Footnote 2

Investigating a Vaccine Against COVID-19

ClinicalTrials.gov Identifier: NCT04400838

Recruitment Status : Recruiting
First Posted : May 26, 2020
Last Update Posted : August 24, 2020

See Contacts and Locations

Sponsor:
University of Oxford

Information provided by (Responsible Party):
University of Oxford

Study Description

Go to

Brief Summary:

A phase 2/3 study to determine the efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine ChAdOx1 nCoV-19 in healthy UK volunteers.

Condition or disease	Intervention/treatment	Phase
Coronavirus	Biological: ChAdOx1 nCoV-19 (Abs 260) Biological: MenACWY vaccine Biological: ChAdOx1 nCoV-19 (Abs 260) + 2.2x10^10vp (qPCR) boost Biological: Two dose MenACWY vaccine Biological: ChAdox1 n-CoV-19 (Abs 260) vaccine low dose Biological: ChAdOx1 nCoV-19 (qPCR) Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Biological: Two dose MenACWY vaccine 4-12 weeks	Phase 2 Phase 3

Detailed Description:

There will be 11 study groups and it is anticipated that a total of 12,330 volunteers will be enrolled. Groups 1, 7 & 9 are adults aged 56-69 years; groups 2, 8 & 10 are adults 70 years and over; group 3 is children aged 5-12 years inclusive; groups 4, 5, 6 & 11 are adults aged 18-55 years.

All subjects will undergo follow-up for a total of 1 year post last vaccination. Additional visits or procedures may be performed at the discretion of the investigators, e.g., further medical history and physical examination, or additional blood tests and other investigations if clinically relevant

Study Design

Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	12330 participants
Allocation:	Randomized
Intervention Model:	Sequential Assignment
Masking:	Single (Participant)
Primary Purpose:	Prevention
Official Title:	A Phase 2/3 Study to Determine the Efficacy, Safety and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19
Actual Study Start Date :	May 28, 2020
Estimated Primary Completion Date :	August 2021
Estimated Study Completion Date :	August 2021

Resource links provided by the National Library of Medicine

MedlinePlus related topics: Coronavirus Infections

Genetic and Rare Diseases Information Center resources: Severe Acute Respiratory Syndrome

U.S. FDA Resources

Arms and Interventions

Go to

Arm	Intervention/treatment
Experimental: Group 1 a1 Volunteers will receive a single dose ChAdOx1 nCOV19 vaccine, 5x10^10vp (Abs 260) delivered intramuscularly	Biological: ChAdOx1 nCoV-19 (Abs 260) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260
Experimental: Group 1 b1 Volunteers will receive two dose ChAdOx1 nCOV19 vaccine, 5x10^10vp (Abs 260) prime and 2.2x10^10vp (qPCR) boost (4-6 weeks apart), delivered intramuscularly	Biological: ChAdOx1 nCoV-19 (Abs 260) + 2.2x10^10vp (qPCR) boost A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260 and 2.2x10^10vp ChAdOx1 nCoV-19 boost measured by qPCR 4-6 weeks later
Experimental: Group 2 a1 Volunteers will receive a single dose ChAdOx1 nCOV19 vaccine, 5x10^10vp (Abs 260) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (Abs 260) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260
Experimental: Group 2 b1 Volunteers will receive two dose ChAdOx1 nCOV19 vaccine, 5x10^10vp (Abs 260) prime and 2.2x10^10vp (qPCR) boost (4-6 weeks apart), delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (Abs 260) + 2.2x10^10vp (qPCR) boost A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260 and 2.2x10^10vp ChAdOx1 nCoV-19 boost measured by qPCR 4-6 weeks later
Experimental: Group 3E Volunteers will receive a single low dose of 2.5x10^10vp ChAdOx1 nCoV-19 (qPCR) delivered intramuscularly.	Biological: ChAdox1 n-CoV-19 (Abs 260) vaccine low dose A single dose of 2.5x10^10vp of ChAdOx1 nCoV-19 measured by qPCR

Experimental: Group 4 a1 Volunteers will receive a single dose ChAdOx1 nCoV19 vaccine, 5x10^10vp (Abs 260) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (Abs 260) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260
Experimental: Group 4 b1 Volunteers will receive two dose ChAdOx1 nCOV19 vaccine, 5x10^10vp (Abs 260) prime and 2.2x10^10vp (qPCR) boost (4-6 weeks apart), delivered intramuscularly	Biological: ChAdOx1 nCoV-19 (Abs 260) + 2.2x10^10vp (qPCR) boost A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260 and 2.2x10^10vp ChAdOx1 nCoV-19 boost measured by qPCR 4-6 weeks later
Experimental: Group 4 c1 Volunteers will receive two dose ChAdOx1 nCOV19 vaccine, 5x10^10vp (Abs260) prime and 2.2x10^10vp (qPCR) boost* (4-6 weeks apart), delivered intramuscularly	Biological: ChAdOx1 nCoV-19 (Abs 260) + 2.2x10^10vp (qPCR) boost A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260 and 2.2x10^10vp ChAdOx1 nCoV-19 boost measured by qPCR 4-6 weeks later
Experimental: Group 5 a1 Volunteers will receive a single dose ChAdOx1 nCoV19 vaccine, 5x10^10vp, (Abs 260) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (Abs 260) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by spectrophotometry at Abs260
Experimental: Group 5 b1 Volunteers will receive a single dose ChAdOx1 nCoV19 vaccine, 5x1010vp, (qPCR) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (qPCR) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by qPCR
Experimental: Group 5 c1 Volunteers will receive a single dose ChAdOx1 nCoV19 vaccine, 5x10^10vp, (qPCR) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (qPCR) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by qPCR
Experimental: Group 5 d1 Volunteers will receive two doses of ChAdOx1 nCoV19 vaccine, 0.5mL (3.5 - 6.5 × 10^10 vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 - 6.5 × 10^10 vp Abs 260, corrected for PS80)

Experimental: Group 6 a1 Volunteers will receive a single dose ofChAdOx1 nCoV19 vaccine, 5x1010vp (qPCR) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (qPCR) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by qPCR
Experimental: Group 6 b1 Volunteers will receive two doses of ChAdOx1 nCoV19 vaccine, 5x1010vp (Abs260) prime and 0.5mL (3.5 - 6.5 × 1010 vp, Abs 260, corrected for PS80)* boost* (4-12 weeks apart, +2 weeks) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 - 6.5 × 10^10 vp Abs 260, corrected for PS80)
Experimental: Group 7 a1 Volunteers will receive a single dose ChAdOx1nCOV19 vaccine, 5x1010vp (qPCR) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (qPCR) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by qPCR
Experimental: Group 7 b1 Volunteers will receive two doses of ChAdOx1nCOV19 vaccine, 5x1010vp (qPCR)* (4-6 weeks apart) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 - 6.5 × 10^10 vp Abs 260, corrected for PS80)
Experimental: Group 8 a1 Volunteers will receive a single dose ChAdOx1nCOV19 vaccine, 5x1010vp (qPCR) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 (qPCR) A single dose of 5x10^10vp of ChAdOx1 nCoV-19 measured by qPCR
Experimental: Group 8 b1 Volunteers will receive two doses of ChAdOx1 nCoV19 vaccine, 0.5mL (3.5 - 6.5 × 10^10 vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 - 6.5 × 10^10 vp Abs 260, corrected for PS80)
Experimental: Group 9 a1 Volunteers will receive two doses of ChAdOx1 nCoV19 vaccine, 0.5mL (3.5 - 6.5 × 10^10 vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 - 6.5 × 10^10 vp Abs 260, corrected for PS80)
Experimental: Group 10 a1 Volunteers will receive two doses of ChAdOx1 nCoV19 vaccine, 0.5mL (3.5 - 6.5 × 10^10 vp,	Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 - 6.5 ×

Abs 260, corrected for PS80)*, (4-6 weeks apart) delivered intramuscularly.	10^10 vp Abs 260, corrected for PS80)
Experimental: Group 11 Volunteers will receive two doses of ChAdOx1 nCoV19 vaccine, 0.5mL (3.5 - 6.5 × 10^10 vp, Abs 260, corrected for PS80)*, (4-6 weeks apart) delivered intramuscularly.	Biological: ChAdOx1 nCoV-19 plus 5x10^10vp boost (qPCR) Two dose ChAdOx1 nCoV-19 0.5mL (3.5 - 6.5 × 10^10 vp Abs 260, corrected for PS80)
Active Comparator: Single dose MenACWY Groups 1 a2, 2 a2, 3 a, 4 a2, 5 a2, 5 b2, 5 c2, 6 a2, 7 a2 & 8 a2 will receive a standard single dose of MenACWY vaccine delivered intramuscularly	Biological: MenACWY vaccine Standard single dose of MenACWY vaccine Other Names: • Menveo • Nimenrix
Active Comparator: Two dose MenACWY Groups 1 b2, 2 b2, 4 b2, 4 c2, 5 d2, 7 b2, 8 b2, 9 a2 & 10 a2 will receive two doses of MenACWY 4-6 weeks apart delivered intramuscularly	Biological: Two dose MenACWY vaccine Two standard doses of MenACWY vaccine 4-6 weeks apart Other Names: • Menveo • Nimenrix
Active Comparator: Two dose MenACWY 4-12 weeks Group 6b2 will receive two doses of MenACWY (4-12 weeks apart, +2 weeks), delivered intramuscularly	Biological: Two dose MenACWY vaccine 4-12 weeks Two standard doses of MenACWY vaccine 4-12 weeks apart, + 2 weeks Other Names: • Menveo • Nimenrix

Outcome Measures

Go to

Primary Outcome Measures :

1. Assess the efficacy of the candidate ChAdOx1 nCoV-19 against COVID-19 in adults aged 18 years and older. [Time Frame: 6 months]

Number of virologically confirmed (PCR positive) symptomatic cases of COVID-19

2. Assess the safety of the candidate vaccine ChAdOx1 nCoV-19 in adults and children [Time Frame: 6 months]

   Occurrence of serious adverse events (SAEs) throughout the study duration.

Secondary Outcome Measures :

1. Assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19: occurrence of solicited local reactogenicity signs and symptoms for 7 days following [Time Frame: 7 days post vaccination]

   Occurrence of solicited local reactogenicity signs and symptoms for 7 days following vaccination

2. Assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19: occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following [Time Frame: 7 days post vaccination]

   Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following vaccination

3. Assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19: occurrence of unsolicited adverse events (AEs) for 28 days following vaccination [Time Frame: 28 days post vaccination]

   Occurrence of unsolicited adverse events (AEs) for 28 days following vaccination (except groups 4 & 6)

4. Assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 through standard blood tests (full blood count, liver and kidney function tests) [Time Frame: 6 months]

   Frequency of participants with clinically significant changes from baseline for safety laboratory measures (haematology and biochemistry blood results; except groups 4 and 6)

5. Assess the safety, tolerability and reactogenicity profile of the candidate vaccine ChAdOx1 nCoV-19 by measuring the number of disease enhancement episodes [Time Frame: 6 months]

   Occurrence of disease enhancement episodes

6. Assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19: hospital admissions [Time Frame: 6 months]

   Number of hospital admissions associated with COVID-19

7. Assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19 [Time Frame: 6 months]

   Number of intensive care unit (ICU) admissions associated with COVID-19

8. Assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19: number of deaths [Time Frame: 6 months]

   Number of deaths associated with COVID-19

9. Assess efficacy of the candidate ChAdOx1 nCoV-19 against severe and non-severe COVID-19 by measuring seroconversion rates [Time Frame: 6 months]

   Proportion of people who become seropositive for non-Spike SARS-CoV-2 antigens during the study

10. Assess humoral immunogenicity of ChAdOx1 nCoV-19: antibody quantification [Time Frame: 28 days post vaccination]

    Quantify antibodies against SARS-CoV-2 spike protein (seroconversion rates)

11. Assess humoral immunogenicity of ChAdOx1 nCoV-19: seroconversion [Time Frame: 28 days post vaccination]

    Proportion of seroconversion to antibodies against SARS-CoV-2 spike protein at Day 28 post-vaccination

12. Assess cellular and humoral immunogenicity of ChAdOx1 nCoV-19 through ELISpot assays (groups 1, 2 and 3 only) [Time Frame: 6 months]

    Interferon-gamma (IFN-γ) enzyme-linked immunospot (ELISpot) responses to SARS-CoV-2 spike protein

13. Assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1 and 2 only): local reactogenicity [Time Frame: 7 days post vaccination]

    Occurrence of solicited local reactogenicity signs and symptoms for 7 days following booster vaccination

14. Assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1 and 2 only): systemic reactogenicity [Time Frame: 7 days post vaccination]

    Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days following booster vaccination

15. Assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1 and 2 only) [Time Frame: 28 days post vaccination]

    Occurrence of unsolicited adverse events (AEs) for 28 days following booster vaccination

16. Assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1 and 2 only) through standard blood tests (full blood count, liver and kidney function tests) [Time Frame: 6 months]

    Frequency of participants with clinically significant changes from baseline from pre-booster for safety laboratory measures (haematology and biochemistry blood results)

17. Assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1 and 2 only) via seroconversion [Time Frame: 56 days post vaccination]

    Antibodies against SARS-CoV-2 spike protein at Day 56 post-vaccination (seroconversion rates)

18. Assess the safety and immunogenicity of a booster dose of ChAdOx1 nCoV-19 in older adults aged 56 years or older (two-dose schedules for groups 1 and 2 only) [Time Frame: 56 days post vaccination]

    Proportion of seroconversion to antibodies against SARS-CoV-2 spike protein at Day 56 post-vaccination

Other Outcome Measures:

1. Exploratory Immunology by virus neutralising antibody assays [Time Frame: 6 months]

    Virus neutralising antibody (NAb) assays against live and/or pseudotype SARS-CoV-2 virus

2. Exploratory Immunology by flow cytometry [Time Frame: 6 months]

    Cell analysis by flow cytometry assays

3. Exploratory Immunology by functional antibody assays [Time Frame: 6 months]

    Functional antibody assays

4. Exploratory Immunology: anti-vector immunity [Time Frame: 6 months]

    Anti-vector immunity induced by 1 or 2 doses of ChAdOx1 nCoV-19

5. Measure exposure to COVID-19 [Time Frame: 6 months]

Reported by weekly survey to collect information about cases amongst household contacts and friends, contact with the general public, infection control procedures

6. Exploratory efficacy against infection: assess efficacy of the candidate ChAdOx1 nCoV-19 against SARS-CoV-2 infection by PCR [Time Frame: 6 months]

   Number of PCR positive cases of COVID-19 infection

7. Exploratory efficacy against infection: assess efficacy of the candidate ChAdOx1 nCoV-19 against SARS-CoV-2 infection [Time Frame: 6 months]

   Measure of differences in viral loads between those with severe, mild, and asymptomatic PCR+ SARS-CoV-2 infections

8. Compare safety, reactogenicity and immunogenicity between different manufacturing batches of ChAdOx1 nCoV-19 used in COV001 and COV002 [Time Frame: 6 months]

   Differences in safety, reactogenicity and immunogenicity profiles between Group 1 in COV001 and Group 5 in COV002 (proportion of Grade 3 solicited AEs, occurrence of fevers, seroconversion rates at D28, neutralising antibody titres and differences in T-cell responses at D14).

9. Compare safety, reactogenicity and immunogenicity between different methods for measuring doses (Abs260, Abs260 corrected for PS80, and qPCR) of ChAdOx1 nCoV-19 [Time Frame: 6 months]

   Differences in safety, reactogenicity and immunogenicity profiles between Groups 1, 2, and 5A compared with Groups, 7, 8, and 5B/C (proportion of Grade 3 solicited AEs, occurrence of fevers, seroconversion rates at D28, neutralising antibody titres and differences in T-cell responses at D14).

10. Assess vaccine induced mucosal immunity: Nasal mucosa IgA levels at D0 and D28 in a subset of individuals [Time Frame: 6 months]

    Nasal mucosa IgA levels at D0 and D28 in a subset of individuals

11. Compare viral shedding on stool samples of SARS-CoV-2 PCR positive individuals [Time Frame: 6 months]

    Differences in viral shedding on stool at 7 days and beyond post SARS-CoV-2 positivity

12. Compare immunogenicity of ChAdOx1 nCoV-19 in participants receiving 1 or 2 doses in groups 1, 2, 7 and 8: differences in antibody titres [Time Frame: 6 months]

    Differences in antibody titres (ELISA and Neutralising antibodies) in participants who received 1 or 2 doses of ChAdOx1 nCoV-19 (groups 1, 2, 7 and 8)

13. Compare immunogenicity of ChAdOx1 nCoV-19 in participants receiving 1 or 2 doses in groups 1, 2, 7 and 8: longevity of immune responses [Time Frame: 6 months]

    Longevity of immune responses in participants who received 1 or 2 doses of ChAdOx1 nCoV-19

14. Describe the impact of previous vaccination with other ChAdOx1 vectored vaccines on safety and immune responses to ChAdOx1 nCoV-19 [Time Frame: 6 months]

    Differences reactogenicity profile, antibody titres and T-cell responses between groups 5d and 11 and their relationship with anti-vector neutralising antibody titres.

Eligibility Criteria

Go to

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	5 Years and older (Child, Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	Yes

Criteria

Inclusion Criteria:

- Adults aged 18 - 55 years (groups 4, 5, 6 and 11)
- Adults aged 56-69 years (groups 1, 7, and 9)
- Adults aged 70 years and older (groups 2, 8, and 10)
- Children aged 5-12 years inclusive (group 3)
- Able and willing (in the Investigator's opinion) to comply with all study requirements.
- Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures.
- For females of childbearing potential only, willingness to practice continuous effective contraception (see below) during the study and a negative pregnancy test on the day(s) of screening and vaccination.

- Agreement to refrain from blood donation during the course of the study.
- Provide written informed consent.
- Parent/Guardian provides informed consent

Exclusion Criteria:

• Participation in COVID-19 prophylactic drug trials for the duration of the study.

Note: Participation in COVID-19 treatment trials is allowed in the event of hospitalisation due to COVID-19. The COV002 study team should be informed as soon as possible.

• Participation in SARS-CoV-2 serological surveys where participants are informed of their serostatus for the duration of the study.

Note: Disclosure of serostatus post enrolment may accidently unblind participants to group allocation. Participation in COV002 can only be allowed if volunteers are kept blinded to their serology results from local/national serological surveys

- Receipt of any vaccine (licensed or investigational) other than the study intervention within 30 days before and after each study vaccination, with the exception of the seasonal influenza vaccination. Participants will be encouraged to receive this vaccination at least 7 days before or after their study vaccine.
- Prior or planned receipt of an investigational or licensed vaccine or product likely to impact on interpretation of the trial data (e.g. Adenovirus vectored vaccines, any coronavirus vaccines). This exclusion criteria will not apply to group 11, as recruitment will be targeted at those volunteers who previously received a ChAdOx1 vectored vaccine.
- Administration of immunoglobulins and/or any blood products within the three months preceding the planned administration of the vaccine candidate.
- Any confirmed or suspected immunosuppressive or immunodeficient state; asplenia; recurrent severe infections and use of immunosuppressant medication within the past 6 months, except topical steroids or short-term oral steroids (course lasting ≤14 days)
- History of allergic disease or reactions likely to be exacerbated by any component of ChAdOx1 nCoV-19 or MenACWY
- Any history of angioedema.
- Any history of anaphylaxis.
- Pregnancy, lactation or willingness/intention to become pregnant during the study.
- Current diagnosis of or treatment for cancer (except basal cell carcinoma of the skin and cervical carcinoma in situ).
- History of serious psychiatric condition likely to affect participation in the study.
- Bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder), or prior history of significant bleeding or bruising following IM injections or venepuncture.
- Continuous use of anticoagulants, such as coumarins and related anticoagulants (i.e. warfarin) or novel oral anticoagulants (i.e. apixaban, rivaroxaban, dabigatran and edoxaban)

- Suspected or known current alcohol or drug dependency.
- Any other significant disease, disorder or finding which may significantly increase the risk to the volunteer because of participation in the study, affect the ability of the volunteer to participate in the study or impair interpretation of the study data.
- Severe and/or uncontrolled cardiovascular disease, respiratory disease, gastrointestinal disease, liver disease, renal disease, endocrine disorder and neurological illness (mild/moderate well controlled comorbidities are allowed)
- History of laboratory confirmed COVID-19. o Seropositivity to SARS-CoV-2 before enrolment (except groups 5d, 9, 10 and 11)

Additional Exclusion criteria to Groups 4, 6, 9 and 10 • History of allergic disease or reactions likely to be exacerbated by Paracetamol

o Note: Caution should be taken when recommending paracetamol to adults who already take paracetamol chronically

Additional Exclusion Criteria to Group 3

- Chronic medical conditions such as chronic lung disease, chronic liver disease, chronic renal failure, chronic heart disease, congenital genetic syndromes (e.g. Trisomy 21)
- Fulfil any of the contraindications to vaccination as specified in The Green Book

Re-vaccination exclusion criteria (two-dose groups only)

- Anaphylactic reaction following administration of vaccine
- Pregnancy
- Any AE that in the opinion of the Investigator may affect the safety of the participant or the interpretation of the study results

Contacts and Locations

Go to

Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): ***NCT04400838***

Contacts

Contact: Volunteer Recruitment Coordinator 01865 611424 vaccinetrials@ndm.ox.ac.uk

Locations

▶ Show 20 study locations

Sponsors and Collaborators

University of Oxford

Investigators

Principal Investigator: Andrew Pollard, Prof University of Oxford

More Information

Go to

Responsible Party:	University of Oxford
ClinicalTrials.gov Identifier:	NCT04400838
Other Study ID Numbers:	COV002
First Posted:	May 26, 2020 Key Record Dates
Last Update Posted:	August 24, 2020
Last Verified:	May 2020

Studies a U.S. FDA-regulated Drug Product:	No
Studies a U.S. FDA-regulated Device Product:	No

Keywords provided by University of Oxford:

Covid-19
ChAdOx1 nCov19
sars-cov-2
vaccine

Additional relevant MeSH terms:

Coronavirus Infections
Coronaviridae Infections
Nidovirales Infections
RNA Virus Infections
Virus Diseases
Vaccines
Immunologic Factors
Physiological Effects of Drugs

TO TOP

For Patients and Families | For Researchers | For Study Record Managers

HOME RSS FEEDS SITE MAP TERMS AND CONDITIONS DISCLAIMER CUSTOMER SUPPORT

Footnote 3

Science. Author manuscript; available in PMC 2015 Apr 29.

Published in final edited form as:

Science. 2014 Apr 4; 344(6179): 49–51.

doi: 10.1126/science.1250672

PMCID: PMC4414116

NIHMSID: NIHMS679843

PMID: 24700849

Immune Activation with HIV Vaccines: Implications of the Adenovirus Vector Experience

Anthony S. Fauci,[1,*] Mary A. Marovich,[1] Carl W. Dieffenbach,[1] Eric Hunter,[2] and Susan P. Buchbinder[3]

Author information Copyright and License information Disclaimer

The development of a safe and effective HIV vaccine is perhaps the most significant and challenging goal remaining in HIV/AIDS research. Recent progress using a poxvirus vector prime and envelope protein boost strategy demonstrated a modest but significant level of efficacy and for the first time established the

concept that a vaccine could prevent HIV infection (1). Because protection waned over time, approaches to boost durability and efficacy are currently in the planning stages (2).

In addition, alternative approaches, particularly those using adenovirus vectors with various HIV gene inserts have been evaluated. In this regard, between 2005 and 2013 two vaccine concepts based on recombinant Adenovirus serotype-5 (rAd5) were evaluated in three efficacy studies (3–5). The first study (Step) using 3 doses of the Merck rAd5-gag/pol/nef vaccine was stopped for futility; of note, a trend toward increased HIV infections in vaccine recipients was observed (3). Once the entire Step dataset accumulated from 18 months of blinded follow-up was analyzed, this trend became statistically significant (6). The Step study showed an overall increased risk of acquisition (HR 1.4, $p< 0.03$); however, the group at highest risk was uncircumcised men who both had sex with men (MSM) *and* had high levels of pre-existing Ad5 antibodies (HR 4.2, $p=0.02$) (6).

Following the release of the Step findings, the Phamibili trial of the same Merck Ad5 vaccine platform conducted in South Africa, was closed and unblinded early during the enrollment period. Few Phamibili participants received the planned three doses of vaccine. Primary analysis of the Phambili follow up data showed no increased risk of HIV infection (5). However, data from the long term unblinded follow-up of Phambili participants suggested an increased risk of infection in vaccinated men compared to unvaccinated controls (7).

In 2009, a different rAd5 vaccine platform advanced to efficacy testing in the HIV Vaccine Trial Network (HVTN) 505 trial. The vaccine contained 3 doses of a DNA prime followed by a single rAd5 boost with inserts expressing HIV envelope and viral structural antigens. As a safety precaution, this study restricted enrollment to circumcised MSM who lacked pre-existing Ad5 antibodies, since no level of increased risk had been seen in this group in the Step Trial (6). The HVTN 505 trial was halted prematurely because it met futility criteria; however, there was no evidence of increased risk of acquisition in the vaccinated subjects (8).

Based upon this information, the National Institute of Allergy and Infectious Diseases (NIAID) convened the Mini-Summit on Adenovirus Platforms for HIV Vaccines on September 19, 2013 (9) to investigate: 1) if rAd5 vectors are associated with increased risk of HIV infection; and 2) whether these problems extend to some or

all of the other recombinant adenovirus vectors currently in development. Additional goals were to evaluate possible mechanisms by which rAd vectors could increase susceptibility to infection. In addition, the question was raised whether increased susceptibility might be seen with any HIV vaccine that activates the immune system rendering activated CD4+ T cells more susceptible to HIV infection, while at the same time inducing little or no protective effect against HIV acquisition (9).

Results of a Meta-Analysis

To better understand the impact of rAd5 vaccination on HIV acquisition, a meta-analysis of the Step, Phambili and HVTN 505 trials was performed by a group of statisticians from the HVTN Statistics and Data Management Center and from NIAID. Combining data from the three studies, the statisticians determined there was an overall hazard ratio of 1.33 ($p<0.01$) associated with vaccination. However, almost all of the increased risk of HIV acquisition was driven by the Merck vaccine (Step and Phambili: HR = 1.41, $p = 0.005$) with the Step trial contributing most infection endpoints. HVTN 505 considered alone did not show any trend toward infection risk (9–10). It could not be determined by this analysis whether the lack of increased susceptibility in the latter trial was due to population or regimen (inclusion of env, DNA prime, single rAd5 boost with differences in vector backbone).

Other Ad-Based Vaccines

HIV acquisition risk following vaccination with other Ad-based vaccines was also investigated. Alternative Ad vectors for use in tuberculosis or malaria vaccines have not been evaluated in trials in sufficient numbers of adults at risk for HIV infection to provide useful information about possible interactions with HIV. However, active duty U. S. Army recruits have been vaccinated with Ad4/7 to prevent highly contagious respiratory illnesses in close quarters during training (11). During the time window of 1999–2011, the U.S. Army interrupted and then resumed vaccination with Ad4/7, creating three separate cohorts for comparison. The serologic data for incidence of HIV infection was reviewed retrospectively for these three cohorts by Dr. A.M. Cost and no changes in HIV incidence was detectable (9).

Potential Mechanisms for rAd5 effects

In 2008, NIAID held an HIV Vaccine Summit to reassess research

directions following the lack of efficacy of the Step trial that had been reported that year. That summit fostered studies to understand the possible mechanisms of the effects seen in the Step study (12). At the 2013 NIAID Mini-Summit, Dr. M. Betts, presenting on behalf of collaborative work with Dr. G. Silvestri, summarized results from non-human primate (NHP) studies of the Merck rAd5-gag/pol/nef vaccine constructs that were used in the Step and Phambili studies. The data revealed an increase in activated CD4+ T cells in the gastrointestinal mucosa after rAd vaccination; and increased SIV acquisition following rAd-SIV vaccination, although immunization with the empty rAd vector did not increase SIV acquisition (13). In this regard, Dr. J. McElrath reported that the human gut biopsies of individuals vaccinated with the DNA prime and rAd5 boost as part of HVTN 204 (low risk) and HVTN 505 (high risk) revealed high levels of activated Ad-specific CD4+ T-cells, with an increase in CCR5 expression, but no HIV specific cells in multiple samples from the rectum and colon (9). Furthermore, the activated T cells were concentrated in unevenly distributed foci making extensive sampling a necessity (14). Although there is no current evidence of increased risk of HIV acquisition for other Ad vectors, the presence of rAd5-activated T-cells in tissue and the known degree of shared T cell epitopes between Ad serotypes needs to be considered as a possible area of concern. Ad serotype cross reactivity can be attributed, in part, to extensive CD4+ and CD8+ T cell recognition of highly conserved hexon regions across most human and primate Ad species (15–17). Therefore, this issue must at least be considered in the risk/benefit analysis of potential HIV vaccine trials using alternate Ad vectors. However, according to Dr. Dan Barouch in a Phase 1 study using a single rAd26-HIV env vaccination, a limited set of rectal biopsies showed no evidence for increased Ad-specific T cell activation in low risk volunteers and a different host gene activation signature from that in Ad5 vaccinated individuals (9). Nonetheless, we feel that a description of the rAd5 experience should be included in informed consents associated with HIV vaccine trials using alternate Ad vectors.

It is conceivable that increased risk of acquisition could be associated with any vaccination strategy that activates T cells, especially at mucosal surfaces. A vaccine must engage the immune system in order to induce a response. If the balance between the induction of protective anti-HIV responses versus Ad-specific responses that activate CD4+ T cells leans towards an anti-HIV response, then protection might be seen despite the presence of susceptible activated CD4+ T cell targets. However, increased

susceptibility to infection may be seen if: the anti-HIV response is weak and does not counterbalance the increased susceptibility of activated CD4+ T cells; if the anti-HIV response wanes faster than the CD4+ T cell activation; or if the Ad-induced response is maintained and boosted by re-exposure to alternative Adenoviruses. Furthermore, cellular immune responses against Ad5, regardless of Ad serostatus, have been shown to diminish anti-HIV responses to rAd5-HIV vaccination in Step (15). In summary, the efficacy or not of an HIV vaccine may reflect a balance of two competing activities—protection driven by anti-HIV responses versus a risk of increased acquisition driven by cellular activation induced by anti-vector or any other immune activating response.

Considerations for the future

Given the increased risk together with the lack of efficacy in trials using rAd5, further HIV vaccine studies testing rAd5 vectors are not appropriate. When considering HIV vaccines that are designed to elicit a component of T-cell immunity, a risk/benefit analysis should consider the balance between anti-HIV responses and vector-directed responses that activate CD4+ T cells, thus rendering them more susceptible to HIV infection, and the potential for re-exposure to vector-related antigens in the environment with subsequent restimulation of the vector response. This is particularly important when evaluating viral vectors, including alternative Ad vectors. Future clinical testing of Ad-based vaccines should evaluate the levels and distribution of both vector and insert responses in target tissues where HIV acquisition is known to occur.

There are a number of research activities that could be pursued to help understand the roles of anti-vector responses in overall HIV vaccine efficacy. First, NHP studies using empty vectors or vectors with non-HIV inserts as placebo controls could define the levels of anti-vector immunity and evaluate the effect on virus acquisition of this vector-related activation of CD4+ T cells independent of an anti-HIV response. Second, the field could benefit from additional NHP studies. For example, the identification of biomarkers in primates that indicate increased risk of acquisition (18) could be valuable to monitor for risk in early phase human studies.

Third, a better understanding of mucosal immune responses to HIV vaccination is needed. The timing, location and number of mucosal biopsies that define the vaccine-induced gut immune responses need clarification. Importantly, understanding the influence of the

mucosal microbiome on vaccination (19) and the impact specifically of the virome will be important. Particularly for Ad-based vectors, understanding components of risk related to the level of Ad exposure and persistence will be essential.

For non-HIV vaccine trials using vectors that induce strong T-cell immunity that are conducted in regions with high HIV incidence, it may be important to monitor for HIV acquisition, depending on the target population. In such studies where the population may be at risk of HIV exposure, HIV incidence should be monitored at the end of the study and for an appropriate follow-up period.

In summary, the experience with rAd5-based HIV vaccines has taught us that vaccine-induced protection against acquisition of HIV infection likely reflects the balance between beneficial anti-HIV responses and deleterious effects of immune activation that increases the susceptibility of CD4+ T cells to infection (Figure 1). Among the spectrum of existing or planned vaccines, this phenomenon is likely unique for an HIV vaccine since the activated CD4+ T cell is the very target for the virus. These observations should be taken into serious consideration in future HIV vaccine research endeavors and underscores the importance of maximizing the specific anti-HIV responses of such candidates.

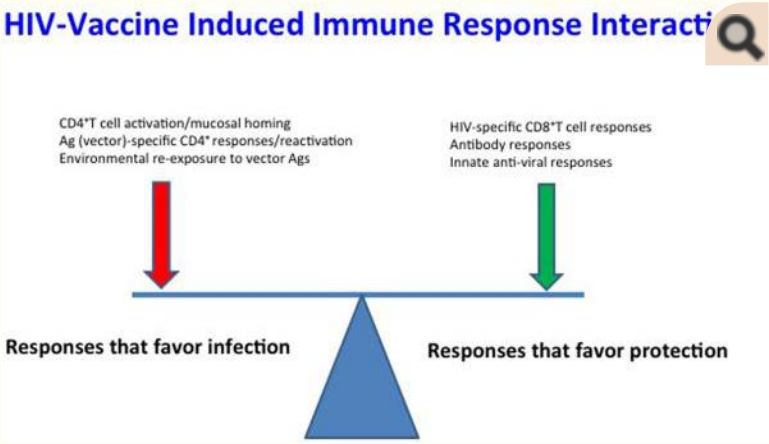


Figure 1

HIV-Vaccine Induced Immune Response Interactions

Immune activation associated with HIV vaccination theoretically can lead to increased infection due to the activation of CD4+ T cells during the immune response. The level of protection seen with a vaccine can be viewed as the balance between the responses to the vaccine that lead to susceptibility to infection counterbalanced by the responses that favor protection.

References

1. Rerks-Ngarm S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361:2209–2220. [PubMed] [Google Scholar]

2. Robb ML, et al. Risk behaviour and time as covariates for efficacy of the HIV vaccine regimen ALVAC-HIV (vCP1521) and AIDSVAX B/E: a post-hoc analysis of the Thai phase 3 efficacy trial RV 144. Lancet Infect Dis. 2012;12(7):531–7. [PMC free article] [PubMed] [Google Scholar]

3. Buchbinder S, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet. 2008;372:1881. [PMC free article] [PubMed] [Google Scholar]

4. McElrath J, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. Lancet. 2008;372:1894. [PMC free article] [PubMed] [Google Scholar]

5. Gray GE, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis. 2011;11(7):507–15. [PMC free article] [PubMed] [Google Scholar]

6. Duerr A, et al. Extended follow-up confirms early vaccine-enhanced risk of HIV acquisition and demonstrates waning effect over time among participants in a randomized trial of recombinant adenovirus HIV vaccine (Step Study) J Infect Dis. 2012;206(2):258–66. [PMC free article] [PubMed] [Google Scholar]

7. Gray GE, et al. Long term follow up of the HVTN503/Phambili Study, a phase 2b HIV vaccine trial, investigating an Ad5 HIV-1 gag/pol/nef vaccine in South Africa. N Engl J Med. 2013 Dec; submitted. [Google Scholar]

8. Hammer SH, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med. 2013;369(22):2083–92. [PMC free article] [PubMed] [Google Scholar]

9. National Institute of Allergy and Infectious Diseases Mini-Summit on Adenovirus Platforms for HIV Vaccines. 2013 Sep 19; webcast available at: http://www.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/Pages/adenovirusPlatforms.aspx.

10. Hammer S, et al. paper presented at AIDS Vaccine Meeting Barcelona, Spain, 2013. AIDS Research and Human Retroviruses. 2013 Nov;29(11):A-1–A-208. [Google Scholar]

11. Hoke CH, Jr, Snyder CE., Jr History of the restoration of adenovirus type 4 and type 7 vaccine, live oral (Adenovirus Vaccine) in the context of the Department of Defense acquisition system. Vaccine. 2013;31(12):1623–32. [PubMed] [Google Scholar]

12. Fauci AS, et al. HIV Vaccine Research: The Way Forward. Science. 2008;321:530–532. [PubMed] [Google Scholar]

13. Qureshi H, et al. Low-dose penile SIVmac251 exposure of rhesus macaques infected with adenovirus type 5 (Ad5) and then immunized with a replication-defective Ad5-based SIV gag/pol/nef vaccine recapitulates the results of the phase IIb step trial of a similar HIV-1 vaccine. J Virol. 2012;86(4):2239–50. [PMC free article] [PubMed] [Google Scholar]

14. McElrath J. paper presented at The Collaboration for AIDs Vaccine Discovery Meeting; Seattle, WA. Decemember. 2013. Sponsored by the Bill and Melinda Gates Foundation. [Google Scholar]

15. Frahm N, et al. Human adenovirus-specific T cells modulate HIV-specific T cell responses to an Ad5-vectored HIV-1 vaccine. J Clin Invest. 2012;122(1):359–67. [PMC free article] [PubMed] [Google Scholar]

16. Hutnick NA, et al. Adenovirus-specific human T cells are pervasive, polyfunctional, and cross-reactive. Vaccine. 2010;28(8):1932–41. [PMC free article] [PubMed] [Google Scholar]

17. Heemskerk B, et al. Extensive cross-reactivity of CD4+ adenovirus-specific T cells: implications for immunotherapy and gene therapy. J Virol. 2003;77(11):6562–6. [PMC free article] [PubMed] [Google Scholar]

18. Martinelli E, et al. The frequency of $\alpha_4\beta_7$(high) memory $CD4^+$ T cells correlates with susceptibility to rectal simian immunodeficiency virus infection. J Acquir Immune Defic Syndr. 2013;64(4):325–31. [PMC free article] [PubMed] [Google Scholar]

19. Williams WB, et al. paper presented at AIDS Vaccine Meeting Barcelona, Spain, 2013. AIDS Research and Human Retroviruses. 2013;29(11):A-1–A-208. [Google Scholar]

Footnote 5

Siri | Glimstad

200 Park Avenue, Seventeenth Floor, New York, NY 10166
sirillp.com | P: (212) 532-1091 | F: (646) 417-5967

VIA ELECTRONIC FILING

July 20, 2020

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
Commissioner Stephen M. Hahn, M.D.
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Dear Commissioner Hahn,

Enclosed is an Amended Citizen Petition filed by Del Bigtree and the Informed Consent Action Network ("ICAN") regarding clinical trials of vaccines for SARS-CoV-2 which raise exigent concerns that demand your immediate attention.

ICAN looks forward to receiving a timely decision and we, as counsel to the petitioners, remain available to answer questions and provide any relevant additional information.

Very truly yours,

/s/ Aaron Siri
Aaron Siri
Elizabeth Brehm
Jessica Wallace
SIRI & GLIMSTAD LLP
200 Park Avenue
17th Floor
New York, NY 10166
Telephone: (212) 532-1091
Facsimile: (646) 417-5967
Email: aaron@sirillp.com

UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
AND THE FOOD AND DRUG ADMINISTRATION

PETITION FOR ADMINISTRATIVE ACTION TO REQUIRE, *INTER ALIA*, PLACEBO CONTROL GROUP IN CLINICAL TRIALS OF COVID-19 VACCINES	**:**	**Docket No. 2020-P-1601**

AMENDED CITIZEN PETITION

The original petition in this matter was submitted on June 17, 2020. In that petition, the undersigned requested that the Food and Drug Administration (the "**FDA**") require, among other things, that all clinical trials of a COVID-19 vaccine include a control group that receives a placebo. This request was submitted because, among other things, on May 22, 2020, the FDA approved a clinical trial of a COVID-19 vaccine in which the control group would receive a MenACWY vaccine instead of a placebo.[1]

In light of the guidance issued by the FDA on June 30, 2020, titled *Development and Licensure of Vaccines to Prevent COVID-19: Guidance for Industry* (the "**FDA COVID-19 Guidance**"), which provided, *inter alia*, that the control group receive a placebo in all clinical trials for COVID-19 vaccines, the undersigned submits this amended petition.

This amended petition is being submitted pursuant to 21 C.F.R. § 10.30 and related relevant provisions of the Federal Food, Drug, and Cosmetic Act and Public Health Service Act, the Public Health and Welfare at, *inter alia*, 42 U.S.C. § 262(a)(2)(A)-(C) and 42 U.S.C. § 262(j), and 42 U.S.C. § 300aa-10 *et seq.*, to request that the Commissioner of Food and Drugs (the "**Commissioner**") require, *inter alia*, that all Phase II and III trials of vaccines against the novel coronavirus, SARS-CoV-2 ("**COVID-19**") track all adverse events for an adequate period of time.

A. Action Requested

1. For Phase II and Phase III trials of COVID-19 vaccines, it is hereby requested that the Commissioner require any and all adverse events and reactions (including, but not limited to, systemic adverse reactions, adverse events, non-serious adverse event, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine) be documented for the entire duration of the clinical trial.

[1] https://www.clinicaltrials.gov/ct2/history/NCT04400838?V_1=View#StudyPageTop (last visited July 10, 2020).

2. For Phase II and III trials of COVID-19 vaccines, it is hereby requested that the Commissioner require all adverse events and reactions for each subject be tracked post-vaccination for a minimum period of twelve months for adults, thirty-six months for children, and sixty months for infants and toddlers.

3. For Phase III trials of COVID-19 vaccines, it is hereby requested that more specific and appropriate guidance on the number of subjects receiving the vaccine and placebo be provided in the FDA COVID-19 Guidance, and that the updated guidance require at least 20,000 subjects receive the COVID-19 vaccine with a 1:1 randomization between vaccine and placebo groups.

4. In the FDA COVID-19 Guidance, the FDA provided that, "Later phase trials, including efficacy trials, should be randomized, double-blinded, and placebo controlled … with 1:1 randomization between vaccine and placebo groups." The foregoing guidance, which comports with our June 17, 2020 requests, is appreciated but it is hereby requested that the FDA formally adopt this industry guidance, with the necessary flexibility, as formal regulatory requirements.

B. Statement of Grounds

5. The need for adequate clinical trials of any potential COVID-19 vaccine is acute for many reasons, including because: (i) according to the most recent CDC estimates, COVID-19 rarely injures children and younger healthy adults; (ii) overall, 99.74% of those infected with COVID-19 recover;[2] (iii) even without social distancing, it appears that only a minority of those in contact with an infected individual become infected; and (iv) the vaccine will likely be administered to at least hundreds of millions of individuals. If the vaccine, for example, causes .3% of children to develop a chronic health condition a year after injection, that could cause lifelong health issues for millions of children. This is why international scientists have declared that "inadequately powered studies should themselves be considered a breach of ethical standards."[3] Without a clinical trial of sufficient size that reviews all potential adverse events for a sufficient duration, this potentially catastrophic result will not be identified prior to licensure.

6. Moreover, states are expected to mandate the vaccine for all their residents. For example, the New York State Bar Association recently issued a report on COVID-19 recommending that "[w]hen the efficacy of a COVID-19 vaccine has been confirmed, enact legislation requiring vaccination of each person unless the person's physician deems vaccination for his or her patient to be clinically inappropriate."[4] Mandating administration of the vaccine, thereby eliminating the right to informed consent, only makes more acute the need to assure that the safety and efficacy of any COVID-19 vaccine is robustly studied in an adequate clinical trial monitoring for any potential adverse events.

---

[2] https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html#box (last visited June 2, 2020).

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2504487/ (last visited July 12, 2020).

[4] https://nysba.org/app/uploads/2020/05/HealthLawSectionTaskForceCOVID-19Report_5.13.20-1.pdf (last visited June 2, 2020).

7. Further heightening this need is the fact that the Secretary of the United States Department of Health & Human Services ("**HHS**") has already granted those developing and selling any COVID-19 product broad immunity from liability for injuries.[5]

8. Reflecting the importance of a robust clinical trial, on May 24, 2020, a member of the FDA's Vaccines and Related Biological Products Advisory Committee ("**VRBPAC**"), Dr. Paul Offit, told CNN News that, in order to determine whether a COVID-19 vaccine is safe and effective, "we are waiting for the big trial… the large prospective placebo controlled trial, we have 20,000 people who get a vaccine, 10,000 people who get a placebo, then and only then will you know whether a vaccine is safe and effective."[6]

a. Tracking All Adverse Events During the Clinical Trial

9. To increase assurance that potential adverse events from the candidate COVID-19 vaccines are captured, all adverse events and reactions (including but not limited to: systemic adverse reactions, adverse events, non-serious adverse event, serious adverse events, medically-attended adverse events, new onset medical conditions, and any other health issue of any degree or type arising or exacerbated post-vaccination, whether suspected, unexpected, expected or otherwise, and whether or not considered related to the vaccine) should be documented for each subject post-vaccination, whether or not they are considered vaccine-related by the investigator or sponsor, for the duration of the clinical trial.[7]

10. The adverse events captured beyond a short duration should not be limited to "serious adverse events," since there are many autoimmune, neurological and chronic health disorders which have a major impact on the quality of life, yet are categorized by the FDA as "adverse reactions" and not categorized as "serious adverse reactions."[8] To wit, there are a myriad of post-licensure adverse reactions reported by consumers and physicians and also listed in the package inserts for one or more vaccines, that any individual living with would categorize as "serious"; yet the FDA, under its current guidelines, may not. These include, but are not limited to: alopecia, autoimmune disease, lupus erythematosus, vasculitis, Bell's Palsy, hypotonia, migraine, myelitis, neuropathy, seizures, mental disorders, rhinitis, and vertigo.[9]

---

[5] https://www.phe.gov/Preparedness/legal/prepact/Pages/default.aspx (last visited June 2, 2020).

[6] https://www.cnn.com/videos/health/2020/05/24/coronavirus-covid-19-vaccine-trials-vaccinologist-concern-ip-vpx.cnn (emphasis added) (last visited June 2, 2020).

[7] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32 (last visited July 10, 2020) (defining "Adverse event" as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related"); https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event (last visited July 10, 2020).

[8] The FDA defines an adverse event to be "serious" if it results in one of the following specific outcomes: "death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect." FDA Guidance for Industry and Investigators, https://www.fda.gov/media/79394/download (last visited June 30, 2020).

[9] *See* https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm (last visited June 30, 2020). Also, the determination of whether an adverse reaction is a "serious adverse event"

11. The current FDA COVID-19 Guidance provides that these adverse events should be captured for only 28 days after vaccination while "serious adverse events" should continue to be captured for at least 6 months. As the Principal Deputy Commissioner of the FDA, along with her colleagues at the FDA, wrote with regard to monitoring safety during a clinical trial: "sponsors are expected to monitor all adverse events, including nonserious ones, during drug development."[10]

12. Given that "serious adverse events" are already being captured for 6 months, it appears foolhardy to not also capture all adverse events. If a COVID-19 vaccine causes a systemic autoimmune issue to arise two months after vaccination, it would be irresponsible and unethical not to capture that reaction because it falls into the artificial zone of being an "adverse event" or "non-serious adverse event" rather than a "serious adverse event."

13. The undersigned therefore respectfully urges that the action requested in paragraph 1 above be adopted forthwith.

b. Minimum Period to Track Adverse Events

14. At a minimum, all adverse events and reactions should be documented for each subject post-vaccination for at least: (i) twelve months for adults, (ii) thirty-six months for children, and (iii) sixty months for infants and toddlers. These minimal timeframes provide an opportunity to capture adverse and non-specific health issues that the COVID-19 vaccine may cause.

15. The importance of capturing all potential health issues for a material duration is reflected in the clinical trials of, for example, the drugs Enbrel[11], Lipitor[12], and Botox,[13] which had safety review periods of 6.6 years, 4.8 years and 51 weeks respectively, with a placebo control group. As another example, the weight loss drug Belviq, indicated only for adult use, was safety tested in a placebo-controlled trial for two years before being licensed by the FDA in 2012.[14] In February 2020 the drug was voluntarily removed from the US market at the request of the FDA

---

is typically left to the discretion of the sponsor of the clinical trial or the clinical investigators, who are paid by the sponsor, and therefore subject to bias. *See* 21 C.F.R. § 312.32, explaining that an adverse event may be categorized as "serious" if "in the view of either the investigator or sponsor, it results in any of the" listed outcomes.

[10] https://www.nejm.org/doi/pdf/10.1056/NEJMp1103464 (last visited July 12, 2020).

[11] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103795s5503lbl.pdf (last visited June 2, 2020).

[12] https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020702s056lbl.pdf (last visited June 2, 2020).

[13] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103000s5302lbl.pdf (last visited June 2, 2020).

[14] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022529lbl.pdf (last visited July 10, 2020).

due to emerging data showing that people who had taken the drug as part of a large clinical trial had an increased occurrence of cancer five years later.[15]

16. The FDA states that the length of study for phase III clinical trials is typically "1 to 4 years"[16] and that the duration of a clinical trial should "reflect the product and target condition."[17] In accord with this guidance, and the fact that a COVID-19 vaccine will be an entirely novel product, the safety review period for adults should be at least 1 year. The need for this minimum safety review period following injection is further supported by the indications that the immunity conferred by a COVID-19 vaccine is expected to last approximately one year or maybe a few years, requiring repeated injections of the product during a person's life.

17. Moreover, taking into account the FDA's guidance that clinical trials should "reflect the product and target condition,"[18] the time frame for the safety review should be longer for minors, and in particular for babies and toddlers, since autoimmune, neurological, and developmental disorders will often not be diagnosed until after babies are at least a few years old.[19] Indeed, a 2019 review, authored by researchers at the FDA and Duke University, reviewed 306 pediatric clinical trials and found that short-term

> pediatric studies may not provide complete safety data across all critical periods of growth and development. This observation may be important because multiple periods of critical pediatric growth and development exist… Although the first 3 years of life are often considered more critical than older ages for brain development, biochemical studies of brain metabolism suggest that high brain metabolic rates characteristic of early childhood may not decline to adult levels until ages 16 to 18 years, suggesting that the school-age and adolescent periods are equally critical periods of brain development. Given this information, even the longest trial duration

---

[15] https://www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market (last visited July 10, 2020); https://www.health.harvard.edu/blog/weight-loss-drug-belviq-recalled-2020040919439 (last visited July 10, 2020).

[16] https://www.fda.gov/patients/drug-development-process/step-3-clinical-research (last visited July 12, 2020).

[17] https://www.fda.gov/media/102332/download (last visited July 12, 2020).

[18] https://www.fda.gov/media/102332/download (last visited July 12, 2020).

[19] For example, according to the CDC, even for a common neurological disorder such as ADHD, "5 years of age was the average age of diagnosis for children reported as having severe ADHD." https://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html (last visited June 2, 2020). As another example, learning disabilities, a group of common developmental issues, are often "identified once a child is in school." https://www.nichd.nih.gov/health/topics/learning/conditioninfo/diagnosed (last visited June 2, 2020). Even for asthma, a very common autoimmune condition, whose symptoms are obvious, diagnosis can be difficult for children under 5 years of age because lung function tests aren't accurate before 5 years of age and "[s]ometimes a diagnosis can't be made until later, after months or even years of observing symptoms." https://www.mayoclinic.org/diseases-conditions/childhood-asthma/diagnosis-treatment/drc-20351513 (last visited June 2, 2020).

> identified in our study (364 weeks/7 years) does not completely evaluate potential critical stages of all pediatric growth and development periods.[20]

The FDA and Duke authors explained that, compared to licensing a drug for adults, "data on drug efficacy and safety in children may require an additional 6 years."[21] Since children have not been seriously affected by this virus, the risk of any vaccine must be fully understood in order to weigh it against any potential benefit.

18. The undersigned therefore respectfully urges that the action requested in paragraph 2 above be adopted forthwith.

c. Number of Subjects

19. The FDA COVID-19 Guidance provides as follows with regard to the number of subjects needed to assess safety:

> The pre-licensure safety database for preventive vaccines for infectious diseases typically consists of at least 3,000 study participants vaccinated with the dosing regimen intended for licensure. FDA anticipates that adequately powered efficacy trials for COVID-19 vaccines will be of sufficient size to provide an acceptable safety database for each of younger adult and elderly populations, provided that no significant safety concerns arise during clinical development that would warrant further pre-licensure evaluation.

20. A Phase III trial of a COVID-19 vaccine with 3,000 subjects cannot produce an adequate safety profile for a COVID-19 vaccine. SARS-CoV-2 poses a statistically insignificant risk of harm to children and young healthy adults. For this enormous cohort of the American population, the threshold for establishing that the COVID-19 vaccine is safer than the infection is exceedingly high and will require highly powered trials. Even within so-called higher risk groups, the percent of individuals suffering serious health issues from SARS-CoV-2 is statistically small on a population level, which again demands a well-powered trial to assess the safety of the vaccine versus natural infection.

21. Reflecting the foregoing, even Dr. Paul Offit, a member of VRBPAC and a staunch advocate for removing hurdles to the licensure of vaccines, has said that to determine whether a COVID-19 vaccine is safe and effective, "we are waiting for the big trial … the large prospective placebo controlled trial, we have **20,000 people who get a vaccine**, **10,000 people who get a placebo**, **then and only then will you know whether a vaccine is safe and effective**."[22]

---

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6526087/ (last visited July 12, 2020).

[21] *Id*.

[22] https://www.cnn.com/videos/health/2020/05/24/coronavirus-covid-19-vaccine-trials-vaccinologist-concern-ip-vpx.cnn (emphasis added) (last visited June 2, 2020).

22. The undersigned therefore respectfully urges that the action requested in paragraph 3 above be adopted forthwith.

d. Converting Guidance to Binding Regulations

23. In the FDA COVID-19 Guidance, the FDA provided that, "[l]ater phase trials, including efficacy trials, should be randomized, double-blinded, and placebo controlled … with 1:1 randomization between vaccine and placebo groups." The foregoing guidance, which comports with the undersigned's June 17, 2020 requests, are appreciated but it is hereby requested that the FDA formally adopt this industry guidance, with the necessary flexibility, as formal regulatory requirements.

24. According to the FDA and the Center for Disease Control and Prevention ("**CDC**"), randomized placebo-controlled trials are the standard for determining the safety and efficacy of a new drug or biological product, including new vaccines. A "placebo" is defined as "[a] substance or treatment that has no effect on human beings."[23] Clinical trials for new pharmaceutical products typically do not use a non-inert substance as a control because, due to its pharmacological effects, a non-inert substance makes it impossible to isolate the effects of just the experimental product being studied.

25. COVID-19 primarily impacts the elderly. The National Institute of Aging, an institute within the National Institutes of Health, explains as follows regarding designing clinical trials:

> In undertaking a clinical trial, researchers don't want to leave anything to chance. They want to be as certain as possible that the results of the testing show whether or not a treatment is safe and effective. The "gold standard" for testing interventions in people is the "randomized, placebo-controlled" clinical trial. ... A placebo is an inactive substance.[24]

26. Where an effective vaccine already exists for an infection, ethical considerations may require using the existing vaccine, rather than a placebo, as the control (an "**active control**"). The FDA's industry guidance explains that an "active control must be a drug whose effect is well defined," which means "historical placebo-controlled trials are available to define the active control effect."[25] The importance of only using an active control that has already been licensed based on a placebo-controlled trial is explained by the FDA as follows:

> The placebo-controlled trial measures the total pharmacologically mediated effect of treatment. In contrast, an active control trial …

[23] https://www.cdc.gov/vaccines/terms/glossary.html (last visited June 2, 2020); *see also* https://www.fda.gov/media/71349/download (last visited July 10, 2020).

[24] https://www.nia.nih.gov/health/why-are-placebos-important (last visited June 2, 2020).

[25] https://www.fda.gov/media/78504/download (last visited June 2, 2020).

> measures the effect relative to another treatment. The placebo-controlled trial also allows a distinction between adverse events due to the drug and those due to the underlying disease or background noise.[26]

Because there is no licensed COVID-19 vaccine, an active control is not appropriate for trials of COVID-19 vaccines, and hence clinical trials of potential COVID-19 vaccines should include a placebo control group.[27]

27. Without a placebo-controlled trial, cause and effect between a potential adverse effect and the vaccine being studied is very difficult and often impossible to establish.[28] Hence, once licensed, studying claims of injury occurring post-licensure becomes exceedingly difficult. This is because after licensure, it will be considered unethical to conduct a placebo-controlled clinical trial of a licensed COVID-19 vaccine. Having a scientifically valid and robust clinical trial prior to licensure will avoid this quagmire.

28. Fortunately, most of the FDA-approved Phase II and III study designs for potential COVID-19 candidate vaccines appear to include a saline placebo control group. For example, the leading candidate COVID-19 vaccine in the United States, developed with the National Institute of Allergy and Infectious Disease ("**NIAID**") lists "Placebo: Saline" as the control for its Phase

---

[26] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e10-choice-control-group-and-related-issues-clinical-trials (last visited June 2, 2020).

[27] Moreover, even after a COVID-19 vaccine has been licensed, there are still many considerations that must be taken into account before using a COVID-19 vaccine as a control, rather than a placebo, for any new potential COVID-19 vaccine. *See* https://www.fda.gov/RegulatoryInformation/Guidances/ucm126501.htm ("There are three principal difficulties in interpreting active-control trials. … One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have powerful stimuli toward assuring study excellence. *Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds of poor study quality that can arise.* The other problem is that a finding of no difference between a test article and an effective treatment may not be meaningful.") (emphasis added) (last visited June 2, 2020).

[28] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html ("establishing evidence for cause and effect on the basis of case reports and case series alone is usually not possible," rather, researchers need "to compare the incidence of the event among vaccinees with the incidence among unvaccinated persons") (last visited June 2, 2020); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3505292/ (The entire advantage of a randomized placebo-controlled trial "is the ability to demonstrate causality" i.e., cause-effect relationship.) (last visited June 2, 2020); https://www.cdc.gov/vaccines/pubs/surv-manual/chpt21-surv-adverse-events.html (The Vaccine Adverse Events Reporting System (VAERS) is unable "to determine causation" because "there is a lack of an unvaccinated group for comparison in VAERS.") (last visited June 2, 2020).

II clinical trial.[29] As another example, the leading COVID-19 vaccines being developed in China both list a placebo control group in their Phase II study designs approved by the FDA.[30]

29. Unfortunately, this does not yet appear to be true for all of the COVID-19 vaccine trials approved by the FDA. For example, the Phase I/II clinical trial of the COVID-19 vaccine ChAdOx1 nCoV-19, currently under development by AstraZeneca, initially provided that the control group would receive a "Saline Placebo."[31] After approving this study design, the FDA inexplicably approved changing the control from a "Placebo Control" to "MenACWY," which is another vaccine for a bacterial infection unrelated to COVID-19. It is ethically and scientifically indefensible to use MenACWY vaccine as a control for a COVID-19 vaccine trial, including because the safety of MenACWY has never been established in a placebo-controlled clinical trial.[32]

30. Permitting clinical trials of a potential COVID-19 vaccine without a placebo control group is inappropriate, scientifically and ethically, especially given the above. The use of a non-inert substance as a control creates significant uncertainty in confirming, among other things, the safety of a COVID-19 vaccine. There is no reason to create such uncertainty or to compromise the scientific validity and robustness of the clinical trial for any candidate COVID-19 vaccine by having a control that is anything other than a saline placebo.

31. With regard to the relative number of subjects between the vaccine and placebo groups, we are pleased that the FDA COVID-19 Guidance provides for "1:1 randomization between vaccine and placebo groups" which comports with the request in the undersigned's original petition that, to assure sufficient power to properly compare the safety profile between the COVID-19 vaccine group and the saline placebo group, the saline placebo group should be at least the size of the group receiving the COVID-19 vaccine.[33]

32. The undersigned therefore respectfully urges that the action requested in paragraph 4 above be adopted forthwith.

---

[29] https://www.clinicaltrials.gov/ct2/show/NCT04405076 (last visited June 2, 2020).

[30] https://www.clinicaltrials.gov/ct2/show/NCT04341389; (last visited June 2, 2020); https://www.clinicaltrials.gov/ct2/show/NCT04383574 (last visited June 2, 2020).

[31] https://clinicaltrials.gov/ct2/history/NCT04324606 (last visited June 2, 2020).

[32] *Ibid*. The trade name for MenACWY vaccine in the United States is Menveo. This product was licensed for adults based on a clinical trial in which the control group of 1,966 participants received either Menomune (209 participants) or Menactra (1,757 participants). https://www.fda.gov/media/78514/download (last visited June 2, 2020). Menactra was licensed based on a clinical trial in which Menomune was the active comparator. https://www.fda.gov/media/75619/download (last visited June 2, 2020). Quizzically, the clinical trials section of the package insert for Menomune only lists the clinical trial in which it was used as a comparator against Menactra. https://www.fda.gov/media/83562/download (last visited June 2, 2020). Meaning, the same clinical trial in which Menactra was studied with Menomune as its active control is apparently relied upon by the FDA to support the safety of both of these products. Using any of these products as an active control for a COVID-19 vaccine is unscientific and unacceptable. The control should be a saline placebo.

[33] https://www.fda.gov/media/87621/download (last visited June 2, 2020); https://www.fda.gov/media/139638/download at p.12 (last visited July 7, 2020).

C. Environmental Impact

33. The undersigned hereby states that the relief requested in this petition will have no environmental impact and therefore an environmental assessment is not required under 21 C.F.R. Sections 25.30 and 25.31.

D. Economic Impact

34. Economic impact information will be submitted upon request of the commissioner.

E. Certification

35. I certify that, to the best of my knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: May 28, 2020 and June 30, 2020. I have not received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Informed Consent Action Network
Del Bigtree, President
2025 Guadalupe Street
Austin, TX, 78705
512-677-6726

Footnote 6

Lancet. Author manuscript; available in PMC 2009 Nov 29.

Published in final edited form as:

Lancet. 2008 Nov 29; 372(9653): 1881–1893.

Published online 2008 Nov 13.

doi: 10.1016/S0140-6736(08)61591-3

PMCID: PMC2721012

NIHMSID: NIHMS108872

PMID: 19012954

Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial

Susan P. Buchbinder, MD,[1] Devan V. Mehrotra, PhD,[2] Ann Duerr, MD, PhD, MPH,[3] Daniel W. Fitzgerald, MD,[4] Robin Mogg, MS,[2] David Li, PhD,[2] Peter B. Gilbert, PhD,[3] Javier R. Lama, MD, MPH,[5] Michael Marmor, PhD,[6] Carlos del Rio, MD,[7] M. Juliana McElrath, MD, PhD,[3] Danilo R. Casimiro, PhD,[2] Keith M. Gottesdiener, MD,[2] Jeffrey A. Chodakewitz, MD,[2] Lawrence Corey, MD,[3] and Michael N. Robertson, MD[2], the Step Study Protocol Team

Author information Copyright and License information Disclaimer

The publisher's final edited version of this article is available at Lancet

See commentary "Immune Activation with HIV Vaccines: Implications of the Adenovirus Vector Experience" in *Science*, volume 344 on page 49.

See commentary "HIV-1 step study." in *Lancet*, volume 373 on page 805.

See commentary "Failure of the Merck HIV vaccine: an uncertain step forward." in *Lancet*, volume 372 on page 1857.

Abstract

Background

Observational data and non-human primate challenge studies suggest that cell-mediated immune (CMI) responses may provide control of HIV replication. The Step Study is the first direct assessment of the efficacy of a CMI vaccine to protect against HIV infection or alter early plasma HIV levels in humans.

Method

HIV-seronegative participants (3000) were randomized (1:1) to receive 3 injections of MRKAd5 HIV-1 gag/pol/nef vaccine or placebo. Randomization was pre-stratified by gender, baseline adenovirus type 5 (Ad5) titer, and study site. Participants were tested ~every 6 months for HIV acquisition; early plasma HIV RNA was measured ~3 months post-HIV diagnosis.

Findings

The vaccine elicited IFN-γ ELISPOT responses in 75% of vaccinees. In a pre-specified interim analysis among participants with baseline Ad5 ≤200, 24 of 741 vaccinees became HIV infected, versus 21 of 762 placebo recipients. All but one infection occurred in men. The early geometric mean plasma HIV RNA was comparable in infected vaccine and placebo recipients. In exploratory multivariate analyses, HIV incidence was higher in vaccinees versus placebo recipients among Ad5 seropositive men (5.1% versus 2.2% per year, respectively) and uncircumcised men (5.2% versus 1.4% per year, respectively). HIV incidence was similar in vaccinees versus placebo recipients among Ad5 seronegative men and circumcised men.

Interpretation

This CMI vaccine did not prevent HIV infection or lower early viral level. Mechanisms for failure of the vaccine to protect and for the increased HIV infection rates in subgroups of vaccinees are being explored. Additional follow-up will determine if elevated HIV incidence in vaccinee subgroups persists.

Keywords: HIV vaccine, efficacy, adenovirus, HIV acquisition, viral load, male circumcision, test of concept

Introduction

The development of an efficacious HIV vaccine is one of the world's greatest public health challenges. The lack of a known correlate of protection and the widespread genetic diversity of the

virus pose significant scientific hurdles (1). Traditional methods of vaccine design, such as use of live attenuated virus, whole killed virus, or subunit proteins are either thought to be too dangerous or have been found to be ineffective in generating robust immune responses or protecting against HIV (2). No effective strategies have yet been developed to generate broadly neutralizing antibody against HIV, although considerable work is being done in this field (3–6). A substantial body of data points to the importance of CMI responses in controlling viral replication and disease progression in long-term nonprogressors (7–13) and in non-human primate challenge models (14–17). Substantial effort has been devoted to designing and evaluating CMI based vaccines.

Adenovirus type 5 (Ad5) vector-based vaccines have proven to be among the most immunogenic of CMI vaccines in Phase I clinical trials (18;19), surpassing immune responses generated by DNA plasmids (20;21), and many poxvirus vectors (22–24). Non-human primate challenge studies have also demonstrated that SIV Ad5 prototype vaccines led to control of viremia, in some, but not all, challenge models (14;25–27).

Building on this early promising data from prototype vaccines containing a single gene (gag)(28), a candidate vaccine using a mixture of rAd5 vectors expressing the HIV-1 *gag*, *pol* and *nef* genes (18)was developed. These antigens were selected because they are commonly recognized during natural infection and are relatively conserved across different clades of HIV-1. This vaccine mixture was shown in phase 1 trials to elicit immune responses in both Ad5 seronegative and Ad5 seropositive, immunocompetent participants (18). However, because of considerable uncertainty about what would be required of a CMI vaccine to control HIV viral replication, we designed a test-of-concept trial (29) to evaluate the potential public health impact of this CMI vaccine. Test-of-concept trials provide a preliminary assessment of efficacy and allow exploration of immune correlates of protection while being substantially smaller than phase III licensure trials (30).

Methods

Study population

The Step Study is a multicenter, double-blind, randomized, placebo-controlled phase II test of concept study of the MRKAd5 HIV-1 gag/pol/nef vaccine in HIV-1 negative individuals at high risk of HIV-1 acquisition. This trial is being conducted in regions of the world where clade B is the predominant HIV-1 subtype. The

trial was initially designed to enroll 1500 participants with low (≤200) Ad5 antibody titers at enrollment, based on reduced levels of immunogenicity seen in persons with higher baseline Ad5 titers (28). After data from a Phase I trial demonstrated robust immune responses even in subjects with pre-existing immunity to Ad5 (18), the trial was expanded to include a cohort of 1500 participants with Ad5 titers >200, to increase the potential global relevance of this vaccine candidate.

Participants were 18–45 years of age, HIV-1 seronegative, with serum alanine transaminase levels ≤ 3 times the upper limit of normal, and at high risk of HIV-1 acquisition based on reported risk behavior in the 6 months prior to enrollment. Men were eligible if they reported: 1) unprotected anal intercourse with a male partner or 2) anal intercourse with ≥ 2 male partners. Heterosexual men from Caribbean sites were also eligible if they reported: 1) a diagnosis of syphilis or genital ulcer disease; 2) ≥2 sexual partners; 3) exchanging sex for money, drugs, services, or gifts; or 4) using crack cocaine ≥3 times. Women were eligible if they reported: 1) unprotected vaginal or anal intercourse with an HIV positive man or an injection drug user; 2) exchanging sex for money, drugs, services, or gifts, or 3) using crack cocaine ≥3 times. Women from Caribbean sites were also included if they reported a diagnosis of syphilis or pelvic inflammatory disease. Participants were excluded if they had a history of immunodeficiency, malignancy, anaphylaxis or allergy to vaccine components, receipt of an experimental HIV vaccine, or other conditions that would interfere with their study participation. Women who were pregnant at screening were excluded; women who became pregnant during the study did not receive further study injections but followed all other study procedures.

Vaccine Description

The MRKAd5 HIV-1 gag/pol/nef vaccine, consisted of a 1:1:1 mixture of 3 separate replication-defective Ad5 vectors, one each expressing the *gag* gene from the HIV-1 strain CAM-1, the *pol* gene from HIV-1 strain IIIB and the *nef* gene from HIV-1 strain JR-FL, as previously described (18). Vaccine was administered as a 1.0 ml injection of 1.5×10^{10} adenovirus genomes, equivalent to the 3×10^{10} viral particle dose used in previous vaccine trials (18). The placebo was a 1.0 ml injection of the vaccine diluent only, with no Ad5 vector.

Study procedures

Participants underwent a thorough written informed consent process. The protocol was approved by the Ethical Review Committee of each site, and the study was conducted in conformance with applicable local and country requirements.

Study participants were randomized in a 1:1 ratio to receive 3 doses of the MRK Ad5 gag/pol/nef vaccine or placebo on Day 1 (study enrollment), Week 4, and Week 26. Randomization was pre-stratified by study site, gender, and baseline Ad5 titer (<18 (lower limit of detection of assay), 18–200, 201–1000, >1000). Study participants were seen at Day 1 and Weeks 2, 4, 8, 12, 26, 30, 52, and every 26 weeks thereafter through week 208. Clinical evaluation and risk reduction counseling were conducted at each visit. Local and systemic reactogenicity was assessed for the 14 days following study injections. Behavioral risk was assessed by self-report at screening and every 26 weeks thereafter, and included standardized interviewer-administered questionnaires about sexual risk, drug use, and sexually transmitted infections in the previous 6 months.

Serum alanine transferase and a complete blood count were measured immediately prior to and two weeks following the first vaccination to assess any hepatic or hematological toxicity from the vaccine. HIV-1 testing was conducted at Day 1, Weeks 12 and 30, 52, and every 26 weeks thereafter through Week 208. If HIV was diagnosed at any visit, stored plasma specimens from earlier time points were tested to accurately time the onset of HIV-1 infection. All HIV-1 tests were performed at a central laboratory. Specimens were screened with an immunoassay (Uni-Gold™ Recombigen® HIV test from Trinity BioTech or the Multispot HIV-1/HIV-2 Rapid Test from Bio-Rad) that only contained HIV envelope antigens, which are not included in the vaccine. Reactive tests were confirmed with an HIV-1 Western blot and HIV-1 plasma viral RNA assay (Amplicor Monitor Version 1.5 from Roche) conducted on the original specimen and a confirmatory specimen. A blinded Endpoint Adjudication Committee consisting of 3 independent experts in HIV-1 diagnostics made the final determination of HIV-1 infection status. All cases were unanimously confirmed by this committee. Participants who became HIV-infected during the study were provided counseling and linkage to local HIV medical and psychosocial care. HIV-1 infected participants underwent clinical and laboratory assessment 1, 2, 8, 12, and 26 weeks after their initial HIV-1 diagnosis, and every 26 weeks thereafter through week 78 post-diagnosis.

Peripheral blood mononuclear cells (PBMC) were isolated from

EDTA-anticoagulated blood obtained at weeks 8, 30, 52, and 104, and were cryopreserved within 12 hours of venipuncture, using previously described methods (31). Validated IFN-γ ELISPOT assays (32) were performed on cryopreserved PBMC at the weeks 8 and 30 timepoints on a random sample of 25% of study participants, stratified by treatment assignment and study site.

Study Objectives and Endpoints

The primary objectives were to demonstrate the safety, tolerability, and efficacy of the MRK Ad5 gag/pol/nef HIV-1 vaccine in the study population with baseline Ad5 titers ≤200. The primary objectives focused on the subpopulation initially targeted for this trial and the one likely to have the most robust immune response, based on data from phase I trials. Efficacy was defined as demonstrating a reduction in HIV-1 acquisition rates (infection endpoint) and/or a decrease in HIV-1 viral load set-point (average of 2 $\log_{10}$ HIV-1 RNA values at ~ 3 months after HIV-1 diagnosis) (viral load endpoint), among vaccine versus placebo recipients.

Secondary objectives were to evaluate the safety, tolerability, and efficacy of the vaccine in the entire study population, regardless of baseline Ad5 titer, and to identify immune responses that correlated with efficacy endpoints. Exploratory objectives included evaluation of associations between the co-primary efficacy endpoints (infection and viral load) and prognostic factors such as gender, baseline Ad5 titer, age, race, HLA type, and circumcision status (for males).

Statistical analysis

Pre-specified analyses

All serious vaccine-related adverse experiences, injection-site reactions (within 5 days of each study injection), body temperatures and systemic adverse events (within 15 days of each study injection), and laboratory measures (at pre-specified time points) were summarized. The safety analyses included all randomized subjects that received at least one dose of vaccine or placebo.

To assess vaccine efficacy for the infection endpoint, the number of acquired HIV-1 infections (“events”) in the vaccine arm was compared to the corresponding number in the placebo arm using a test for stratified Poisson data (33). To assess vaccine efficacy for the viral load endpoint, viral load set-points for subjects who became HIV-1 infected were compared between treatment groups using a stratified Wilcoxon rank sum test; a pre-specified multiple imputation approach was used to resolve the problem of altered or

missing viral load data associated with antiretroviral therapy (ART) initiation or premature study discontinuation, respectively (34).

Two analysis populations were pre-defined. The per-protocol (PP) analysis population included all randomized subjects who received the first two doses of either vaccine or placebo, except those who were either diagnosed with HIV-1 infection before or at week 12 (i.e., 8 weeks post-dose 2) and/or were identified as protocol violators based on predefined criteria. The modified intention-to-treat (MITT) analysis population included all randomized subjects who received at least one dose of vaccine or placebo, except those who had a positive HIV-1 screening test prior to randomization.

The Step Study was an event-driven trial, designed to accrue at least 50 PP events in the Ad5 ≤ 200 stratum and 50 PP events in the Ad5 > 200 stratum (100+ events overall). An alpha-spending interim analysis for the primary efficacy hypotheses was to be conducted when 30 PP events had accrued in the Ad5 ≤ 200 stratum and the corresponding viral load set-point data for the HIV-1 infected subjects were available. Similarly, an alpha-spending interim analysis for the secondary efficacy hypotheses was to be conducted when 30 PP events had accrued in the Ad5 > 200 stratum and at least 30 PP events had accrued in the Ad5 ≤ 200 stratum (60+ total PP events), and the corresponding viral load data for the HIV-1 infected subjects were available. At the interim analysis for the primary efficacy hypothesis, statistical success for the infection and viral load endpoints was defined as the 1-tailed p-value (in the direction of a vaccine benefit) being less than alpha allocated levels of 0.00025 and 0.025, respectively. The corresponding p-value thresholds for success at the interim analysis for the secondary efficacy hypothesis were 0.000125 and 0.0125, respectively. Futility criteria associated with strong evidence of a lack of vaccine efficacy were also specified upfront: at either planned interim analysis, the vaccine was to be declared ineffective if the 1-tailed p-value was greater than 0.50 for both of the co-primary efficacy endpoints.

For the primary efficacy hypothesis (Ad5 ≤ 200 stratum), 30 events provided 80% power to detect a 1 $\log_{10}$ copies/ml difference (placebo – vaccine) in mean viral load set-point, and 50 events provided 80% power to detect a 60% reduction in the HIV-1 infection rate for vaccine versus placebo. The power calculations were based on a total alpha allocation of 0.05 for the two primary efficacy endpoints, and they accounted for the alpha spending at the interim analysis. Similarly, for the secondary efficacy hypothesis (Ad5 ≤ 200 and Ad5 > 200 strata combined), 60 events provided

80% power to detect a 0.75 $\log_{10}$ copies/ml difference in mean viral load set-point, and 100 events provided 80% power to detect a 50% reduction in the HIV-1 infection rate, based on a total alpha allocation of 0.025 for the two co-primary efficacy endpoints and accounting for the planned interim analysis.

Exploratory analyses Because the study unexpectedly met the pre-specified futility boundaries at the first interim analysis (see Results), additional analyses were initiated to explore reasons for the vaccine's lack of efficacy and potential for increased HIV-1 acquisition. Data accrued through October 17, 2007, prior to public announcement of study results and participant unblinding, were included in these analyses.

Univariate Cox proportional hazards models were used to quantify treatment effects for various subgroups defined by demographic and/or baseline behavioral risk factors. The time-to-event variable for the Cox model analyses was defined as the time from initial vaccination to the midpoint between the date of the last HIV seronegative visit and the date of the first evidence of HIV infection, as determined by the blinded Endpoint Adjudication Committee. Participants who never showed any evidence of HIV infection were right-censored on the date of their last study visit prior to October 17, 2007. Kaplan-Meier plots were generated to graphically illustrate the treatment effect across the four design-based Ad5 strata (baseline Ad5 titer ≤18, 19–200, 201–1000, >1000). Treatment effects were quantified using estimated hazard ratios (vaccine/placebo) with associated Wald-based 95% confidence intervals (CIs) and two-tailed p-values. Interaction tests were conducted to evaluate whether the treatment effect differed between two given subgroups.

Multivariate Cox models were used to estimate the treatment effect after adjusting for potential confounding variables. Candidate confounders were pre-selected on the basis of their plausibility to impact HIV infection risk. The candidate confounders were all dichotomous for simplicity, stabilizing the model fitting, and reducing the modeling assumptions. The backwards elimination procedure for building the multivariate models used a Wald p-value threshold of 0.15 for removing variables; similar results were observed using a threshold of 0.10.

Role of the Data Safety Monitoring Board

The trial was monitored by an independent Data Safety Monitoring Board (DSMB) consisting of seven experts in clinical trials, vaccinology, statistics, and bioethics. The DSMB met three times

per year to review safety data; serious adverse events were reviewed by the DSMB chair in real time. In September 2007, the DSMB met to review the unblinded data on HIV acquisition and viral load endpoints at the pre-specified interim analysis.

Role of the funding sources

This study was funded by Merck Research Laboratories; the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), in the US National Institutes of Health (NIH); and the NIH-sponsored HIV Vaccine Trials Network (HVTN). Each of the partners was involved in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Results

The Step Study opened in December 2004 to study participants with Ad5 titers ≤200 at screening, and was amended to include participants with Ad5 titers >200 at screening in July 2005. Three thousand participants were enrolled through March 2007 at 34 sites in North America, the Caribbean, South America, and Australia. Protocol adherence was excellent, with 94% of the vaccine and placebo groups receiving all 3 study injections (Figure 1). Overall, 6.5% and 5.8% of vaccine and placebo recipients, respectively, had discontinued follow-up in the study. Baseline demographic and risk characteristics are shown in Table 1, stratified by gender and baseline Ad5 titer. Overall, the study cohort was diverse and reported substantial levels of HIV risk. More than 75% of each stratum reported multiple male sex partners of unknown HIV serostatus, while a substantial proportion of men also reported having known HIV- positive male partners; only 68 men were exclusively heterosexual. Pregnancy rates in female vaccine and placebo participants were 12.8% and 9.9%, respectively, at the time of the interim analysis, indicating substantial levels of unprotected vaginal sex. Within pre-specified Ad5 strata, vaccine and placebo recipients were well-matched on demographic and risk characteristics at baseline. However, there were substantial differences in several important demographic and HIV risk factors between individuals in the low vs. high Ad5 strata. For example, men with baseline Ad5 titers >200 were significantly more likely to have been enrolled outside of North America, to be non-white, and to be uncircumcised. Men with high Ad5 titers were also less likely to have known HIV-positive partners or to use recreational drugs.

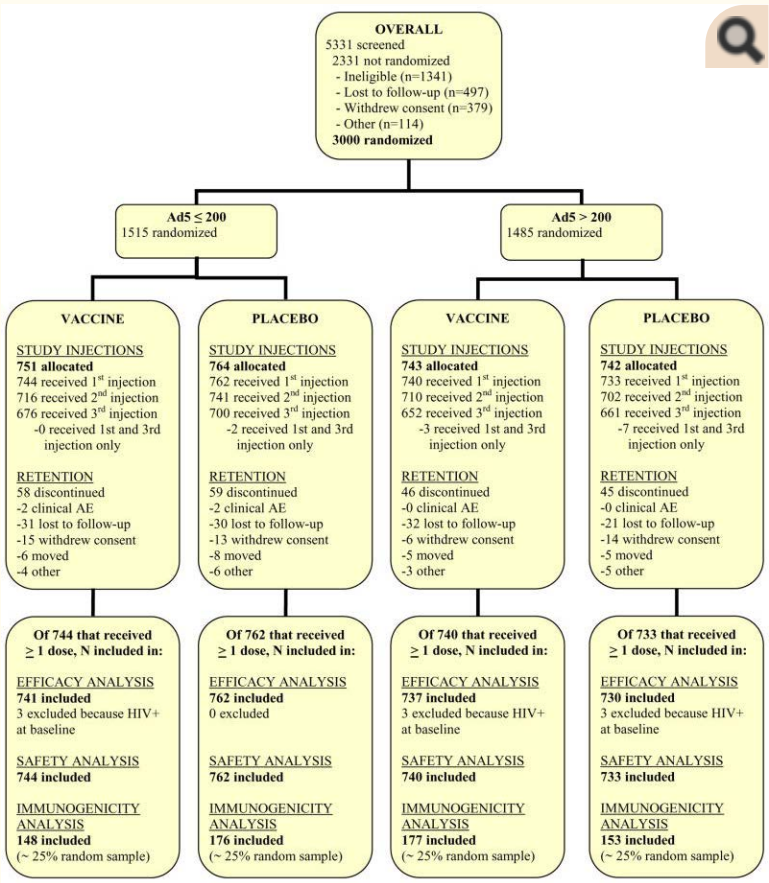


Figure 1

Trial profile. Discontinued includes study participants who were unwilling or unable to continue follow-up in the trial at the time the dataset was frozen. All participants who received at least one dose of vaccine or placebo were included in the safety analysis; efficacy analysis was limited to the modified intent-to-treat subgroup who were also HIV negative at baseline. The immunogenicity analysis was performed on a 25% random sample of the entire cohort.

Table 1

Baseline characteristics, stratified by gender and baseline Ad5 antibody titer

	Men			
	Ad5 ≤ 200		Ad5 > 200	
	Vaccine N=525	Placebo N=536	Vaccine N=394	Placebo N=389

Baseline Characteristics	n(%)	n (%)	n (%)	n (%)
Demographics				
Age				
Median	31	31	28	28
Range	18–45	18–45	18–46	18–45
Race/ethnicity				
Black	53 (10.1)	51 (9.5)	41 (10.4)	40 (10.3)
Hispanic	39 (7.4)	42 (7.8)	44 (11.2)	50 (12.9)
Multiracial	104 (19.8)	100 (18.7)	161 (40.9)	149 (38.3)
White	312 (59.4)	332 (61.9)	136 (34.5)	133 (34.2)
Other	17 (3.2)	11 (2.1)	12 (3.0)	17 (4.4)
Circumcision status				
Circumcised	345 (65.7)	349 (65.1)	159 (40.4)	150 (38.6)
Uncircumcised	165 (31.4)	167 (31.2)	231 (58.6)	228 (58.6)
Unknown	15 (2.9)	20 (3.7)	4 (1.0)	11 (2.8)

*self-reported gonorrhea or chlamydia

Side effects from the vaccine were similar to those reported earlier (18). Injection site pain (70% of vaccinees and 34% of placebo recipients) and headache (32% of vaccinees and 27% of placebo recipients) were most common. There were no clinically significant differences in safety laboratory results between vaccine and placebo recipients. Of 40 serious adverse events reported by blinded study investigators, only 2 (fever, rigors) were reported in the vaccine group that were deemed related to study vaccine.

Among the 25% pre-specified random sample of study volunteers evaluated for IFN-γ ELISPOT responses at the week 8 time-point,

75% of vaccinees responded to one or more HIV antigens, with geometric mean titers of several hundred (Table 2). Response rates were higher among those with baseline Ad5 titers ≤200 than those with Ad5 >200; overall responses did not differ between men and women.

Table 2

IFN-gamma ELISPOT summaries at week 8 for the vaccine group

	Frequency (%) of Responders *Geometric Mean (SFC/10^6 PBMC)*		
	Ad5 ≤ 200	**Ad5 > 200**	**Overall**
	n = 166	**n = 188**	**n = 354**
Gag	125 (75%) *277*	102 (54%) *170*	227 (64%) *213*
Pol	118 (71%) *489*	88 (47%) *245*	206 (58%) *339*
Nef	116 (70%) *251*	97 (52%) *164*	213 (60%) *200*
≥ 1 antigen	140 (84%)	127 (68%)	267 (75%)
≥ 2 antigens	122 (73%)	96 (51%)	218 (62%)
All 3 antigens	97 (58%)	64 (34%)	161 (45%)

"Responder": ELISPOT ≥ 55 SFC/10^6 PBMC and ≥ 4-fold over negative control. Week 8 is 4 weeks after the 2nd vaccination. ELISPOT assay was done for a random sample of approximately 25% of the study cohort; volunteers with evidence of HIV infection by week 8 were excluded from the summaries. Geometric mean is based on data for responders and non-responders combined.

Interim efficacy results

As pre-specified in the protocol, an interim analysis of HIV incidence and early HIV-1 viral load was conducted when there were 30 per-protocol events in the Ad5 ≤200 stratum. Results of this interim analysis are presented in Table 3. Overall HIV-1 seroincidence at the time of the interim analysis in the modified intention-to-treat (MITT) population was 3.6% per year in men

(95% CI 2.6 – 4.8) and 0.2% per year in women (95% CI 0.0 - 1.3). HIV infection rates and mean viral load setpoint were no different or slightly higher in vaccine than placebo recipients in both the PP and MITT analysis subsets. The p-values for a beneficial effect exceeded 0.5 for both primary endpoints, thereby meeting the pre-specified futility criteria. Based on these results, the Step Study Protocol Team immediately halted all additional immunizations in the trial, and began notifying the study investigators, study participants, and the general public of the trial results within 72 hours of the DSMB meeting. After extensive discussions with study investigators, staff, and community representatives about the benefits of continuing blinded versus unblinded follow-up, the Step Study Protocol team decided to unblind study participants in November 2007.

Table 3

Results of Pre-specified Interim Analysis for the Ad5 ≤ 200 Subgroup (Infection and Viral Load (VL)[#] Endpoints)

Analysis Population	Gender	Treatment Group	N	n	Person-years of Follow-up[*]	HIV infection rate(% per year)
Per Protocol (PP)	Male	Vaccine	489	19	475	4.00
		Placebo	495	10	471	2.12
	Female	Vaccine	183	0	145	0.00
		Placebo	196	1	152	0.66
1-tailed p-values (to assess a potential vaccine benefit): 0.949 for inf and 0.528 for VL endpoint.						
Modified Intent-to-Treat (MITT)	Male	Vaccine	522	24	607	3.95
		Placebo	536	20	618	3.24
	Female	Vaccine	219	0	215	0.00
		Placebo	226	1	218	0.46
1-tailed p-values (to assess a potential vaccine benefit): 0.743 for inf						

and 0.656 for VL endpoint.

N=Number in respective analysis population; n = number of events; NA = Not applicable.

PP analysis includes all vaccinated subjects who received at least two vaccinations except those diagnosed as HIV+ on or before Week 12 visit and/or identified as protocol violators per the statistical analysis plan. MITT analysis includes all vaccinated subjects except those diagnosed as HIV+ on or before Day 1 visit.

*For the PP (MITT) population, follow-up was calculated as the time from the day of the Week 12 (Day 1) visit to the last day of study follow-up for uninfected subjects and to the day of HIV diagnosis for infected subjects.
#Viral load (VL) setpoint was the average of $\log_{10}$ HIV-1 RNA values at 2 and 3 months after HIV diagnosis.

Exploratory efficacy analyses in male participants

Because the study unexpectedly met the pre-specified futility boundaries at the first interim analysis, additional analyses were initiated to explore reasons for the vaccine's lack of efficacy. The interim data were expanded to include an additional 8 HIV-1 infections in participants with Ad5 titers ≤200 and 30 in participants with Ad5 titers >200 accrued through October 17, 2007. Because only 1 HIV-1 infection had occurred in a female participant, all subsequent analyses are limited to male participants in the MITT population.

In this expanded analysis of data through October 17, 2007, 49 of the 914 male vaccine recipients became HIV infected (annual HIV incidence 4.6%, 95% CI 3.4 to 6.1) and 33 of the 922 male placebo recipients became HIV infected (annual incidence 3.1%, 95% CI 2.1 to 4.3). The overall treatment effect hazard ratio from the univariate Cox model was 1.5 (95% CI 0.97 to 2.3, p=0.07). As randomization occurred within each of 4 pre-specified Ad5 strata, data are presented for each stratum (Figure 2). Although HIV acquisition rates were similar in vaccine and placebo recipients with baseline Ad5 titers ≤18 (Ad5 seronegative participants), surprisingly, rates appeared to be more than twice as high in vaccinees compared with placebo recipients in Ad5 strata >18, (overall HIV acquisition rate 5.1% vs. 2.3%/year, unadjusted two-tailed p-value 0.013). There was also evidence that the hazard ratio increased with increasing $\log_{10}$(Ad5) (univariate Cox model trend

test p-value = .06).

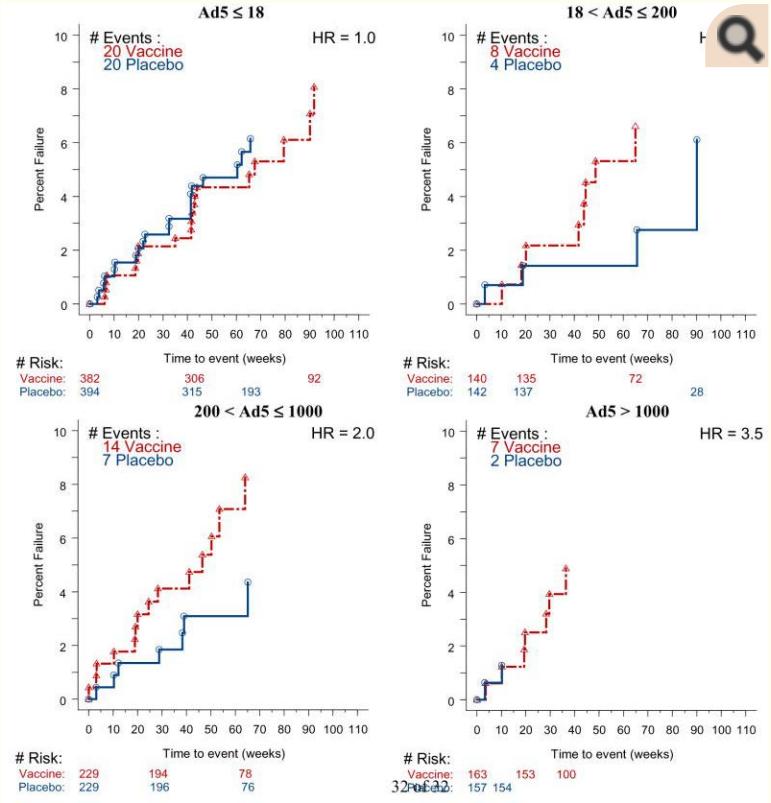


Figure 2

Kaplan Meier plots of HIV infection for male vaccine and placebo groups by A) baseline Ad5 ≤18; B) baseline Ad5 >18 and ≤200; C)baseline Ad5 >200 and ≤1000; and D) baseline Ad5 >1000. Each hazard ratio (HR) is from a univariate Cox regression model.

Viral load setpoints were not materially different between vaccine and placebo recipients in either the Ad5 seronegative or Ad5 seropositive stratum (Figure 3, p>.25 for all comparisons).

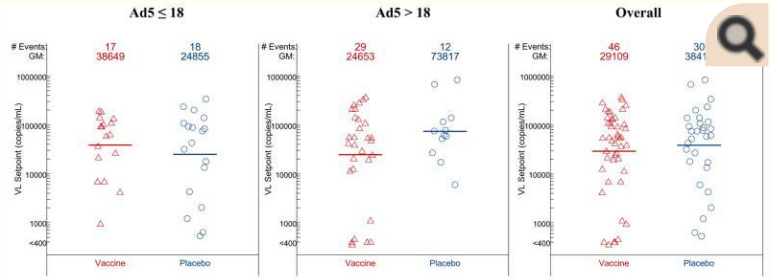


Figure 3

Early plasma viral load (VL) at ~ 3 months after detection of infection in male study participants by A) baseline Ad5 ≤ 18; B) baseline Ad5 >18; and C) all participants. The bar in each panel denotes the geometric mean titers of the plasma VL.

Factors associated with HIV infection risk

Univariate Cox proportional hazard analyses were conducted to evaluate if vaccine effects on HIV acquisition rates were different for different subgroups of participants (Table 4). The hazard ratio (HR) of HIV acquisition in vaccine versus placebo recipients was consistently close to 1.5 among all subgroups defined by age, race, unprotected receptive anal sex, unprotected insertive anal sex, drug use, and number of male sex partners. The elevated risk of HIV acquisition seen in Ad5 seropositive men appeared absent in Ad5 seronegative men (HR 2.3 versus 1.0 respectively, interaction test p = .08). Similarly, the HR was elevated in uncircumcised men, but not in circumcised men (HR = 3.8 vs. 1.0, interaction test p = .01). The univariate results did not materially change after adjusting for other baseline and demographic covariates in multivariate models (data not shown).

Table 4

Hazard Ratios of HIV Infection for Male Subgroups Defined by Demographic and Baseline Behavioral Risk Factors (Univariate Cox Model Analyses)

MITT Population	N	Number of HIV infections		HIV infection rate (% per year)	
		Vaccine	Placebo	Vaccine	Placebo
Demographic factors					
Ad5– (titer ≤ 18)	776	20	20	4.1	4.0
Ad5+ (titer > 18)	1060	29	13	5.1	2.2
Circumcised	999[b]	26	26	4.1	4.2
Uncircumcised	788[b]	22	6	5.2	1.4

Whites	907	24	18	4.4	3.2
Non-Whites	929	25	15	4.8	2.9
Age≤ 30 yrs	970	28	19	5.0	3.5
Age > 30 yrs	866	21	14	4.1	2.6
North America	1171	37	29	5.2	4.0
Others	665	12	4	3.4	1.1
Behavioral risk factors					
UIAS: yes	1097	36	25	5.6	3.9
UIAS: no	739	13	8	3.1	1.8
URAS: yes	916	37	25	7.2	4.7
URAS: no	920	12	8	2.2	1.5
Any drug use:	792	29	19	6.2	4.3

UIAS = unprotected insertive anal sex, URAS = unprotected receptive anal sex; behavioral risk data are based on self-reported behavior within 6 months prior to randomization. N = number of men in the univariate Cox model analysis;

[a]2-tailed p-value for a test of difference between the hazard ratios for the two subgroups, not corrected for multiplicity;
[b]circumcision data unknown for 49/1836 males, including one infected male from each of the vaccine and placebo groups.

To evaluate whether Ad5 serostatus or circumcision status were independent risk factors for HIV infection in the placebo group alone, we applied the Cox model adjusting for baseline demographic and risk variables. The adjusted hazard ratio was 1.6 (95% CI 0.7 to 3.6, p=0.23) for Ad5 >18 versus Ad5 ≤18 placebo recipients, and 2.5 (95% CI 0.7 to 8.7, p=0.14) for circumcised versus uncircumcised placebo recipients. These results do not support either variable as a significant independent predictor of HIV infection; however, they must be interpreted with caution because the study did not randomize participants to Ad5 or circumcision groups, only to vaccine or placebo.

Because circumcision rates were substantially higher in the Ad5 seronegative than Ad5 seropositive participants (77.6% vs. 40.4%,

p<0.001), hazard ratios were calculated for 4 different subpopulations of men in the trial, based on Ad5 and circumcision status. The unadjusted hazard ratio for risk of HIV acquisition among vaccinees compared with placebo recipients was highest among uncircumcised, Ad5 seropositive men (n= 620, HR 3.9, 95% CI 1.3 – 11.9). Risk was intermediate among uncircumcised, Ad5 seronegative men (n=168, HR 3.3, 95% CI 0.7 – 15.8) and circumcised, Ad5 seropositive men (n=421, HR 1.6, 95% CI 0.7 – 3.8). Risk did not appear to be elevated in men who were both circumcised and Ad5 seronegative (n=578, HR 0.7, 95% CI 0.3 – 1.4). These results did not change significantly when using adjusted hazard ratios from any of several multivariate Cox models.

To evaluate whether the increased hazard of HIV acquisition seen within these subgroups occurred only in peri-vaccination periods or persisted over time, the relative HIV incidence (vaccine:placebo) was evaluated during 3 semi-annual periods from the time of enrollment (Figure 4). Overall and within subgroups, HIV incidence was approximately constant over time for both vaccinees and placebo recipients through 78 weeks of follow-up.

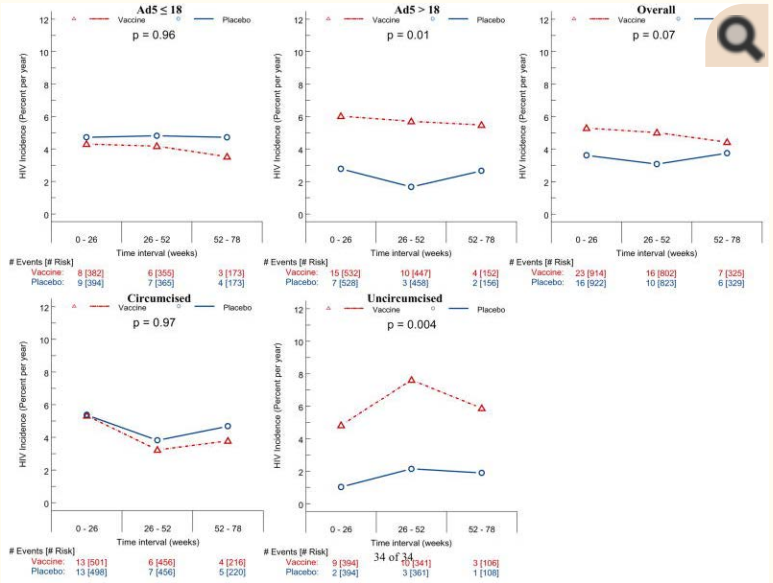


Figure 4

HIV incidence during 6-month time intervals for male vaccine and placebo groups by A) baseline Ad5 titer ≤18; B) baseline Ad5 >18; C) overall; D) circumcised; and E) uncircumcised. Each 2-tailed p-value (p) is from a univariate Cox regression model.

Risk behavior

If the vaccine increased the risk of HIV acquisition in uncircumcised male participants, a likely mechanism would be through insertive anal sex exposures and therefore, relative hazards should be particularly high in men reporting this risk. Therefore, the relative hazard of HIV infection was compared between men who had and had not reported unprotected insertive anal sex with HIV positive or unknown serostatus partners at baseline. Among uncircumcised men, the hazard ratios appeared to be even higher in men who reported unprotected insertive anal sex at baseline than in men who did not report this risk (HR 6.1 vs. 2.5 respectively). No such relationship was seen with unprotected receptive anal sex with HIV positive or unknown partners; the hazard ratio for uncircumcised men who reported this risk at baseline was lower than in uncircumcised men who did not report this risk (HR 3.7 vs. 5.7 respectively). Among circumcised men, hazard ratios were consistently near 1.0, regardless of reported baseline risk.

The difference in infection rates between vaccine and placebo recipients could be attributed to differences in risk practices between vaccine and placebo groups, particularly if any substantial levels of unblinding had occurred. Risk data were compared between vaccine and placebo recipients through 18 months of follow-up. For both vaccine and placebo recipients, the proportion of study participants reporting risk declined substantially during the first 6 months of the study, and then remained relatively level throughout follow-up (data not shown). The frequency of all measured risk behavior variables was similar for Ad5 seropositive vaccine and placebo recipients over time, and for uncircumcised vaccine and placebo recipients over time (all p-values > 0.20 data not shown).

Discussion

This is the first completed efficacy evaluation of a CMI-based HIV vaccine. Thirty-three months after the first participant was enrolled in the Step Study, this trial determined that the MRKAd5 gag/pol/nef HIV-1 vaccine neither prevented HIV-1 infection nor lowered viral load setpoint in participants with baseline Ad5 titers ≤200, despite generating IFN-γ ELISPOT responses in the majority of vaccinees. High levels of protocol adherence provide further confidence in this study's conclusions about the vaccine's lack of protective efficacy. Unfortunately, vaccine efficacy could not be conclusively evaluated in women in this trial because of low HIV acquisition rates, possibly driven by low HIV prevalence in male partners. The challenge of identifying high-seroincidence cohorts

of women has been demonstrated in a number of other studies (35;36).

Because CMI vaccines act by killing HIV infected cells, they would likely have their biggest impact in controlling viral replication, rather than preventing infection (37). However, there was no indication that early plasma viral levels were reduced in vaccinees compared with placebo recipients in this study. A companion manuscript explores the immunologic response among vaccinees in greater detail, and begins to explore potential explanations for the failure of this vaccine to provide protection. What is not yet clear is whether the magnitude, quality, specificity, or homing of the immune response generated by this specific vaccine was insufficient to control viral replication, or if this represents a more fundamental challenge of CMI vaccines to alter the clinical course of HIV disease. By providing the first direct test of a CMI vaccine to alter clinical outcome, the STEP study has provided important data for the field, and a repository of specimens with which to explore reasons for failure (e.g., mismatch between vaccine-induced immune response and viral sequences, inadequate magnitude or quality of the vaccine-induced immune response) and potential immune correlates of protection (e.g., presence or magnitude of a functional assay associated with lower viral load in subgroups of vaccinees).

Surprisingly, there was an increase in the number of HIV-1 infections in male vaccine recipients. These effects appeared to be limited to men who were Ad5 seropositive and/or uncircumcised on multivariate analyses, and not to be confounded by other measured baseline demographic and risk variables. However, this does not rule out confounding by as-yet unmeasured variables such as baseline herpes simplex type 2 (HSV-2) serostatus or host genetic factors, which are currently being measured in cryopreserved specimens. Other potential confounders, such as sexual network clustering, are being explored through viral genotyping.

There is little in the published literature that point to a mechanism for increased acquisition risk associated with this candidate or other adenovirus-based HIV vaccines. Antibody-dependent enhancement has been described for a number of viral infections (38;39). To date, such enhancement has been directed at surface envelope proteins and the MRKAd5 trivalent vaccine did not contain envelope inserts. There is one published report of a candidate HIV vaccine using a recombinant varicella-zoster virus (VZV) vector that led to enhanced SIV replication and disease progression in

rhesus macaques, although the effects on SIV acquisition were not assessed (40). The VZV vaccine elicited a robust SIV-specific CD4+ T cell response without a measurable CD8+ T cell response, quite different from the immunologic profile of the Merck trivalent vaccine.

The mechanism for enhanced HIV acquisition risk in vaccinated Ad5 seropositive men is likely to be complex. All vaccinees are likely to have developed both Ad5 antibodies as well as T cell responses to the vector; thus, none of the vaccinees were likely Ad5 seronegative after the first immunization. However, natural Ad5 infection occurs via the nasopharynx or gut, may persist at mucosal surfaces over several years, and preferentially infect lymphocytes that home to mucosa (41). Vaccinees with pre-existing Ad5 immunity may generate an Ad5-specific immune response that homes to mucosal surfaces, while those with vaccine-induced Ad5 immunity may not. Studies are underway to further explore differences in the mucosal immune response between participants with and without pre-existing Ad5 immunity. Conversely, the repeated administration of the Ad5 vector may cause an as yet undefined effect on the immune response that led to increased HIV acquisition. It is not yet clear whether the effects of this vaccine apply to other adenovirus-based HIV vaccines, including those using alternate serotypes. Until the mechanism for these effects can be clarified, clinical trials of novel adenovirus-based HIV vaccine candidates should include safeguards to minimize potential risk to study volunteers (e.g., limiting study enrollment to subgroups without evidence of vaccine-associated elevated risk, close study monitoring, and extensive discussion of risk during informed consent).

Circumcision has been shown to be associated with a halving of the risk of HIV acquisition in MSM in a longitudinal study (42), although data from cross-sectional studies and smaller longitudinal studies have been mixed (43–45). The protective effect of circumcision may be more difficult to demonstrate for men who engage in both insertive and receptive anal sex, and may therefore be most concentrated among men reporting unprotected insertive anal sex with HIV positive or unknown serostatus partners. In this study, uncircumcised vaccinees were at increased risk of HIV acquisition compared with uncircumcised placebo recipients, especially among men reporting high-risk insertive anal sex. Conversely, the risk of HIV acquisition did not appear to be more concentrated in uncircumcised men reporting high-risk receptive anal sex at baseline, nor did circumcised men appear to be at elevated risk, regardless of their sexual practices. These results call

for further inquiry into evaluating the mucosal response to this and other vaccines, and the potential interaction of mucosal immune responses to pre-existing vector immunity.

The Step Study has also been a landmark trial in deepening our understanding of the potential, and potential pitfalls, of current non-human primate challenge models. A prototype replication incompetent Ad5 vaccine based on an earlier Merck Ad5 gag-only vaccine provided substantial and durable control of viral replication against SHIV 89.6P challenge (14), particularly in animals with genetic markers associated with virologic control (25;25;27;27). The Step trial results suggest that this model is not a useful predictor of the clinical utility of T cell based vaccines (46). Other non-human primate challenge studies of this candidate vaccine have demonstrated more transient protection against $SIV_{mac}239$ that may depend upon a DNA prime (25) or inclusion of additional gene inserts (26); however, the utility of these challenge models is also as yet unproven (47). If vector-based immunity plays an important role in the quality of the immune response generated to vaccines, animal models may not predict clinical experience, particularly when the vector's host range is limited.

The Step Study successfully addressed the pre-specified primary study outcomes. Furthermore, it has challenged the field to more fully understand the role of vector-based immunity, the potential for vaccine-induced increased acquisition, and to mine the wealth of data and specimens in this human trial of a CMI vaccine, to understand the vaccine's failure. It will take the additional, coordinated efforts of laboratory, non-human primate, and clinical scientists to provide definitive answers to these questions, and ultimately to develop a safe and effective HIV vaccine.

Acknowledgments

The authors would like to thank the Step Study volunteers; the staff and community members at each of the Step Study sites; the staff at the HVTN Administrative Core, SCHARP Statistical Center; and Central Laboratory; the staff at Merck & Co., Inc. including Clinical Research Specialist Organization (CRSO), Worldwide Clinical Data Management Operations (WCDMO), Clinical Research Operations (CROps), and Serology Laboratory; and Drs. Margaret Johnston, Carl Dieffenbach, Alan Fix, and Jorge Flores at the Division of AIDS in the National Institute of Allergy and Infectious Diseases.

Partial support for this trial was provided by the Emory CFAR (P30

AI050409).

Footnotes

Conflicts of Interest

DVM, RM, DRC, KMG, JAC, MNR all are paid employees of Merck & Co., Inc and own Merck stock and have Merck stock options; DL has Merck stock; SPB, MM and MJM have all served as investigators on Merck-funded research; AD, DWF, PB, JRL, CDR, and LC have no conflicts of interest.

Data from this manuscript were presented at the Conference on Retroviruses and Opportunistic Infections, February 3–6, 2008, Boston, MA, USA and the Keystone Symposium, HIV Vaccines, Progress and Prospects, March 27–30, 2008, Banff, Alberta, Canada.

The study was registered at Clinicaltrials.gov with number NCT00095576.

Step Study Protocol Team

Sydney, Australia—Tony Kelleher

Rio de Janeiro, Brazil— Paulo Barroso, Mauro Schechter

Sao Paulo, Brazil— Artur Kalichman, Esper Kallas

Montreal, Canada—Julie Bruneau

Toronto, Canada—Mona Loutfy

Vancouver, Canada—Mark Tyndale

Santo Domingo, Dominican Republic—Yeycy Donastorg, Ellen Koenig

Port-au-Prince, Haiti—Patrice Joseph, Jean Pape

Kingston, Jamaica—Peter Figueroa

Iquitos, Peru—Martin Casapia

Lima, Peru— Robinson Cabello, Jorge Sanchez

San Juan, Puerto Rico—Carmen Zorrilla

United States Atlanta, Georgia—Paula Frew, Mark Mulligan

Birmingham, Alabama—Paul Goepfert

Boston, Massachusetts— Lindsey Baden, Ken Mayer

Chicago, Illinois—Richard Novak

Denver, Colorado—Frank Judson

Houston, Texas—Patricia Lee, Steven Tyring

Los Angeles, California—Steve Brown

Miami, Florida—Steven Santiago

New York, New York— Demetre Daskalakis, Scott Hammer, Beryl Koblin

Newark, New Jersey—Ronald Poblete

Philadelphia, Pennsylvania—Ian Frank

Rochester, New York—Mike Keefer

Saint Louis, Missouri—Sharon Frey

San Francisco, California—Jonathan Fuchs

Seattle, Washington—Karen Marks

HIV Vaccine Trial Network—Sarah Alexander, Gail Broder, Lisa Bull, Tirzah Griffin, Soyon Im, Ellen Maclachlan, Steve Self, Steve Wakefield, Margaret Wecker

Merck & Co., Inc.— Cheryl Ewing, Lori Gabryelski, Robin Isaacs, Randi Leavitt, Colleen Linehan, Audrey Mosley, Gabriela O'Neill, Melissa Shaughnessy, Amanda Vettori, Amy Zhou

National Institute of Allergy and Infectious Diseases—Dale Lawrence

Community—Derrick Mapp, Dewayne Mullis

Author Contributions

SPB, DVM, AD, DWF, PBG, MJM, DRC, KMG, JAC, LC, and MNR participated in the design of the study; SPB, MNR, and DVM co-chaired the study and together with AD, oversaw study implementation; KMG and LC served on the Oversight Committee; JRL, MM, and CDR participated in the conduct of the study; MJM and DRC led the laboratory components of this study and conducted the immunologic assays; DVR, RM, DL, PBG analyzed the study data; SPB, DVM, PBG and MNR drafted the manuscript and all coauthors participated in revising the manuscript.

References

1. Letvin NL. Progress and obstacles in the development of an AIDS vaccine. Nat Rev Immunol. 2006 Dec;6(12):930–9. [PubMed] [Google Scholar]

2. Duerr A, Wasserheit JN, Corey L. HIV vaccines: new frontiers in vaccine development. Clin Infect Dis. 2006 Aug 15;43:500–11.

[PubMed] [Google Scholar]

3. Burton DR, Desrosiers RC, Doms RW, Koff WC, Kwong PD, Moore JP, et al. HIV vaccine design and the neutralizing antibody problem. Nat Immunol. 2004 Mar;5(3):233–6. [PubMed] [Google Scholar]

4. Haynes BF, Montefiori DC. Aiming to induce broadly reactive neutralizing antibody responses with HIV-1 vaccine candidates. Expert Rev Vaccines. 2006 Aug;5(4):579–95. [PubMed] [Google Scholar]

5. Polonis VR, Brown BK, Rosa BA, Zolla-Pazner S, Dimitrov DS, Zhang MY, et al. Recent advances in the characterization of HIV-1 neutralization assays for standardized evaluation of the antibody response to infection and vaccination. Virology. 2008 Jun 5;375(2):315–20. [PubMed] [Google Scholar]

6. Vishwanathan SA, Hunter E. Importance of the membrane-perturbing properties of the membrane-proximal external region of human immunodeficiency virus type 1 gp41 to viral fusion. J Virol. 2008 Jun;82(11):5118–26. [PMC free article] [PubMed] [Google Scholar]

7. Pereyra F, Addo MM, Kaufmann DE, Liu Y, Miura T, Rathod A, et al. Genetic and immunologic heterogeneity among persons who control HIV infection in the absence of therapy. J Infect Dis. 2008 Feb 15;197(4):563–71. [PubMed] [Google Scholar]

8. Emu B, Sinclair E, Hatano H, Ferre A, Shacklett B, Martin JN, et al. HLA class I-restricted T-cell responses may contribute to the control of human immunodeficiency virus infection, but such responses are not always necessary for long-term virus control. J Virol. 2008 Jun;82(11):5398–407. [PMC free article] [PubMed] [Google Scholar]

9. Altfeld M, Kalife ET, Qi Y, Streeck H, Lichterfeld M, Johnston MN, et al. HLA alleles associated with delayed progression to AIDS contribute strongly to the initial CD8+ T cell response against HIV-1. PLoS Med. 2006 Oct;3(10):1851–64. [PMC free article] [PubMed] [Google Scholar]

10. Rosenberg ES, Billingsley JM, Caliendo AM, Boswell SL, Sax PE, Kalams SA, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia [see comments] Science. 1997 Nov 21;278(5342):1447–50. [PubMed] [Google Scholar]

11. Kalams SA, Goulder PJ, Shea AK, Jones NG, Trocha AK, Ogg

GS, et al. Levels of human immunodeficiency virus type 1-specific cytotoxic T-lymphocyte effector and memory responses decline after suppression of viremia with highly active antiretroviral therapy. J Virol. 1999 Aug;73(8):6721–8. [PMC free article] [PubMed] [Google Scholar]

12. Harrer T, Harrer E, Kalams SA, Elbeik T, Staprans SI, Feinberg MB, et al. Strong cytotoxic T cell and weak neutralizing antibody responses in a subset of persons with stable nonprogressing HIV type 1 infection. AIDS Res Hum Retroviruses. 1996 May 1;12(7):585–92. [PubMed] [Google Scholar]

13. Klein MR, van Baalen CA, Holwerda AM, Kerkhof GS, Bende RJ, Keet IP, et al. Kinetics of Gag-specific cytotoxic T lymphocyte responses during the clinical course of HIV-1 infection: a longitudinal analysis of rapid progressors and long-term asymptomatics. J Exp Med. 1995 Apr 1;181(4):1365–72. [PMC free article] [PubMed] [Google Scholar]

14. Shiver JW, Fu TM, Chen L, Casimiro DR, Davies ME, Evans RK, et al. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. Nature. 2002 Jan 17;415(6869):331–5. [PubMed] [Google Scholar]

15. Ellenberger D, Otten RA, Li B, Aidoo M, Rodriguez IV, Sariol CA, et al. HIV-1 DNA/MVA vaccination reduces the per exposure probability of infection during repeated mucosal SHIV challenges. Virology. 2006 Aug 15;352(1):216–25. [PubMed] [Google Scholar]

16. Jin X, Bauer DE, Tuttleton SE, Lewin S, Gettie A, Blanchard J, et al. Dramatic rise in plasma viremia after $CD8^+$ T cell depletion in simian immunodeficiency virus-infected macques. J Exp Med. 1999;189(6):991–8. [PMC free article] [PubMed] [Google Scholar]

17. Schmitz JE, Kuroda MJ, Santra S, Sasseville VG, Simon MA, Lifton MA, et al. Control of viremia in simian immunodeficiency virus infection by $CD8^+$ lymphocytes. Science. 1999;283:857–60. [PubMed] [Google Scholar]

18. Priddy FH, Brown D, Kublin J, Monahan K, Wright DP, Lalezari J, et al. Safety and immunogenicity of a replication-incompetent adenovirus type 5 HIV-1 clade B gag/pol/nef vaccine in healthy adults. Clin Infect Dis. 2008 Jun 1;46(11):1769–81. [PubMed] [Google Scholar]

19. Catanzaro AT, Koup RA, Roederer M, Bailer RT, Enama ME, Moodie Z, et al. Phase 1 safety and immunogenicity evaluation of a

multiclade HIV-1 candidate vaccine delivered by a replication-defective recombinant adenovirus vector. J Infect Dis. 2006 Dec 15;194(12):1638–49. [PMC free article] [PubMed] [Google Scholar]

20. Gorse GJ, Baden LR, Wecker M, Newman MJ, Ferrari G, Weinhold KJ, et al. Safety and immunogenicity of cytotoxic T-lymphocyte poly-epitope, DNA plasmid (EP HIV-1090) vaccine in healthy, human immunodeficiency virus type 1 (HIV-1)-uninfected adults. Vaccine. 2008 Jan 10;26(2):215–23. [PubMed] [Google Scholar]

21. Boyer JD, Cohen AD, Vogt S, Schumann K, Nath B, Ahn L, et al. Vaccination of seronegative volunteers with a human immunodeficiency virus type 1 env/rev DNA vaccine induces antigen-specific proliferation and lymphocyte production of beta-chemokines. J Infect Dis. 2000 Feb;181(2):476–83. [PubMed] [Google Scholar]

22. Jaoko W, Nakwagala FN, Anzala O, Manyonyi GO, Birungi J, Nanvubya A, et al. Safety and immunogenicity of recombinant low-dosage HIV-1 A vaccine candidates vectored by plasmid pTHr DNA or modified vaccinia virus Ankara (MVA) in humans in East Africa. Vaccine. 2008 May 23;26(22):2788–95. [PubMed] [Google Scholar]

23. Mulligan MJ, Russell ND, Celum C, Kahn J, Noonan E, Montefiori DC, et al. Excellent safety and tolerability of the human immunodeficiency virus type 1 pGA2/JS2 plasmid DNA priming vector vaccine in HIV type 1 uninfected adults. AIDS Res Hum Retroviruses. 2006 Jul;22(7):678–83. [PubMed] [Google Scholar]

24. Kelleher AD, Puls RL, Bebbington M, Boyle D, Ffrench R, Kent SJ, et al. A randomized, placebo-controlled phase I trial of DNA prime, recombinant fowlpox virus boost prophylactic vaccine for HIV-1. AIDS. 2006 Jan 9;20(2):294–7. [PubMed] [Google Scholar]

25. Casimiro DR, Wang F, Schleif WA, Liang X, Zhang ZQ, Tobery TW, et al. Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with dna and recombinant adenoviral vaccine vectors expressing Gag. J Virol. 2005 Dec;79(24):15547–55. [PMC free article] [PubMed] [Google Scholar]

26. Wilson NA, Reed J, Napoe GS, Piaskowski S, Szymanski A, Furlott J, et al. Vaccine-induced cellular immune responses reduce plasma viral concentrations after repeated low-dose challenge with

pathogenic simian immunodeficiency virus SIVmac239. J Virol. 2006 Jun;80(12):5875–85. [PMC free article] [PubMed] [Google Scholar]

27. Liang X, Casimiro DR, Schleif WA, Wang F, Davies ME, Zhang ZQ, et al. Vectored Gag and Env but not Tat show efficacy against simian-human immunodeficiency virus 89.6P challenge in Mamu-A*01-negative rhesus monkeys. J Virol. 2005 Oct;79(19):12321–31. [PMC free article] [PubMed] [Google Scholar]

28. Harro C, Edupuganti S, Goepfert P, Priddy F, Lally M, Shiver J, et al. Safety and Immunogenicity of Adenovirus Type 5 (Ad5) HIV-1 gag Vaccines. 12th Conference on Retroviruses and Opportunistic Infections Poster 504, G-115; 2005. [Google Scholar]

29. WHO/UNAIDS/IAVI expert group. Executive summary and recommendations from the WHO/UNAIDS/IAVI expert group consultation on ‘Phase IIB-TOC trials as a novel strategy for evaluation of preventive HIV vaccines’, 31 January-2 February 2006, IAVI, New York, USA. AIDS. 2007 Feb%19;21(4):539–46. [PubMed] [Google Scholar]

30. Mehrotra DV, Li X, Gilbert PB. A comparison of eight methods for the dual-endpoint evaluation of efficacy in a proof-of-concept HIV vaccine trial. Biometrics. 2006 Sep;62(3):893–900. [PubMed] [Google Scholar]

31. Kierstead LS, Dubey S, Meyer B, Tobery TW, Mogg R, Fernandez VR, et al. Enhanced rates and magnitude of immune responses detected against an HIV vaccine: effect of using an optimized process for isolating PBMC. AIDS Res Hum Retroviruses. 2007 Jan;23(1):86–92. [PubMed] [Google Scholar]

32. Dubey S, Clair J, Fu TM, Guan L, Long R, Mogg R, et al. Detection of HIV vaccine-induced cell-mediated immunity in HIV-seronegative clinical trial participants using an optimized and validated enzyme-linked immunospot assay. J Acquir Immune Defic Syndr. 2007 May 1;45(1):20–7. [PubMed] [Google Scholar]

33. Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC Sci Publ. 1987;(82):1–406. [PubMed] [Google Scholar]

34. Mogg R, Mehrotra DV. Analysis of antiretroviral immunotherapy trials with potentially non-normal and incomplete longitudinal data. Stat Med. 2007 Feb 10;26(3):484–97. [PubMed] [Google Scholar]

35. Seage GR, III, Holte SE, Metzger D, Koblin BA, Gross M, Celum C, et al. Are US populations appropriate for trials of human immunodeficiency virus vaccine? The HIVNET Vaccine Preparedness Study. Am J Epidemiol. 2001 Apr 1;153(7):619–27. [PubMed] [Google Scholar]

36. Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, Para MF. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis. 2005 Mar 1;191(5):654–65. [PubMed] [Google Scholar]

37. McMichael AJ. HIV vaccines. Annu Rev Immunol. 2006;24:227–55. 227–55. [PubMed] [Google Scholar]

38. Tirado SM, Yoon KJ. Antibody-dependent enhancement of virus infection and disease. Viral Immunol. 2003;16(1):69–86. [PubMed] [Google Scholar]

39. Iankov ID, Pandey M, Harvey M, Griesmann GE, Federspiel MJ, Russell SJ. Immunoglobulin g antibody-mediated enhancement of measles virus infection can bypass the protective antiviral immune response. J Virol. 2006 Sep;80(17):8530–40. [PMC free article] [PubMed] [Google Scholar]

40. Staprans SI, Barry AP, Silvestri G, Safrit JT, Kozyr N, Sumpter B, et al. Enhanced SIV replication and accelerated progression to AIDS in macaques primed to mount a CD4 T cell response to the SIV envelope protein. Proc Natl Acad Sci U S A. 2004 Aug 31;101(35):13026–31. [PMC free article] [PubMed] [Google Scholar]

41. Garnett CT, Erdman D, Xu W, Gooding LR. Prevalence and quantitation of species C adenovirus DNA in human mucosal lymphocytes. J Virol. 2002 Nov;76(21):10608–16. [PMC free article] [PubMed] [Google Scholar]

42. Buchbinder SP, Vittinghoff E, Heagerty PJ, Celum CL, Seage GR, III, Judson FN, et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. J Acquir Immune Defic Syndr. 2005 May 1;39(1):82–9. [PubMed] [Google Scholar]

43. Millett GA, Ding H, Lauby J, Flores S, Stueve A, Bingham T, et al. Circumcision status and HIV infection among Black and Latino men who have sex with men in 3 US cities. J Acquir Immune Defic Syndr. 2007 Dec 15;46(5):643–50. [PubMed] [Google Scholar]

44. Kreiss JK, Hopkins SG. The association between circumcision status and human immunodeficiency virus infection among homosexual men. J Infect Dis. 1993 Dec;168(6):1404–8. [PubMed] [Google Scholar]

45. Grulich AE, Hendry O, Clark E, Kippax S, Kaldor JM. Circumcision and male-to-male sexual transmission of HIV. AIDS. 2001 Jun 15;15(9):1188–9. [PubMed] [Google Scholar]

46. Feinberg MB, Moore JP. AIDS vaccine models: challenging challenge viruses. Nat Med. 2002 Mar;8(3):207–10. [PubMed] [Google Scholar]

47. Staprans SI, Feinberg MB. The roles of nonhuman primates in the preclinical evaluation of candidate AIDS vaccines. Expert Rev Vaccines. 2004 Aug;3(4 Suppl):S5–32. [PubMed] [Google Scholar]

Footnote 9

Immunity
Review

Immunologic Basis of Vaccine Vectors

Margaret A. Liu[1,2,*]
[1]ProTherImmune, 3656 Happy Valley Road, Lafayette, CA 94549, USA
[2]Department of Microbiology and Tumor Cell Biology, Karolinska Institutet, Nobels väg 16, SE-17 177 Stockholm, Sweden
*Correspondence: liu@protherimmune.com
DOI 10.1016/j.immuni.2010.10.004

Efforts to make vaccines against infectious diseases as well as immunotherapies for cancer, autoimmune diseases and allergy have utilized a variety of heterologous expression systems, including viral and bacterial vectors, as well as DNA and RNA constructs. This review explores the immunologic rationale and provides an update of insights obtained from preclinical and clinical studies of such vaccines.

Introduction

Traditional means of making vaccines against infectious disease have been highly successful for a number of pathogens with a resultant decrease in their rates of infection. However, the usual approaches have had limitations for certain diseases such as HIV and for diseases either not due to infections, or in which the appropriate target antigen is unclear, such as for certain cancers and autoimmune diseases. Challenges for making such vaccines include knowing the type of immunity that is needed or thought to be needed for particular pathogens or diseases, as well as unique biological and pathophysiological characteristics of a given pathogen or disease process. For example, attenuated virus vaccines are extremely effective, and they are perhaps the best way to stimulate all the components of immunity (including at least some degree of memory) that infection with the pathogenic organism does, without the obvious morbidity and mortality of wild-type infection. But not only are some pathogens considered perhaps too risky even in attenuated form, but also the immune responses elicited by wild-type infection are not necessarily effective for clearing a pathogen after an infection. Infection with HIV is an obvious example in which infection does not induce effective immunity, and hence the immune responses that occur after HIV infection may not be good predictors of the type of immunity that a vaccine should generate. Inactivated pathogen or subunit vaccines, such as for influenza, are generally used for pathogens for which a humoral immune response is considered the primary protective immune response and as such would be inadequate for inducing the appropriate forms of cellular immunity needed for certain diseases. Therefore new technologies have been developed and explored for making vaccines that elicit the forms of immunity thought to be most important for a given infectious agent or disease. Inducing primarily antibodies or cytolytic T cells or modifying the type of T cell help, such as for preventing or treating autoimmune or allergic diseases, might be best accomplished by different vaccine technologies that deliver the antigen in such a way as to induce a particular arm of immunity or to bias the type of immune response. Vectors are delivery systems often derived from pathogens and are used to deliver genes encoding antigens of a different pathogen. In other words, a modified bacterium, virus, plasmid, or gene sequence derived from a pathogen that is used to deliver a gene encoding an antigen is a vector that when given to a vaccinee results in the in situ production of the antigen. This distinguishes it from a traditional vaccine that involves the direct administration of the pathogen or some part of the pathogen (versus a gene encoding it) against which the immune response is desired. This review will explain the rationale for different types of vectors, then compare vectors under development. Vectors for vaccine delivery include plasmid DNA, RNA, viral vectors, and bacteria. Some of the attributes are shown in Table 1.

Immunologic Rationale for Vaccine Vectors

New vaccine modalities have been explored that could generate the appropriate forms (and duration) of immune responses while simultaneously focusing the immune response on the desired antigen (Nabel et al., 2010). For viral infections and cancer, for example, cellular responses, such as cytolytic T cells (CTLs), are thought to be an important part of the immune responses, and in addition to targeting the virally infected cells (versus the virus itself) or the tumor cells directly, they can target epitopes that are conserved between different strains of a virus or between different tumors, which often are internal or functional proteins, and hence are less accessible to antibodies. Thus efforts have been made to generate vaccines (and immunotherapies) that can generate CTL responses. This is one of the main rationales for developing vectored vaccines because they are able to deliver heterologous antigens into the antigen-processing pathways needed to stimulate MHC class I-restricted CTL responses (Liu, 2010). The intent is to generate an immune response against epitopes from proteins that are more highly conserved between viral strains or tumor antigens that are common to a particular type of tumor in order to make a vaccine that is broadly protective or useful against tumors arising in different individuals. These approaches are not meant to imply that the humoral response is not an important component of vectored vaccines, but rather they are a way to generate a cellular response that heretofore had been difficult to stimulate without using a live attenuated vaccine. Vector vaccines can also result in antibodies (as well as the cellular responses) directed against the encoded antigen.

Although it is possible to directly introduce proteins into the MHC class I processing pathway, such as through the use of certain particles (Oh et al., 1997) including hepatitis B surface antigen particles (Schirmbeck et al., 1998), it is more universally feasible to deliver a gene encoding the antigen into cells from which the relevant peptide epitopes could ultimately be appropriately presented on the MHC class I molecules (Donnelly

Table 1. Examples of Vaccine Vectors

Vector	Potential Advantages	Issues/Concerns
Nucleic Acids		
Plasmid DNA	Licensed veterinary vaccines	Low human potency without heterologous boost
	Relatively generic construction and production	Use of delivery device or technology will increase complexity and cost
	Potent prime in animal studies	
RNA	Considered to have fewer safety regulatory issues than other vectors, e.g., no integration, no issue of autoimmunity	Instability; likely require formulation and/or delivery technology
	Facile production with high purity	
Viruses		
Poxviruses	Licensed veterinary vaccine vector	Possible issue of pre-existing immunity for vaccinia (smallpox) vaccinees
	MVA known clinical safety	Probably will need prime, increasing complexity and cost
	Room for large gene insert	
	Various strains available	
Adenovirus	Historic oral adenovirus vaccine	Pre-existing immunity to certain human strains may not preclude use as vectors, but results of HIV STEP trial need to be understood re: safety for high-titered vaccinees relative to subsequent risk of HIV infection if exposed
	Strong immune responses	Human Ad strains oncogenic in animals
	Many strains available	
Adeno-associated virus	Apparent efficacy as vector in small gene therapy trial for eye disease[a]	Disputed risk of integration
	Safety shown in small gene-Rx trials	Limited gene insert capacity
Alphaviruses	Virus particles or DNA replicons	Modest gene capacity
	High expression	
	No risk of integration because RNA particle can target DCs	
Herpes virus	Broad tropism including DCs	Neurotropism may be safety issue
		Possible pre-existing immunity
Measles virus	Mucosal delivery possible	Possible pre-existing immunity
	RNA virus (no integration issue)	
Vesicular stomatitis virus	Broad tropism including DCs	Neurotropism[b] may be safety issue
	High expression	
Bacteria		
Salmonella/Shigella	Oral delivery	Concern about heterologous gene if on plasmid
	Infect M cells (gut antigen uptake cells)	Potential stability of antigen gene if on plasmid
BCG	Extensive safety of BCG vaccine	Bacterial (versus mammalian) posttranslational modifications
Listeria	Efficient mechanisms for CTL induction	Concerns re: vector virulence in immunocompromised

[a] Maguire et al., 2008.
[b] Johnson et al., 2007.

et al., 1997). A variety of techniques were used to accomplish this, including direct cell transfection, and the use of vectors, initially viral vectors, but also bacteria and plasmid DNA (Liu, 2010).

Other developments that increased the interest in vectored vaccines included the focus on particular antigens or even epitopes. Early vaccines were based on whole organisms (e.g., vaccinia, BCG), but attention moved to key proteins, such as the toxins of diphtheria and tetanus, or the surface antigen of hepatitis B. The rationale was that those molecules were essential targets for antibody responses. Subsequently, a new strategy for targeting different proteins was developed for those proteins that are not necessarily accessible to antibodies, but rather that are more conserved between viral strains due to their function and/or location (Rolland et al., 2007). For example, early studies of the genetics of HIV strains revealed that Gag and Pol proteins are more highly conserved than Env (Peeters et al., 1991) (Alizon and Montagnier, 1987), and Env contains highly variable regions (Gao et al., 1996), which rapidly mutate in response to antibody responses. Similarly, influenza subtypes,

which are classified on the basis of the hemagglutinin (Schweiger et al., 2002) and neuraminidase surface proteins, which mutate frequently (Xu et al., 1996), readily escape antibody-based viral neutralization by minor mutations in these proteins necessitating the annual reformulation of the influenza vaccines (Doherty et al., 2006). Yet they have much less variability in their nucleoproteins, even between influenza viruses of different subtypes and between such epidemic strains separated by many years (Thomas et al., 2006).

A study in humans demonstrated that CTLs have cross-reactivity with another strain of influenza. In that study, people were intentionally infected with a strain of influenza, and those who had CTLs cleared infection whether or not they had pre-existing antibody directed against the virus, and their CTLs were found to be able to kill cells infected with the challenge virus even if they had no evidence of previous infection with the challenge virus, i.e., their CTLs were able to cross-react with a new subtype of virus. (McMichael et al., 1983). As the HIV-AIDS epidemic develops, the cellular immune responses, notably $CD4^+$ T cell help (Day and Walker, 2003), and $CD8^+$ CTL responses (Harrer et al., 1996; Goulder et al., 1996) were found to play a role in viral containment (Rowland-Jones et al., 1999). Human memory CTLs have also been found to be effective against different strains of virus (Gianfrani et al., 2000). Certain of these cellular responses were directed against epitopes that were conserved between different strains (Johnson et al., 1991). This led to two aspects for the development and use of vectors: the first being to find means to deliver antigens in a way as to generate both CTL and appropriate T helper cell responses, and to be able to deliver just the key antigens desired, which could easily be accomplished by the use of vectors rather than attenuated organisms. The utilization of only certain proteins or even epitopes to focus the immune response on critical (e.g., neutralizing) (Muster et al., 1994) or conserved regions (Hammond et al., 1991) (Nishino et al., 1994) (Johnson et al., 1994) is an effort to ensure that the immune response would be effective for controlling viremia and would be effective against a broad array of viral strains (Kuwano et al., 1989; Ulmer et al., 1993). Another rationale for limiting the proteins delivered, or excluding portions of proteins, was to eliminate proteins with deleterious functions (such as the transforming capabilities of human papilloma virus E6 [Sedman et al., 1991]). Thus, vectors could be used to deliver the genes encoding only the specific antigens against which an immune response is desired and can deliver the gene or antigen such that the desired immune responses are generated.

Different vectors and delivery modes were found to stimulate or bias different T helper responses. The type of T cell help is thought to not only affect the type of immune response (e.g., antibodies versus CTLs) but to potentially play a role in limiting disease progression (e.g., in HIV [Rosenberg and Walker, 1998]). Thus, there are increased efforts to develop specific vectors not only to generate specific CTLs and/or antibody responses but also to promote the type of T cell help (i.e., T helper 1 [Th1] or Th2) for diverse applications, such as for prevention of infectious diseases or asthma and diabetes, respectively (Liu, 2010).

Efforts to develop vectors have taken into account a variety of other factors such as the ease of manipulation of the vectors, gene capacity, expression of the heterologous protein, production of the vectors, and safety. One aspect that was little understood in the early days, and that is still too complicated to fully factor in, is the immune response against the vector itself. This includes issues related to reuse of a vector, or the use of vector in persons who have been previously exposed to the virus or a related virus, such as for smallpox vectors in previously immunized individuals. Additionally, stimulation of innate immunity by the vectors themselves (Ulmer et al., 2006; Zhu et al., 2007) is considered an attribute that can increase the potency of vectored vaccines, although clearly the interactions between the innate and adaptive immune systems are poorly understood.

The final aspect of the rationale for utilizing vectors to deliver vaccines is the targeting of delivery, not just to the antigen-processing pathways but to particular cells or subsets of cells. Although adenovectors target a broad range of cells, this in some ways may be a limitation of their utility because of the efficiency with which they bind to nonantigen presenting cells (non-APCs), such as liver cells (Arnberg, 2009). Efforts to specifically direct vectors to or away from certain cell types have included the addition or deletion of targeting motifs on the vectors (Einfeld et al., 2001) and formulation of DNA plasmids in or on particles to enhance their uptake by APCs (Denis-Mize et al., 2000).

Throughout this discussion, it must be remembered that although vaccine research and development has targeted particular immune responses, and particular antigens, we have a relatively incomplete understanding of all of the components of the immune response that comprise a protective response, even for licensed vaccines. That is, except for certain vaccines, a particular antibody titer is generally used as the correlate of protection. For other vaccines we do not have an antibody titer, nor a measure of cellular responses that can be considered protective, particularly when the cellular immunity is thought to be crucial. Moreover, our usual source of sampling for immune responses, especially in large-scale efficacy studies, is peripheral blood, which gives us a very incomplete picture of the protective immune responses at the initial sites of infection (mucosal surfaces) or target organs. Measurement of single types of immune responses gives a limited understanding of the composite and interactive nature of the various responses. Thus this discussion of the immune responses, and comparisons between different vectors, is akin to the proverbial description of an elephant by six blind men, in which the measured immune responses only reveal a portion of the complex immune response. It must also be remembered that although this review will focus on the immune responses of the vectored vaccines, any particular vaccine can be made and will be utilized on the basis of the sum of its attributes, which include not only immune responses (which may vary in different populations), but foremost safety, as well as ease and cost of manufacture, distribution, and administration.

Viral Vectors

Various viral vectors have been developed and reached clinical trials. Interestingly, several of these were also the basis for gene therapy efforts when an immune response against the gene product would not be desired. The intrinsic characteristics of the vectors lead to specialized applications or determine their potency as vaccine vectors. For example, herpes virus vectors are under development not only as vaccine vectors but also as

immunotherapies for brain tumors and for the delivery of genes encoding therapeutic agents to the CNS because of their tropism for the nervous system (Manservigi et al., 2010). Vesicular stomatitis virus (VSV) has been shown to target DCs, perhaps accounting for the potent immune responses seen when it is used as a vector (Boudreau et al., 2009). The vectors that have the most data from clinical trials include adenovectors and pox vectors, including both canary pox and modified vaccinia ankara (MVA). The measured immune responses for vaccines and immunotherapy focus on: (1) immune responses directed against the heterologous antigen, (2) the adaptive immune responses directed against the vector, and how these affect the use and reuse of the vector, and (3) the innate responses against the vector, and the impact upon the antigen-specific immune responses.

The immunological rationale for selecting a particular viral vector includes how well the heterologous gene is expressed because the quantity of antigen may affect the extent of the immune response. In addition, the type of cells that produce the antigen following transfection by the virus vector, may affect the nature and potency of the immune response. Another factor influencing the choice of vector is the persistence of the virus (e.g., herpes [Liu et al., 2009]), which might be useful for prolonging immunity. Because so many of the factors governing the induction of optimal immunity are incompletely understood (such as the activation of the innate immune system by various components of vectors and the effect upon the adaptive immunity), it is hard to know exactly what would make the best vector for any given vaccine. Given the expensive and long development process required for clinical testing, the choice of one vector over another for the vaccines described below has been largely based upon key characteristics of a vector and extensive preclinical studies for that vector rather than exhaustive head-to-head comparisons of vectors and administration protocols, since regimens, doses, and matrices of prime-boost combinations could lead to innumerable variables.

Pox Virus Vector

Pox viruses are selected as potential vectors for several reasons: the extensive use of the smallpox vaccine (and the related modified vaccinia ankara), which provided knowledge of the human safety parameters; the large gene capacity for the insertion of a heterologous gene encoding the antigen of interest; the broad tropism of the virus for mammalian cells that could then result in a number of cells expressing the heterologous antigen; the production of antigen for a relatively short period of time (making the kinetics of the production of the heterologous protein more akin to antigen production from an acutely infecting pathogen, but less useful for gene therapy applications); and the location of the virus in the cytoplasm, thus avoiding integration risks that might occur with a retroviral vector, for example (Mastrangelo et al., 2000). The earliest vector for delivery of a heterologous antigen is a licensed veterinary vaccine employing a modified vaccinia ankara vector to deliver a rabies antigen (Mackowiak et al., 1999). The vaccine was developed in order to be delivered as bait for wild animals. The vector not only expressed the heterologous antigen, but as a smallpox vaccine had been tested in 150,000 humans including immunocompromised individuals (McCurdy et al., 2004). The success of using a vector to deliver an antigen that generated immunity sufficient to protect animals and curtail outbreaks in the wild, via oral delivery of bait (hence with imprecise dosing), in a variety of animal species, demonstrates many of the advantages of an ideal vectors, in this case efficacy, safety, and even ease of distribution (oral delivery), which would not have been as facile with a nonvectored vaccine.

Various pox vectors have undergone human clinical testing as HIV vaccines (Hanke et al., 2002a; Hanke et al., 2002b; Peters et al., 2007; Vasan et al., 2010; Wee et al., 2002). In the largest clinical trial, a canary pox vector coding for HIV antigens was utilized as the first component of a prime-boost regimen (see below) in a clinical trial of an HIV vaccine involving 16,000 individuals (Rerks-Ngarm et al., 2009). This study utilized a recombinant protein boost and demonstrated modest protective efficacy. In another heterologous prime-boost vaccination protocol for prophylaxis of HIV, the priming is being done with a DNA plasmid, followed by an MVA vector boost (http://clinicaltrials.gov/ct2/show/NCT00820846?term=DNA+%2B+MVA+for+HIV&rank=5).

Adenovirus Vector

The STEP trial was a proof-of-concept human clinical trial for prevention of infection with HIV and utilized an adenovirus vector encoding HIV proteins (Buchbinder et al., 2008; McElrath et al., 2008). Because of the concern that pre-existing adenovirus (Ad5) antibodies would make such a vaccine less effective, by binding to the vaccine and diminishing its activity, the study was done both in individuals with high and low titers of pre-existing adenovirus antibody. The human trial was stopped when it was clear that it would not be possible to demonstrate that the vaccine had efficacy (so called "futility" of the trial) (Buchbinder et al., 2008). However, one result that came out of the study was that more individuals who had high titers of adenovirus antibodies before being immunized became HIV infected than did similar patients who received the placebo. No differences in rates of HIV infection were seen in patients receiving vaccine or placebo in individuals who had low pre-existing adenovirus antibody titers.

One possible explanation for these results, aside from it being stochastic, is that in patients with high anti-Ad5 titers, (i.e., presumably indicative of prior infection with adenovirus 5, and hence also with pre-existing Ad5 T helper cell responses) activated Ad5-specific T cells were more susceptible to infection by HIV. Two subsequent studies seemed to indicate that this mechanism was not responsible, by their demonstration of a lack of correlation between the titer of Ad5 antibodies and the frequency of Ad5-specific T cells either before or after immunization (Hutnick et al., 2009; O'Brien et al., 2009). However, a further study showed that when T cells from individuals who had pre-existing antibodies against adenovirus were stimulated with adenovirus, an increase in memory $CD4^+$ T cells occurred, and these T cells were more easily infected with HIV (Benlahrech et al., 2009). In addition, these T cells homed to mucosa, which could provide an explanation for the results of the two prior studies that had sampled peripheral blood lymphocytes rather than mucosal lymphocytes (Benlahrech et al., 2009). These studies highlighted, among other issues, that many of the readouts of immunologic parameters have utilized peripheral blood lymphocytes, which may not reflect cells or immune conditions in organs or at the sites of infection.

As noted above, another concern about using vectors is the pre-existing immunity either from natural infection or from prior

administration of the Ad5 vector. In a nonhuman primate study evaluating the effect of prior immunization with an adenovector not encoding an HIV gene, which was included in the vector used for the second injection, the immune response against the HIV antigen was diminished but not eliminated compared to adenovirus vector-naive monkeys (Casimiro et al., 2003). For humans, pre-existing immunity would include both prior infection with wild-type Ad5 and prior use of Ad5 as a vector (Quirk et al., 2008), (Harro et al., 2009). However, this may not be an issue for all vectors. In a clinical trial employing an MVA vector encoding several HIV genes, older individuals, who by dint of their age had been previously immunized against smallpox (a practice discontinued in 1980 after smallpox was declared eradicated in 1977) did indeed have lower immune responses than people not previously immunized for smallpox (Gudmundsdotter et al., 2009). But it is possible that the lower immune responses were due to the fact that the former group was older, because cellular immunity, in particular, is known to diminish with age.

The desire to increase the ability to reuse adenovectors has led to efforts to develop Ad5 constructs lacking various adenovirus genes (in addition to the genes already removed to make the vectors incapable of replication) to eliminate the immunogenicity of the expressed proteins (Gabitzsch et al., 2009), (Weaver et al., 2009), (Koup et al., 2009). Other groups have turned to adenoviruses that do not normally infect humans such as those derived from chimpanzees (Rodríguez et al., 2009), (Santra et al., 2009), (Tatsis et al., 2009). In addition, approaches are being evaluated for decreasing immune responses against the vector (Thacker et al., 2009). Nonreplicating adenovectors have been the primary focus of vaccine development because of concerns related to use of replication-competent adenovirus in immunodeficient individuals and concerns about the animal oncogenicity of human adenovirus strains. But replicating adenovectors yield more potent cellular and antibody responses against heterologous antigens (Robert-Guroff, 2007) and could be administered orally (Gómez-Román et al., 2006). Thus replicating adenovectors for use as an HIV vaccine are under development, and have been explored as primes for heterologous prime-boost regimens (Patterson and Robert-Guroff, 2008), more fully discussed below.

Bacteria Vector

Several attributes of bacteria led to their development as vaccine vectors. These included the ability to deliver them via the oral route, which is the natural route of infection for a variety of bacteria such as Salmonella (Fouts et al., 1995a; Fouts et al., 1995b), (Chin'ombe et al., 2009), (Huang et al., 2009), Shigella (Fennelly et al., 1999), and certain Mycobacteria such as M. bovis (Ferrari et al., 2000). Of note, attenuated bacteria are used. The heterologous (i.e., vaccine) antigen could either be made as a bacterial protein, or the bacteria could be used to deliver a plasmid encoding the antigen under control of a viral promoter for protein production by the infected mammalian host cell. The immunologic rationale for bacterial vectors has therefore also been that intracellular bacteria, could deliver the antigen or the plasmid into cells for intracellular production of the antigen, with subsequent introduction of the antigen into the MHC class I processing pathway. Thus both humoral and cellular immune responses can be generated. Interestingly, in a study of Salmonella vectors used to deliver plasmid encoding antigen, it was determined that prokaryotic production of the antigen was necessary for immunogenicity rather than simply the mammalian production in the host cell (Gahan et al., 2009). A potential issue for bacterial vaccine vectors given orally, is the concern that the heterologous gene, if present on a plasmid, could be transferred to other bacteria (Zhang et al., 2008). In addition, for bacterial delivery of plasmid DNA vaccines, high copy plasmid numbers are generally used, and these may be unstable (Huang et al., 2010).

DNA and RNA Vectors

DNA, RNA and oligonucleotides have been directly delivered into cells in vitro as a means to have recombinant proteins expressed in situ, or to affect the synthesis of endogenously encoded proteins (such as with the delivery of siRNA). Because intracellular bacteria and viruses have specific structures and mechanisms for their infection of cells, the direct transfection of cells by DNA or RNA was considered too inefficient to transfect cells in vivo, particularly given the degradability of the genetic material. So the demonstration that plasmid DNA could directly transfect muscle cells when injected directly in vivo, and that the encoded gene could be expressed (Wolff et al., 1990) was unexpected. Moreover, because DNA plasmids when injected are primarily taken up by, and expressed in, muscle cells (Wolff et al., 1990), the observation that immune responses could be generated against the encoded protein, including MHC class I-restricted CTLs that could protect against infectious challenge with a heterosubtypic virus (Ulmer et al., 1993), was even more surprising. The immunologic mechanism was only understood when it was shown that cross-priming could occur, whereby antigen produced in non-APCs could be somehow transferred in a way to professional APCs (Fu et al., 1997), and that a low number of APCs could also be directly transfected (Ulmer and Otten, 2000).

Another mechanism for the immune responses against proteins encoded by DNA vaccines is the innate responses directed against the plasmid itself. Studies demonstrated that addition of noncoding plasmid to plasmid coding for antigen resulted in greater immune responses (Donnelly et al., 1995), (Sato et al., 1996). Because the plasmid is bacterial in origin, its sequences contain CpG motifs that stimulate Toll-like receptor 9 (TLR9) (Klinman et al., 1997), (Hemmi et al., 2000) with a resultant augmentation of the cognate immune response against the antigen encoded by the plasmid. However studies in *Tlr9* $^{+/+}$ and *Tlr9* $^{-/-}$ mice yield different conclusions. Tudor and colleagues demonstrate that TLR9 signaling is not needed for generation of the cognate immunity, but did appear to augment the immunity against the antigen encoded by the DNA (Tudor et al., 2005), whereas Babiuk and colleagues demonstrate that both types of mice generated similar immune responses (Babiuk et al., 2004), and Spies and colleagues showed that although DNA vaccines activate DCs via TLR9 they could activate responses in TLR9-deficient mice (Spies et al., 2003). Efforts to increase the potency of DNA plasmid vaccines by the addition of immunostimulatory CpG sequences have met with limited success, although synthetic CpG oligonucleotides do increase the potency of protein antigens. A recent study has provided a possible explanation for the different outcomes of the above studies, by demonstrating that the role of the CpG motifs in activating DCs may be important for a prime

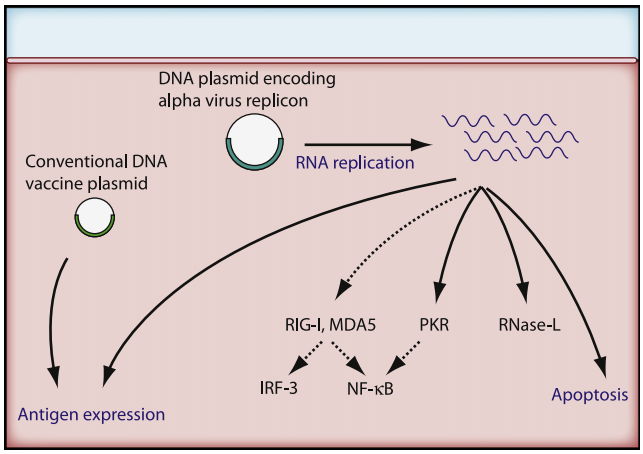


Figure 1. Induction of Immune Responses after Transfection of Plasmid DNA Encoding an Alpha Virus Replicon versus Simple Plasmid DNA

The replicon DNA encodes both the heterologous antigen and the alpha virus proteins needed to replicate the genetic material but not the alpha virus structural proteins. Thus, the RNA is self-replicating and results in the production of larger amounts of heterologous antigen than from a usual DNA plasmid driven by a typical CMV promoter. Innate responses are also stimulated by the alpha virus proteins and double-stranded RNA along with apoptosis. The net effect is a highly potent immune response against the encoded heterologous antigen. Proposed mechanisms are shown by dashed lines, with solid lines denoting proven pathways.

Mechanisms to increase the potency of DNA and RNA Vaccines

Plasmid alterations
- Changes in promoters to increase gene expression
- Codon optimization
- Augmentation of innate immune responses (increasing CpG motifs?)
- Coexpression of immune modulators: cytokines, costimulatory molecules, targeting molecules
- Encoding replicons

Increasing the stability of the DNA or RNA
- Formulations
- Encapsulation

Delivery
- Gene gun
- Electroporation
- Propelling devices
- Mucosal delivery

Augmentation of Immunity
- Coadministration of protein cytokines and adjuvants

Box 1. Mechanisms to Increase the Potency of DNA and RNA Vaccines

with a DNA vaccine for a viral infection, but not for a prime-boost regimen (Rottembourg et al., 2010).

Other oligonucleotides that may prove useful include linear DNA, which can be produced enzymatically in cell-free systems (Vilalta et al., 2007). RNA has also been studied for vaccines and immunotherapy of cancer (Pascolo, 2006), as well as for immunotherapy of allergy (Weiss et al., 2010) but the increased susceptibility to degradation of RNA compared to DNA has required additional stabilizing technologies (Kuhn et al., 2010). Clinical trials have been performed for patients with melanoma utilizing mRNA coding for melanoma antigens or using mRNA derived by extracting total RNA from a resected melanoma metastasis to make cDNA libraries which could then be transcribed to produce mRNA for immunotherapy (Weide et al., 2008; Weide et al., 2009). RNA has long been known to activate the innate immune system, and mRNA condensed on protamine in order to render it less susceptible to degradation has been shown to stimulate DCs via TLR-7 and TLR-8 (Scheel et al., 2005).

Additionally, DNA or RNA encoding alphavirus replicons are under development and evaluation. Replicons encode not simply the antigen, but by encoding viral enzymes of an alpha virus, generate self-amplifying RNA. Both DNA and RNA replicons have been made and have been based on several alpha viruses (Liu et al., 2006). They result in production of high amounts of antigen, although for a short period of time (Karlsson and Liljeström, 2004), as well as stimulating innate (anti-viral) responses directed against the dsRNA (Leitner et al., 2003) and apoptosis (Leitner et al., 2004) (see Figure 1) with the net effect to be increased immunogenicity compared to when comparable doses of regular plasmid DNA are used. However, the size of replicon DNA plasmids may limit their ability to transfect cells in vivo, because they are several-fold larger than the typical DNA plasmids. Indeed a primate study comparing DNA replicons with regular plasmid DNA demonstrated similar immune responses (Otten et al., 2004), although a another study demonstrated that a chimeric replicon could protect both juvenile and infant macaques from measles (Pan et al., 2010).

Although efforts to increase the potency of viral vectors have centered on issues specific for the virus, such as pre-existing immunity, and increasing or decreasing the innate and virus-specific immune responses, the approaches for DNA vaccines can be described as ways to build back in those attributes of a pathogen that enhance immunity, but in more surgical way than might be possible by starting with a pathogen as a vector (Box 1). These efforts fall into two main categories: improved formulation and delivery to the relevant immune system, and the provision of additional immunologic help in the form of adjuvants and cytokines, whether via the innate or adaptive immune systems. DNA formulation and delivery encompass a broad array of approaches meant to stabilize the DNA, enable it to be delivered more facilely, (e.g., orally), result in higher antigen expression (Wang et al., 2006), and to deliver the DNA to APCs (or increase cross-priming) or specifically augment the immune response against the cognate antigen. Of course some of the technologies have multiple effects, such as a cationic lipid formulation designed to protect the DNA which also has adjuvant activity (Hartikka et al., 2009) (Sedegah et al., 2010). These concepts have been recently reviewed elsewhere (Nabel et al., 2010).

Because particles (1–10 microns diameter) are taken up by APCs, one approach has been to formulate DNA into or onto microparticles, which should serve to protect the DNA as well as to direct it to APCs rather than to either muscle cells or

degradation (Xiang et al., 2010), (DeLong et al., 2009), (Denis-Mize et al., 2003). DNA coated onto gold beads has also been delivered via propulsion into the skin. In this case, the DNA is directed into any cell in its pathway, including Langerhans cells. This direct transfection of APCs may be responsible for the potency of such ''gene-gun'' delivered DNA compared to intramuscularly injected plasmid. In clinical trials performed in individuals who had not responded to the licensed recombinant protein vaccine, injection of gold beads coated with a DNA vaccine resulted in the production of antibodies (Rottinghaus et al., 2003). However, the dose of DNA that can be delivered per ''shot'' means that multiple injections into multiple sites are required, limiting the attractiveness of the technology. Another device, the Biojector, shoots the liquid-formulated plasmid into the skin, in an effort to also directly transfect Langerhans cells (Rao et al., 2006), (Bråve et al., 2005). In vivo electroporation enables a substantial increase in uptake of DNA into cells, with a resultant increase in protein production and immunogenicity (Chiarella et al., 2010). The safety (in terms of risk of integration) and clinical applicability of this technology is under evaluation.

During the years following the development of the recombinant Hepatitis B vaccine, vaccine efforts focused on the development of ''surgical'' types of vaccines that depended on single antigens, or even limited epitopes, to generate protection. However, it became clear that for most vaccines, even though a particular antibody might be critical in terms of being responsible for the neutralization of the virus, or the lysis of a bacteria, that a variety of immunologic cells and factors played key roles in generating the response that received credit for the protection. A DNA vaccine lends itself to being able to specifically add back in those elements of the immune system to either augment a response, or to modify the response toward the desired phenotype. This could easily be accomplished by co-administration of cytokines or chemokines or their genes (as DNA plasmids) (Barouch, 2006), (Stevenson, 2004). Efforts to harness the innate immune system have been discussed above for both plasmids and viral vectors.

Additional immunologic manipulations have included efforts to cause apoptosis of the cell expressing the antigen (Parsania et al., 2010) (Bergmann-Leitner et al., 2009) to increase cross-priming, and hence to augment the immune response. However, in other systems, an anti-apoptosis gene increases the immunogenicity (Dharmapuri et al., 2009) (Kim et al., 2004). In one case, the beneficial effect of the anti-apoptosis gene appears to be due to inhibition of gp140-mediated cytolosis, resulting in higher amounts of expression of gp140 (the antigen) (Su et al., 2008). Another explanation may be that different degrees of apoptosis determine the immunological outcome (Kojima et al., 2007). It may be that the effect is dependent upon whether the antigen expression occurs in professional APCs (in which case, prolonged expression of the antigen would yield a greater immune response), versus in non-APCs, wherein apoptosis would enhance the cross-priming (Chattergoon et al., 2000).

Prime-Boost Immunization

Perhaps the most interesting, and immunologically poorly understood approach to increasing the potency of vectored vaccines has been the use of a mixed-modality vaccine wherein a prime (or series of priming immunizations) is given with one type of vaccine, such as a DNA vaccine, followed by a boost (or series of boosts) with another type of vaccine, such as a viral vector, or a recombinant protein. The concept of heterologous prime-boosting arose when an initial immunization with plasmid DNA followed by a viral vector, both encoding the same antigen, was more potent for generating immune responses than either the DNA or viral vector alone or given in the opposite order, and provided better protective immunity to malarial challenge (Schneider et al., 1998). Preclinical and clinical trials of combinations of various modalities (DNA vaccines, viral vectors, bacterial vectors, recombinant proteins) have been performed (Nabel et al., 2010), with the most extensive being the 16,000 patient trial for an HIV vaccine described above, consisting of a pox vector followed by a recombinant protein boost (Rerks-Ngarm et al., 2009). Additional HIV vaccine trials include a Phase II study utilizing plasmid DNA then a boost with an Adenovector5 (http://clinicaltrials.gov/ct2/show/NCT00865566?term=DNA+ad5+HIV+phase+II&rank=1, or ClinicalTrials.gov Identifier NCT00865566), a Phase I study using a DNA plasmid prime boosted with either an Ad 35 or an Ad5 vector (http://clinicaltrials.gov/ct2/results?term=NCT+00801697, or Clinical Trials.gov Identifier NCT 00801697), and a phase II study utilizing adenovectors delivered by either needle or Biojector (http://clinicaltrials.gov/ct2/show/NCT00709605?term=Biojector&rank=3; identifier NCT 00709605).

The immunologic explanation for the increased immune responses in prime boost protocols and the reason that the sequence of priming with DNA plasmid followed by another modality, whether recombinant protein or viral vector, is necessary are not well understood. However, the lack of additional viral antigens (of the vector) when DNA is the prime, may help focus the immune response on the key antigen (de Mare et al., 2008). The additional innate antiviral responses, and cytokine milieu that develop following the viral vector boost, may augment the booster response. Recombinant protein has been utilized as a boost to increase the antibody responses, as DNA vaccines have often been considered better at inducing CTLs than antibodies in higher species (Liu, 2010).

Vectored Vaccines for Veterinary Applications

Several vector-based vaccines have been licensed for animal applications including the MVA-vectored rabies vaccine described above and several DNA vaccines. The DNA vaccines span the range of a fish vaccine against infectious hematopoietic necrosis virus (IHNV) for use in salmon (Kurath, 2005) to a melanoma immunotherapeutic vaccine for dogs (Bergman et al., 2003), and an equine vaccine against West Nile virus (Turell et al., 2003). The relatively easy success of generating immune responses and protection against disease in a host of preclinical models, followed by either poor immunogenicity, or good immunogenicity but lack of, or modest, protection in human clinical trials of vaccines (see above) compared to the efficacy of these vaccines in animals raises the question of what is immunologically different about these specific vaccines or the target host. Clearly size alone is not the sole factor, since the West Nile DNA vaccine is effective in horses. Nor is the reason simply that DNA vaccines somehow work in fish but not in humans (Kurath, 2005). The effectiveness for the salmon and West Nile vaccine may in part

be due to the intrinsic immunogenicity of the target antigen. Because the IHNV G protein triggers innate immune responses in addition to the cognate immunity and memory responses (Purcell et al., 2006), the combination of interferon (Acosta et al., 2006), (Yasuike et al., 2007), neutralizing antibodies and T cells (Corbeil et al., 2000), specifically induced by the G protein may point as much to the antigen and its induction of a diverse immune responses as to the vaccine modality. For West Nile virus, the PreM-E antigen when given as a DNA vaccine was immunogenic and effective against viral challenge in mice and horses (Davis et al., 2001). A DNA vaccine coding for the Pre-M and E antigens and core has been shown to generate neutralizing antibodies and $CD4^+$ and $CD8^+$ T cell responses in humans (Martin et al., 2007 and ClinicalTrials.gov identifier NCT00106769).

Any discussion of the immune mechanisms of vector vaccines, must discuss the use of vectors to not simply generate de novo immune responses against pathogens, but to bias the immune response for therapy or prevention of allergies and autoimmune diseases, as well as to break tolerance against self antigens for immunotherapy of cancer. For the latter, the use of DNA encoding human tyrosinase is the basis for the licensed dog melanoma therapy mentioned above (Liao et al., 2006). Although these studies raise the specter of autoimmune diseases, it is interesting that DNA vaccines are specifically being developed to generate tolerance for therapy of autoimmune diseases. The rationale behind such efforts is that through the use of plasmid DNA encoding a protein such as proinsulin, tolerance can be induced to the insulin resulting in a lower rate of diabetes in diabetogenic mice (Solvason et al., 2008). The effect was due to the generation of Th1 helper responses, with the production of γ-interferon, and could be manipulated by the protocol of administration of the DNA vaccine as well as factors such as the amount of, and intracellular location of the production of the protein. The induction of Th1 cell responses has also been beneficial in preclinical models of allergies, where DNA vaccines bias toward a Th1 cell type of response versus the pro allergenic Th2 cell and IgE antibodies directed against the allergens (Chua et al., 2009).

Concluding Remarks

The rationales for vaccine vectors are myriad: generation of specific types of immune responses, including CTLs and particular types of T cell help, the ability to target antigens to certain cell types and certain intracellular processing compartments, the ability to deliver antigens orally to generate mucosal immune responses (as well as for the ease of delivery), and for harnessing various antigen-specific and innate immune responses. The applications range from prophylactic vaccines for infectious diseases to immunotherapy of cancer, allergies, and autoimmune diseases, highlighting the diversity of immunologic mechanisms. While the human clinical development of vectored vaccines has been frustrating with the failure of one HIV vaccine, and the very modest results of another, the efficacy of animal vector vaccines, and the insights gained from the preclinical and clinical studies of vector vaccines point toward the enormous potential of the vectors for developing vaccines and immunotherapies as well as for illuminating the incredible complexities of the immune system.

REFERENCES

Acosta, F., Collet, B., Lorenzen, N., and Ellis, A.E. (2006). Expression of the glycoprotein of viral haemorrhagic septicaemia virus (VHSV) on the surface of the fish cell line RTG-P1 induces type 1 interferon expression in neighbouring cells. Fish Shellfish Immunol. *21*, 272–278.

Alizon, M., and Montagnier, L. (1987). Genetic variability in human immunodeficiency viruses. Ann. N Y Acad. Sci. *511*, 376–384.

Arnberg, N. (2009). Adenovirus receptors: Implications for tropism, treatment and targeting. Rev. Med. Virol. *19*, 165–178.

Babiuk, S., Mookherjee, N., Pontarollo, R., Griebel, P., van Drunen Littel-van den Hurk, S., Hecker, R., and Babiuk, L. (2004). TLR9-/- and TLR9+/+ mice display similar immune responses to a DNA vaccine. Immunology *113*, 114–120.

Barouch, D.H. (2006). Rational design of gene-based vaccines. J. Pathol. *208*, 283–289.

Benlahrech, A., Harris, J., Meiser, A., Papagatsias, T., Hornig, J., Hayes, P., Lieber, A., Athanasopoulos, T., Bachy, V., Csomor, E., et al. (2009). Adenovirus vector vaccination induces expansion of memory CD4 T cells with a mucosal homing phenotype that are readily susceptible to HIV-1. Proc. Natl. Acad. Sci. USA *106*, 19940–19945.

Bergman, P.J., McKnight, J., Novosad, A., Charney, S., Farrelly, J., Craft, D., Wulderk, M., Jeffers, Y., Sadelain, M., Hohenhaus, A.E., et al. (2003). Long-term survival of dogs with advanced malignant melanoma after DNA vaccination with xenogeneic human tyrosinase: A phase I trial. Clin. Cancer Res. *9*, 1284–1290.

Bergmann-Leitner, E.S., Leitner, W.W., Duncan, E.H., Savranskaya, T., and Angov, E. (2009). Molecular adjuvants for malaria DNA vaccines based on the modulation of host-cell apoptosis. Vaccine *27*, 5700–5708.

Boudreau, J.E., Bridle, B.W., Stephenson, K.B., Jenkins, K.M., Brunellière, J., Bramson, J.L., Lichty, B.D., and Wan, Y. (2009). Recombinant vesicular stomatitis virus transduction of dendritic cells enhances their ability to prime innate and adaptive antitumor immunity. Mol. Ther. *17*, 1465–1472.

Bråve, A., Ljungberg, K., Boberg, A., Rollman, E., Isaguliants, M., Lundgren, B., Blomberg, P., Hinkula, J., and Wahren, B. (2005). Multigene/multisubtype HIV-1 vaccine induces potent cellular and humoral immune responses by needle-free intradermal delivery. Mol. Ther. *12*, 1197–1205.

Buchbinder, S.P., Mehrotra, D.V., Duerr, A., Fitzgerald, D.W., Mogg, R., Li, D., Gilbert, P.B., Lama, J.R., Marmor, M., Del Rio, C., et al; Step Study Protocol Team. (2008). Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): A double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet *372*, 1881–1893.

Casimiro, D.R., Chen, L., Fu, T.M., Evans, R.K., Caulfield, M.J., Davies, M.E., Tang, A., Chen, M., Huang, L., Harris, V., et al. (2003). Comparative immunogenicity in rhesus monkeys of DNA plasmid, recombinant vaccinia virus, and replication-defective adenovirus vectors expressing a human immunodeficiency virus type 1 gag gene. J. Virol. *77*, 6305–6313.

Chattergoon, M.A., Kim, J.J., Yang, J.S., Robinson, T.M., Lee, D.J., Dentchev, T., Wilson, D.M., Ayyavoo, V., and Weiner, D.B. (2000). Targeted antigen delivery to antigen-presenting cells including dendritic cells by engineered Fas-mediated apoptosis. Nat. Biotechnol. *18*, 974–979.

Chiarella, P., Fazio, V.M., and Signori, E. (2010). Application of electroporation in DNA vaccination protocols. Curr. Gene Ther. *10*, 281–286.

Chin'ombe, N., Bourn, W.R., Williamson, A.L., and Shephard, E.G. (2009). Oral vaccination with a recombinant Salmonella vaccine vector provokes systemic HIV-1 subtype C Gag-specific CD4+ Th1 and Th2 cell immune responses in mice. Virol. J. *6*, 87.

Chua, K.Y., Kuo, I.C., and Huang, C.H. (2009). DNA vaccines for the prevention and treatment of allergy. Curr. Opin. Allergy Clin. Immunol. *9*, 50–54.

Corbeil, S., Kurath, G., and LaPatra, S.E. (2000). Fish DNA vaccine against infectious hematopoietic necrosis virus: Efficacy of various routes of immunisation. Fish Shellfish Immunol. *10*, 711–723.

Davis, B.S., Chang, G.J., Cropp, B., Roehrig, J.T., Martin, D.A., Mitchell, C.J., Bowen, R., and Bunning, M.L. (2001). West Nile virus recombinant DNA vaccine protects mouse and horse from virus challenge and expresses

in vitro a noninfectious recombinant antigen that can be used in enzyme-linked immunosorbent assays. J. Virol. *75*, 4040–4047.

Day, C.L., and Walker, B.D. (2003). Progress in defining CD4 helper cell responses in chronic viral infections. J. Exp. Med. *198*, 1773–1777.

de Mare, A., Lambeck, A.J., Regts, J., van Dam, G.M., Nijman, H.W., Snippe, H., Wilschut, J., and Daemen, T. (2008). Viral vector-based prime-boost immunization regimens: A possible involvement of T-cell competition. Gene Ther. *15*, 393–403.

DeLong, R.K., Akhtar, U., Sallee, M., Parker, B., Barber, S., Zhang, J., Craig, M., Garrad, R., Hickey, A.J., and Engstrom, E. (2009). Characterization and performance of nucleic acid nanoparticles combined with protamine and gold. Biomaterials *30*, 6451–6459.

Denis-Mize, K.S., Dupuis, M., MacKichan, M.L., Singh, M., Doe, B., O'Hagan, D., Ulmer, J.B., Donnelly, J.J., McDonald, D.M., and Ott, G. (2000). Plasmid DNA adsorbed onto cationic microparticles mediates target gene expression and antigen presentation by dendritic cells. Gene Ther. *7*, 2105–2112.

Denis-Mize, K.S., Dupuis, M., Singh, M., Woo, C., Ugozzoli, M., O'Hagan, D.T., Donnelly, J.J., 3rd, Ott, G., and McDonald, D.M. (2003). Mechanisms of increased immunogenicity for DNA-based vaccines adsorbed onto cationic microparticles. Cell. Immunol. *225*, 12–20.

Dharmapuri, S., Aurisicchio, L., Biondo, A., Welsh, N., Ciliberto, G., and La Monica, N. (2009). Antiapoptotic small interfering RNA as potent adjuvant of DNA vaccination in a mouse mammary tumor model. Hum. Gene Ther. *20*, 589–597.

Doherty, P.C., Turner, S.J., Webby, R.G., and Thomas, P.G. (2006). Influenza and the challenge for immunology. Nat. Immunol. *7*, 449–455.

Donnelly, J.J., Friedman, A., Martinez, D., Montgomery, D.L., Shiver, J.W., Motzel, S.L., Ulmer, J.B., and Liu, M.A. (1995). Preclinical efficacy of a prototype DNA vaccine: Enhanced protection against antigenic drift in influenza virus. Nat. Med. *1*, 583–587.

Donnelly, J.J., Ulmer, J.B., Shiver, J.W., and Liu, M.A. (1997). DNA vaccines. Annu. Rev. Immunol. *15*, 617–648.

Einfeld, D.A., Schroeder, R., Roelvink, P.W., Lizonova, A., King, C.R., Kovesdi, I., and Wickham, T.J. (2001). Reducing the native tropism of adenovirus vectors requires removal of both CAR and integrin interactions. J. Virol. *75*, 11284–11291.

Fennelly, G.J., Khan, S.A., Abadi, M.A., Wild, T.F., and Bloom, B.R. (1999). Mucosal DNA vaccine immunization against measles with a highly attenuated Shigella flexneri vector. J. Immunol. *162*, 1603–1610.

Ferrari, G., Kostyu, D.D., Cox, J., Dawson, D.V., Flores, J., Weinhold, K.J., and Osmanov, S. (2000). Identification of highly conserved and broadly cross-reactive HIV type 1 cytotoxic T lymphocyte epitopes as candidate immunogens for inclusion in Mycobacterium bovis BCG-vectored HIV vaccines. AIDS Res. Hum. Retroviruses *16*, 1433–1443.

Fouts, T.R., Lewis, G.K., and Hone, D.M. (1995a). Construction and characterization of a Salmonella typhi-based human immunodeficiency virus type 1 vector vaccine. Vaccine *13*, 561–569.

Fouts, T.R., Tuskan, R.G., Chada, S., Hone, D.M., and Lewis, G.K. (1995b). Construction and immunogenicity of Salmonella typhimurium vaccine vectors that express HIV-1 gp120. Vaccine *13*, 1697–1705.

Fu, T.M., Ulmer, J.B., Caulfield, M.J., Deck, R.R., Friedman, A., Wang, S., Liu, X., Donnelly, J.J., and Liu, M.A. (1997). Priming of cytotoxic T lymphocytes by DNA vaccines: Requirement for professional antigen presenting cells and evidence for antigen transfer from myocytes. Mol. Med. *3*, 362–371.

Gabitzsch, E.S., Xu, Y., Yoshida, L.H., Balint, J., Amalfitano, A., and Jones, F.R. (2009). Novel Adenovirus type 5 vaccine platform induces cellular immunity against HIV-1 Gag, Pol, Nef despite the presence of Ad5 immunity. Vaccine *27*, 6394–6398.

Gahan, M.E., Webster, D.E., Wesselingh, S.L., Strugnell, R.A., and Yang, J. (2009). Bacterial antigen expression is an important component in inducing an immune response to orally administered Salmonella-delivered DNA vaccines. PLoS ONE *4*, e6062.

Gao, F., Morrison, S.G., Robertson, D.L., Thornton, C.L., Craig, S., Karlsson, G., Sodroski, J., Morgado, M., Galvao-Castro, B., von Briesen, H., et al. (1996). Molecular cloning and analysis of functional envelope genes from human immunodeficiency virus type 1 sequence subtypes A through G. The WHO and NIAID Networks for HIV Isolation and Characterization. J. Virol. *70*, 1651–1667.

Gianfrani, C., Oseroff, C., Sidney, J., Chesnut, R.W., and Sette, A. (2000). Human memory CTL response specific for influenza A virus is broad and multispecific. Hum. Immunol. *61*, 438–452.

Gómez-Román, V.R., Grimes, G.J., Jr., Potti, G.K., Peng, B., Demberg, T., Gravlin, L., Treece, J., Pal, R., Lee, E.M., Alvord, W.G., et al. (2006). Oral delivery of replication-competent adenovirus vectors is well tolerated by SIV- and SHIV-infected rhesus macaques. Vaccine *24*, 5064–5072.

Goulder, P.J., Bunce, M., Krausa, P., McIntyre, K., Crowley, S., Morgan, B., Edwards, A., Giangrande, P., Phillips, R.E., and McMichael, A.J. (1996). Novel, cross-restricted, conserved, and immunodominant cytotoxic T lymphocyte epitopes in slow progressors in HIV type 1 infection. AIDS Res. Hum. Retroviruses *12*, 1691–1698.

Gudmundsdotter, L., Nilsson, C., Brave, A., Hejdeman, B., Earl, P., Moss, B., Robb, M., Cox, J., Michael, N., Marovich, M., et al. (2009). Recombinant Modified Vaccinia Ankara (MVA) effectively boosts DNA-primed HIV-specific immune responses in humans despite pre-existing vaccinia immunity. Vaccine *27*, 4468–4474.

Hammond, S.A., Obah, E., Stanhope, P., Monell, C.R., Strand, M., Robbins, F.M., Bias, W.B., Karr, R.W., Koenig, S., and Siliciano, R.F. (1991). Characterization of a conserved T cell epitope in HIV-1 gp41 recognized by vaccine-induced human cytolytic T cells. J. Immunol. *146*, 1470–1477.

Hanke, T., McMichael, A.J., Mwau, M., Wee, E.G., Ceberej, I., Patel, S., Sutton, J., Tomlinson, M., and Samuel, R.V. (2002a). Development of a DNA-MVA/HIVA vaccine for Kenya. Vaccine *20*, 1995–1998.

Hanke, T., McMichael, A.J., Samuel, R.V., Powell, L.A., McLoughlin, L., Crome, S.J., and Edlin, A. (2002b). Lack of toxicity and persistence in the mouse associated with administration of candidate DNA- and modified vaccinia virus Ankara (MVA)-based HIV vaccines for Kenya. Vaccine *21*, 108–114.

Harrer, T., Harrer, E., Kalams, S.A., Barbosa, P., Trocha, A., Johnson, R.P., Elbeik, T., Feinberg, M.B., Buchbinder, S.P., and Walker, B.D. (1996). Cytotoxic T lymphocytes in asymptomatic long-term nonprogressing HIV-1 infection. Breadth and specificity of the response and relation to in vivo viral quasispecies in a person with prolonged infection and low viral load. J. Immunol. *156*, 2616–2623.

Harro, C.D., Robertson, M.N., Lally, M.A., O'Neill, L.D., Edupuganti, S., Goepfert, P.A., Mulligan, M.J., Priddy, F.H., Dubey, S.A., Kierstead, L.S., et al; Merck V520-007/012 Study Teams. (2009). Safety and immunogenicity of adenovirus-vectored near-consensus HIV type 1 clade B gag vaccines in healthy adults. AIDS Res. Hum. Retroviruses *25*, 103–114.

Hartikka, J., Bozoukova, V., Yang, C.K., Ye, M., Rusalov, D., Shlapobersky, M., Vilalta, A., Wei, Q., Rolland, A., and Smith, L.R. (2009). Vaxfectin, a cationic lipid-based adjuvant for protein-based influenza vaccines. Vaccine *27*, 6399–6403.

Hemmi, H., Takeuchi, O., Kawai, T., Kaisho, T., Sato, S., Sanjo, H., Matsumoto, M., Hoshino, K., Wagner, H., Takeda, K., and Akira, S. (2000). A Toll-like receptor recognizes bacterial DNA. Nature *408*, 740–745.

Huang, H., Wang, Y.J., White, A.P., Meng, J.Z., Liu, G.R., Liu, S.L., and Wang, Y.D. (2009). Salmonella expressing a T-cell epitope from Sendai virus are able to induce anti-infection immunity. J. Med. Microbiol. *58*, 1236–1242.

Huang, J.M., Sali, M., Leckenby, M.W., Radford, D.S., Huynh, H.A., Delogu, G., Cranenburgh, R.M., and Cutting, S.M. (2010). Oral delivery of a DNA vaccine against tuberculosis using operator-repressor titration in a Salmonella enterica vector. Vaccine, in press. 10.1016/j.vaccine.2010.09.001.

Hutnick, N.A., Carnathan, D.G., Dubey, S.A., Makedonas, G., Cox, K.S., Kierstead, L., Ratcliffe, S.J., Robertson, M.N., Casimiro, D.R., Ertl, H.C., and Betts, M.R. (2009). Baseline Ad5 serostatus does not predict Ad5 HIV vaccine-induced expansion of adenovirus-specific CD4+ T cells. Nat. Med. *15*, 876–878.

Johnson, R.P., Trocha, A., Yang, L., Mazzara, G.P., Panicali, D.L., Buchanan, T.M., and Walker, B.D. (1991). HIV-1 gag-specific cytotoxic T lymphocytes recognize multiple highly conserved epitopes. Fine specificity of the gag-specific response defined by using unstimulated peripheral blood mononuclear cells and cloned effector cells. J. Immunol. *147*, 1512–1521.

Johnson, R.P., Hammond, S.A., Trocha, A., Siliciano, R.F., and Walker, B.D. (1994). Induction of a major histocompatibility complex class I-restricted cytotoxic T-lymphocyte response to a highly conserved region of human immunodeficiency virus type 1 (HIV-1) gp120 in seronegative humans immunized with a candidate HIV-1 vaccine. J. Virol. *68*, 3145–3153.

Johnson, J.E., Nasar, F., Coleman, J.W., Price, R.E., Javadian, A., Draper, K., Lee, M., Reilly, P.A., Clarke, D.K., Hendry, R.M., and Udem, S.A. (2007). Neurovirulence properties of recombinant vesicular stomatitis virus vectors in non-human primates. Virology *360*, 36–49.

Karlsson, G.B., and Liljeström, P. (2004). Delivery and expression of heterologous genes in mammalian cells using self-replicating alphavirus vectors. Methods Mol. Biol. *246*, 543–557.

Kim, T.W., Hung, C.F., Zheng, M., Boyd, D.A., He, L., Pai, S.I., and Wu, T.C. (2004). A DNA vaccine co-expressing antigen and an anti-apoptotic molecule further enhances the antigen-specific CD8+ T-cell immune response. J. Biomed. Sci. *11*, 493–499.

Klinman, D.M., Yamshchikov, G., and Ishigatsubo, Y. (1997). Contribution of CpG motifs to the immunogenicity of DNA vaccines. J. Immunol. *158*, 3635–3639.

Kojima, Y., Jounai, N., Takeshita, F., Nakazawa, M., Okuda, K., Watabe, S., Xin, K.Q., and Okuda, K. (2007). The degree of apoptosis as an immunostimulant for a DNA vaccine against HIV-1 infection. Vaccine *25*, 438–445.

Koup, R.A., Lamoreaux, L., Zarkowsky, D., Bailer, R.T., King, C.R., Gall, J.G., Brough, D.E., Graham, B.S., and Roederer, M. (2009). Replication-defective adenovirus vectors with multiple deletions do not induce measurable vector-specific T cells in human trials. J. Virol. *83*, 6318–6322.

Kuhn, A.N., Diken, M., Kreiter, S., Selmi, A., Kowalska, J., Jemielity, J., Darzynkiewicz, E., Huber, C., Türeci, O., and Sahin, U. (2010). Phosphorothioate cap analogs increase stability and translational efficiency of RNA vaccines in immature dendritic cells and induce superior immune responses in vivo. Gene Ther. *17*, 961–971.

Kurath, G. (2005). Overview of recent DNA vaccine development for fish. Dev. Biol. (Basel) *121*, 201–213.

Kuwano, K., Scott, M., Young, J.F., and Ennis, F.A. (1989). Active immunization against virus infections due to antigenic drift by induction of crossreactive cytotoxic T lymphocytes. J. Exp. Med. *169*, 1361–1371.

Leitner, W.W., Hwang, L.N., deVeer, M.J., Zhou, A., Silverman, R.H., Williams, B.R., Dubensky, T.W., Ying, H., and Restifo, N.P. (2003). Alphavirus-based DNA vaccine breaks immunological tolerance by activating innate antiviral pathways. Nat. Med. *9*, 33–39.

Leitner, W.W., Hwang, L.N., Bergmann-Leitner, E.S., Finkelstein, S.E., Frank, S., and Restifo, N.P. (2004). Apoptosis is essential for the increased efficacy of alphaviral replicase-based DNA vaccines. Vaccine *22*, 1537–1544.

Liao, J.C., Gregor, P., Wolchok, J.D., Orlandi, F., Craft, D., Leung, C., Houghton, A.N., and Bergman, P.J. (2006). Vaccination with human tyrosinase DNA induces antibody responses in dogs with advanced melanoma. Cancer Immun. *6*, 8.

Liu, M.A. (2010). Gene-based vaccines: Recent developments. Curr. Opin. Mol. Ther. *12*, 86–93.

Liu, M.A., Wahren, B., and Karlsson Hedestam, G.B. (2006). DNA vaccines: Recent developments and future possibilities. Hum. Gene Ther. *17*, 1051–1061.

Liu, X., Broberg, E., Watanabe, D., Dudek, T., Deluca, N., and Knipe, D.M. (2009). Genetic engineering of a modified herpes simplex virus 1 vaccine vector. Vaccine *27*, 2760–2767.

Mackowiak, M., Maki, J., Motes-Kreimeyer, L., Harbin, T., and Van Kampen, K. (1999). Vaccination of wildlife against rabies: Successful use of a vectored vaccine obtained by recombinant technology. Adv. Vet. Med. *41*, 571–583.

Maguire, A.M., Simonelli, F., Pierce, E.A., Pugh, E.N., Jr., Mingozzi, F., Bennicelli, J., Banfi, S., Marshall, K.A., Testa, F., Surace, E.M., et al. (2008). Safety and efficacy of gene transfer for Leber's congenital amaurosis. N. Engl. J. Med. *358*, 2240–2248.

Manservigi, R., Argnani, R., and Marconi, P. (2010). HSV Recombinant Vectors for Gene Therapy. Open Virol J *4*, 123–156.

Martin, J.E., Pierson, T.C., Hubka, S., Rucker, S., Gordon, I.J., Enama, M.E., Andrews, C.A., Xu, Q., Davis, B.S., Nason, M., et al. (2007). A West Nile virus DNA vaccine induces neutralizing antibody in healthy adults during a phase 1 clinical trial. J. Infect. Dis. *196*, 1732–1740.

Mastrangelo, M.J., Eisenlohr, L.C., Gomella, L., and Lattime, E.C. (2000). Poxvirus vectors: Orphaned and underappreciated. J. Clin. Invest. *105*, 1031–1034.

McCurdy, L.H., Larkin, B.D., Martin, J.E., and Graham, B.S. (2004). Modified vaccinia Ankara: Potential as an alternative smallpox vaccine. Clin. Infect. Dis. *38*, 1749–1753.

McElrath, M.J., De Rosa, S.C., Moodie, Z., Dubey, S., Kierstead, L., Janes, H., Defawe, O.D., Carter, D.K., Hural, J., Akondy, R., et al; Step Study Protocol Team. (2008). HIV-1 vaccine-induced immunity in the test-of-concept Step Study: A case-cohort analysis. Lancet *372*, 1894–1905.

McMichael, A.J., Gotch, F.M., Noble, G.R., and Beare, P.A. (1983). Cytotoxic T-cell immunity to influenza. N. Engl. J. Med. *309*, 13–17.

Muster, T., Guinea, R., Trkola, A., Purtscher, M., Klima, A., Steindl, F., Palese, P., and Katinger, H. (1994). Cross-neutralizing activity against divergent human immunodeficiency virus type 1 isolates induced by the gp41 sequence ELDKWAS. J. Virol. *68*, 4031–4034.

Nabel, G.J., Kaslow, D.C., Ulmer, J.B., and Liu, M.A. (2010). DNA vaccines. In New Generation Vaccines, M.M. Levine, G. Dougan, M.F. Good, M.A. Liu, G.J. Nabel, J.P. Nataro, and R. Rappuoli, eds. (New York, NY, USA: Marcel Dekker), pp. 386–395.

Nishino, Y., Kameoka, M., Okada, Y., Zhong, Q., Kimura, T., Azuma, I., and Ikuta, K. (1994). In vivo induction of human immunodeficiency virus type 1-specific cytotoxic T lymphocytes and delayed-type hypersensitivity by a 23-amino acid peptide from the highly conserved region in major core protein p24. Vaccine *12*, 485–491.

O'Brien, K.L., Liu, J., King, S.L., Sun, Y.H., Schmitz, J.E., Lifton, M.A., Hutnick, N.A., Betts, M.R., Dubey, S.A., Goudsmit, J., et al. (2009). Adenovirus-specific immunity after immunization with an Ad5 HIV-1 vaccine candidate in humans. Nat. Med. *15*, 873–875.

Oh, Y.K., Harding, C.V., and Swanson, J.A. (1997). The efficiency of antigen delivery from macrophage phagosomes into cytoplasm for MHC class I-restricted antigen presentation. Vaccine *15*, 511–518.

Otten, G., Schaefer, M., Doe, B., Liu, H., Srivastava, I., zur Megede, J., O'Hagan, D., Donnelly, J., Widera, G., Rabussay, D., et al. (2004). Enhancement of DNA vaccine potency in rhesus macaques by electroporation. Vaccine *22*, 2489–2493.

Pan, C.H., Greer, C.E., Hauer, D., Legg, H.S., Lee, E.Y., Bergen, M.J., Lau, B., Adams, R.J., Polo, J.M., and Griffin, D.E. (2010). A chimeric alphavirus replicon particle vaccine expressing the hemagglutinin and fusion proteins protects juvenile and infant rhesus macaques from measles. J. Virol. *84*, 3798–3807.

Parsania, M., Bamdad, T., Hassan, Z.M., Kheirandish, M., Pouriayevali, M.H., Sari, R.D., and Jamali, A. (2010). Evaluation of apoptotic and anti-apoptotic genes on efficacy of DNA vaccine encoding glycoprotein B of Herpes Simplex Virus type 1. Immunol. Lett. *128*, 137–142.

Pascolo, S. (2006). Vaccination with messenger RNA. Methods Mol. Med. *127*, 23–40.

Patterson, L.J., and Robert-Guroff, M. (2008). Replicating adenovirus vector prime/protein boost strategies for HIV vaccine development. Expert Opin. Biol. Ther. *8*, 1347–1363.

Peeters, M., Piot, P., and van der Groen, G. (1991). Variability among HIV and SIV strains of African origin. AIDS *5* (*Suppl 1*), S29–S36.

Peters, B.S., Jaoko, W., Vardas, E., Panayotakopoulos, G., Fast, P., Schmidt, C., Gilmour, J., Bogoshi, M., Omosa-Manyonyi, G., Dally, L., et al. (2007). Studies of a prophylactic HIV-1 vaccine candidate based on modified vaccinia virus Ankara (MVA) with and without DNA priming: Effects of dosage and route on safety and immunogenicity. Vaccine *25*, 2120–2127.

Purcell, M.K., Nichols, K.M., Winton, J.R., Kurath, G., Thorgaard, G.H., Wheeler, P., Hansen, J.D., Herwig, R.P., and Park, L.K. (2006). Comprehensive gene expression profiling following DNA vaccination of rainbow trout against infectious hematopoietic necrosis virus. Mol. Immunol. *43*, 2089–2106.

Quirk, E.K., Mogg, R., Brown, D.D., Lally, M.A., Mehrotra, D.V., DiNubile, M.J., and Robertson, M.N. (2008). HIV seroconversion without infection after receipt of adenovirus-vectored HIV type 1 vaccine. Clin. Infect. Dis. *47*, 1593–1599.

Rao, S.S., Gomez, P., Mascola, J.R., Dang, V., Krivulka, G.R., Yu, F., Lord, C.I., Shen, L., Bailer, R., Nabel, G.J., and Letvin, N.L. (2006). Comparative evaluation of three different intramuscular delivery methods for DNA immunization in a nonhuman primate animal model. Vaccine *24*, 367–373.

Rerks-Ngarm, S., Pitisuttithum, P., Nitayaphan, S., Kaewkungwal, J., Chiu, J., Paris, R., Premsri, N., Namwat, C., de Souza, M., Adams, E., et al; MOPH-TAVEG Investigators. (2009). Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N. Engl. J. Med. *361*, 2209–2220.

Robert-Guroff, M. (2007). Replicating and non-replicating viral vectors for vaccine development. Curr. Opin. Biotechnol. *18*, 546–556.

Rodríguez, A., Mintardjo, R., Tax, D., Gillissen, G., Custers, J., Pau, M.G., Klap, J., Santra, S., Balachandran, H., Letvin, N.L., et al. (2009). Evaluation of a prime-boost vaccine schedule with distinct adenovirus vectors against malaria in rhesus monkeys. Vaccine *27*, 6226–6233.

Rolland, M., Nickle, D.C., and Mullins, J.I. (2007). HIV-1 group M conserved elements vaccine. PLoS Pathog. *3*, e157.

Rosenberg, E.S., and Walker, B.D. (1998). HIV type 1-specific helper T cells: A critical host defense. AIDS Res. Hum. Retroviruses *14* (*Suppl 2*), S143–S147.

Rottembourg, D., Filippi, C.M., Bresson, D., Ehrhardt, K., Estes, E.A., Oldham, J.E., and von Herrath, M.G. (2010). Essential role for TLR9 in prime but not prime-boost plasmid DNA vaccination to activate dendritic cells and protect from lethal viral infection. J. Immunol. *184*, 7100–7107.

Rottinghaus, S.T., Poland, G.A., Jacobson, R.M., Barr, L.J., and Roy, M.J. (2003). Hepatitis B DNA vaccine induces protective antibody responses in human non-responders to conventional vaccination. Vaccine *21*, 4604–4608.

Rowland-Jones, S.L., Dong, T., Dorrell, L., Ogg, G., Hansasuta, P., Krausa, P., Kimani, J., Sabally, S., Ariyoshi, K., Oyugi, J., et al. (1999). Broadly cross-reactive HIV-specific cytotoxic T-lymphocytes in highly-exposed persistently seronegative donors. Immunol. Lett. *66*, 9–14.

Santra, S., Sun, Y., Korioth-Schmitz, B., Fitzgerald, J., Charbonneau, C., Santos, G., Seaman, M.S., Ratcliffe, S.J., Montefiori, D.C., Nabel, G.J., et al. (2009). Heterologous prime/boost immunizations of rhesus monkeys using chimpanzee adenovirus vectors. Vaccine *27*, 5837–5845.

Sato, Y., Roman, M., Tighe, H., Lee, D., Corr, M., Nguyen, M.D., Silverman, G.J., Lotz, M., Carson, D.A., and Raz, E. (1996). Immunostimulatory DNA sequences necessary for effective intradermal gene immunization. Science *273*, 352–354.

Scheel, B., Teufel, R., Probst, J., Carralot, J.P., Geginat, J., Radsak, M., Jarrossay, D., Wagner, H., Jung, G., Rammensee, H.G., et al. (2005). Toll-like receptor-dependent activation of several human blood cell types by protamine-condensed mRNA. Eur. J. Immunol. *35*, 1557–1566.

Schirmbeck, R., Wild, J., and Reimann, J. (1998). Similar as well as distinct MHC class I-binding peptides are generated by exogenous and endogenous processing of hepatitis B virus surface antigen. Eur. J. Immunol. *28*, 4149–4161.

Schneider, J., Gilbert, S.C., Blanchard, T.J., Hanke, T., Robson, K.J., Hannan, C.M., Becker, M., Sinden, R., Smith, G.L., and Hill, A.V. (1998). Enhanced immunogenicity for CD8+ T cell induction and complete protective efficacy of malaria DNA vaccination by boosting with modified vaccinia virus Ankara. Nat. Med. *4*, 397–402.

Schweiger, B., Zadow, I., and Heckler, R. (2002). Antigenic drift and variability of influenza viruses. Med. Microbiol. Immunol. (Berl.) *191*, 133–138.

Sedegah, M., Rogers, W.O., Belmonte, M., Belmonte, A., Banania, G., Patterson, N.B., Rusalov, D., Ferrari, M., Richie, T.L., and Doolan, D.L. (2010). Vaxfectin enhances both antibody and in vitro T cell responses to each component of a 5-gene Plasmodium falciparum plasmid DNA vaccine mixture administered at low doses. Vaccine *28*, 3055–3065.

Sedman, S.A., Barbosa, M.S., Vass, W.C., Hubbert, N.L., Haas, J.A., Lowy, D.R., and Schiller, J.T. (1991). The full-length E6 protein of human papillomavirus type 16 has transforming and trans-activating activities and cooperates with E7 to immortalize keratinocytes in culture. J. Virol. *65*, 4860–4866.

Solvason, N., Lou, Y.P., Peters, W., Evans, E., Martinez, J., Ramirez, U., Ocampo, A., Yun, R., Ahmad, S., Liu, E., et al. (2008). Improved efficacy of a tolerizing DNA vaccine for reversal of hyperglycemia through enhancement of gene expression and localization to intracellular sites. J. Immunol. *181*, 8298–8307.

Spies, B., Hochrein, H., Vabulas, M., Huster, K., Busch, D.H., Schmitz, F., Heit, A., and Wagner, H. (2003). Vaccination with plasmid DNA activates dendritic cells via Toll-like receptor 9 (TLR9) but functions in TLR9-deficient mice. J. Immunol. *171*, 5908–5912.

Stevenson, F.K. (2004). DNA vaccines and adjuvants. Immunol. Rev. *199*, 5–8.

Su, J., Willert, C., Comanita, L., Peters, A., Gilbert, P.A., Strathdee, C., O'Connell, P.J., McFadden, G.D., and Dekaban, G.A. (2008). Inclusion of the viral anti-apoptotic molecule M11L in DNA vaccine vectors enhances HIV Env-specific T cell-mediated immunity. Virology *375*, 48–58.

Tatsis, N., Lasaro, M.O., Lin, S.W., Haut, L.H., Xiang, Z.Q., Zhou, D., Dimenna, L., Li, H., Bian, A., Abdulla, S., et al. (2009). Adenovirus vector-induced immune responses in nonhuman primates: Responses to prime boost regimens. J. Immunol. *182*, 6587–6599.

Thacker, E.E., Timares, L., and Matthews, Q.L. (2009). Strategies to overcome host immunity to adenovirus vectors in vaccine development. Expert Rev. Vaccines *8*, 761–777.

Thomas, P.G., Keating, R., Hulse-Post, D.J., and Doherty, P.C. (2006). Cell-mediated protection in influenza infection. Emerg. Infect. Dis. *12*, 48–54.

Tudor, D., Dubuquoy, C., Gaboriau, V., Lefèvre, F., Charley, B., and Riffault, S. (2005). TLR9 pathway is involved in adjuvant effects of plasmid DNA-based vaccines. Vaccine *23*, 1258–1264.

Turell, M.J., Bunning, M., Ludwig, G.V., Ortman, B., Chang, J., Speaker, T., Spielman, A., McLean, R., Komar, N., Gates, R., et al. (2003). DNA vaccine for West Nile virus infection in fish crows (Corvus ossifragus). Emerg. Infect. Dis. *9*, 1077–1081.

Ulmer, J.B., and Otten, G.R. (2000). Priming of CTL responses by DNA vaccines: Direct transfection of antigen presenting cells versus cross-priming. Dev. Biol. (Basel) *104*, 9–14.

Ulmer, J.B., Donnelly, J.J., Parker, S.E., Rhodes, G.H., Felgner, P.L., Dwarki, V.J., Gromkowski, S.H., Deck, R.R., DeWitt, C.M., Friedman, A., et al. (1993). Heterologous protection against influenza by injection of DNA encoding a viral protein. Science *259*, 1745–1749.

Ulmer, J.B., Wahren, B., and Liu, M.A. (2006). Gene-based vaccines: Recent technical and clinical advances. Trends Mol. Med. *12*, 216–222.

Vasan, S., Schlesinger, S.J., Chen, Z., Hurley, A., Lombardo, A., Than, S., Adesanya, P., Bunce, C., Boaz, M., Boyle, R., et al. (2010). Phase 1 safety and immunogenicity evaluation of ADMVA, a multigenic, modified vaccinia Ankara-HIV-1 B′/C candidate vaccine. PLoS ONE *5*, e8816.

Vilalta, A., Jimenez, G., Rusalov, D., Planchon, R., Lalor, P., Carner, K., Chaplin, J.A., Komai, M., Manthorpe, M., Kaslow, D.C., and Rolland, A. (2007). Vaccination with polymerase chain reaction-generated linear expression cassettes protects mice against lethal influenza A challenge. Hum. Gene Ther. *18*, 763–771.

Wang, S., Farfan-Arribas, D.J., Shen, S., Chou, T.H., Hirsch, A., He, F., and Lu, S. (2006). Relative contributions of codon usage, promoter efficiency and leader sequence to the antigen expression and immunogenicity of HIV-1 Env DNA vaccine. Vaccine *24*, 4531–4540.

Weaver, E.A., Nehete, P.N., Buchl, S.S., Senac, J.S., Palmer, D., Ng, P., Sastry, K.J., and Barry, M.A. (2009). Comparison of replication-competent, first generation, and helper-dependent adenoviral vaccines. PLoS ONE *4*, e5059.

Wee, E.G., Patel, S., McMichael, A.J., and Hanke, T. (2002). A DNA/MVA-based candidate human immunodeficiency virus vaccine for Kenya induces multi-specific T cell responses in rhesus macaques. J. Gen. Virol. *83*, 75–80.

Weide, B., Carralot, J.P., Reese, A., Scheel, B., Eigentler, T.K., Hoerr, I., Rammensee, H.G., Garbe, C., and Pascolo, S. (2008). Results of the first phase I/II clinical vaccination trial with direct injection of mRNA. J. Immunother. *31*, 180–188.

Weide, B., Pascolo, S., Scheel, B., Derhovanessian, E., Pflugfelder, A., Eigentler, T.K., Pawelec, G., Hoerr, I., Rammensee, H.G., and Garbe, C.

(2009). Direct injection of protamine-protected mRNA: Results of a phase 1/2 vaccination trial in metastatic melanoma patients. J. Immunother. *32*, 498–507.

Weiss, R., Scheiblhofer, S., Roesler, E., Ferreira, F., and Thalhamer, J. (2010). Prophylactic mRNA vaccination against allergy. Curr. Opin. Allergy Clin. Immunol., in press. Published online September 18, 2010. 10.1016/j.vaccine.2010.09.001.

Wolff, J.A., Malone, R.W., Williams, P., Chong, W., Acsadi, G., Jani, A., and Felgner, P.L. (1990). Direct gene transfer into mouse muscle in vivo. Science *247*, 1465–1468.

Xiang, S.D., Selomulya, C., Ho, J., Apostolopoulos, V., and Plebanski, M. (2010). Delivery of DNA vaccines: An overview on the use of biodegradable polymeric and magnetic nanoparticles. Wiley Interdiscip Rev Nanomed Nanobiotechnol *2*, 205–218.

Xu, X., Cox, N.J., Bender, C.A., Regnery, H.L., and Shaw, M.W. (1996). Genetic variation in neuraminidase genes of influenza A (H3N2) viruses. Virology *224*, 175–183.

Yasuike, M., Kondo, H., Hirono, I., and Aoki, T. (2007). Difference in Japanese flounder, Paralichthys olivaceus gene expression profile following hirame rhabdovirus (HIRRV) G and N protein DNA vaccination. Fish Shellfish Immunol. *23*, 531–541.

Zhang, X.L., Jeza, V.T., and Pan, Q. (2008). Salmonella typhi: From a human pathogen to a vaccine vector. Cell. Mol. Immunol. *5*, 91–97.

Zhu, J., Huang, X., and Yang, Y. (2007). Innate immune response to adenoviral vectors is mediated by both Toll-like receptor-dependent and -independent pathways. J. Virol. *81*, 3170–3180.

Footnote 11

Policy ForumPUBLIC HEALTH

Toward an HIV vaccine: A scientific journey

Anthony S. Fauci[1,*], Hilary D. Marston[2]

[1]*Anthony S. Fauci M.D. is the Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, Bethesda, MD 20892, USA.*

[2]*Hilary D. Marston M.D., M.P.H. is a Medical Officer and Policy Advisor for Global Health at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, Bethesda, MD 20892, USA.*

[*]Corresponding author. E-mail: afauci{at}niaid.nih.gov

See allHide authors and affiliations

Science 24 Jul 2015:
Vol. 349, Issue 6246, pp. 386-387
DOI: 10.1126/science.aac6300

Article
Figures & Data
Info & Metrics
eLetters
PDF

You are currently viewing the summary.

View Full Text

Summary

In the face of a global pandemic, the search for an effective vaccine against the human immunodeficiency virus (HIV) remains an urgent priority. From the first HIV vaccine trials in the 1980s to the present, a tension has existed between the desire to move quickly to clinical trials to stem the spread of the epidemic and the view that research into HIV pathogenesis and host immunity were necessary predicates to and informative of vaccine design. Those advocating the first strategy—an empirical (or inductive) approach—argued that in vitro and animal studies were poorly predictive of the human response to HIV infection and that the only way to gauge vaccine efficacy was to test candidates in humans. Those advocating the second strategy—a theoretical (or deductive) approach—hoped to establish an understanding of the immune response to natural infection and to find ways to recapitulate and enhance that response through vaccination. Today, these approaches are coalescing into concomitant paths toward a safe and effective HIV vaccine.

View Full Text

Science

Vol 349, Issue 6246
24 July 2015

Table of Contents
Print Table of Contents
Advertising (PDF)
Classified (PDF)
Masthead (PDF)

Article Tools

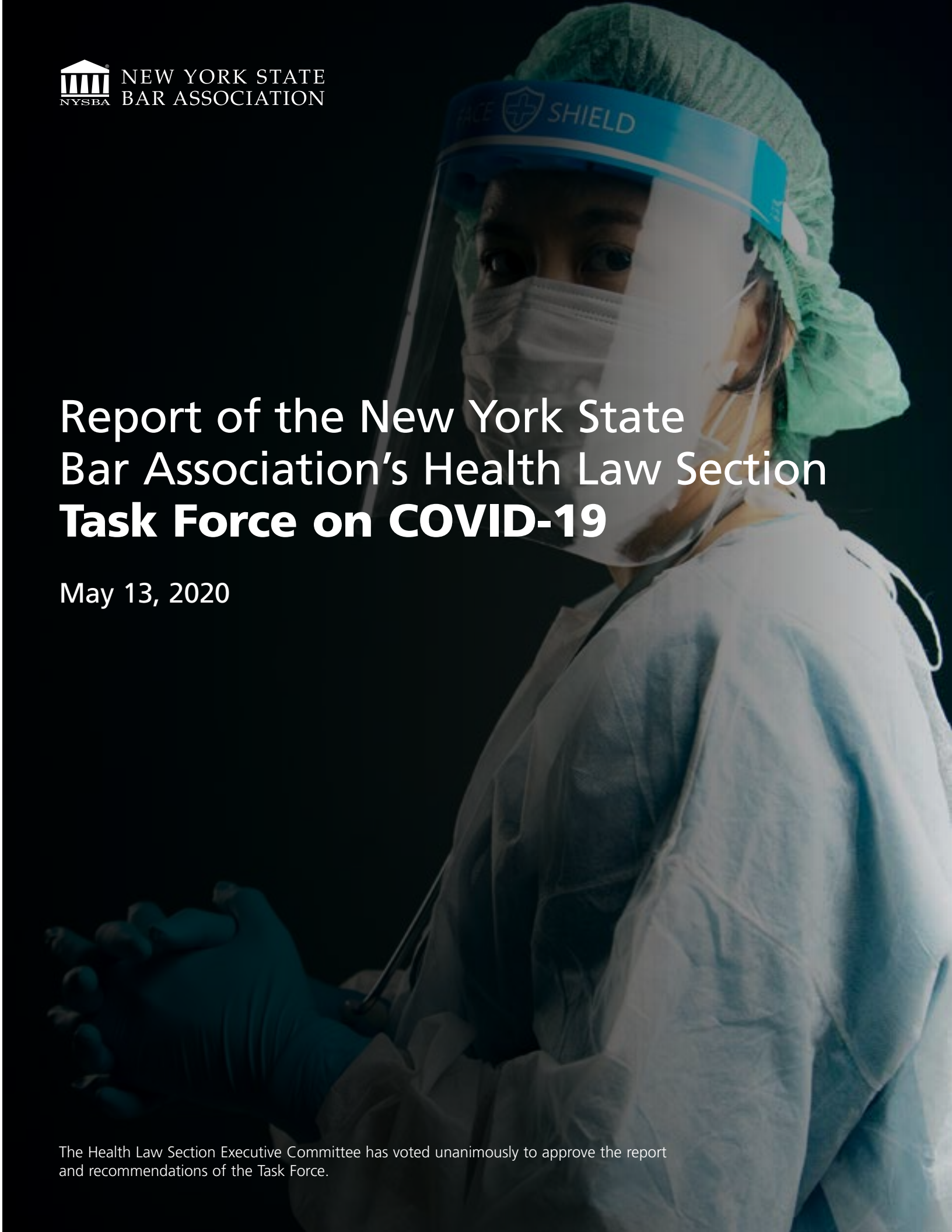
Email
Download Powerpoint
Print

Working Life

Data-driven advice for grad school

Footnote 12

NEW YORK STATE
NYSBA BAR ASSOCIATION



Report of the New York State Bar Association's Health Law Section **Task Force on COVID-19**

May 13, 2020

The Health Law Section Executive Committee has voted unanimously to approve the report and recommendations of the Task Force.

This report is dedicated to New York's health care workers and workers in service jobs on the front lines of the pandemic.

TABLE OF CONTENTS

Executive Summary

The COVID-19 crisis and New York on PAUSE[1] have presented a unique set of circumstances for New York healthcare providers, professionals and workers, and the persons, families and communities they serve. Over 22,000 New Yorkers have lost their lives to date, based upon New York State Department of Health data, including nursing home and adult care facility COVID-19 related deaths statewide, reported through the period ending May 13, 2020.[2] While the apex of the pandemic appears to be flattening in New York, deaths are still hovering at an unacceptably high number, and emerging data and evidence suggest heightened risk for young children. The health system as a whole has been struggling to deal with executive orders and overwhelmed capacities and capabilities, across the continuum of care, as well as the surge in capacity that occurred over a very short time period. Through drastic social control measures (i.e., closing businesses and enforcing social distancing), supported by innovation and resourcefulness (for example, in adaptation of equipment such as shared ventilators), explicit rationing of resources may have been averted in some parts of the system, or mitigated in others, at least for now, particularly as such rationing concerns allocation of ventilators in the hospital system. It has come to light that the long-term care system has not fared nearly as well, and there have been continuing shortages of personal protective equipment and staff in both the hospital and long-term care systems. Notwithstanding the unparalleled bravery we have witnessed at all levels of the system, issues concerning rationing scarce resources, including implicit forms of rationing, remain relevant while the pandemic continues to devastate populations and health care workers. This is particularly apparent in the long-term care sector. To the extent that crisis standards of care remain in place during the period the pandemic continues to flatten, as well as in future waves of COVID-19, there will continue to be concern about rationing.

In addressing the legal and ethical issues confronted by the health system, we must not forget the human face of COVID-19, the persons, families and communities affected by the pandemic, and the unspeakable assaults on the fabric of human life – loved ones dying alone in sterile hospital rooms, unemployment and food insecurity, the loss of sociality, and depths of bereavement and despair unknown in generations, at least in the western world. Communities of color and those historically disadvantaged and marginalized, including Black/African Americans and Latinos with illness burden, isolated and vulnerable older adults, nursing home residents, persons with disabilities, persons who are homeless, workers in low-income jobs and on the frontlines, and inmates and immigrants, have been the hardest hit by the pandemic, reflecting the intersectionality of age, race and ethnicity, class, gender, and disability and immigration status. In these contexts, there has been a lack of systematic attention to the psychosocial needs of those affected by the pandemic,[3] or the role of the helping professions including psychology and social work, perhaps with the exception of palliative care which is playing a central role in the pandemic. Palliative care physicians, nurses, nurse practitioners, social workers, psychologists, and chaplains are trained in working with families, goals of care discussions, pain assessment and mitigation of suffering, and providing bereavement support. Efforts to locate palliative care practitioners and teams in emergency rooms during the pandemic, as reported by hospital systems here in New York, are helping to relieve the stress of front-line workers,

---

[1] N.Y EXEC. ORDER, *New York State on Pause:10 Point Plan*, Mar. 22, 2020, https://coronavirus.health.ny.gov/new-york-state-pause.

[2] NEW YORK STATE, Department of Health, COVID-19 Tracker, *Fatalities,* May 14, 2020, https://covid19tracker.health.ny.gov/views/NYS-COVID19-Tracker/NYSDOHCOVID-19Tracker-Fatalities?%3Aembed=yes&%3Atoolbar=no&%3Atabs=n; *Nursing Home and ACF COVID Related Deaths Statewide*, May 13, 2020, https://www.health.ny.gov/statistics/diseases/covid-19/fatalities_nursing_home_acf.pdf.

[3] UNITED NATIONS, Policy Brief: COVID-19 and the Need for Action on Mental Health, May 13, 2020, https://www.un.org/sites/un2.un.org/files/un_policy_brief-covid_and_mental_health_final.pdf.

and provide critical support to patients and their family members as they confront the assaults of the virus and imminent risk of death.[4]

As the crisis began to unfold, New York State Bar Association (NYSBA) President Hank Greenberg asked that the Health Law Section prepare a report on the legal issues presented by the COVID-19 epidemic. To meet the request, Section Chair Hermes Fernandez appointed a Task Force to address the unique legal and ethical questions raised by COVID-19.[5] The Health Law Section Task Force began work in early March.[6]

The Task Force was charged with examining legal issues presented by the pandemic. As the Task Force pursued its work, it identified gaps in the law and legal and regulatory barriers to care delivery that have emerged during the pandemic. The Task Force also chose to make recommendations to address such gaps and barriers in the rapidly changing legal environment, based upon present knowledge.

Cluster groups were organized to examine public health, ethics, provider systems, telehealth, reimbursement, business and liability, workforce and vulnerable population issues.

The members of the Task Force and its various cluster groups convened approximately twice a week, starting on March 13 through April 24, to identify goals and priorities, and also consulted with experts in medicine and bioethics on issues of concern. The members of the Task Force and cluster groups followed consensus processes of decision making throughout its work. During this time, governmental leadership has managed many of the issues the Task Force addresses through a series of declarations and emergency orders.[7] The Task Force acknowledges the value and impact of such steps.

This report reflects the consensus of the Task Force on a wide range of legal and ethical issues and recommendations to further ease the challenges presented now and anticipated in the future. The following limitations of the report are noted: although we touch upon the interaction of federal and state law, the principal focus of the report is New York law; the key issues identified and examined by the Task Force members are by no means exhaustive; and as of this date, sources of reliable data and evidence about the pandemic remain limited. A summary set of Task Force recommendations, based upon current knowledge, may be found at the end of the report.[8] These recommendations will need to be re-assessed over the course of the pandemic, and as more knowledge is gained about the science of COVID-19, health system vulnerabilities, and population outcomes.

[4] Dana Lustbader & Sean Morrison, *Palliative Care on the Front Lines of COVID-19,* GNYHA (webinar), Apr. 20, 2020, https://www.gnyha.org/event/palliative-care-on-the-front-lines-of-covid-19-webinar/.

[5] *See* a full list of appointed members of the Task Force, as well as consulting advisors, scholars and legal professionals, and attorney and law student volunteers who provided support to the Task Force, Appendix H.

[6] The opinions expressed herein are those of the Health Law Section, and not those of the New York State Bar Association until approved by the House of Delegates or the Executive Committee, or the individual members of the Task Force. The New York State Bar Association is a statewide bar association with 74,000 members. We are proud to have a robust Health Law Section with active members in diverse areas of practice concentration and legal scholarship.

[7] *See* New York State Bar Association Health Law Section Task Force Letter to Governor and Department of Health, March 26, 2020, footnotes 4, 5, 6 and 7, Appendix A.

[8] *See* Task Force Recommendations, Appendix G.

I. Public Health Law Framework

Introduction

Public health law focuses on the legal powers and duties of the state to protect the public health, as well as limitations on state power to preserve the legally protected interests of individuals. Public health law provides critical tools to support the response of federal, state, and local governments to public health emergencies (PHEs).[9]

Legal Reforms

Legal reforms have sought to improve planning and response for PHEs through development of legal response capabilities, comprehensive federal and state declarations, and improved classifications of PHEs utilizing modern approaches to react to current threats.[10] Public health law experts and academics have promoted adoption of model emergency preparedness acts to equip government officials with the legal tools to respond to novel and emerging public health threats. For example, the Model State Emergency Health Powers Act (MSEHPA), developed by the Center for Law and the Public's Health at Georgetown and Johns Hopkins Universities in 2001, provides a set of model provisions for state and local government to respond to public health crises.[11] The MSEHPA balances individual and communal interests when government is responding to a public health threat that may result in a large number of deaths and/or mass morbidity. It provides a framework for governments to respond efficiently and effectively to public health emergencies without unjustly infringing upon individual rights.[12,13]

New York can benefit from examining the principles established in the model legislation for coordinating an effective public health response during the coronavirus pandemic. Knowledge of a uniform structure of laws in New York for enabling a public health emergency response is especially important in protecting community health as more residents become infected, demanding more resources from the state's healthcare system. Once the pandemic is over, New York should review and consider adopting the MSEHPA provisions, as is or as otherwise amended, using the Columbia University Center for Health Policy Gap Analysis,[14] developed at the impetus of, and in collaboration with, the NYSBA Public Health Law Committee.

New York State Executive Law Article 2-B,[15] as significantly expanded in April 2020 (Ch. 23, Laws 2020),[16] grants emergency powers to both local heads of government and to the Governor. Epidemics are included in its definition of what is an emergency.[17] The chief executive of a town or city in which an epidemic is occurring may issue directives to safeguard the health of the public that include setting curfews and restricting people from gathering in public places.[18] If an epidemic cannot be contained by local action,

---

[9] JAMES G. HODGE, JR., PUBLIC HEALTH LAW IN A NUTSHELL, 227-247 (West Academic Publishing 2014).
[10] James G. Hodge, Jr. et al., *From Anthrax to Zika: Key Lessons in Public Health Legal Preparedness*, 15 INDIANA L. REV., 23, 25-26 (2018).
[11] *See* Lawrence O. Gostin et al., *Model State Emergency Health Powers Act*, CENTER FOR LAW AND THE PUBLIC'S HEALTH (Georgetown University 2001), http://publichealthlaw.net/MSEHPA/MSEHPA.pdf.
[12] *See* Lawrence O. Gostin & James G. Hodge, *State Public Health Law Assessment Report*, TURNING POINT PUBLIC HEALTH STATUTE MODERNIZATION NATIONAL COLLABORATIVE (2002).
[13] *See id*.
[14] Benjamin Mason Meier & Jocelyn Getgen, *Gap Analysis: Comparing the Model State Emergency Health Powers Act with Corresponding New York State And New York City Statutory Authority*, CENTER FOR HEALTH POLICY (Columbia University 2008).
[15] N.Y. EXEC. L. Art. 2-B – State and Local Natural and Man-Made Disaster Preparedness.
[16] Ch. 23, Laws 2020.
[17] N.Y. EXEC. L. §20(2)(B).
[18] N.Y. EXEC. L. §24.

the Governor may declare a disaster and issue directives to protect the public. Applicable laws require implementation of the least restrictive measures to protect the public, as well as reliance on specialists to prevent adverse effects of any public health emergency measures during the pandemic. The Public Health Manual, recently updated by the New York State Bar Association and New York's Office of Court Administration, provides an overview of the laws that apply to public health issues. [19] As evidenced by the numerous Executive Orders issued over the past several months, more review, analysis, and legislation potentially, are needed.

Developing a systematic framework to prioritize scarce resources in the face of the coronavirus pandemic is essential to protect both individual rights and the public's health. This requires a robust evaluation of constitutional rights, ethical triage of scarce resources, guidance regarding existing advance care directives, and adverse effects of decisions on vulnerable populations and communities of color – all components of legal and ethical decision-making to ensure fairness, transparency and equity. Issues of equity present the most challenging allocation decisions and call upon us to grapple with questions of implicit bias and risks of discrimination in crisis standards and decision processes. For example, if people of color or with co-morbidities and other burdens are less likely to survive hospitalization due to social and economic determinants of health that have compromised their health status over the life years and resulted in advance illness and compromise, is it ethical to consider long-term survival in making allocation decisions? Federal law bars discrimination on the basis of disability, and in the case of discriminatory triage guidelines, enforcement actions may result.[20]

Crisis Standards of Care

New York State, and other jurisdictions, have lacked sufficient resources (e.g., practitioners, personal protective equipment, ventilators, and dialysis machines) to provide critical care during the coronavirus pandemic and may face similar situations in possible future surges. Rationing resources may thus be unavoidable at such times. The development of a framework to guide decision making in a crisis -- a pervasive (e.g., pandemic) or catastrophic (e.g., earthquake) disaster[21] -- is important to preserve the rule of law and maintain focus on ethical considerations. Crisis standards of care ensure that scarce resources during these times are allocated based on evidence and data, with the participation of a broad range of public and private stakeholders, and that decisions are communicated in a transparent manner to preserve the community's trust.[22]

The Institute of Medicine, in a 2009 letter and 2012 report, set forth a comprehensive approach to the development and implementation of crisis standards of care. The Crisis Standards of Care (CSC) proposed by the IOM provide one path for shifting from usual healthcare operation to crisis response required to address the need for a surge response.[23] They acknowledge the interdependency of public and private emergency responders and suggest a process to adjust the state's response to address medical surge and scarce resources. The CSC ensure provider and community engagement to adjust the delivery of care based

---

[19] NYS PUBLIC HEALTH LEGAL MANUAL, A GUIDE FOR JUDGES, ATTORNEYS AND PUBLIC HEALTH PROFESSIONALS, 2d Edition, Currently available as free ebook at: https://nysba.org/products/new-york-state-public-health-legal-manual-second-edition-ebook/?numberOfItemsInCart=1&salesOrderId=a1J1U000002yZ5PUAU&status=SUCCESS.

[20] 42 U.S.C. §12132 (1990); 42 U.S.C. §12182 (1990); *See* HHS OFFICE OF CIVIL RIGHTS, *OCR Reaches Early Case Resolution With Alabama After It Removes Discriminatory Ventilator Triaging Guidelines*, Apr. 8, 2020, https://www.hhs.gov/about/news/2020/04/08/ocr-reaches-early-case-resolution-alabama-after-it-removes-discriminatory-ventilator-triaging.html?; *See* also discussion of these issues, *infra*, Sections II and VII.

[21] INSTITUTE OF MEDICINE, CRISIS STANDARDS OF CARE: A SYSTEMS FRAMEWORK FOR CATASTROPHIC DISASTER RESPONSE: VOLUME 1, (Dan Hanfling, et al., eds., The National Academies Press 2012), https://doi.org/10.17226/13351, https://commed.vcu.edu/IntroPH/2012/crisisManagement_IOM.pdf.

[22] *Id*.

[23] James G. Hodge et al., *Practical, Ethical, and Legal Challenges Underlying Crisis Standard of Care,* J. L. MED. & ETHICS, Spring 2013 at 2.

on fair and equitable principles. Furthermore, the CSC offer guidelines to enable providers to make difficult life and death decisions and reduce suffering.[24]

The development of consensus standards of care can be particularly beneficial to New York State when navigating crises, such as the coronavirus pandemic, because it focuses on adherence to ethical and professional standards.[25] The IOM's standards are based on three substantive principles: fairness, duty of care, and duty to steward resources. Underlying the concept of fairness in allocating resources is the duty to base decisions on ethically sound principles. This presupposes the allocation of resources in a consistent and standardized way across all types of provider types and settings. Furthermore, it contemplates the rigorous assessment of decisions against professional ethics. A process for resource allocation should be developed based on specified goals.[26] For example, if healthcare practitioners will receive priority for being placed on a ventilator, public health officials must clearly identify the goals and rationale for establishing this priority. The process must be based on non-discriminatory and reasonable standards for protecting the public's health.[27]

The CSC planning approach seeks to facilitate community and provider trust through transparency, consistency, proportionality, and accountability. Adoption requires public health officials to strictly adhere to ethical principles, as well as the development of standardized processes, and transparent communication with providers and the community about the processes.[28] Standardization protects and supports healthcare providers in resource allocation by providing a clear framework. The CSC planning approach promotes trust through transparency about the resource allocation process with the community.

Ideally, the CSC planning approach should be implemented before a public health emergency, when difficult decision-making can occur without the threat of immediate harm and private-public relationships can be cultivated. However, CSC can and should be implemented even during the crisis to create clear guidelines for practitioner and public health decision-making. While this report recommends adoption of a CSC planning approach, which requires long term planning outside of a PHE, it will also identify components of crisis standards of care that can be considered for potential implementation, on a temporary basis, during a crisis.

Provider and Community Engagement

Protecting the public health during the coronavirus pandemic requires a commitment from a multitude of stakeholders, from public health agencies, private organizations, emergency response personnel, and bordering state agencies. Cooperation and collaboration are critical for sharing of resources and equipment. As part of a CSC planning process, New York State should consider establishing memoranda of understanding and other agreements to facilitate interjurisdictional cooperation and coordination among

---

[24] *Id*.
[25] *Id.* at 3.
[26] *Id.* at 3-4.
[27] Of course, the IOM standards, based on ethical, legal, and medical principles, must comport with federal and New York law, including New York's Constitution, statutes, and case law. New York State has long recognized the individual right to self-determination in health care and has a robust law of informed consent, including the right to refuse medical treatment, and the right to information and access to palliative care. The sensitive question of ventilator allocation must also satisfy federal and New York law. For example, under the Americans with Disabilities Act, as interpreted in Supreme Court decisions, health care providers may not discriminate against any patient in the provision of care based on the patient's disability, as discussed *infra* in Section II. Similarly, all providers have an ethical and legal duty not to abandon their patients, as discussed *infra* in Section II.
[28] James G. Hodge et al., *Practical, Ethical, and Legal Challenges Underlying Crisis Standard of Care,* J. L. MED. & ETHICS, Spring 2013 at 5.

different entities.[29] Agreements can ensure consistency with existing New York laws, as well as address specific concerns about resource allocation.[30]

Provider and community engagement are essential for the delivery of healthcare services during the pandemic. Using the CSC planning framework, public health officials can work with healthcare organizations and the community to develop mechanisms to ensure compliance with surveillance, reporting, testing, screening, quarantine, social isolation, or other public health mandates. Patient issues, such as accommodations for disabled patients, preserving informed consent, and protecting patient privacy, can be addressed through engagement.[31]

Adoption and Communication of Consistent Methods of Resource Allocation

Achieving consistency in allocation of scarce resources can impact community and individual health outcomes. The CSC planning approach would establish meaningful guidance on shifting standards of care during PHEs, as well as establish legal authority. Recognition of changing standards of care in a declared emergency alleviates healthcare practitioner concerns regarding liability when allocating resources. By changing the scope of practice during a declared emergency, public health officials can also suspend certain licensure requirements to meet increased healthcare demands.[32] Licensure and other requirements can be temporarily revised to allow healthcare providers to practice at the top of their license (e.g., reducing supervision requirements or authorizing practitioners with overlapping skills to fulfill service gaps).[33] (See Section III for a full discussion of licensure issues.)

Continuous Performance Improvement

The coronavirus pandemic has resulted in fluid decision-making as more information is released from the federal government and more patients recover from the virus. The CSC planning approach would promote continuous performance improvement to refine processes to provide the best level of care possible, even during the crisis. It would allow for the use of data and evidence-based decision making to make mid-course corrections, even during the crisis.[34]

Provider Education About the CSC

Healthcare providers are trained to focus on individual patient needs and improving clinical outcomes. Coordinating the allocation of scarce medical resources could well require a dramatic shift in their approach to healthcare and difficult choices regarding patient care. Practitioners would need education on the CSC framework, and the conditions under which the crisis standards would come into play.[35]

The CSC is based on modern public health principles to provide a consistent and ethically sound approach to delivering the best level of healthcare services to the community during the coronavirus pandemic. New York State should consider educating healthcare practitioners about the CSC to ensure transparency and fairness in all healthcare decision-making processes. Consistent application of CSC would also be important

---

[29] U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION, Public Health Law/Publications and Resources/Emergency Preparedness, https://www.cdc.gov/phlp/publications/topic/emergency.html (last reviewed: Apr.10, 2020).
[30] INSTITUTE OF MEDICINE, CRISIS STANDARDS OF CARE: A SYSTEMS FRAMEWORK FOR CATASTROPHIC DISASTER RESPONSE: VOLUME 1, 1-6 (Dan Hanfling, et al., eds., The National Academies Press 2012), https://doi.org/10.17226/13351, https://commed.vcu.edu/IntroPH/2012/crisisManagement_IOM.pdf.
[31] *Id*.
[32] JAMES G. HODGE, JR., PUBLIC HEALTH LAW IN A NUTSHELL, 227-247 (West Academic Publishing 2014).
[33] *Id.* at 4.
[34] INSTITUTE OF MEDICINE, CRISIS STANDARDS OF CARE: A SYSTEMS FRAMEWORK FOR CATASTROPHIC DISASTER RESPONSE: VOLUME 1, 1-3 (Dan Hanfling, et al., eds., The National Academies Press 2012), https://doi.org/10.17226/13351, https://commed.vcu.edu/IntroPH/2012/crisisManagement_IOM.pdf.
[35] *Id.* at 1-33-1-34.

specifically in broadly reducing geographic variability or inconsistency in applications to evolving standards of care. Even variability can occur across health systems in the same metropolitan region.

Constitutional Protections and Civil Liberties

New York's ability to respond to public health emergencies is derived from its police powers and parens patriae powers.[36] The New York Constitution under Article XVII, Section 3 states, "The protection and promotion of the health of the inhabitants of the state are matters of public concern and provision therefor shall be made by the state and by such of its subdivisions and in such manner, and by such means as the legislature shall from time to time determine." With this constitutional authority, on March 2, 2020, the legislature, passed an amendment to Executive Law §29-a granting the Governor broad discretion to address the emergent COVID-19 Pandemic.

The steps that New York has taken to control this novel virus are largely unprecedented. Exercising its power to address the coronavirus pandemic, the State implemented social distancing measures to protect public health during the pandemic, stay-at-home orders, the shutdown of "non-essential businesses," a moratorium on elective health procedures, and other directives that significantly infringe upon the rights of New York citizens. Such actions should be sparingly used, and only when there is a compelling reason to believe that these extreme measures are necessary to save lives. Accordingly, when implementing them, government officials must continually balance individual civil liberties against the need to protect the public health. They must be transparent about why such steps are needed, and they must impose the restrictions fairly and for only as long as they are needed.

For example, restrictions of movement should only be employed when they are necessary and public health officials can cite clear and compelling evidence that the disease, because of its communicability and severity, poses a grave risk to public health.[37] The government should ensure fair and equitable treatment, avoiding stigma or discrimination against individuals or groups. Furthermore, public health measures should be no more restrictive than necessary to accomplish public health objectives.[38] The evidence about the coronavirus and recovery outcomes are changing daily; therefore, New York should continually review the public health restrictions against evolving scientific evidence. Public health officials should revise executive orders and adjust restrictions accordingly to ensure least restrictive and fair measures.

Additionally, New York public health officials should implement safeguards to protect patient privacy during the pandemic. Patients have a right to privacy pursuant to the Health Information Portability and Accountability Act (HIPAA), as well as a state constitutional right to privacy. However, the right to privacy is not an absolute right; public health reporting is a standard exemption for providers, and public health officials and healthcare covered entities may share protected health information to advance public health surveillance and reporting activities.[39] While such data sharing promotes transparency, covered entities and public health officials must carefully consider protecting patient information by disclosing the minimum necessary information to achieve public health objectives.

Fair due process procedures are required when the government deprives an individual of property or liberty. The level of due process afforded must be commensurate with the extent of deprivation of life or liberty. Determining whether an informal process or a formal judicial process will preserve civil liberties rests on the level of coercive measures imposed, the risk of an erroneous decision, and the burden of additional

[36] *Jacobson v. Massachusetts*, 197 U.S. 11 (1905); Lawrence O. Gostin, Public Health Law: Power, Duty, and Restraint, 92-98 (Univ. of California Press 2008).
[37] Wendy Parmet & Michael Sinha, *COVID-19: The Law and Limits of Quarantine*, 15 NEW ENG. J. MED. 28 (2020).
[38] *Id*.
[39] 45 C.F.R. 160 (2012).

judicial procedures.[40] In New York, access to the courts has been curtailed temporarily due to the pandemic; however, virtual proceedings are increasingly available.

II. Ethical Issues in the Management of COVID-19

Introduction

There are two central ethical issues presented by the COVID-19 pandemic in the United State: i) the fair allocation of scarce resources; and ii) the balancing of autonomy, that is, individual rights and liberty interests, versus protection of the public's health. These are separate issues and merit consideration as such.

Allocation of Life-Saving Equipment

Allocating limited resources during the pandemic is among the greatest challenges in balancing our obligation to save the most lives against concerns of equity and the right to liberty. Such resources include tests to determine who is infected, personal protective equipment (PPE) to prevent spread, life-saving medical equipment – notably ventilators – and trained health care workers. Even items as mundane as hospital beds are scarce and must be allocated fairly.

Virus Testing

As other countries have demonstrated,[41] the value of assuring adequate testing early enough to tailor social distancing measures can significantly reduce the apex of infection and prevent strain on life-saving resources. Test-availability and test access triage are variable across domestic regions, which both reflects and reinforces inequities across socioeconomic lines. This has created unjustifiable disparities: in access to better protection measures and treatment stratified by financial and social means.

There is evolving discussion about two specific types of testing now - diagnostic testing and post-exposure (antibody) testing. Both need to be in place and scaled. In light of the Governor's expressed intent to strategically execute a phased plan for reopening, a coordinated state-wide plan for diagnostic testing is needed to ensure: i) frontline health care workers are prioritized in access to testing on the basis of moral obligation; and ii) the most vulnerable New Yorkers from both a health and business operations standpoint have equitable access to testing.[42] Frontline and essential employees who are forced to engage in significant close contact with other essential employees to perform their duties, and cannot easily be replaced, are critical to ensure that essential businesses are able to continue to operate effectively in support of our community members, while also proactively protecting our community members who rely on services and products from these entities.

PPE

The United States is also severely short on PPE for health care workers, such as gowns, face masks, eye protection, and surgical masks,[43] which leads to difficult questions about who among them should have access to the existing limited supply. Production and distribution should have ramped up sooner, preventing such shortages. Members of the general public are understandably inclined to use PPE to protect themselves, but such use could be limited according to actual effectiveness and curtailed according to the far greater

---

[40] LAWRENCE O. GOSTIN, PUBLIC HEALTH LAW: POWER, DUTY, AND RESTRAINT, 130-132 (Univ. of California Press 2008); *Mathews v. Eldridge*, 424 U.S. 319, 335 (1976).

[41] Heather Stewart, *UK Must Learn from German Response to COVID-19, says Whitty*, THE GUARDIAN, Apr. 7, 2020, https://www.theguardian.com/world/2020/apr/07/uk-must-learn-from-german-response-to-COVID-19-says-whitty.

[42] NEW YORK STATE, Amid Ongoing Covid-19 Pandemic, Governor Cuomo Outlines Phased Plan to Re-open New York Starting with Construction and Manufacturing, Apr. 26, 2020, available at: https://www.governor.ny.gov/news/amid-ongoing-covid-19-pandemic-governor-cuomo-outlines-phased-plan-re-open-new-york-starting.

[43] Andrew Jacobs et al., *'At War With No Ammo': Doctors Say Shortage of Protective Gear is Dire*, N.Y. TIMES, Mar. 19, 2020, https://www.nytimes.com/2020/03/19/health/coronavirus-masks-shortage.html.

need of health care workers. Whereas socially distanced members of the public can effectively protect themselves and others with carefully placed cloth coverings,[44] health care workers require more advanced N95 respirators because they are intimately and unavoidably exposed to infected people. Those hoarding PPE[45] represent the extreme violation of our collective ethical duty to steward precious resources.

Ventilators and Other Scarce Equipment

Allocation of life-saving equipment such as ventilators, which enable breathing for patients whose lung function is compromised by coronavirus infection, is the starkest exercise of justice during the pandemic. Access to a ventilator may make the difference between life and death for many individuals. Based upon all reports, there has been no explicit rationing of ventilators by providers upstate, and upstate systems actually sent available ventilators downstate. However, providers downstate were forced to adapt equipment to meet need, such as through ventilator sharing. It is not clear whether any patient was expressly denied access to a ventilator or other scarce equipment, although the state was on the brink of such decisions, and may very well not have enough scare equipment for everyone in future waves of the pandemic,, as experienced in Italy.[46] Accordingly, we may be faced in the future with difficult decisions about who will have access and for how long, and hence, must be adequately prepared.

Several organizations foresaw the possibility of pandemic-related ventilator shortage and developed guidelines for how to allocate fairly. These guidelines, including those produced by the New York State Task Force on Life and the Law (NYSTFLL) in 2015,[47] first issued in 2008, as well as the University of Pittsburgh,[48] the North Carolina Protocol for Allocating Scarce Inpatient Critical Care Resources in a Pandemica,[49] Maryland[50] and other states, and the Catholic Health Association of the United States,[51] follow certain similar patterns. It is of note, however, that the updated 2015 New York Task Force on Life and the Law (NYSTFLL) Guidelines do not grant priority to health care workers. Some existing guidelines do give priority to health care workers, based upon the implicit assumption that such professionals can receive limited ventilation and then return to the workforce while the need still exists, which remains uncertain from both an individual and systems perspective.[52] Furthermore, the definition of a health care worker is unclear. Is it just physicians and nurses, or just those who serve during a pandemic, or just those with expertise to treat pandemic patients? For example, should a Florida dermatologist who let his license lapse be prioritized in a New York hospital? The issue of the treatment of health care workers in the event

---

[44] Prevent Getting Sick, CTRS FOR DISEASE CONTROL & PREVENTION, Apr. 13, 2020, https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/diy-cloth-face-coverings.html.

[45] Marty Stempniak, *Feds seize 900,000-plus pieces of PPE from hoarding price gouger, distribute to providers*, RADIOLOGY BUSINESS, Apr. 2, 2020, https://www.radiologybusiness.com/topics/policy/ppe-COVID-19-pandemic-coronavirus-william-barr-doj.

[46] Marco Pavesi, *I'm a Doctor in Italy. We Have Never Seen Anything Like This*, N.Y. TIMES, Mar. 18, 2020, https://www.nytimes.com/2020/03/18/opinion/coronavirus-italy.html.

[47] New York State Task Force on Life and the Law, Ventilator Allocation Guidelines, Nov. 2015, https://www.health.ny.gov/regulations/task_force/reports_publications/docs/ventilator_guidelines.pdf. *See* University of Rochester Medical Center grid attached, Appendix B.

[48] *Allocation of Scarce Critical Care Resources During a Public Health Emergency*, U. PITTSBURGH, DEPT. OF CRITICAL CARE MED. Apr.15, 2020, https://ccm.pitt.edu/sites/default/files/UnivPittsburgh_ModelHospitalResourcePolicy_2020_04 _15.pdf.

[49] North Carolina Protocol for Allocating Scarce Inpatient Critical Care Resources in a Pandemica, Douglas White, *A Model Hospital Policy for Allocating Scarce Critical Care Resources*, U. PITTSBURGH SCHOOL OF MED. Mar. 23, 2020, https://ccm.pitt.edu/?q=content/model-hospital-policy-allocating-scarce-critical-care-resources-available-online-now.

[50] *Maryland Framework for the Allocation of Scarce Life-sustaining Medical Resources in a Catastrophic Public Health Emergency*, U. MARYLAND SCHOOL OF LAW, Aug. 24, 2017, https://www.law.umaryland.edu/media/SOL/pdfs/Programs/Health-Law/MHECN/ASR%20Framework_Final.pdf.

[51] Ethical Guidelines for Scarce Resources in a Pandemic, CATHOLIC HEALTH ASSOCIATION OF THE UNITED STATES 2020, https://www.chausa.org/docs/default-source/ethics/ethical-guidelines-for-scarce-resources-in-a-pandemic.pdf?sfvrsn=2.

[52] Mark A. Rothstein, *Should Health Care Providers Get Treatment in an Influenza Pandemic?*, 38 J. L. MED. & ETHICS, 412-419 (2010).

of scarce ventilator resources calls for re-examination in light of the experience and knowledge gained during the COVID-19 pandemic.

Most frameworks prioritize survival benefit, which means prioritizing patients for whom ventilator use will lead to hospital discharge and return to normal life. Such evaluations can be quite sophisticated in separating cases that seem similar. For example, the NYSTFLL guidelines recommend using the Sequential Organ Failure Assessment (SOFA) score[53] that quantifies the possibility of mortality based on the degree of dysfunction of six organ systems. Most frameworks then allow for the possibility that such a comparison will not be able to differentiate all patients, leading to the need for "tie-breakers." A recent article in the New England Journal of Medicine[54] describes such tie-breakers as involving assessment of co-morbid conditions that would indicate which patients would likely have better post-treatment life-length and life-quality, or age, for which younger patients would get priority because they have yet to experience the full life-cycle. Advocates for those with disabilities have raised serious questions about the ethics of any guidelines that would discriminate against persons with disabilities,[55] and the HHS Office of Civil Rights has cautioned that such discrimination on the basis of disability or age is barred by federal law.[56]

Many allocation frameworks describe the importance of avoiding decisions that in practice discriminate on non-medical grounds and suggest the use of a lottery only if all other factors are equal. While objective and utilitarian, decisions that differentiate patients on grounds such as assessment of co-morbidities and age cannot be free from unintentional discrimination. Many with co-morbid conditions are so affected because of prior social injustices, leading to their inability to access adequate care or maintain healthy lifestyles.[57] Accordingly, this prioritization scheme will inevitably save the lives of many whose health was better before the pandemic, which demonstrates the tension between the goal of saving the most lives and achieving distributive justice. Early data already suggest this pandemic is disproportionately affecting Black/African Americans and Latinos,[58] something that should be studied carefully and potentially used to ensure that social and economic determinants of health are considered in the fair allocation of life-saving resources.

Age has also been suggested as an allocation criterion. Older persons have historically been marginalized, but the value of remaining life is not necessarily diminished by age, which draws age into question as an

---

[53] *Sequential Organ Failure Assessment (SOFA) Score*, MD+CALC, (last accessed Apr. 24, 2020), https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score.

[54] Ezekiel Emanuel et al., *Fair Allocation of Scarce Medical Resources in the Time of COVID-19*, NEW ENG. J. MED., Mar. 23, 2020, https://www.nejm.org/doi/full/10.1056/NEJMsb2005114.

[55] Ari Ne'eman, *When It Comes To Rationing Disability Rights Law Prohibits More than Prejudice*, Bioethics Forum Essay, HASTINGS CTR., Apr. 10, 2020, https://www.thehastingscenter.org/when-it-comes-to-rationing-disability-rights-law-prohibits-more-than-prejudice/; Joseph J. Fins, *Disabusing the Disability Critique of the New York State Task Force Report on Ventilator Allocation*, HASTINGS CTR., Apr. 1, 2020, https://www.thehastingscenter.org/disabusing-the-disability-critique-of-the-new-york-state-task-force-report-on-ventilator-allocation/; Joseph J. Fins, *New York State Task Force on Life and the Law Ventilator Allocation Guidelines: How Our Views on Disability Evolved*, HASTINGS CTR., Apr. 7, 2020, https://www.thehastingscenter.org/new-york-state-task-force-on-life-and-the-law-ventilator-allocation-guidelines-how-our-views-on-disability-evolved/.

[56] HHS OFFICE OF CIVIL RIGHTS, Bulletin: *Civil Rights, HIPAA, and the Coronavirus Disease 2019 (COVID-19)*, Mar. 28, 2020, https://www.hhs.gov/sites/default/files/ocr-bulletin-3-28-20.pdf; Patient Protection and Affordable Care Act, 42 U.S.C. § 18001 et seq. (2010).

[57] SHORTER LIVES, POORER HEALTH (Steven H. Wolf and Landon Aaron, eds., National Academies Press 2013); FROM NEURONS TO NEIGHBORHOODS: THE SCIENCE OF EARLY CHILDHOOD DEVELOPMENT (Jack P. Shonkoff and Deborah A. Phillips, eds., National Academies Press, 2000).

[58] Kenya Evelyn, *'It's a Racial Justice Issue': Black Americans are Dying in Greater Numbers from COVID-19*, THE GUARDIAN, Apr. 8, 2020, https://www.theguardian.com/world/2020/apr/08/its-a-racial-justice-issue-black-americans-are-dying-in-greater -numbers-from-COVID-19.

allocation criterion. Yet some take the position that we may have a duty to help children and younger adults experience more life when possible, meaning that the value of experiencing more life-phases might necessitate age comparison in some cases. Clearly, an age difference of just one year or two will rarely be ethical grounds on which to allocate, but our intuitions might sometimes support a decision to ventilate a 9-year old over a 79-year old when ventilator access would give them an equal chance of hospital discharge. This intuition reflects a basic human impulse to afford special protection to small children, as reflected for example in child abuse laws.

Many allocation frameworks provide thoughtful yet general guidelines. The challenge in their development is to be prescriptive enough so that overburdened health care workers can make confident decisions without fear of liability, yet general enough to allow flexibility when similar scenarios should be handled differently. For example, if one ventilator must be allocated between two patients equally likely to survive the acute respiratory infection yet one has a heart condition that would indicate fewer remaining life-years, a co-morbidities assessment would favor the unaffected patient. However, if the heart condition is congenital due to Down Syndrome, guidance might suggest avoiding allocation decisions that hinge on the presence of disability, even if indirectly. If the heart condition is the product of a poor diet from living in poverty, guidance might suggest avoiding allocation decisions based on factors that grow out of oppressive socio-economic structures. Relevant facts should thus inform ethical decisions to maximize lives saved while also avoiding unjust discrimination. At the same time, the allocation criteria should be sufficiently clear and concise that they can be understood and implemented by all front-line health care workers.

The development of a ventilator triage framework based on ethical principles should consider the social and cultural norms of the implementing system. It is also important to ensure healthcare staff are trained on the policy and processes and that they are universally applied. All clinicians should know how they are expected to assess survival benefit in accordance with a standardized, consistent process. Adherence to the accepted framework should serve to protect clinicians' allocation decisions, such as withdrawing care from someone who will not survive with maximum care to make resources available to another patient who is likely to benefit. There are mechanisms to relieve the attending health care staff of making the most difficult decisions that risk unjust discrimination on nonmedical grounds should not be made by the attending health care staff. To alleviate some of their burden and further insulate them from liability during this morally challenging time, a triage committee, or ethics committee, can be established and available to carefully apply the allocation policy and reach consensus about justified decisions in these cases. It is an unfortunate reality that many institutions do not have the capacity to train their staff on policy implementation or provide triage or ethics committee support for hard cases.

Withdrawal, DNR, and Futility

Usually, ventilator supply exceeds need. Under normal circumstances, when a ventilated patient will not likely survive after ventilator withdrawal, decisions regarding the course of care will involve a discussion of patient and family wishes, and appropriate implementation of palliative care to mitigate suffering, with limitations in public health emergency contexts such as the present one. Similarly, decisions to resuscitate a patient who is at risk of cardiac arrest will be informed by the patient's previously expressed wishes, or the family's wishes.[59] Such respect for patient autonomy represents the ideal of shared decision making in

[59] N.Y. PHL Art. 29-B, formerly the "DNR Law," now only applies in psych units and hospitals. It provides that, "It shall be lawful" for practitioners to write a DNR based on patient or agent/surrogate consent, or in the case of an isolated patient (i.e., a patient who lacks capacity and has no agent or surrogate) for two physicians to write a DNR based on medical futility. N.Y. PHL Art. 29-CC, the Family Health Care Decisions Act, authorizes decisions – including DNR – by surrogates for incapable patients who meet clinical criteria, and by two physicians for isolated patients when treatment would be in effect futile. N.Y. CLS SCPA § 1750-b relates to patients who have an intellectual disability. It authorizes decisions – including DNR – by surrogates for incapable patients who meet clinical criteria, and by a surrogate decision-making committee for isolated patients when treatment would be in effect futile.

modern western medicine. One way to better respect patient autonomy during the pandemic is to lower the existing bar for individuals to designate health care proxies, such as the recent Executive Order enabling remote witnessing of such legal designations.[60] In light of severely restricted access to serving as a witness for patients, more could be done including dropping the required two witnesses to one, or if none is available only requiring a remote notary.[61]

There will be many cases for which the existence of a health care proxy will not morally bear on the need to justly allocate or reallocate resources. Honoring the ideal of patient autonomy in all cases where advance directives and surrogate decision makers ask for continued care that meets the definition of futility during the pandemic would prevent distribution of resources to those who would survive hospital discharge and would lead to significantly more deaths. This said, some guidelines include a variation of "first come first served," which means that once patients are on ventilators, if the family or the patient objects to withdrawal, this resource cannot be re-allocated to another patient who might benefit even if continued care meets the definition of futility. One potential foundation for this principle is that reallocation necessitates a direct and unjust comparison of the worth of two lives. This might be refuted by the fact that reallocation would only be considered if the presently-ventilated patient has negligible existing quality of life that can never be improved, whereas the new patient could have full quality of life with access to care.

Crisis standards of care[62] protect withdrawing and withholding care from patients when such care would be medically futile. The challenge arises when the patient's advance directive conflicts, or the surrogate decision-maker disagrees, with the decision to withdraw or withhold care. Although laws exist in states like California and Texas[63] that protect a clinical determination of futility leading to a do not resuscitate (DNR) order or the withdrawal of a ventilator against a surrogate's wishes if the patient is still alive (with adequate time given to say goodbye), New York does not have such laws. This can lead to unhelpful resuscitation attempts in futile cases when families demand it. First, it exposes the resuscitation team to a high risk of infection – a risk not usually present in resuscitation attempts in non-pandemic circumstances. However, the issuance of a DNR without consent or over objection is not explicitly prohibited, leading to ambiguous territory especially during the pandemic. While we unavoidably need to ask health care professionals to risk their lives to save patients, we cannot ethically ask them to do so when there is no realistic prospect of saving the patient's life. Moreover, even apart from that consideration, directing resuscitation attempts when there is no prospect of benefit to the patient is morally injurious to staff, and reallocation of resources can save far more lives.

Although an Executive Order has been issued[64] protecting health care workers from liability for making decisions in accordance with existing law or other executive orders,[65] there are no laws in New York that would protect physicians making decisions based on futility over family objection. This could lead to significant litigation and liability for all health systems for making ethical decisions to protect the greatest number of human lives, unless such an order is issued. A statute or Executive Order could override several existing laws, including PHL 308, PHL § 2504, PHL Art. 30-D, PHL Articles 29-B, 29-C, 29-CC and 29-CCC, MHL Art. 33, MHL Art. 47, and Surrogate's Court Procedure Act section 1750-b, Penal Law Title H, SSL Art. 11, the Justice Center Act, and other laws to the extent that such laws, and any regulations

[60] N.Y. EXEC. ORDER No. 202.10, Mar. 23, 2020.
[61] *See* Health Care Proxy proposal, Appendix C.
[62] INSTITUTE OF MEDICINE, CRISIS STANDARDS OF CARE: A SYSTEMS FRAMEWORK FOR CATASTROPHIC DISASTER RESPONSE: Volume 1, 1-3 (Dan Hanfling, et al., eds., The National Academies Press 2012), https://doi.org/10.17226/13351, https://commed.vcu.edu/IntroPH/2012/crisisManagement_IOM.pdf.
[63] Michael D. Cantor et al., *Do-Not-ResU.S.C.itate Orders and Medical Facility*, 163 (22) ARCH. INTERN. MED. 2689 (2003).
[64] N.Y. EXEC. ORDER No. 202.10, Mar. 23, 2020, https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.
[65] N.Y. PHL Art. 30.

promulgated pursuant to them, constrain the ability of an attending practitioner, as defined by PHL 2994-a, to issue a do-not-resuscitate order based on a determination that resuscitation would be "medically futile," as defined in PHL 2961.12, provided there is a concurring determination by a second practitioner. It is also recommended that such determinations be documented in the medical record.

Balancing of Autonomy Versus Protection of Public Health

The second issue concerns the extent to which individual rights and liberty interests[66] may be superseded by measures to protect public health. This determination hinges on the magnitude of the affected population, the severity of symptoms, and the degree of resource limitation. As of this writing, in the United States the coronavirus has infected nearly 1.4 million people and resulted in nearly 84,000 deaths.[67] New York has suffered nearly 22,000 deaths,[68] primarily in the New York Metropolitan area. Of course, these numbers are changing rapidly, and questions have been raised about the accuracy of official death counts and possible undercounting.[69] As there is presently no vaccine available for COVID-19, the primary resources are the ability to test for its presence, the use of personal protective equipment (PPE) to reduce transmission, clinical support equipment, such as ventilators to support respiratory function of those with compromised lung capacity, and as of May 1, 2020, the investigational antiviral drug remdesevir, recently approved by the U.S Food and Drug Administration through emergency authorization.[70] Many regions have only enough tests for those who must be hospitalized,[71] hospital systems are creating makeshift PPE out of trash bags,[72] and in New York (the U.S. COVID-19 epicenter), while it appears that catastrophic shortages of ventilators in the March-April surge were avoided, New York must be prepared to deal with shortages in future surges.[73] The issue is whether, and the extent to which, the speed, breadth, and lethality of COVID-19, and our inadequate preparation, create a ground for restricting liberty in order to save lives.

As the right to liberty is fundamental,[74] burdening or restricting the right must be limited to just those means that will prevent avoidable loss of life or property. Additional facts about this pandemic inform prevention efforts, specifically those aimed at reducing spread in the general community. While the virus is highly contagious, based on information presently available, it appears that many infected are asymptomatic for many days, many will remain asymptomatic, and a significant portion will only experience mild symptoms. Although it would seem at this point without rigorous research evidence that the risk of significant health

---

[66] *Jacobson v. Massachusetts*, 197 U.S. 11 (1905); LAWRENCE O. GOSTIN, PUBLIC HEALTH LAW: POWER, DUTY, AND RESTRAINT, 92-98 (Univ. of California Press 2008).

[67] CTR. FOR DISEASE CONTROL AND PREVENTION, CORONAVIRUS DISEASE 2019, *Cases in the U.S.*, (last updated May 14, 2020), https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html.

[68] NEW YORK STATE, Department of Health, COVID-19 Tracker, *Fatalities,* May 12, 2020, https://covid19tracker.health.ny.gov/views/NYS-COVID19-Tracker/NYSDOHCOVID-19Tracker-Fatalities?%3Aembed=yes&%3Atoolbar=no&%3Atabs=n; *Nursing Home and ACF COVID Related Deaths Statewide*, May 11, 2020, https://www.health.ny.gov/statistics/diseases/covid-19/fatalities_nursing_home_acf.pdf.

[69] Sarah Kliff & Julie Bosman, *Official Counts Understate the Official U.S. Coronavirus Death Toll*, N.Y.TIMES, Apr. 7, 2020, https://www.nytimes.com/2020/04/05/us/coronavirus-deaths-undercount.html.

[70] *See*, U.S. FOOD & DRUG ADMIN., CORONAVIRUS (COVID-19) UPDATE: FDA ISSUES EMERGENCY USE AUTHORIZATION FOR POTENTIAL COVID-19 TREATMENT, May 1, 2020, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.

[71] *New Coronavirus Testing Guidelines*, NYC Health and Hospitals, https://www.nychealthandhospitals.org/coronavirus-testing-guidelines/.

[72] Chris Brooks, *Using Trash Bags for Gowns: Interview with a New York Nurse*, LABORNOTES, Mar. 30 2020, https://www.labornotes.org/2020/03/using-trash-bags-gowns-interview-new-york-nurse.

[73] *COVID-19 Projections*, INS. FOR HEALTH METRICS & EVALUATION, https://Covid19.healthdata.org/united-states-of-america, (last visited Apr. 17, 2020).

[74] *Jacobson v. Massachusetts*, 197 U.S. 11 (1905); LAWRENCE O. GOSTIN, PUBLIC HEALTH LAW: POWER, DUTY, AND RESTRAINT, at 92-98 (Univ. of California Press 2008).

consequences is lower for young healthy people, the evidence is not all in, and the risk is not negligible.[75] There are recent New York City Health Department reports of an inflammatory illness affecting children that may possibly be related to COVID-19[76] Moreover, the younger population can infect more vulnerable populations at great risk of dying. We have increasing evidence that suggests how the virus is transmitted and how long it lasts, but such data are not yet supported by robust scientific evidence and no curative treatment exists. Presently, it may serve society to be overprotective rather than under protective. Individuals do not have adequate information to engage in their own risk calculus regarding where to go and with whom to interact. Such decisions have enormous impact on others and the state's exercise of its police power in these circumstances to protect the population as a whole may justify a curtailment on the exercise of individual liberty.[77] As we have seen, those limitations, among other things, have been extensive, including prohibitions on gatherings, social distancing, the wearing of face coverings, and restrictions on the operations of businesses. Accordingly, it can be argued that the executive orders putting New York on PAUSE[78] and urgent campaigns to get us to stay home are ethically warranted. However, more draconian measures, such as quarantine with penalties as issued in China,[79] run so deeply counter to the core values of liberty and self-determination in the U.S. that they would only be considered if several measures more drastic than PAUSE prove insufficient, and even then might prove impossible to implement.

The harms of being overprotective run far beyond the boredom of being stuck indoors. Shutting down the economy is leading to extraordinary unemployment and financial suffering, which over the long term adversely affects health outcomes, for example, such as risks of drug use and suicide in some cases. Deferring the availability of essential services, elective medical procedures, and medicine production for vulnerable populations may lead to harm and death.[80] However, studies suggest that social distancing and mitigation strategies reduce the community spread of COVID-19 and concomitant mortality.[81] Enacted protection measures must constantly balance these harms by being responsive to new discoveries about the disease and the best scientific predictions about the consequences of revisions to social distancing policies, such as allowing limited return to work.

---

[75] Sanjay Gupta, *The Mystery of Why Coronavirus Kills Some Young People*, CNN, Apr. 6, 2020, https://www.cnn.com/2020/04/05/health/young-people-dying-coronavirus-sanjay-gupta/index.html.

[76] J. Goldstein, *15 Children Are Hospitalized With Mysterious Illness Possibly Tied to COVID-19*, N.Y.TIMES, May 8, 2020, https://www.nytimes.com/2020/05/05/nyregion/children-Kawasaki-syndrome-coronavirus.html?campaign_id=16&emc=edit_ml_20200508&instance_id=18295&nl=well-family&regi_id=70461562&segment_id=26869&te=1&user_id=a25ad6bf8443b5ca142cd1840c7794d2; NYC HEALTH DEPARTMENT, 2020 Health Alert #13: *Pediatric Multi-System Inflammatory Syndrome Potentially Associated with COVID-19*, https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf

[77] *See Jacobson v Massachusetts*, 197 U.S. 11 (1905).

[78] NEW YORK STATE, *New York State on Pause: 10 Point Plan*, Mar. 22, 2020, https://coronavirus.health.ny.gov/new-york-state-pause.

[79] Hilary Brueck et al., *China Took at Least 12 Strict Measures to Control the Coronavirus. They Could Work for the U.S. but Would Likely Be Impossible to Implement*, BUSINESS INSIDER, Mar. 24, 2020, https://www.businessinsider.com/chinas-coronavirus-quarantines-other-countries-arent-ready-2020-3#the-country-postponed-non-urgent-medical-care-and-moved-many-doctors-visits-online-not-all-patients-were-given-the-critical-care-they-needed-during-the-outbreak-though-3; Lawrence O. Gostin & James. G. Hodge, *US emergency Legal Responses to Novel Coronavirus Balancing Public Health and Civil Liberties*, JAMA, Feb. 13, 2020, doi:10.1001/jama.2020.2025.

[80] Robert Arnott & Stephen Moore, *Shutdown is Killing the Economy -and is Also No Good For Our Health*, THE HILL, Mar. 25, 2020, https://thehill.com/opinion/finance/489566-shutdown-is-killing-the-economy-and-is-also-no-good-for-our-health.

[81] Brian Resnik, *12 Things Everyone Needs to Know About the Coronavirus Pandemic*, VOX, Apr. 2, 2020, https://www.vox.com/science-and-health/2020/4/2/21197617/coronavirus-pandemic-COVID-19-death-rate-transmission-risk-factors-lockdowns-social-distancing; Rochelle P. Walensky & Carlos del Rio, *From Mitigation to Containment of the COVID-19 Pandemic Putting the SARS-CoV-2 Genie Back in the Bottle*, JAMA, Apr. 17, 2020, doi:10.1001/jama.2020.6572.

Essential Services

Despite the fact that we must all consider ourselves at risk and despite the effectiveness of social distancing, "essential services" are excluded from government orders prohibiting in-person operations. However, the exemption imposes greater risk on those who provide essential services. It is unclear which employees providing such services have an ethical duty to continue working. What constitutes an essential service is debatable, even with New York's executive order laying out categorical descriptions.[82] Arguably, some essential services must remain open to prevent complete societal collapse, but few professionals are ethically bound to serve others at the expense of their own wellbeing.

Medical Research

Research to study both the nature of this coronavirus and how to treat it must proceed during this time.

Ethical Considerations

The pandemic heightens research ethics concerns regarding equal respect for those participating in research and fairness in terms of who is included in trials,[83] as well as not allowing either profit motive or fear to drive unjust or reckless trial development.[84] It also places enormous pressure on the procedures and safeguards that have been put in place over years to protect research subjects. We must commit to ensuring sufficient resources for studying the disease and treatment, and not move too fast with unproven treatments, whether to treat the general infected population or to treat infected frontline health care workers. We must also protect the vulnerable from incurring greater risk in dangerous trials, but also include traditionally marginalized populations in appropriate research without exploiting them. Moreover, we must not divert resources from proven methods of risk mitigation, and find the most careful ways to preserve non-pandemic essential health services.

Incapacitated subjects

Many patients who are on ventilators, such as advanced COVID-19 patients, are incapacitated and unable to agree to participate in a clinical trial. It is important that the rights and dignity of such patients, as well as all other individuals who lack capacity to consent, be respected should they be considered for enrollment as study subjects. We recommend that researchers follow the guidelines set forth in, "Report and Recommendations For Research with Human Subjects Who Lack Consent Capacity," of the New York State Task Force on Life and the Law.[85]

Sharing of Data and Specimen

We encourage the sharing of data and specimen among interested researchers to expand the breadth of potential research in COVID-19 related matters with adequate informed consent from research subjects. In all cases, the results of all studies should be made available to the public so that other researchers may better understand study results and limitations. These steps will also help support a research environment that encourages rapid funding of well-designed studies, advancing understanding of the disease, effective preventive measures and the development of novel treatments and a vaccine.

---

[82] Press Release, *Governor Cuomo Issues Guidance on Essential Services Under The 'New York State on PAUSE' Executive Order*, Mar. 20, 2020, https://www.governor.ny.gov/news/governor-cuomo-issues-guidance-essential-services-under-new-york-state-pause-executive-order.

[83] Beatriz Da Costa Thome, *Research in the Time of Coronavirus: Keep it Ethical*, STAT REP., Mar. 2, 2020, https://www.statnews.com/2020/03/02/research-public-health-emergencies-ethics/.

[84] Olivia Goldhill, *The Race to Develop Coronavirus Treatments Pushes the Ethics of Clinical Trials*, QUARTZ, Mar. 28, 2020, https://qz.com/1826431/the-ethics-of-clinical-trials-for-coronavirus-treatments/.

[85] *See* NEW YORK STATE TASK FORCE ON LIFE AND THE LAW, *Report And Recommendations For Research With Human Subjects Who Lack Consent Capacity*, Jan. 2014, https://www.health.ny.gov/regulations/task_force/docs/report_human_subjects_research.pdf.

Health Care Workers as Study Subjects

We should be particularly sensitive to studies involving our frontline health care workers. We should not place additional stress on them or their families by engaging them in research that may have marginal or no direct benefit to them or result in increased risk of infection. For example, if sufficient PPE is available at an institution, the health care workers should not be enrolled into a study testing an experimental new mask or face shield as such mask or shield will not have been shown to be as effective as the PPE already available.

However, we recommend consideration of qualitative inquiry and employment of diverse qualitative methods, including oral histories, to document the experience of health care workers both during the pandemic and the post-pandemic recovery period. Such research can be conducted during the pandemic with sensitivity to health care workers who consent to be research participants, and interviews arranged and conducted based upon their availability and comfort, including accommodating their needs as to place and time and limiting length of interview. Qualitative approaches may actually give health care workers an opportunity to share their experience of moral distress during the pandemic.

III. Provider Systems and Issues

Introduction

Hospitals, long-term care facilities, home health care, and physicians, nurses, and other health care workers, are in the front lines of our battle with COVID-19. We as members of the New York State Bar Association need to do all that we can to advocate for the removal of legal and regulatory obstacles that hinder health care providers' ability to fully respond to the challenges posed by the pandemic. This section covers many potential legal and regulatory barriers confronted by health care providers that can impede the thorough response to the pandemic. They include impediments relating to the following topics: supplies, bed capacity, resident work hours, facility licensure, anti-kickback and Stark laws, telehealth, and testing, as well as recommendations for overcoming such hurdles.

Purchasing Necessary Supplies for Hospitals and Other Health Care Providers during a State of Emergency

Health care facilities, as well as other health care providers, should be protected from price gouging and excessive pricing due to extraordinary market conditions for necessary supplies during the disruption of the marketplace due to a state of emergency.

The extent of such abusive business behavior nationwide is evident from the enormous and continually increasing number of complaints filed with the Federal Trade Commission.[86] Over 23,000 complaints were filed as of April 21, 2020.[87] One of the responsive federal actions includes the United States joint federal, state, and local COVID-19 Fraud Task Force to combat coronavirus-related fraud.[88]

---

[86] *See* FEDERAL TRADE COMMISSION, *Coronavirus (COVID-19) Consumer Complaint Data,* https://www.ftc.gov/coronavirus/complaint-data.

[87] *See* FEDERAL TRADE COMMISSION, *FTC COVID-19 Complaints, January 1, 2020-April 21, 2020*, https://www.ftc.gov/system/files/attachments/coronavirus-COVID-19-consumer-complaint-data/COVID-19-daily-public-complaints-042120.pdf.

[88] *See* UNITED STATES ATTORNEY'S OFFICE, District of Arizona, *United States Attorney Michael Bailey and Arizona Attorney General Mark Brnovich Launch COVID-19 Fraud Task Force*, U.S. DEPT. OF JUSTICE, Apr. 8, 2020, https://www.justice.gov/usao-az/pr/us-attorney-bailey-and-ag-brnovich-launch-COVID-19-fraud-task-force.

In New York, the Department of Consumer and Worker Protection ("DCWP") promulgated an emergency Rule under the City's Consumer Protection Law[89] that makes price gouging illegal for any personal or household good or any service that is needed to prevent or limit the spread of or treat COVID-19. The Rule makes it illegal to increase prices by 10 percent or more, follows DCWP's previous declaration that face masks, hand sanitizer, and disinfectant wipes are in short supply, and expands the Agency's ability to protect New Yorkers from price gouging.[90] This emergency rule "is in effect ([since]March 16, 2020) and, under the city's emergency rulemaking process, will be valid for 60 days. The Rule can be extended once for an additional 60 days." [91]

In the absence of any violation of the antitrust laws,[92] there does not appear to be any prior New York Law governing exorbitant pricing due to profiteering from an emergency situation that is directly applicable to supplies used by health care facilities and health care providers, such as ventilators, surgical gowns, and face masks. New York General Business Law Sec. 396-r[93] is intended to protect consumers against excessive pricing of necessary consumer goods (goods used, bought or rendered primarily for personal, family or household purposes) and services during an abnormal disruption of the market at the time of extraordinarily adverse circumstances, such as the stress of weather, climate events or disasters, failure or shortage of electric power or other source of energy, strike, civil disorder, war, military action, national or local emergency. It empowers the New York State Attorney General to bring an action on behalf of the state to enjoin the activity, obtain civil penalties, and get restitution for the aggrieved individuals. There must be a nexus between the emergency situation and the specific goods at issue.

During periods of abnormal disruption of the market caused by strikes, power failures, severe shortages or other extraordinary adverse circumstances, market forces competing for necessary products will cause crucial supplies to inordinately rocket upwards in price. Moreover, there also may be instances of suppliers engaging in price gouging taking advantage of the circumstances. Where those supplies are critical to hospitals and other health care providers for the care and treatment of patients, it becomes a matter of public safety for the state to ensure access to those supplies. Regardless of whether it is market forces or price gouging, the law must provide a means to protect the distribution of such products at reasonable prices. While national leadership is needed during these times to organize national purchasing and distribution of needed supplies, in the absence of such national initiative, the state should enact laws that encourage and facilitate the creation of buying cooperatively under these circumstances. In the short term, the Emergency Rule discussed above should be extended through the end of the pandemic. Subsequently, consumer protections extant under the General Business Law ought to be extended to cover hospitals and health care providers.

Ability to Exceed Certified Bed Capacity for Acute Care Hospitals

In a state of emergency that requires an immediate increase in acute care bed capacity to handle the surge of acutely ill persons within the state, we examine whether the regulatory restrictions limiting the number of inpatients at acute care hospitals to the respective total number of certified beds should be waived, thereby permitting each facility to go beyond the number of certified beds during the pendency of the emergency.

---

[89] N.Y.C. ADMIN. CODE § 20-701(b).
[90] NEW YORK CITY DEPT. OF CONSUMER AFFAIRS, *Notice of Adoption of Emergency Rule Prohibiting Price Gouging of Certain Personal and Household Goods and Services*, Mar. 15, 2020, https://www1.nyc.gov/assets/dca/downloads/pdf/about/Emergency-Rule-Adoption-Price-Gouging.pdf.
[91] *Id.*
[92] FEDERAL TRADE COMMISSION & US DEPARTMENT OF JUSTICE, *Joint Antitrust Statement Regarding COVID-19,* (regarding expedited antitrust procedure and guidance), Mar. 2020, https://www.ftc.gov/system/files/documents/public_statements/1569593/statement_on_coronavirus_ftc-doj-3-24-20.pdf.
[93] N.Y. GBL §396-r.

The total number of beds for which the facility has approval from the Commissioner of Health to operate is the number of beds that appears on the operating certificate.[94]

In the 1974, the National Health Planning and Resources Development Act[95] was enacted to, among other things, control the costs and regulate the expansion of health care facilities and redundancy in medical services nationwide. As part of that federal legislation, states received grants for their Health Services Agencies to coordinate health care planning and to establish a "certificate of need" ("CON") process acceptable to the U.S. Department of Health Education and Welfare, now known as, Health and Human Services. The CON process governs the establishment, construction, renovation and major medical equipment acquisitions of health care facilities, such as hospitals, nursing homes, home care agencies, and diagnostic and treatment centers. It seeks to determine where there is sufficient demand for new hospital or expanded hospital services within a given service area of the state. In addition to the need component of the process, there is financial feasibility, and character and competency aspects to the CON review process. This process then culminates in a review and approval by the Department of Health that can establish a new facility, or an expansion of an existing facility, with a set number of certified beds approved by the New York State Department of Health ("DOH"). The facilities are legally charged with operating at or below the number of certified beds approved DOH.

In the circumstances of a statewide emergency, where the need for increased hospital beds is urgently required, the limitation on the number of approved certified beds can present an obstacle to delivering necessary services to the people of New York State. Moreover, the time element for seeking an increase in bed capacity is contraindicated, and the CON process does not contemplate situations involving temporary need. Presently, Governor Cuomo's Executive Order 202.1[96] accomplishes that goal by providing waivers of section 401.3 and section 710.1 of Title 10 of the NYCRR,[97] to the extent necessary, to allow hospitals to make temporary changes to physical plant, bed capacities, and services provided, upon approval of the Commissioner of Health, in response to a surge in patient census. The Executive Order was reissued in 202.10.[98]

The waiver of the New York State Department of Health regulations governing certified bed restrictions resulting from the Governor's Executive Orders 202.1 and 202.10 should be continued during the pendency of the state of emergency in New York.

Limitation on Resident Hours Working in Acute Care Hospitals

New York State was a pioneer in the adoption of limits on resident working hours, and they remain among the strictest in the country. Among other limitations, residents are not allowed to be scheduled to work more than 80 hours in a week, or 24 hours straight, or more than 12 consecutive hours in the emergency department.[99]

In ordinary circumstances, limiting the number of hours that post-graduate trainees (residents) are permitted to work best serves the interests of patient care and the residents' training experiences. However, where there is an extraordinary need for health care professions to care for numerous patients in a pandemic, and the state is requesting help from retired physicians and physicians from other jurisdictions, it is not helpful

[94] 10 NYCRR §441.60.
[95] PUB. L. NO. 93-641, 42 U.S.C. §§300k et seq.
[96] N.Y. EXEC. ORDER No. 202.1, Mar. 12, 2020, https://www.governor.ny.gov/news/no-2021-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.
[97] 10 NYCRR §§401.3, 710.1.
[98] N.Y. EXEC. ORDER No. 202.10, Mar. 23, 2020, https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.
[99] 10 NYCRR §405.4(b)(6).

to limit the number of hours that graduate medical doctors can attend to patients at hospitals. It is anticipated that relaxation of these requirements will be implemented in a judicious manner that will not expose patients to unnecessary risk but will provide needed care to patient. By dint of Governor Cuomo's original Executive Order 202,[100] a broadly worded waiver of section 405 that includes regulation of resident work hours was issued, providing that, Section 405 of Title 10 of the NYCRR[101] was waived to the extent necessary to maintain the public health with respect to treatment or containment of individuals with or suspected to have COVID-19. That Executive Order has been reissued in Executive Order 202.10.[102]

It is recommended that the waiver of the resident hour requirements during the pendency of an emergency state in response to the pandemic be continued.

Temporary Changes to Existing Hospital Facility Licensed Services, and the Construction and Operation of Temporary Hospital Locations and Extensions

Finally, we look at whether Article 28 of the New York State Public Health Law and DOH regulations governing the approval for changing hospital licensed services, and the construction and operation of temporary hospital locations and extensions, should be waived during the pendency of a state of emergency to permit hospitals to modify their services, and create temporary extension and other locations to better address the health care needs of the people of New York State.

New York State envisions that hospitals plan to achieve efficiency and economy of operation while producing care of high quality. To that end, the State has a comprehensive review and approval process for considering proposed changes to licensed hospital services, as well as the construction and operation of temporary hospital and location sites.

Public Health Law section 2803,[103] and DOH regulations at 10 NYCRR sections 400, 401, 405, 409, 710, 711 and 712,[104] govern the process for approval. They provide a comprehensive and elaborate scheme to regulate the building, alteration, reconstruction, improvement, extension or modification of a hospital facility, including its equipment and services. Among other things, the following types of proposals, regardless of cost, generally are subject to CON application and review requirements:

(i) the addition, modification or decertification of a licensed service, or the addition or deletion of approval to operate part-time clinics;
(ii) a change in the method of delivery of a licensed service, regardless of cost;
(iii) the initial acquisition or addition of any equipment,;
(iv) a conversion of beds.

Moreover, there are certain limited proposals that are eligible for administrative review. They mainly must be within specific cost limitations, or involve supporting certain policy objectives of the New York State Department of Health.

[100] N.Y. EXEC. ORDER No. 202, Mar. 7, 2020, https://www.governor.ny.gov/news/no-202-declaring-disaster-emergency-state-new-york.
[101] 10 NYCRR §405.
[102] N.Y. EXEC. ORDER No. 202.10, Mar. 23, 2020, https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.
[103] N.Y. PHL §2803.
[104] 10 NYCRR §§400, 401, 405, 409, 710, 711 and 712.

In response to the PHE, Governor Cuomo has issued a number of Executive Orders to expand the availability of health care resources and staff. On March 7, in Executive Order 202,[105] the Governor waived all regulatory provisions that might limit the use of hospital beds. Thereafter, as the crises exceeded capacity, on March 23, the Governor issued Executive Order 202.10,[106] which suspended the application of the law and regulations cited above, "to the extent necessary to permit and require general hospitals to take all measures necessary to increase the number of beds available to patients."

New York State utilizes complex regulatory processes to govern changes in hospital service, as well as construction and operation of temporary hospital locations and extension sites. Some procedures are solely administrative and can be expedited, while others generally require a more in-depth review by bodies within the New York State Department of Health. These reviews are intended to validate the need, the costs, and the ability to competently operate the approved services and patient care sites. In a state of emergency, responding to the public health needs of the people of the state of New York is of paramount concern. The health facilities that regularly serve their communities are in the best position in the first instance to assess the needs of their respective service areas. Moreover, those facilities also are trusted, indeed required, to deliver the necessary service within their respective existing sites, as well as any additional locations that they deem essential to providing important health care interventions. Finally, the rapid response to the emergency conditions is critical for the health and safety of all New Yorkers. Therefore, the Governor appropriately removed all legal or regulatory barriers to the timely delivery of expanded, crucial health care services, and did not require the consent of DOH (though notice was anticipated) nor the recommendation of the Public Health and Health Planning Council or other applicable body.

We recommend continuation of the waiver provided under Executive Orders 202.1[107] and 202.10[108] of state requirements that would restrict the ability of hospitals to reconfigure and expand operations as necessary to deal with the PHE.

Issues in Long-Term Care, Residential and Home Health Care, and Correctional and Detention Facilities: Human Rights Crisis

Long-term care providers, and other institutional, residential, and home health care settings, are facing numerous challenges during this pandemic. These settings include, for example, group homes for persons with disabilities; religious communities maintaining nursing home residences on their campuses; correctional facilities housing older inmates, inmates with dementia, and inmates who experience accelerated aging and accompanying disease burden at younger ages; and detention facilities housing immigrants and refugees and their family members. This is not just a matter of a public health emergency, but it is also a human rights crisis.

Policies implemented largely by executive orders have not adequately addressed the problems that nursing homes, adult care facilities (ACFs), home care providers and group homes continue to face. In non-health care settings housing persons with healthcare needs, there has been a near total failure in developing and implementing policy or guidance to protect inmates and immigrants, who are often living in sub-human conditions with very limited access to health or mental health services under optimal circumstances, and remain at very high risk of COVID-19 as conditions have exacerbated.

---

[105] N.Y. EXEC. ORDER No. 202, Mar. 7, 2020, https://www.governor.ny.gov/news/no-202-declaring-disaster-emergency-state-new-york.
[106] N.Y. EXEC. ORDER No. 202.10, Mar. 23, 2020, https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.
[107] N.Y. EXEC. ORDER No. 202.1, Mar. 12, 2020, https://www.governor.ny.gov/news/no-2021-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.
[108] N.Y. EXEC. ORDER No. 202.10, Mar. 23, 2020, https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.

The plight of vulnerable older adults and other vulnerable persons in diverse facility and residential settings demands immediate attention as the COVID-19 pandemic continues to ravage these communities. This is not only a legal obligation, but a moral imperative. The 2012 Crisis Standards of Care make clear there is a duty of care and a duty of non-abandonment to all persons under disaster and emergency conditions.[109]

More specifically, with respect to nursing homes, the New York State Department of Health issued an advisory on March 25th, 2020, prohibiting nursing homes from denying admission or re-admission to a nursing home solely based on a confirmed or suspected diagnosis of COVID-19.[110] It also prohibited nursing homes from requiring a hospitalized resident who was determined medically stable to be tested for COVID-19 prior to admission or readmission.[111] The Department of Health issued a nearly identical advisory for ACFs.[112] The foregoing mandates may have substantially contributed to increased risk of spread of infection in nursing homes and adult care facilities. It is also worthy of note that during the same period these mandates were in effect and until more recently, nursing homes continued to have much more limited access to PPE emergency stockpiles than hospitals. Comments by the Governor suggested that the rationale for this decision was that many of these facilities were privately owned, and therefore it was the owner/operator's responsibility to purchase and provide PPE.

An Executive Order (EO) issued on May 10, 2020[113] imposes new requirements on nursing homes and ACFs and rescinds the nursing home directives as referenced in the preceding paragraph.

The May 10th EO No. 202.30, as applicable to Nursing homes and ACFs, mandates the following and imposes penalties for non-compliance:

- Testing of all personnel including employees, contract staff, medical staff, operators and administrators pursuant to a written plan filed with the Department of Health (DOH) no later than May 13, 2020;
- Reporting of all positive test results to DOH by 5 pm the day following receipt of test results;
- Filing of Certificate of Compliance with EO 202.30 and all other directives of DOH and Commissioner of Health no later than May 15, 2020; and
- Suspension or revocation of operating certificate if failure to comply with EO 202.30 or any other regulations or directives; financial penalties of $2,000 per violation per day, including repeat violation penalty of $10,000 per violation per day.

The following provisions of EO 202.30 are applicable to hospital discharges to nursing homes only, and not ACFs:

- Art. 28 hospitals cannot discharge a patient to a nursing home unless the nursing home first certified that is able to properly care for such patient; and
- Art. 28 hospitals cannot discharge a patient to a nursing home without first performing a diagnostic COVID-19 test and obtaining a negative result.

---

[109] INSTITUTE OF MEDICINE, CRISIS STANDARDS OF CARE: A SYSTEMS FRAMEWORK FOR CATASTROPHIC DISASTER RESPONSE: VOLUME 1, 1-3, (Dan Hanfling, et al., eds., The National Academies Press 2012), https://doi.org/10.17226/13351, https://commed.vcu.edu/IntroPH/2012/crisisManagement_IOM.pdf.

[110] NYS DOH Advisory: Hospital Discharges and Admissions to Nursing Homes, Mar. 25, 2020, previously available at: https://coronavirus.health.ny.gov/system/files/documents/2020/03/doh_Covid19_nhadmissionsreadmissions_032520.pdf, page no longer available.

[111] *Id.*

[112] NYS DOH Advisory: Hospital Discharges and Admissions to Adult Care Facilities, Apr. 7, 2020, available at: https://coronavirus.health.ny.gov/system/files/documents/2020/04/doh_covid19_acfreturnofpositiveresidents_040720.pdf.

[113] N.Y. EXEC. ORDER No. 202.30, May 10, 2020, https://www.governor.ny.gov/news/no-20230-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.

On May 11, 2020, DOH issued a Dear Administrator Letter[114] providing guidance on these new requirements. Nevertheless, there are many questions about how the above directives will be operationalized and more broadly, whether nursing homes and ACFs can reasonably comply with the mandates given the lack of access to COVID-19 testing and limited resources. Employee rights are also an area ripe for legal challenges.

In addition to the recent mandates referenced above, long-term care institutions have faced obstacles due to other state requirements, which have generally imposed new burdens on under-staffed facilities and administrators during the pandemic, taking precious time away from disease prevention efforts and reporting activities under applicable requirements. For example, the Governor signed S.8091/A.10153 to enact the COVID-19 Paid Sick Leave Law. This was followed by a liberal interpretation of the law by the Department of Labor in its related guidance.[115] Further, as mentioned above, supply chain challenges and PPE shortages have exacerbated staffing challenges.

Conditions in the nursing home sector have also been inaccurately represented in the media reports. For example, media sources have described nursing home failures, including not adequately communicating to the state and to families of residents the status of coronavirus in facilities.[116] CMS has issued new guidance tightening nursing home COVID-19 reporting requirements.[117] However, media reports of nursing home failures need to be balanced by available evidence that communications with families and next of kin have become increasingly challenging due to a number of factors, including limitations on visitation by families imposed by New York State, and the very nature of operations in long-term care facilities, especially during the pandemic, including the growing numbers of both COVID-19 positive cases and deaths, staffing and PPE equipment shortages, and historically low reimbursement rates that threaten the stability of the long-term care sector. Many frail residents need assistance with activities of daily living and require staff to be in close contact with the residents they serve. There is ample evidence that health care workers in nursing homes count among the bravest in the battle against COVID-19 and have a high potential risk of infection themselves without the appropriate PPE. Allocation of sufficient resources to nursing homes during the pandemic must be a New York State priority. In sum, under-resourced nursing homes amount to a form of implicit rationing, detrimentally affecting New York's most vulnerable older adult populations.

In light of the heightened vulnerability of nursing home residents and nursing home staff to COVID-19 infection, as well as increased risk to all vulnerable persons in institutional, residential or home health care settings, including correctional[118] and detention facilities, and the legal and ethical obligations to older

---

[114] N.Y.S. DEP'T OF HEALTH, ACF DAL #20-14, NH-20-07 Required COVID-19 Testing for all Nursing Home and Adult Care Facility Personnel, May 11, 2020, available at: https://www.health.ny.gov/professionals/hospital_administrator/letters/2020/docs/dal_20-14_covid_required_testing.pdf.

[115] New York Paid Family Leave COVID-19, Mar. 18, 2020, Frequently Asked Questions, https://paidfamilyleave.ny.gov/new-york-paid-family-leave-COVID-19-faqs; Guidance For Obtaining An Order For Mandatory Or Precautionary Quarantine, https://paidfamilyleave.ny.gov/system/files/documents/2020/03/obtaining-order-of-quarantine.pdf.

[116] Jan Ransom, *Coronavirus Entered My Father's Nursing Home and Nobody Warned Me. I Did Not Get the Chance to Save Him*, PROPUBLICA, Apr. 21, 2020, https://www.propublica.org/article/coronavirus-entered-my-fathers-nursing-home-and-nobody-warned-me-i-did-not-get-the-chance-to-save-him; John Leland, *At Least 14 N.Y. Nursing Homes Have Had More Than 25 Virus Deaths*, N.Y. TIMES, Apr. 17, 2020, https://www.nytimes.com/2020/04/17/nyregion/new-york-nursing-homes-coronavirus-deaths.html; Michael Goodwin, *Andrew Cuomo's Coronavirus Nursing Home Policy Proves Tragic: Goodwin*, The Post, Apr. 21, 2020, https://nypost.com/2020/04/21/cuomo-coronavirus-nursing-home-policy-proves-tragic-goodwin/?utm_campaign=iphone_nyp&utm_source=mail_app; Bernadette Hogan, Carl Campanile, Priscilla DeGregory & Tamar Lapin, *Woman Kept In Dark About Dad's Condition By Coronavirus-Stricken NYC Nursing Home*, THE POST, Apr. 21, 2020, https://nypost.com/2020/04/21/coronavirus-in-ny-nursing-home-kept-woman-in-dark-about-dads-condition/.

[117] CMS, Center for Clinical Standards and Quality/Quality, Safety & Oversight Group, Ref: QSO-20-26-NH, Apr. 19, 2020, https://www.cms.gov/files/document/qso-20-26-nh.pdf.

[118] *See* Josiah Bates, 'We Feel Like All of Us Are Gonna Get Corona.' Anticipating COVID-19 Outbreaks, Rikers Island Offers Warning For U.S. Jails, Prisons, TIME (Magazine), Mar. 24, 2020, https://time.com/5808020/rikers-island-coronavirus/.

adults and such other vulnerable persons, health care workers and workers in service jobs, we recommend that the following actions be duly considered and implemented by the Governor, Department of Health and other government agencies, as applicable:

Older Adults, Nursing Home Providers and Nursing Home Residents:

Governor, Department of Health (DOH), DOH Bureau of Long Term Care and State Office for Aging to ensure:

1. Equitable allocation of scarce resources from the Public Health and Social Services Emergency Fund—established by the CARES Act—to older adults and their health care providers, prioritizing under-resourced long-term care providers;[119]
2. Adequate provision of personal protective equipment (PPE);
3. Adequate levels of staffing;
4. Adequate funding of employee testing, as required under Executive Order 202.30;
5. Consistent and timely tracking and reporting of case and death data;
6. Adoption of non-discriminatory crisis standards and ethics guidelines;
7. Recognition and honoring of Older New Yorkers' right to health and human rights, as protected under international conventions; and
8. Adequate resources for the Office of the State Long Term Care Ombudsman, which provides advocacy for nursing home residents and families and helps residents understand and exercise their rights to quality care and quality of life.

Persons with Disabilities in Residential Facilities or Group Homes:

Governor, Department of Health and OPWDD to ensure:

1. Access of persons with disabilities to adequate COVID-19 testing and appropriate medical care, mental health and other supportive services, including appropriate day services to substitute for community-based day programs that need to be discontinued during a pandemic;
2. Adequate and appropriate staffing, of residential facilities and group homes, for both day and evening shifts, and provision of appropriate funding for such staff and for appropriate COVID-19 staff training;
3. Access of residential facility and group home staff to adequate testing and appropriate medical care and mental health and other supportive services;
4. Oversight of residential facilities and group homes and programs to assure non-discriminatory management of persons with disabilities during the COVID-19 crisis conditions; and
5. Recognition and honoring of persons with disabilities' right to health and human rights, as protected under international conventions.

Inmates and Correctional Facilities:

Governor, NYS Department of Corrections and NYC Department of Corrections, to ensure:

[119] U.S. SENATE COMMITTEE ON FINANCE, Senator Charles E. Grassley, Chairman, Letter to HHS Secretary Alex Azar and CMS Administrator Verma, Apr. 17, 2020, (asking about the federal response to COVID-19 in nursing homes, group homes, and assisted living facilities, and expressing concerns about testing capacity, data tracking inconsistencies, lack of personal protective equipment (PPE) for nursing home staff, and federal spending transparency) https://www.finance.senate.gov/imo/media/doc/HHSCOVIDLetter17Apr2020Final.pdf.

1. Adequate access of inmates to COVID-19 testing, medical care and mental health and supportive services;
2. COVID-19 testing of correctional staff and adequate provision of gloves, masks and other protective equipment;
3. Release to the community of older inmates and inmates with advanced illness who do not pose a danger to the community; and
4. Adequate funding of prison-to-community transitions including access to housing, meals, and supportive services, and non-discriminatory access to employment opportunities.
5. Recognition and honoring of inmates' right to health and human rights, as protected under international conventions.

Immigrants in Detention Facilities:

In its exercise of its police powers in the COVID-19 public health emergency, New York State, in cooperation with federal agencies, must take step, similar to those outlined above, to ensure:

1. Reduction of risk of the spread of COVID-19 among immigrants being held in detention centers.[120]

Anti-Kickback and Stark Law Compliance During the COVID-19 Emergency

During the PHE, routine anti-kickback and compliance activities at hospitals and in other provider settings are largely suspended, contractual arrangements are being re-structured or ignored, and routine requirements of arms-length transactions, such as commercial reasonableness and fair market value ("FMV"), are often simply not considered, or if considered, not subject to standard verification. Under the circumstances, compliance with the federal and state Anti-Kickback statutes ("AKS") and Physician Self-Referral ("Stark") laws is particularly challenging. While the Centers for Medicare and Medicaid Services ("CMS") has provided a broad (but not unlimited) waiver of the Stark law as necessary to respond to the epidemic, and the Office of the Inspector General of the United States Department of Health and Human Services ("OIG") has issued a "comfort letter" regarding AKS enforcement, uncertainty remains.

Federal and state AKS and Stark laws, and their associated regulations, set standards governing certain behaviors of and arrangements between medical professionals, institutions, and associated contractors, affiliates, and other interested parties.

The federal AKS is a criminal statute that prohibits the knowing or willing offering, paying, soliciting, or receiving any remuneration, rebate, kickback, bribe, or thing of value, directly or indirectly, in cash or in kind to induce or in exchange for the recommending of or actual purchasing, leasing, ordering of any good, facility, or item under federal health care programs.[121] The federal AKS covers those who both pay for and receive kickbacks or remuneration (i.e. anything of value), "including any kickback, bribe, or rebate) directly or indirectly, overtly or covertly, in cash or in kind."[122] However, a payment of remuneration or similar scheme may violate AKS if "one purpose" is to wrongfully induce referrals, even if there are alternative valid motivations.[123] While the statute is interpreted broadly,[124] there are various narrow regulatory exceptions, called "safe harbors," for practices recognized as beneficial.[125]

---

[120] *See* Cole J.P Cole, Federal and State Quarantine Isolation Authority, CONGRESSIONAL RESEARCH SERVICE, Oct. 19, 2014, https://www.ncsl.org/documents/statefed/health/FedandStateQIAuth.pdf.
[121] 42 U.S.C. § 1320a-7b(b).
[122] 42 C.F.R. § 1001.951.
[123] *United States v. Greber*, 760 F.2d 68 (3d Cir. 1985), cert. denied, 474 U.S. 988 (1985).
[124] *United States v. Kats*, 871 F.2d 105 (9th Cir. 1989); *United States v. Greber*, 760 F.2d 68 (3d Cir.), cert. denied, 474 U.S. 988 (1985).
[125] *See* 42 U.S.C. 6 1320a-7b(b)(3); 42 C.F.R. § 1001.952.

The federal Stark law is a strict liability statute that prohibits physicians from referring patients to receive certain "designated health services" under federal health care programs from entities with which the physician or an immediate family member has a financial relationship.[126] The Stark law prohibits the submission, or causing the submission of claims that violate the prohibitions.[127] The Stark law also has certain regulatory exceptions for practices and arrangements that are sufficiently and strictly tailored as to avoid impropriety of referrals.[128]

However, if violations are found, they can form the basis of direct liability under the applicable statute, which can include substantial legal penalties, such as civil monetary penalties per violation or per claim, plus up to three times the remuneration involved, exclusion from participation in federal health care programs, including Medicare and Medicaid, and in the case of AKS violations, potential criminal penalties.[129]

In addition, these providers also face federal False Claims Act ("FCA") liability,[130] which imposes civil (and potentially criminal[131]) liability on persons who knowingly submit false or fraudulent claims for reimbursement to government health care programs.[132] The FCA is a particularly useful tool for fraud and abuse enforcement because it enables civil actions to be brought the Attorney General, or as a *qui tam* action initiated by whistleblowing "relators" who have independent knowledge of wrongdoing and who can recover between 15 and 30 percent of monetary proceeds, plus attorney fees, from successful judgments.[133] Note that with available treble damages, plus more than $22,000 per false claim,[134] these judgments can quickly become catastrophic.

Notably, in October of 2019, the Department of Health & Human Services ("HHS") proposed changes to the AKS and Stark law regulations aimed at reducing regulatory burdens on the expansion of value-based care, which have yet to be finalized.[135]

New York State ("NYS") has state law versions of both AKS and Stark law. The NYS AKS largely tracks the federal statute, is tied to Medicaid, but includes separate provisions detailing that violations are also considered professional misconduct, which could lead to administrative professional licensure penalties in addition to civil and criminal penalties.[136] The NYS Stark law is broader in scope of persons covered than is the federal Stark law as it applies to referrals from a broader range of "practitioners," not only from "physicians," but it is more limited in the services covered.[137] The NYS Stark law also covers claims submitted to all payors, not only to government payors, and does not have as many exceptions as does its federal counterpart, but the exceptions broadly apply to hospital/practitioner relationships. Although

---

[126] 42 U.S.C. § 1395nn(a); 42 C.F.R 411.351.
[127] *Id.*
[128] 42 U.S.C. § 1395nn(b); 42 C.F.R. § § 411.355-57.
[129] *See generally*, OFFICE OF ATT'Y GENERAL, DEP'T OF HEATH AND HUMAN SERVICES, A Roadmap for New Physicians, Fraud & Abuse Laws, https://www.oig.hhs.gov/compliance/physician-education/01laws.asp.
[130] 42 U.S.C. § 1320a-7b(g); 42 U.S.C. § 1395nn(g).
[131] 18 U.S.C. § 287.
[132] 31 U.S.C. §3729-33.
[133] 18 U.S.C. § 3730(b), (c) & (d).
[134] 31 U.S.C. § 3729; 28 C.F.R. § 85.3(a)(9). For updated figures, see https://www.ecfr.gov/cgi-bin/text-idx?rgn=div5&node=28:2.0.1.1.37.
[135] For Department of Health and Human Services Office of Inspector General proposed regulations concerning AKS, *see* 84 FED. REG. 55694-765 (Oct. 17, 2019). For Centers for Medicare and Medicaid Services proposed regulations concerning Stark law, *see* 84 FED. REG. 55766-847 (Oct. 17, 2019).
[136] N.Y. ED. LAW §§ 6530(18) & (19); N.Y. Social Services Law § 366-d.
[137] N.Y. PHL §§ 238-a - 238-e.

penalties under the NYS Stark law are limited and there is no private right of action, New York has a parallel False Claims Act, with substantial treble damages, per claim penalties and attorney fee provisions, which can be used for violations of the NYS Stark law and AKS.[138]

There is no general pandemic exception to the application of the federal AKS and Stark laws. However, on March 30, 2020, each of the OIG and CMS issued guidance designed to assist providers in responding to the epidemic.

CMS limited the application of the federal Stark law until the end of the PHE caused by COVID-19 through a waiver and attendant guidance.[139] CMS announced that it will waive penalties for violations of the Stark law in regard to compensation relationships between physicians and entities, such as hospitals, to which they refer if "solely related to" the COVID-19 pandemic. In particular, the waiver applies, among other things, to:

- violations of FMV requirements in the services, space and equipment lease exceptions,
- medical staff incidental benefits in excess of the regulatory cap,
- non-monetary or in-kind compensation to physicians that exceeds the regulatory cap,
- interest-free or low-interest loans,
- use of space by group practices that does not meet the "same building" requirements, and
- violations of the signature and documentation requirements.

The following are examples of actions that would be deemed "related to the COVID-19 pandemic":

- diagnosis and treatment of COVID-19 patients,
- securing the services of physicians to provide services even if unrelated to COVID-19,
- ensuring the ability and expanding the capacity of providers to meet patient needs,
- shifting patient care locations to alternative sites, and
- addressing medical practice or business interruptions.

CMS cites a number of specific examples of permissible or expected activity, including:

- paying a premium or below market compensation,
- providing free office space,
- offering non-monetary services and incidental benefit increases (e.g., food, childcare, housing, clothing) beyond regulatory limits,
- providing hospital staff to assist private physicians' offices in staff training related to COVID-19, patient intake and treatment, and care coordination tied to the crisis,
- paying physicians' 15% electronic health records subsidy obligation,
- a group practice performing Stark-covered services at an expansion site that would otherwise be impermissible,
- ambulatory surgical center ("ASC") owners continuing to refer to the ASC even though the ASC is licensed as a hospital during the PHE,
- providing services to patients in rural areas, and

[138] N.Y. STATE FINANCE LAW §§ 187-194.
[139] CMS, *Blanket Waivers of Section 1877(g) of the Social Security Act*, https://www.cms.gov/files/document/COVID-19-blanket-waivers-section-1877g.pdf.

- failing to obtain a signature or writing as required for a compensation relationship that is otherwise compliant.

The waiver only applies, "absent the government's determination of fraud and abuse." In this regard, the premise of the waiver is that the party is acting in good faith and is unable to meet the otherwise generally applicable exceptions, which may limit the benefit if interpreted literally. How does "unable" apply when technical compliance is feasible but at unnecessary delay and expense? Another concern is the use of the word "solely" before "related," because very few things are "solely" the product of another. Nevertheless, the examples of the types of arrangements that CMS would appear to bless provide some comfort as to how "unable" and "solely related" will be defined.

The waiver is effective March 1, 2020 and will last for the duration of the PHE.

The OIG simultaneously issued a "message from leadership on minimizing burdens on providers."[140] It notes that the "OIG places a high priority on providing the health care community with the flexibility to provide needed care during the emergency."[141] "[R]especting the great challenges currently facing the health care industry," the OIG, "to the extent possible" will try to "minimize burdens on providers and be flexible where [it] can.[142] Providers are encouraged to reach out to the OIG if they need extensions of deadlines. Finally, and perhaps most significantly, "For any conduct during the emergency that may be subject to OIG administrative enforcement, OIG will carefully consider the context and intent of the parties when assessing whether to proceed with any enforcement action."[143] The latter comment may well be a feature of defenses of direct and certainly FCA *qui tam* claims concerning conduct during the PHE.

Subsequently, on April 3, the OIG responded explicitly to the CMS Stark waiver of March 30.[144] It agreed to not to seek administrative sanctions against most of the behavior specifically permitted by CMS during the PHE. There are, however, differences. The OIG was not willing to accept, on a blanket basis, the CMS exceptions for referring to (i) an owned hospital that has expanded (or former ASC now operating as a hospital), (ii) an owned home care company, or (iii) a group practice for covered services at otherwise impermissible expansion sites or at a patient's residence.[145] In addition, the blanket CMS waivers for patients in rural areas, and for arrangements that are compliant but for documentation requirements, are not accepted by the OIG.[146]

The OIG has also established a process for obtaining prompt informal and non-binding advice during the PHE, including in regard to the Civil Monetary Penalty Law provisions on beneficiary inducements.[147]

As of now, there are no waivers of the NYS Stark law or AKS for the PHE.

---

[140] DEP'T OF HEALTH & HUMAN SVCS, OFFICE OF INSPECTOR GENERAL, *Message From Leadership On Minimizing Burdens On Providers*, Mar. 30, 2020, https://oig.hhs.gov/coronavirus/letter-grimm-03302020.asp.
[141] *Id.*
[142] *Id.*
[143] *Id.*
[144] OIG Policy Statement Regarding Application of Certain Administrative Enforcement Authorities Due to Declaration of Coronavirus Disease 2019 (COVID-19) Outbreak in the United States as a National Emergency, DEP'T OF HEALTH & HUMAN SVCS, OFFICE OF INSPECTOR GENERAL, Apr. 3, 2020, https://oig.hhs.gov/coronavirus/OIG-Policy-Statement-4.3.20.pdf; DEP'T OF HEALTH & HUMAN SVCS, OFFICE OF INSPECTOR GENERAL, *FAQs – Application of OIG's Administrative Enforcement Authorities to Arrangements Directly Connected to the Coronavirus Disease 2019 (COVID-19) Public Health Emergency*, Apr. 24, 2020, https://oig.hhs.gov/coronavirus/authorities-faq.asp.
[145] *Id.*
[146] *Id.*
[147] *Id.*

Provider/Referring practitioner relationships always need to be structured with care to assure compliance with the technical requirements of the Stark law and AKS exceptions and safe harbors, and to assure that the agreements are commercially reasonable, and the compensation thereunder is FMV. In the usual course, agreements are often subject to independent valuation consultant review to assure compliance. However, in the current crisis environment, these relationships are being created, modified and terminated "on the fly," and without the normal regulatory review. Under the circumstances, providers should not have to be concerned about technical compliance, "absent any determination of fraud or abuse" (the words of the federal Stark law waiver). This would have the effect of focusing on the reality of the relationship and not the technicalities of the exceptions and safe harbors that cannot be met.

Given the statements from CMS and the OIG that are helpful in this regard, an order for the NYS Stark law and AKS from either the Governor of New York or the New York State Department of Health that is substantially similar to the CMS Stark law waiver and OIG letters would be prudent. Some might say that no waiver is needed since well-intentioned providers would not be charged with a violation in the absence of fraud and abuse. However, often the AKS safe harbors are treated as requirements by providers, and the failure to provide explicit grace in this context will both delay necessary implementation of restructurings between providers and practitioners and place those providers and practitioners at risk for potentially catastrophic damages. Moreover, the Stark Law does not require intent; it is a strict liability statute, so its suspension is very important.

The waivers provided by CMS and the letters provided by the OIG are helpful in providing some security to providers that enforcement discretion will be exercised in regard to reasonable responses to the PHE (the inconsistencies between the CMS and OIG guidance are unfortunate, but likely not curable and providers will need to navigate the inconsistencies). The waivers and guidance should be adopted in substantially similar form by NYS for the State versions of the Stark law and AKS, each as tailored for the particular statute at issue.

Expanded Use of Telehealth During the COVID-19 Emergency

Telehealth is a valuable tool to deliver healthcare, but longstanding statutory and regulatory barriers, including in the area reimbursement, have stunted the growth of telehealth and delayed its implementation.

The federal telehealth statute[148] imposes five requirements for Medicare fee-for-service coverage. Of these, one of the most significant hurdles to the expansion of telehealth has been the Medicare "originating site" requirement. Prior to COVID-19, Medicare fee-for-service reimbursement was available only when the patient receiving the telehealth service was in a designated rural area, and in a physician's office or in a specified healthcare facility. The definition of a rural location is narrow, limited in general to an area either outside a Metropolitan Statistical Area or in a Health Professional Shortage Area within a rural census tract.[149] Additionally, only eligible practitioners[150] could provide Medicare telehealth services. In New York,[151] state law allows a wide range of professionals[152] to deliver services through telehealth in New

[148] 42 U.S.C. § 1395m(m).
[149] HEALTH RESOURCES AND SERVICES ADMINISTRATION, *Medicare Telehealth Payment Eligibility Analyzer*, https://data.hrsa.gov/tools/medicare/telehealth, (providing guidance on whether a particular site is eligible for Medicare telehealth payment).
[150] Under 42 U.S.C. § 1395m(m)(3)(A) and 42 C.F.R. § 410.78(b), Medicare-eligible telehealth practitioners are: physicians, physician assistants, nurse practitioners, clinical nurse specialists, nurse-midwives, clinical psychologists, clinical social workers, registered dieticians and nutritional professionals, and certified registered nurse anesthetists.
[151] N.Y. PHL § 2999-dd(1); N.Y. SOC. SERVS. LAW § 367-u(2).
[152] Under N.Y. PHL § 2999-cc(2), New York Medicaid-eligible telehealth practitioners are: physicians, physician assistants, dentists, nurse practitioners, registered professional nurses, podiatrists, optometrists, psychologists, social workers, speech language pathologists and audiologists, midwives, physical therapists, occupational therapists, certified diabetes educators,

York, to patients located in a wide range of originating sites, including in the patient's own home.[153] In February 2019, however, in a Special Medicaid Telehealth,[154] New York instituted limitations, including the rule that for dual individuals (those eligible for both Medicare and Medicaid), "[i]f a service is within Medicare's scope of benefits (e.g., physician), but Medicare does not cover the service when provided via telehealth, Medicaid will defer to Medicare's decision and will not cover the telehealth encounter at this time." The effect is to deny Medicaid for telehealth services outside of rural originating sites, and from non-Medicare-eligible practitioners for dually eligible beneficiaries,

The pre-COVID-19 federal and state reimbursement rules limited the expansion of telehealth. As a result, when the coronavirus spread in New York, the healthcare system was woefully underprepared to deploy this important tool quickly and effectively to minimize the spread of infection. The delay, in turn, allowed the disease to gain a foothold in the community and impeded efforts to limit exposure to and slow the viral spread.

The coronavirus pandemic ushered in a new age for telehealth reimbursement. In a major public policy shift, on March 6, 2020, Congress enacted the "Telehealth Services during Certain Emergency Periods Act of 2020," [155] which lifted the "originating site" requirement for Medicare telehealth payment during certain public health emergencies. This statute authorized the waiver of Medicare requirements in a public health emergency to allow qualified providers – those with a pre-existing relationship with the patient – to deliver telehealth to beneficiaries: (i) outside of rural areas, (ii) in their homes, and (iii) by means of a telephone with audio and video capabilities. On March 27, 2020, Congress enacted the "Coronavirus Aid, Relief, and Economic Security Act" (CARES Act).[156] In addition to injecting trillions into the economy, the CARES Act authorized the waiver of the pre-existing relationship requirement and other telehealth expansions. On March 23, 2020, the U.S. Department of Health and Human Services (HHS) Office of Civil Rights (OCR), which enforces the Health Insurance Portability and Accountability Act (HIPAA), announced the exercise of enforcement discretion for HIPAA restrictions that might otherwise have limited the use of telehealth services during the PHE.[157] These changes allowed for Medicare reimbursement for the delivery of health care services using smartphones.

Likewise, in New York, the New York State Department of Health ("DOH") took action to promote the use of telehealth and telephonic evaluation. An Executive Order issued March 12, 2020,[158] suspended the New York telehealth statute and regulations, to the extent necessary to allow additional telehealth provider categories and modalities, to permit other types of practitioners to deliver services within their scopes of practice and to authorize the use of certain technologies for the delivery of health care services to established patients. Beginning on March 10, 2020, DOH issued a series of guidance documents regarding the use of

---

certified asthma educators, certified genetic counselors, hospitals, residential healthcare facilities serving special needs populations, home care services agencies, hospices, credentialed alcoholism and substance abuse counselors, early intervention program providers, clinics licensed or certified by the Office of Mental Health or funded or operated by the Office for People with Developmental Disabilities, and others subject to agency determination.

[153] *Id.*, § 2999-cc (3).

[154] New York Medicaid Update, Special Edition, Expansion of Telehealth Vol. 35, No. 2, N.Y.S. DEP'T OF HEALTH, Feb. 2019, https://www.health.ny.gov/health_care/medicaid/program/update/2019/feb19_mu_speced.pdf.

[155] Coronavirus Preparedness and Response Supplemental Appropriations Act, Pub. L. § 116-123, Mar. 6, 2020, https://www.congress.gov/116/plaws/publ123/PLAW-116publ123.pdf.

[156] Coronavirus Aid, Relief, and Economic Security Act, PUB. L. § 116-136, Mar. 27, 2020, https://www.congress.gov/116/bills/hr748/BILLS-116hr748enr.pdf.

[157] Notification of Enforcement Discretion for Telehealth Remote Communications During the COVID-19 Nationwide Public Health Emergency, HHS OFFICE OF CIVIL RIGHTS, last reviewed Mar. 30, 2020, https://www.hhs.gov/hipaa/for-professionals/special-topics/emergency-preparedness/notification-enforcement-discretion-telehealth/index.html.

[158] N.Y. EXEC. ORDER No. 202.1, Mar. 12, 2020, https://www.governor.ny.gov/news/no-2021-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency.

telehealth, including telephonic services, for dates of service on or after March 1, 2020 and through the duration of the New York State COVID-19 emergency.[159] These guidance documents alleviate some of the barriers to telehealth by allowing clinicians and health care organizations to bill for telephonic services if they cannot provide the audiovisual technology traditionally referred to as "telemedicine."

In the midst of the coronavirus, the temporary rollback of regulatory restrictions enabled providers to marshal telehealth to expand the delivery of services while reducing the spread of infection. This reduced the strain on the healthcare system and prevent further spread of disease. But why only temporary? Though telehealth, providers can deliver medical care much more quickly and serve more patients, without the need for them to travel long distances to the provider's office to receive care. Telehealth proved itself under fire, and its benefits extend well beyond the emergency context. Moving forward, the coronavirus experience argues for the need for updated reimbursement policies to encourage the use of telehealth to provide proper, effective and efficient care for patients.

Testing During Pandemic

We examine the issue as to whether private research laboratories should be authorized to do serology testing for epidemiological studies during an emergency pandemic.

NYS PHL § 580 states, "[n]othing in this title shall be construed as affecting facilities which perform laboratory tests solely for research purposes, nor as affecting laboratory testing by a public health officer as part of an epidemiological investigation in which no patient identified result is reported for diagnostic purposes to a health care provider or the subject of the test."[160]

Essentially, section 580 of the Public Health Law exempts and authorizes research laboratories to pursue tests so long as clinical diagnoses of patients for treatment are not being conducted. At present, 10 NYCRR Part 58-1[161] prevents research laboratories from reporting their results to individual patients.[162]

Serological tests measure the number of antibodies or proteins present in the blood when the body is responding to a specific infection, like COVID-19. In other words, the test detects the body's immune response to the infection caused by the virus rather than detecting the virus itself. This may potentially be used to help determine, together with other clinical data, that such individuals are no longer susceptible to infection and can return to work. In addition, these test results can aid in determining who may donate a part of their blood called convalescent plasma, which may serve as a possible treatment for those who are seriously ill from COVID-19.

Research laboratories present an untapped resource to scale mass testing to respond to COVID-19. The only portion of the Public Health Law that prevents a general research laboratory from engaging in epidemiological serology testing is the requirement that the testing be conducted by a public health officer.

---

[159] 2020 DOH Medicaid Updates, Volume 36, N.Y.S. DEP'T OF HEALTH, rev'd Apr. 2020, https://www.health.ny.gov/health_care/medicaid/program/update/2020/index.htm.

[160] N.Y. PHL § 580.

[161] 10 NYCRR § 58-1.

[162] The Health Law Section of the New York State Bar Association has proposed a rulemaking for the DOH that would permit research laboratories to report results to the health care provider designated by a study subject under specific limited conditions. Such health care provider may then determine if confirmatory tests should be pursued utilizing CLEP approved diagnostic testing in a CLEP approved laboratory. The Committee recommended the following be added as 10 NYCRR § 58-1.8b: "Results of tests conducted in the context of IRB approved research protocols by non-permitted research laboratories may be reported to the research subject's designated health care provider solely for the purpose of referral of the subject for confirmatory testing by a permitted laboratory using approved test methodology." *See* Letter from Ronald Kennedy, Director of Government Relations, NYSBA, to Stephanie Schulman, Ph.D., Director CLEP, Regarding Proposed Rule by NYSBA Health Law Section, April 3, 2018, Appendix D.

To the extent private research laboratories have capacity and are capable of assisting with epidemiological testing, the Governor should exercise his authority under NYS Executive Law § 29-a[163] to suspend that portion of NYS PHL § 580[164] that requires the testing to be provided by a public health officer to enable private research labs to assist with scaling serology testing.
Nevertheless, as of this writing, certain significant ambiguities regarding hospital clinic payment rates remain.

IV. Business/Contracts/Risk Management

Introduction

There is no doubt that the COVID-19 pandemic has had tremendous economic impact upon businesses. The Wall Street Journal reports that, "U.S. economy in the first quarter shrank at its fastest pace since the last recession as the coronavirus pandemic shut down much of the country."[165] As non-essential businesses are put on "pause" and many essential businesses' operations are limited, both individuals and businesses will be hard pressed to meet contractual obligations and must look to risk mitigation strategies to manage the financial impact. Although many businesses have insurance policies that are meant to kick in when disaster strikes, such business interruption coverage typically requires physical damage to the workplace making it impossible for workers to do their job. Quarantines and travel bans imposed by federal and state authorities in an effort to control contagion can make it just as impossible for workers to do their jobs as destruction from a fire, flood or earthquake, but do not cause the physical damage to workplaces that is necessary to trigger successful business interruption claims.[166] From an insurance perspective, such policies are not designed to cover the widespread business interruption caused by the shuttering of businesses across the country. Losses due to bacteria and virus such as the COVID-19 pandemic impacts the entire risk pool, leaving insurers at significant risk because such policies are designed to cover losses resulting from individual insured's chance events and not catastrophic events that impact the entire risk pool.[167]

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act") was signed into law as a $2.2 trillion stimulus package designed to mitigate the cataclysmic economic impact resulting from the COVID-19 pandemic. The CARES Act provided substantial economic relief, but also includes several temporary modifications to chapter 7 and chapter 13 of the U.S. Bankruptcy Code that modify the definition of "current monthly income" to exclude payments made under federal law relating to a declared national emergency and permit chapter 13 debtors with prior-confirmed plans to seek modifications due to Covid-19 related hardships.[168] These provisions provide some relief for consumers, but do not address the risk of city and state bankruptcies as tax revenues fall due to plummeting gas prices, lack of tourism, and shuttering of the hospitality industry, and emergency spending on unemployment claims soars.[169] On April 22, 2020, U.S. Senate Majority Leader Mitch McConnell "opened the door to allowing U.S. states to file

[163] N.Y. EXEC. L. § 29-a.
[164] N.Y. PHL § 580.
[165] Harriet Torry, *Virus Shrinks Economy by 4.8%,* WALL STREET JOURNAL, Apr. 30, 2020 (Last accessed 04/30/2020), https://www.wsj.com/articles/first-quarter-gdp-us-growth-coronavirus-11588123665.
[166] Mary Williams Walsh, *Coronavirus Will Cost Businesses Billions. Insurance May Not Help*, N.Y. TIMES, Mar. 5, 2020, https://www.nytimes.com/2020/03/05/business/coronavirus-business-insurance.html (Last accessed Apr. 10, 2020).
[167] Jim Sams, *Some Insurance Regulators Skeptical About Business Interruption Claims*, CLAIMS JOURNAL, Apr. 27, 2020, (Last accessed May 3, 2020).
[168] K&L Gates, LLP. *COVID-19: How the CARES Act Will Impact Chapter 7 and Chapter 13 Consumer Bankruptcies.* JDSUPRA.COM, Mar. 31, 2020, https://www.jdsupra.com/legalnews/covid-19-how-the-cares-act-will-impact-48826/ (Last accessed Apr. 30, 2020).
[169] Richard McGahey, *COVID-19 Could Bankrupt Your State,* FORBES, Apr. 6, 2020, www.forbes.com/sites/richardmcgahey/2020/04/06/covid-19-could-bankrupt-your-state/#72fd)d565489 (Last accessed 04/30/2020).

for bankruptcy to deal with economic losses stemming from the coronavirus outbreak that are punching big holes in their budgets."[170] However, whether such relief is available to U.S. states remains a looming legal issue. Federal, state and local public health authorities must consider innovation solutions to (i) allow essential businesses to collaborate under CSC and channel resources to address the PHE; (ii) permit essential licensed health care workers in good standing to cross state lines and health care systems to help manage patient surges wherever they occur; and (iii) protect good faith efforts to maintain workplace and public safety and control the spread of contagion where is scarce. Likewise, business leaders should identify the weaknesses in their respective business operations and consider immediate, mid-term and long-term risk management strategies to assure recovery, resiliency, and financial stability.[171]

Potential liability for breach of contract during coronavirus pandemic

We examine whether nonperformance of contractual obligations during the coronavirus pandemic may result in liability for breach of contract.

Ordinarily, a failure to perform under a contract results in potential liability for the party who is in breach of his or her obligations. A supplier of goods, for example, may be held liable if he or she fails to deliver the goods as promised. Or a purchaser of goods may be held liable if he or she fails to pay for goods purchased from a supplier. Similarly, a lease contract may result in liability if either the tenant or the landlord breaches his or her obligations. Or a service provider may be held liable for failure to perform services, or the recipient may be held liable for failure to pay for the services. The law is clear: If you breach a contractual obligation, you may be held liable for the breach.

But what happens if a party does not – or cannot – perform his or her obligations under a contract in the middle of a pandemic? This question has taken on increased urgency in recent days, as companies across a wide range of industries have begun to alter their business practices and contractual arrangements in response to the outbreak of COVID-19. Will the COVID-19 outbreak excuse the nonperformance of a contract?

Under New York law, there are a limited set of circumstances under which the COVID-19 outbreak might excuse contractual non-performance. Those circumstances include: (1) when the relevant contract contains a provision that excuses performance—such as a *force majeure* clause; (2) when certain common law doctrines—such as the doctrines of frustration of purpose or impossibility – excuse non-performance.

Finally, New York's Uniform Code Section 2-615(a) excuses delay or non-delivery under a contract for sale under certain circumstances, including where performance has been made impracticable by an event that goes to the heart of the contract or where the delay or non-delivery was caused by good faith compliance with governmental regulation.

Force Majeure

Some contracts contain provisions that excuse nonperformance due to circumstances beyond the control of the parties. These provisions are known as *force majeure* clauses.[172] A *force majeure* clause generally allows a party relief if a specified event materially impacts, or renders impossible, the performance of the contract. Typically, if a *force majeure* clause applies, the parties' obligations under the contract are

[170] *McConnell says he favors state bankruptcy over more federal aid,* Apr. 22, 2020, REUTERS, reuters.com/article/us-health-coronavirus-usa-states/mcconnell-says-he-favors-state-bankruptcy-over-more-federal-aid-idUSKCN2242U7, (Last accessed 04/30/2020).
[171] *See*, *The world remade by COVID-19*, DELOITTE, COVID-19/Collection Perspectives, www2.deloitte.com/global/en/about-deloitte/articles/covid-19-scenarios-and-impacts-for-business-and-society-world-remade.html.
[172] *Kel Kim v. Central Mkts.*, 70 N.Y.2d 900, 902 (1987).

suspended during the pendency of the event, and, if the event continues for a certain period of time, the parties may have a right to terminate the contract.

Under New York law, *force majeure* clauses are narrowly construed and applied. As one New York court recently explained, *force majeure* clauses are designed to limit damages "where the reasonable expectation of the parties and the performance of the contract have been frustrated by circumstances beyond the control of the parties."[173] Moreover, the courts will generally strictly construe the types of events that give rise to relief under a *force majeure* event. "[O]nly if the *force majeure* clause specifically includes the event that actually prevents a party's performance will that party be excused."[174] When the parties have themselves defined the contours of *force majeure* in their agreement, "those contours dictate the application, effect, and scope of *force majeure*."[175]

Some contracts may include "epidemic" as a specific example of a *force majeure* event.[176] Other contracts may not specifically list epidemic as a *force majeure* event, but may include a catch-all provision. If the coronavirus pandemic is sufficiently similar to the events listed in the *force majeure* clause, then—under the rule of contract construction known as *ejusdem generis* – the coronavirus pandemic may be considered a *force majeure* event.[177]

Common law doctrines: Frustration of purpose and impossibility

In the absence of a *force majeure* clause, two common law doctrines are potentially applicable: the doctrine of impossibility and the doctrine of frustration of purpose. Under New York law, the doctrine of impossibility provides only a limited path to relief and has been narrowly applied by the courts "due in part to judicial recognition that the purpose of contract law is to allocate the risks that might affect performance and that performance should be excused only in extreme circumstances."[178] Under the doctrine of impossibility, a party's performance will be excused "only when the destruction of the subject matter of the contract or the means of performance makes performance objectively impossible."[179] "Moreover, the impossibility of performance must be produced by an unanticipated event that could not have been foreseen or guarded against in the contract."[180] "Thus, where impossibility or difficulty of performance is occasioned only by financial difficulty or economic hardship, even to the extent of insolvency or bankruptcy, performance of a contract is not excused."[181]

The frustration of purpose doctrine excuses non-performance when a change in circumstances is such that one party's performance would no longer give the other party what induced him to make the bargain in the first place.[182] Like the doctrine of impossibility, the doctrine of frustration of purpose is a narrow one. Its application is "limited to instances where a virtually cataclysmic, wholly unforeseeable event renders the contract valueless to one party."[183] In order to successfully invoke the doctrine of frustration of purpose, a party must show that the purpose that is frustrated is the principal purpose of that party in making the contract. "The object must be so completely the basis of the contract that, as both parties understand, without

---

[173] *Constellation Energy Servs. of N.Y. v. New Water St.*, 146 A.D.3d 557, 558 (1st Dept. 2017).
[174] *Id*.
[175] *Id*.
[176] *See, e.g.*, *Touche Ross & Co. Manufacturers Hanover Trust Co.,* 107 Misc. 2d 438, 441 (Sup. Ct. N.Y. County 1980) (quoting contract that defines *force majeure* as including "flood, epidemics, earthquake, [and] war").
[177] *See Kel Kim*, 70 N.Y.2d 900 at 903.
[178] *Id*. at 902.
[179] *Id*.
[180] *Id*.
[181] *407 East 61st Garage, Inc. v. Savoy Fifth Ave. Corp.,* 23 N.Y.2d 275, 281-282 (1968).
[182] *Bierer v. Glaze, Inc.*, 2006 U.S. Dist. LEXIS 73042, *21-22 (E.D.N.Y. Oct. 6, 2006); *U.S. v. General Douglas MacArthur Senior Village, Inc.*, 508 F.2d 377, 381 (2d Cir. 1974).
[183] *Id*.

it the transaction would make little sense."[184] Restatement (Second) of Contracts § 265 (comment). The doctrine does not apply where performing under a contract would merely cause some degree of financial hardship.

New York's Uniform Commercial Code Section 2-615

Finally, even in the absence of a force majeure provision, New York's Uniform Commercial Code may excuse non-performance. Section 2-615(a) of the N.Y. U.C.C. provides that "[d]elay in delivery or non-delivery . . . is not a breach under a contract for sale if performance as agreed has been made impracticable by the occurrence of a contingency the non-occurrence of which was a basic assumption on which the contract was made or by compliance in good faith with any applicable foreign or domestic governmental regulation or order whether or not it later proves to be invalid." Under this provision, a seller is excused where its performance is "commercially impracticable because of unforeseen supervening circumstances not within the contemplation of the parties at the time of contracting."[185] There is an important caveat to Section 2-615(a): Where a seller's ability to supply is only partially impacted, the seller must allocate production/supply among its customers in a fair and reasonable manner.[186]

With respect to impracticability caused by government regulation or order, such "governmental interference cannot excuse unless it truly 'supervenes' in such a manner as to be beyond the seller's assumption of risk."[187] Moreover, a party cannot rely on supervening government action if he or she brought about the action that renders performance impracticable. "[A]ny action by the party claiming excuse which causes or colludes in inducing the governmental action preventing his performance would be in breach of good faith and would destroy his exemption."[188]

If the contract does not contain a *force majeure* clause, then courts will look to the language of the provision to determine if the clause excuses non-performance under the circumstances. *Force majeure* clauses vary widely, and the precise language will be critical. Some *force majeure* clauses specifically reference "epidemic" as a *force majeure* event; others do not. Even in the absence of a specific reference to epidemic, a *force majeure* clause may apply if it contains a catch-all provision and an epidemic event is sufficiently similar to the listed triggering events.

In the absence of a *force majeure* clause, nonperformance may be excused under the limited circumstances permitted by the doctrines of impossibility or frustration of purpose. These common law doctrines are applied narrowly by the courts of New York. The impossibility doctrine applies when an unanticipated and unforeseeable event occurs and, as a result of the event, the destruction of the subject matter of the contract or the means of performance makes performance objectively impossible. The frustration of purpose doctrine applies when a wholly unforeseeable event renders the contract valueless to one party and the principal purpose of the contract is no longer achievable.

Finally, New York's Uniform Code Section 2-615(a) may excuse breach of certain sales contracts where performance has been made impracticable by an unforeseen supervening occurrence or where the breach was caused by good faith compliance with governmental regulation.

---

[184] RESTATEMENT (SECOND) OF CONTRACTS § 265 (comment).
[185] UCC § 2-615, Official Comment 1.
[186] UCC § 2-615(b).
[187] UCC § 2-615, Official Comment 11.
[188] *Id*.

Paycheck Protection Program

It is important to note that the U.S. Small Business Administration established the Paycheck Protection Program (PPP) specifically designed to support small businesses experiencing economic harm from the pandemic and to encourage employers to maintain or rehire their employees, by offering forgiveness for those entities who use the loan proceeds to cover payroll costs and related costs at a specified level for a specified period of time and employee and compensation levels are maintained.[189] As such funding has been depleted quickly due to overwhelming response, additional funds have been granted through an amendment to the CARES Act.[190] Economic initiatives such as this which provide direct funding are critical to ensuring that New Yorkers remain employed and businesses across professional sectors are able to continue operating. However, it is evident that greater care must be given to ensuring that the business entities with greatest need are not dominated by those with greatest resources and influence.

Immunity

Federal Immunity Declarations in Response to COVID-19

CMS Blanket Waivers for Health Care Providers

Pursuant to section 319 of the Public Health Service Act,[191] if the President declares a major disaster or emergency, the Department of Health and Human Services ("HHS") may declare a Public Health Emergency ("PHE") which triggers the authority of the Secretary of HHS under section 1135 of the Social Security Act[192] to temporarily waive or permit flexibility of certain Medicare, Medicaid and HIPAA requirements. These 1135 waivers are adopted to allow hospitals, laboratories, nursing homes, hospice, psychiatric hospitals and critical access hospitals and other regulated organizations and facilities[193] to provide timely care to as many people as possible and may impact the following requirements:

- Conditions of participation and other certification requirements;
- Program participation and similar requirements;
- Preapproval requirements;
- Requirements that physicians and other health care professionals be licensed in the State in which they are providing services, so long as they have equivalent licensing in another State, subject to any applicable State laws governing licensure;
- Emergency Medical Treatment and Labor Act (EMTALA);
- Stark self-referral sanctions; and
- Limitations on payment for health care items and services furnished to Medicare Advantage enrollees by non-network providers.[194]

These waivers allow for unconventional adjustments to operations governed by federal law to control contagion, assure sufficient staffing levels, efficiently treat patients, and allocate scarce resources to preserve and save as many lives as possible during the pandemic under CSC principles while using best efforts to assure the safety of its clinical staff and patient milieu, sometimes at the expense of individual

---

[189] *See* U.S. SMALL BUS. ADMIN., Coronavirus (COVID-19): Small Business Guidance & Loan Resources, https://www.sba.gov/page/coronavirus-COVID-19-small-business-guidance-loan-resources.

[190] Paycheck Protection Program and Health Care Enhancement Act, H.R. 266, 116th Cong. (2020), https://www.congress.gov/amendment/116th-congress/senate-amendment/1580/all-info?s=4&r=1.

[191] 42 U.S.C. § 201 et seq.

[192] 42 U.S.C. § 301 et seq.

[193] EMERGENCY MEDICAL TREATMENT & ACTIVE LABOR ACT, 42 U.C.S § 1395dd.

[194] CMC, CMS Declaration of Waivers under 1135, https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertEmergPrep/1135-Waivers (last visited Apr. 22, 2020).

patient's rights.[195] Such curtailment of individual patient rights however, may lead to regulatory complaints and investigation, penalties, and/or civil and criminal litigation when outcomes are not optimal. Likewise, notwithstanding these waivers, health care organizations and facilities must take caution to avoid fraud and abuse and other overt violations of the laws and regulations governing the health care delivery system. In addition, health care organizations and facilities remain subject to applicable state laws and regulations not under federal jurisdiction. Hence, the immunity afforded by both federal and state authorities to health care organizations and facilities as they navigate the health care delivery system during the coronavirus pandemic is critical to the implementation of CSC. Without such immunity, health care organizations and facilities could be exposed to liability ranging from medical malpractice, violation of federal and state non-discrimination laws, violations of regulatory requirements which may lead to investigation, prosecution under the False Claims Act, and possibly exclusion of federal and commercial payment programs.

CARES Act

As noted above, the Federal Coronavirus Appropriations Package or CARES Act, was enacted largely to stimulate the U.S. economy, but there are several provisions included in the legislation that also aim to relax typical restrictions on the healthcare industry workforce that is on the "frontlines" in providing patient care amid the pandemic, including a liability protection for health care providers who volunteer to provide health care services relating to the diagnosis, prevention or treatment of COVID-19 or the assessment or care of a person who has or is suspected to have COVID-19 (CARES Act § 3215). To qualify for the protection, a healthcare provider must be licensed, registered, and/or certified to provide health care services under State or Federal law and providing services within the scope of their license, registration or certification in good faith (*see id.*). Additionally, an individual must not be compensated for providing the services at issue (*see id.*). The protection is limited in time to the duration of the period of the PHE declared by the U.S. Health and Human Services.

PREP Act

The Public Readiness and Emergency Preparedness Act or PREP Act (42 USC §§ 247d-6d-6e), permits U.S. HHS to issue a declaration to provide liability protections to individuals and entities (referred to as "covered persons") who manufacture, distribute or administer "medical countermeasures" in response to a public health crisis. After determining COVID-19 constituted a PHE, on January 31, 2020, the U.S. HHS Secretary issued a declaration under PREP.[196] Thereafter, consistent with the PREP Act, on March 10, 2020, the U.S. HHS Secretary issued a declaration under PREP that set forth specific covered persons and medical countermeasures that receive liability protection during the COVID-19 pandemic.[197] The covered persons include manufacturers, distributors, and program planners of medical countermeasures and their agents and employees and persons who prescribe, administer, deliver, distribute or dispense medical countermeasures.[198] The medical countermeasures include the following: any antiviral, other drug, biologic, diagnostic, other device or vaccine used to treat, diagnose, cure, prevent or mitigate COVID-19 or any virus mutating therefrom; or any device used in the administration of such product and the components and materials of same.[199]

---

[195] *See id*.

[196] DEP'T OF HEALTH AND HUMAN SERVICES, Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, Mar. 17, 2020, FEDERAL REGISTER, https://www.federalregister.gov/documents/2020/03/17/2020-05484/declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical-countermeasures#footnote-1-p15198 (last visited Apr. 17, 2020).

[197] *See* 85 C.F.R.15198.

[198] Declaration Under the Public Readiness and Emergency Preparedness Act for Medical Countermeasures Against COVID-19, Mar. 17, 2020, https://www.federalregister.gov/documents/2020/03/17/2020-05484/declaration-under-the-public-readiness-and-emergency-preparedness-act-for-medical-countermeasures#footnote-1-p15198 (last visited Apr. 17, 2020).

[199] *See id*.

Since the these official pronouncements by the US HHS Secretary, on April 14, 2020, HHS's Office of General Counsel has issued an Advisory Opinion discussing the declarations and the purpose and limitations of same ("the Advisory Opinion").[200] The stated goal of the Advisory Opinion was to respond to the scores of questions HHS has apparently received as to what is and what is no covered by the liability protections offered under the PREP Act. Notably, the Advisory Opinion indicates the scope of liability protections afforded under the PREP Act is intended to be broad, and, as such, it is the opinion of the General Counsel's Office that if a person or entity that qualifies as a "covered person," that person or entity will likely not "lose" the immunity intended by the law if it turns out later a product believed in good faith to be a "medical countermeasure" was not actually a "medical countermeasure" outlined in the PREP declaration.[201]

Finally, because covered persons are immune from suit, absent gross negligence, under the PREP Act, there is a Countermeasures Injury Compensation Program ("CICP") that provides compensation to individuals who are seriously injured or killed from medical countermeasures.[202] Notably, however, CICP is a "payor of last resort," and will only pay for medical costs not otherwise covered by third-party payors, including personal medical insurers, lost income, and survival benefits in some cases.[203] To file for compensation under CICP, claimants must submit their requests for same within one (1) year of receipt of the countermeasure.[204] It is too soon to tell whether CICP claims will increase beyond what is typical, but it seems very likely they will with what we know at this time.

New York State-Specific Immunity Declarations in Response to COVID-19

Organizational Immunity: Negligent Credentialing

Health care organizations and health care facilities are mandated by New York State laws and regulations to duly credential health care practitioners providing health care services at their facilities.[205] Organizations have a duty to select and retain competent practitioners. Failure to meet established standards of credentialing and privileging may lead to regulatory exposure and/or organizational liability for negligent credentialing in the event of patient harm caused by a credentialed practitioner. Typical strategies employed by health care facilities and their governing boards to minimize risk in the credentialing process are time consuming and may prove impractical in the face of the coronavirus pandemic situation. Typical strategies include:

- Identifying red flags in a practitioner's history (e.g., NPDB reports)
- Thoroughly documenting the practitioner's professional competence through references
- Using a consistent, evidence-based evaluation process
- Collecting performance data on an on-going basis
- Establishing and enforcing standard evaluation parameters
- Assuring adequate facility resources to perform health care services in a safe, effective and efficient manner

[200] Advisory Opinion on The Public Readiness and Emergency Preparedness Act and the March 10, 2020 Declaration Under The Act (Dep't of Health & Human Services, Office of the Sec'y Apr. 14, 2020), https://www.hhs.gov/sites/default/files/prep-act-advisory-opinion-april-14-2020.pdf.
[201] *See id*. at 4.
[202] Countermeasures Injury Compensation Program, 76 FED. REG. 62, 306 (Oct. 7, 2011), https://www.hrsa.gov/sites/default/files/cicp/about/forms/adminfinalrule.pdf (last visited Apr. 23, 2020).
[203] Frequently Asked Questions For Individual Requesters/Recipients, Health Resources & Services Administration, https://www.hrsa.gov/cicp/faq/requesters.html (last visited Apr. 23, 2020).
[204] *See id*.
[205] N.Y. PHL § 2805-k.

- Leadership oversight of the credentialing process (Board review and approval of candidates after careful review of a complete application)

The Governor's EOs appropriately extend to health care entities and facilities immunity from liability resulting from reliance on credentialing processes of other health care organizations and health care facilities in New York and any other state.[206]

Individual Immunity

Likewise, individual practitioners who cross state lines to offer professional medical services to manage patient surges risk professional liability exposure. It is deemed professional misconduct for any licensed practitioner to practice in the State of New York without a valid license. As healthcare practitioners cross state lines to address patient surges, they risk being charged with professional misconduct on the grounds that they are practicing in New York without a license.[207] Similarly, as practitioners and other healthcare workforce members are re-deployed or otherwise take on additional administrative and clinical duties and responsibilities outside the scope of their employment contracts, will health care organizations and health care facilities offer coverage and/or indemnification for potential liability exposure that may arise in the course of treating patients with COVID-19 given the relaxation of other regulatory requirements governing the delivery of health care and patients' rights? The Governor's EO 202.5 provides individual civil and criminal immunity to those duly licensed practitioners crossing state lines without a license to practice in New York state to assist their New York state colleagues in managing the surge of patients needing acute clinical care beyond that which health systems in New York can handle. More recently, EO 202.18 expanded civil and criminal immunity to those individual practitioners ranging from physicians to licensed clinical social workers to laboratory staff and pharmacy staff who are licensed and in current good standing in any province or territory of Canada. Such immunity however is limited to those acts of omission or commission in the management of COVID-19 consistent with the CSC.

Finally, from a risk management perspective, health care organizations and facilities should assure that termination of interjurisdictional credentialing arrangements and expansion of delineation of privileges should terminate contemporaneously with termination of the current public health emergency crisis as determined by governmental entities or when the health organization has sufficient capacity to handle census. Health care organizations and facilities should clarify for individual practitioners that termination does not amount to a termination or other denial of clinical privileges that would otherwise be deemed an adverse event triggering a report to the state Office of Professional Medical Conduct, Office of Professions or National Practitioner Data Bank.[208]

More significant, however, is the individual immunity necessary for health care workers who must make the life and death decisions about allocation of scarce resources such as ventilators, PPE and clinical staff when emergency departments and intensive care units are overwhelmed beyond their capacity. In this regard, EO 202.10 provides health care professionals with immunity from civil liability. Unfortunately, the immunity provision does not extend to individual criminal liability, nor does it extend to the health care facility at which the services are provided. Article 30-D of the Public Health Law,[209] signed by Governor Cuomo on April 3, 2020, as part of the New York State budget extends "immunity for any liability, civil

[206] *See* N.Y. EXECUTIVE ORDER No. 202.10, "Continuing Suspension and Modification of Laws Relating to the Disaster Emergency," Mar. 23 2020, https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency (last accessed Apr. 17, 2020).

[207] N.Y. ED. L., Art. VIII.

[208] 42 U.S.C. § 1320a, 42 C.F.R.§ 1003.810, Failure to report to NPDB may result in significant Civil Monetary Penalties.

[209] N.Y. PUB. H. L. § 3080 et seq.

and criminal, for any health care professional or facility alleged to have been sustained as a result of any act or omission" in the provision of care pursuant to a COVID-19 emergency rule or is otherwise lawful.[210]

HIPAA Privacy Rule

The Health Insurance Portability and Accountability Act ("HIPAA") is likely best known for its privacy protections. Indeed, HIPAA sets forth national standards to protect against the wrongful disclosure of information contained in patients' medical records, as well as the disclosure of other personal health information.[211] Importantly, the restrictions set forth in HIPAA apply to "covered entities," which is defined to include health plans (i.e., individual or group plans that provide or pay the cost of medical care), heath care clearinghouses (i.e., public or private entities that process or facilitate the processing of health information received from another entity, including, but not limited to billing companies), and health care providers who typically transmit health information in electronic form (and their "business associates"); and ordinarily restrict those entities from disclosing "health information," defined as "any information… that relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual" without certain required consent from patients or their representatives or in certain limited defined exceptions.[212]

Several of those defined exceptions are applicable now amid the COVID-19 crisis. There is an exception that permits covered entities to disclose otherwise protected health information to public health authorities "for the purpose of preventing or controlling disease… including, but not limited to, the reporting of disease" and where a patient "may have been exposed to a communicable disease or may otherwise be at risk of contracting or spreading a disease or condition."[213] There is also an exception that allows covered entities to disclose information to a patient's family members or other persons identified by the patient as being involved with his/her/their care if the information is directly relevant to the patient's care – e.g., that certain precautions need to be taken if the patient has or is suspected to have COVID-19.[214]

Related to this, there is also an additional exception that allows covered entities to disclose health information to when it is "necessary to prevent or lessen a serious and imminent threat to the health or safety of a person or the public," and that disclosure can be made to any "person or persons reasonably able to prevent or lessen the threat."[215] Notably, however, in a bulletin issued on February 3, 2020 ("the February Bulletin"), HHS cautions that this exception should only be used when the "professional judgment of health professionals" indicate it is necessary because of the nature and severity of the threat.[216] The February Bulletin also warns against reporting health information to the media or the public at large, absent a patient's consent to do so, and reminds covered entities and their business associates that they must make reasonable efforts to limit the disclosed information to the "minimum necessary." Meaning, it would be permissible for a hospital to provide a public health authority requesting information on COVID-19 status, but the hospital should refrain from also provide information about that patient's surgical history and other unrelated medical conditions, absent a reason for doing so.[217]

---

[210] N.Y. PUB. H. L. § 3082.
[211] *See* 45 C.F.R.§ 160 et seq.
[212] *See* 45 C.F.R.§ 160.103; *see also* 45 C.F.R.164.500 et seq.
[213] *See* 45 C.F.R.164.512(b)(i) and (b)(iv).
[214] *See* 45 C.F.R.164.510(b).
[215] *See* 45 C.F.R.164.512(j).
[216] U.S. DEP'T OF HEALTH AND HUMAN SERVICES, HIPAA Privacy and Novel Coronavirus, Feb. 2020, https://www.hhs.gov/sites/default/files/february-2020-hipaa-and-novel-coronavirus.pdf (last visited Apr. 23, 2020).
[217] *See id*.

In March 2020, HHS issued another HIPAA-related bulletin for the stated purpose of addressing the question of whether covered entities could share names of patients and other identifying information about patients who have been infected with or exposed to COVID-19 with law enforcement, paramedics, other first responders, and public health authorities ("the March Bulletin").[218] The March Bulletin references the exceptions discussed above, and provides examples of how those exceptions apply.[219]

In sum, while HHS has not "waived" the privacy restrictions that are set forth in the HIPAA Privacy Rule, the available exceptions that already exist in the law appear sufficient to provide public health authorities with the information they need to stop the spread of the pandemic. Importantly, in both the February Bulletin and the March Bulletin, HHS made clear patient confidentiality is extremely important and reasonable efforts should be made to ensure it is maintained to the greatest extent possible.

Workplace Liability Exposure

Employment Practices

As non-essential businesses press "pause" in response to the COVID-19 Pandemic, and as essential businesses reallocate their workforce, many employers have conducted layoffs, furloughs and implemented workshare programs to reduce salary and other overhead expenses during a time of limited cash flow. As more fully discussed in the Workforce Section of this Report, Federal and State laws governing paid sick leave, unemployment benefits, and FMLA have been expanded to account for some of the workforce reductions and lessen the devastating impact on individuals and the economy. However, as employers implement the difficult decisions pertaining to their employees, they must be cognizant of civil rights laws that prohibit discrimination in the workplace.[220] Decisions pertaining to sick leave, layoffs, furloughs, workshare and reassignment of duties must be made in a non-discriminatory manner to avoid allegations of adverse employment actions, failure to provide reasonable accommodations, and wrongful termination. In addition, when implementing workshare or other reductions in work hours, employers must strictly comply with wage and hour provisions to protect employees' right to unemployment benefits and avoid unnecessary liability for overtime hours worked. Finally, prior to implementing such reductions in force, employers subject to the Worker Adjustment and Retraining Notification Act must be sure to provide adequate notice as may be required by law.[221]

Workplace Safety

Inevitably, essential workers risk exposure to COVID-19 and may suffer illness as a result. Such illness, when it is demonstrated that it was contracted during work-related activity in the course of employment, will be covered by workers' compensation coverage. However, demonstrating a direct causal effect may prove difficult where employees may be exposed to the virus in their normal course of daily activities, likely leaving employers to work through workers' compensation claims long after the crisis abates.

On the other hand, where employers do not or are not able to comply with OSHA and other workplace safety requirements, they may be exposed to organizational liability including, but not limited to significant civil monetary penalties imposed by the Department of Labor under the Federal Civil Penalties Inflation

---

[218] U.S. DEP'T OF HEALTH AND HUMAN SERVICES, COVID-19 and HIPAA: Disclosures to law enforcement, paramedics, other first responders and public health authorities, https://www.hhs.gov/sites/default/files/COVID-19-hipaa-and-first-responders-508.pdf (last accessed Apr. 23, 2020).

[219] *See id*.

[220] *See* Age Discrimination in Employment Act of 1967, 29 U.S.C. §§ 621-634; Title VII of the Civil Rights Act of 1964, (Pub. L. 88-352) 42 U.S.C. § 2000e et seq; Americans with Disabilities Act of 1990, 42 U.S.C. ch. 126 § 12101 et seq; Consolidated Omnibus Reconciliation Act of 1985, IRC §4980B and 29 U.S.C. §§ 1161-1168; Family Medical Leave Act, 29 U.S.C. ch. 28 §§ 2601-2654.

[221] Worker Adjustment and Retraining Notification Act of 1988, 29 U.S.C. §§ 2101-2109.

Adjustment Act of 1990, as amended.[222] Failure to assure that adequate risk management strategies are adopted to minimize the risk of infection for employees, customers and others who interact directly with the public may expose employers to not only significant regulatory penalties, but claims arising from customers who may be exposed. Essential businesses including, but not limited to, grocery stores and other food markets, child-care centers, and utility providers must adopt infection prevention protocols such as standard and universal precautions that they, unlike health care delivery providers, may not otherwise be familiar with. Employers must assure that PPE and hand sanitizer is readily available and properly used, and that environmental surfaces and equipment are cleansed and disinfected effectively and often, and that social distancing policies are strictly enforced.

Given the health care services workers' shortage and patient surges during the COVID-19 Pandemic, the CDC has adopted guidance for occupational health programs and public health officials making decisions about return to work for healthcare personnel with confirmed COVID-19 or who have suspected COVID-19 but have not been tested.[223] Healthcare services employers must balance the risk of early return to work with their local need for healthcare services personnel on the front lines to manage patient care needs and adopt standard policies that are consistently enforced to avoid unnecessary exposure for deviations from accepted CSC.

V. Workforce Issues Associated with COVID-19

Introduction to Workforce

Implementation of crisis standards of care in response to a public health emergency mandates that the interests of the public's health be deemed paramount and that all efforts and resources be devoted toward saving as many lives as possible. Governmental entities must determine how businesses and entities and their respective employees, independent contractors and volunteers are legally distinguished for the purpose of coordinating essential services while maintaining public and worker safety**.** The Centers for Disease Control ("CDC") and other public health authorities have acknowledged community spread of COVID-19 in the United States and have issued precautions to slow the spread, such as significant restrictions on public gatherings. In addition, numerous state and local authorities have issued directives to minimize the risk of contagion by requiring quarantine, suspending non-essential commercial business operations, closing schools and taking other measures to prevent public gatherings in close quarters.

Governor Andrew Cuomo's Executive Orders ("EOs") coordinating restrictions on in-person business operations, school closures, and stay-at-home mandates across New York State in response to the ongoing COVID-19 pandemic have had a catalytic impact on New York State's economy, workforce, and education system, while also incidentally hindering access to essential resources and health care services for many individuals.[224] Despite desperate efforts by federal, state and local government officials to minimize the inevitable harms associated with a deadly pandemic such as this, the debilitating effect of the existing mandates has exposed societal weaknesses specific to public health and safety which cannot be easily rectified in the present. Nonetheless, such efforts and the results thereof provide insight regarding potential opportunities to remedy recognized weaknesses and build upon discovered strengths.

---

[222] 28 U.S.C. § 2461.

[223] CTRS FOR DISEASE CONTROL & PREVENTION, *Return to Work for Healthcare Personnel with Confirmed or Suspected COVID-19*, Apr. 13, 2020, https://www.cdc.gov/coronavirus/2019-ncov/hcp/return-to-work.html (last accessed Apr. 23, 2020).

[224] *See* N.Y. EXEC. ORDER No. 202.14 (Extends restrictions on public and private businesses; postponement or cancellation of all non-essential gathering of individuals of any size for any reason, and closure of schools stateside until 11:59 on April 29, 2020).

Through a series of EOs, the Governor necessarily categorized businesses into non-essential and essential whereby workers in non-essential businesses, or non-essential positions in essential businesses, must "shelter-in-place."[225] Timely and definitive guidance on what constitutes an essential business, or an essential worker, is critical to balance societal access to vital resources with control over contagion to avoid overwhelming our health care systems. This requires thoughtful allocation of human resources where the public need is greatest. As a result, tensions between public health interests including those of vulnerable populations, with those of individual workers inevitably rise to the surface.

As the Governor's office, the New York City Mayor's office and other related stakeholders try to determine the appropriate timing and manner in which the economy should reopen in collaboration with surrounding states, Governor Cuomo has continued to emphasize the inseverable symbiotic relationship between businesses, schools, workforce, and transportation, while clearly stating that one cannot reopen independent of the others.[226] This section highlights the tight interconnections among business, workforce and education and the associated issues that quasi "shelter-in-place" mandates have surfaced to date.

Allocation of Human Resources

Beginning in mid-March 2020, Governor Cuomo began issuing executive orders requiring government entities and businesses to have non-essential personnel work from home or take leave without charging accruals.[227] Effective March 20, 2020, Executive Order 202.6 required all businesses and not-for-profit entities to utilize telecommuting or work from home procedures to the maximum extent possible. Within days, a new executive order was issued, reducing the in-person workforce at any work locations by 100% no later than March 22, 2020 with a limited exemption for essential businesses.[228] This mandate, though undeniably one of the most successfully impactful State initiatives to "flatten the curve," triggered a whirlwind of anxiety and uncertainty amongst employers and employees alike as they diligently attempted to comply with often vague and ever-changing "essential business/employee" definitions; fiscally and logistically manage business operations; balance employer/employee rights and responsibilities; and fully engage in public health efforts to mitigate spread of the virus in the workplace, homes, communities, throughout the State and worldwide. As New York State prepares to reopen and embrace the "new normal," it is important to reflect on the past, identify and acknowledge the lessons learned as the emergency period continues to unfold, and commit to embracing an innovative future.

Essential and Non-Essential Business Categorization

As Governor Cuomo's workplace mandates evolved over time, the following business and employee categories emerged and shifted from a workforce population percentage standpoint as restrictions became more stringent.

Essential Businesses

- First Responders (Medical)
- First Responders (Non-medical)
- Essential – significant contact with public and co-workers (grocery, manufacturing, shipping, transportation, etc.)
- Essential – limited or no contact with public

[225] *See* N.Y. EXEC. ORDER Nos. 202.6; 202.13; Appendix F.
[226] Governor Cuomo Press Conference, Apr. 18, 2020, https://www.rev.com/blog/transcripts/andrew-cuomo-new-york-COVID-19-briefing-transcript-april-18 (last accessed 04/20/2020).
[227] *See* N.Y. EXEC. ORDER No. 202.4, Mar. 17, 2020.
[228] *See* Empire State Dev., Guidance for Determining Whether a Business Enterprise is Subject to a Workforce Reduction Under Recent Executive Orders, Apr.19, 2020, https://esd.ny.gov/guidance-executive-order-2026 (last visited Apr. 23, 2020).

Non-Essential Businesses

- On-site
- Telecommuting

Each category of professionals referenced above faces its own unique set of challenges, beyond those shared amongst all, as a consequence of the diverse roles and expected contributions required by society present day. Governor Cuomo reported that according to the Center for Economic and Policy Research, "41 percent of frontline workers are people of color, and of those frontline workers." In addition, "45 percent of transit workers, 57 percent of building cleaning service workers and 40 percent of health care workers are people of color. People of color are also disproportionately represented in delivery and childcare services."[229] Furthermore, each category consists of numerous sub-categories of families and individuals who may be "sheltering" with family or loved ones; forced to "shelter" independently in isolation; working remotely with high productivity expectations which exceed the norm; or working with a reduced workload due to the economic impact of the pandemic. Each of these familial and individual categories are also differently situated socioeconomically, and thus must be closely scrutinized to ensure that unintended consequences do not result from overgeneralizing the perceived benefits and harms of existing and future initiatives, especially as we continue to navigate unchartered waters toward our "new normal."

As previously suggested, the greatest challenges for business leaders beyond revenue related considerations have been associated with employee rights as related to employment, benefits, and protection from work-related exposure to COVID-19. In-person workforce reduction and quasi "shelter in-place" mandates significantly impacted demand for existing and new business almost instantaneously. Furthermore, many companies have not been able to collect payment for past services rendered, thus forcing them to determine how to effectively prioritize and allocate their employees and related business projects and tasks. Concerted efforts to prevent spread of the virus within the workplace have been futile to date as employees have continued to test positive since the pandemic was declared. Consequently, numerous human rights related concerns such as the "right to stay home" and "freedom of speech" have arisen and escalated in response to the highly contagious and deadly nature of the virus, which are addressed in a later section.

Employer Workplace Considerations

In light of the unprecedented impact of the COVID-19 pandemic economically, socially, and emotionally, employers must make every effort to maintain a supportive and legally sound work environment, recognizing the significant bearing workplace culture has on employee morale, trust and performance. Considering this, all operating businesses (non-essential and essential) should make a concerted effort to design and diligently implement a plan that is both employer and employee focused to ensure compliance with the legal and ethical practices, while fostering a supportive work environment. Employees should be provided with reputable state and federal resources to effectively follow best practices in mitigating the spread of the virus. Employers should closely follow public health guidelines and offer any equipment and materials necessary, including personal protective equipment (PPE), to not only support a healthy work environment, but convey a clear message to employees that the health and safety of themselves and their loved ones are of utmost importance. The New York State Nurses Association has challenged the adequacy of the PPE provided by certain hospitals during the PHE. The hospitals' perspective is that the PPE was compliant with guidance during the pandemic.[230]

---

[229] Governor Cuomo Press Conference, *Amid Ongoing COVID-19 Pandemic, Governor Cuomo Calls on Federal Government to Provide Hazard Pay to Essential Public Workers*, Apr. 20, 2020, https://www.governor.ny.gov/news/amid-ongoing-COVID-19-pandemic-governor-cuomo-calls-federal-government-provide-hazard-pay.

[230] The case against one of the hospitals was dismissed on May 1, 2020. The cases against the other hospital are proceeding. Proskauer Rose LLP represents the hospitals in the NYSNA cases noted above. Edward S. Kornreich, a Proskauer Partner, is a

In light of the recent release of federal guidelines for reopening businesses,[231] it is important that public health considerations remain at the foundation of any decision-making associated with business operations to mitigate spread.[232] On May 4, 2020, Governor Cuomo announced four core factors that the State intends to monitor to determine which regions can re-open.[233] Such considerations include the number of new infections, health care capacity, diagnostic testing capacity, and contract tracing capacity.[234] Furthermore, businesses are required to document and put in place new safety precautions upon reopening to mitigate risk of virus spread.[235] Such precaution requirements include the following:

- Workplace hours and shift design must be adjusted as necessary to reduce density in the workplace;
- Social distancing protocols must be enacted;
- Non-essential travel for employees must be restricted;
- All employees must be required to wear masks if infrequent contact with others;
- Strict cleaning and sanitation standards must be implemented;
- A continuous health screening process must be enacted for individuals to enter the workplace;
- Cases must be traced, tracked and reported on an ongoing basis; and
- Liability processes must be developed.

Business practices established during the early phase of the pandemic response which err on the side of caution, such as encouraging remote work when reasonably feasible, limiting non-essential travel and using reasonable discretion when employees display flu-like symptoms, will undeniably help expedite long-term health and economic success locally, nationally, and globally in the hours, days, and months to come. Considering this, such policies and procedures must not only be established, but implemented consistently and uniformly on an ongoing basis to ensure such efforts are worthwhile and have the long-term effect desired.

Employee Benefits

The following economically focused benefits and initiatives are designed to support employees impacted by exposure to or diagnosis of the COVID-19 virus, furloughs and layoffs.

Sick Leave, Paid Time-Off (PTO), Unemployment

The Family First Coronavirus Response Act (FFCRA) and the Coronavirus Aid, Relief and Economic Security Act (CARES Act)

The Family First Coronavirus Response Act (FFCRA) is a Congressional Act designed to respond to the economic impact of the ongoing pandemic. The Act contains numerous provisions including, paid leave for workers affected by the pandemic. The Coronavirus Aid, Relief and Economic Security Act (CARES Act) builds upon such efforts by providing additional support for individuals and businesses, including pandemic emergency unemployment compensation, pandemic unemployment assistance, extended benefits, short-

---

member of the Task Force. Mr. Kornreich did not participate in the creation of this section of the Report, or any other sections of the Report related to workforce issues, or to the Force Majeure and Impossibility discussions, and did not approve their contents. This Report does not represent the views of Proskauer, which disclaims any responsibility for, or association with, its contents.

[231] THE WHITE HOUSE, Guidelines: Opening Up America Again (2020), https://www.whitehouse.gov/wp-content/uploads/2020/04/Guidelines-for-Opening-Up-America-Again.pdf?mod=article_inline&mod=article_inline.

[232] Jennifer Maloney, Mike Colias, Paul Ziobro, *Businesses Strive to Reopen From Coronavirus Shutdown*, WALL ST. J., Apr. 20, 2020, https://www.wsj.com/articles/the-corporate-coronavirus-plan-to-reopen-make-it-up-as-you-go-11587404618.

[233] Governor Cuomo Press Conference, *Amid Ongoing COVID-19 Pandemic, Governor Cuomo Outlines Additional Guidelines for When Regions Can Re-Open*, May 4, 2020, available at: https://www.governor.ny.gov/news/amid-ongoing-covid-19-pandemic-governor-cuomo-outlines-additional-guidelines-when-regions-can.

[234] *Id.*

[235] *Id.*

term compensation, trade readjustment allowances, disaster unemployment assistance, and payments under the self-employment assistance program.

Under both the FFCRA and the CARES Act, laws and policies that affect employee wages, scheduling, and overtime remain unchanged from the current statutory regime under title 29 of the United States Code. Federal wage standards governed under 29 U.S.C. §209 hold that employers must pay employees a minimum wage. Furthermore, 29 U.S.C. §207(a)(1) requires employers to pay employees who work an excess of forty hours a week overtime pay "at a rate not less than one and one-half times the regular rate at which he is employed." Exempt employees, such as contractual employees or employees subject to existing collective bargaining agreements, may be exempted from overtime pay under §209(a)(1) if such contract or agreement specifies an expectation that the workweek would exceed forty hours in accordance with 29 U.S.C. §209(b). These laws are designed to work in concert with State law. Under circumstances in which State benefits are more generous than federal benefits, such as that for family leave, the eligible individual will be able to obtain the difference of the amount owed from the State.[236]

WARN – Worker Adjustment and Retraining Notifications

The FFRCA and the CARES Act do not alter the provisions of the Worker Adjustment and Retraining Notification statutes.[237] Under the federal WARN statutes, if a covered employer seeks a permanent or temporary shutdown – of a single site of employment, or one or more facilities or operating-units within a single site of employment – results in a reduction of fifty or more employees for a minimum of thirty days, then the covered employer must provide sixty day notice to those employees and relevant federal, state, and local government agencies of the pending closure.[238] When a natural disaster causes a shutdown – such as the COVID-19 pandemic – an employer is not required to adhere to the sixty day notice requirement.[239] The employer is still obligated to provide notice "as is practicable" and shall provide a brief statement of the basis of reducing the notification period.[240]

Sick Leave and Paid Time-Off (PTO), Paid Family Leave Benefits

In New York State, a detailed paid family leave framework was enacted to provide sick leave, paid family leave and other benefits to employees subject to an order for mandatory or precautionary quarantine due to COVID-19.[241] The provisions outline categories of eligible businesses, employee salary ranges, paid family leave or disability benefit eligibility standards and guaranteed job protections granted to individuals under the law.[242] For the purposes of these provisions, "disability" is defined as "any inability of any employee to perform the regular duties of his or her employment or the duties of any other employment which his or her employer may offer him or her as a result of a mandatory or precautionary order of quarantine or isolation" issued by specified entities.[243] Furthermore, "family leave" includes any leave "taken by an employee from work when an employee is subject to a mandatory or precautionary order of quarantine or isolation" issued by specified entities due to COVID-19 or any leave taken "to provide care for a minor dependent child of the employee who is subject to a mandatory or precautionary order of quarantine or isolation" issued by the same specified entities due to COVID-19.[244] Under the FFCRA, employees who

[236] N.Y. Legis. 25 (2020), 2020 Sess. Law News of N.Y. Ch. 25 (S. 8091) (McKINNEY'S).
[237] 29 U.S.C. §2101(a).
[238] 20 C.F.R. § 639.4.
[239] 29 U.S.C. § 2102(b)(2)(B).
[240] 29 U.S.C. § 2107(b)(3).
[241] N.Y. Legis. 25 (2020), 2020 Sess. Law News of N.Y. Ch. 25 (S. 8091) (McKINNEY'S); New York State Paid Family Leave, Fact Sheets, COVID-19 Paid Sick Leave Employees, https://paidfamilyleave.ny.gov/system/files/documents/2020/03/COVID-19-sick-leave-employees.pdf, (last visited Apr. 23, 2020).
[242] *Id.*
[243] *Id*.
[244] *Id*.

work for businesses which employ over 50 but under 500 employees can also qualify for paid sick leave if the leave is related to the COVID-19 health emergency.[245] There are six conditions that trigger these provisions, which are more expansive than New York State law. These conditions include:

(1) The employee is subject to federal, state or local order to quarantine or self-isolate;
(2) A health care provider advises the employee to quarantine or self-isolate related to COVID-19;
(3) The employee is experiencing symptoms of COVID-19;
(4) The employee is caring for an individual who is subject to quarantine/isolations;
(5) The employee is caring for a son or daughter under the age 18 because school closures and child care is unavailable;
(6) The employee is experiencing any other substantially similar condition specified by the Secretary of Health and Human Services, in consultation with the Secretaries of Labor and Treasury.[246]

The U.S. Department of the Treasury, the IRS, and the U.S. Department of Labor have collaborated to provide small and midsized business tax credits to help such entities recover the cost of such benefits.

It is important to note that if an employer has reduced an employee's normal work hours, the employee is not eligible to use sick leave or the expanded family and medical leave to replace the lost hours, unless a qualifying condition stated above renders the employee unable to work.[247] Even so, the extraordinary impact of these benefits is notable. As of May 3, 2020, there were over 170,000 confirmed cases of novel coronavirus, 43,045 hospitalizations, and approximately 13, 536 deaths associated with the virus in New York City alone.[248] Considering this, expanded paid leave and health insurance benefits have been critical to facilitating public health and safety for New Yorkers, in concert with the unemployment benefit initiatives referenced below.

Unemployment Benefits

An unprecedented number of employees have been laid-off, furloughed, or in some way severed from employment due to lack of work as a result of the pandemic.[249] For the week of April 25, 2020, the total number of individuals filing initial claims for unemployment benefits was close to four million, bringing the total number of initial claims to over thirty million nationally.[250] In New York, unemployment applications spiked 16,000 percent.[251] Individuals may qualify for unemployment insurance benefits offered through the state and federal government, including pandemic specific assistance provided under the Cares Act referenced above, depending on their employee category and status.[252] In New York, individuals seeking unemployment insurance must (a) have adequate past earnings; (b) be unemployed for

[245] *See* U.S. DEP'T OF LABOR, Families First Coronavirus Response Act: Employee Paid Leave Rights (2020), https://www.dol.gov/agencies/whd/pandemic/ffcra-employee-paid-leave (Last accessed Apr. 12, 2020).
[246] *Id.*
[247] *Id*.
[248] NEW YORK CITY HEALTH, COVID, COVID-19: DATA, (May 3, 2020), https://www1.nyc.gov/site/doh/covid/covid-19-data.page.
[249] New York Dept. of Labor, Number of Unemployment Insurance Beneficiaries and Benefit Amounts Paid Regular Unemployment Insurance New York State, Region and County February 2020 and Cumulative Since January 1, 2020, https://labor.ny.gov/stats/UI/Beneficiaries-and-Amounts-by-Region-and-County-February-2020.pdf, (total including out of state residents is 194,400 in Feb. 2020).
[250] U.S. DEP'T OF LABOR, Unemployment Insurance Weekly Claims (Apr. 30, 2020), https://www.dol.gov/ui/data.pdf; https://oui.doleta.gov/unemploy/archive.asp (Last accessed May 3, 2020).
[251] NEW YORK DEP'T OF LABOR, *Facing Unprecedented Spike in COVID-19 Related Unemployment Insurance Applications, NYS Department of Labor Announces Partnerships to Boost Tech Capacity and Make It Easier for New Yorkers to File*, Apr. 9, 2020, https://labor.ny.gov/pressreleases/2020/april-09-2020.shtm, (increase of application by 16,000%).
[252] *See* U.S. DEP'T OF LABOR, Families First Coronavirus Response Act: Questions and Answers (2020), https://www.dol.gov/agencies/whd/pandemic/ffcra-questions (Last accessed 04/21/2020); CARES Act: sec. 6428 (S. Res. 3548, 116th Cong. §6428 (2020) https://www.congress.gov/116/bills/s3548/BILLS-116s3548is.pdf.

each day claimed; (c) be unemployed "through no fault of their own"; and be actively and viably seeking reemployment, in accordance with Section 500 of the New York State Labor Law.[253] On March 12, 2020, Governor Cuomo signed an executive order waiving the 7-day waiting period for individuals claiming unemployment insurance through New York State as a result of the COVID-19 pandemic.[254] Typically, unemployment benefits would exclude certain employee categories and be deemed considerably inadequate to financially support individuals, let alone families, under crisis circumstances such as this. However, New York State and the federal government have each made a concerted effort offer benefits at a livable wage and broaden the scope of employees eligible to receive them.

Under Title II of the CARES Act, unemployment insurance eligibility has been extended to self-employed workers, independent contractors, gig economy workers, clergy and others who are typically ineligible under a new temporary federal program called Pandemic Unemployment Assistance (PUA). [255] Additionally, eligible parties are entitled to additional payment per week, on top of regular state benefits for an additional 13 weeks beyond the 26 weeks regularly provided, for a total of 39 weeks of coverage.[256]

Individuals are eligible under the CARES Act under the following circumstances:

i. The individual has been diagnosed with COVID-19 or is experiencing symptoms of COVID-19 and is seeking a medical diagnosis;
ii. A member of the individual's household has been diagnosed with COVID-19;
iii. The individual is providing care for a family member or a member of the individual's household who has been diagnosed with COVID-19;
iv. A child or other person in the household for which the individual has primary caregiving responsibility is unable to attend school or another facility that is closed as a direct result of the COVID-19 public health emergency and such school or facility care is required for the individual to work;
v. The individual is unable to reach the place of employment because of a quarantine imposed as a direct result of the COVID-19 public health emergency;
vi. The individual is unable to reach the place of employment because the individual has been advised by a health care provider to self-quarantine due to concerns related to COVID-19;
vii. The individual was scheduled to commence employment and does not have a job or is unable to reach the job as a direct result of the COVID-19 public health emergency;
viii. The individual has become the breadwinner or major support for a household because the head of the household has died as a direct result of COVID-19;
ix. The individual has to quit his or her job as a direct result of COVID-19; or
x. The individual's place of employment is closed as a direct result of the COVID-19 public health emergency.

These pandemic specific economic initiatives strive to keep both essential and non-essential businesses viable and individuals employed. It is important to note there are technical differences between furloughed and laid-off workers which should be taken into consideration when making employment decisions, such as the anticipated length of time the impacted individual is intended to be out of work and benefit eligibility. In order to most effectively take advantage of the various benefits highlighted above, in addition to others

[253] 18 N.Y. LAB. LAW § 500 et. seq.
[254] NEW YORK STATE, Know Your Rights, https://coronavirus.health.ny.gov/know-your-rights#insurance; N.Y. EXEC. ORDER No. 202.1, Mar. 7, 2020, https://www.governor.ny.gov/sites/governor.ny.gov/files/atoms/files/EO_202_1.pdf.
[255] *Id.*
[256] *Id.*

included in the CARES Act, employers and employees should seek guidance from the Department of Labor and professional and/or non-profit entities specializing in such matters.

Schools and Child Care

On April 11, 2020, the New York Times published an article highlighting diverging perspectives between the Mayor of New York City, Mayor Bill de Blasio, and the Governor of New York State, Governor Andrew Cuomo, regarding when schools and businesses should open, and which government leader has the authority to make such decision.[257] The Mayor publicly announced that New York City schools, which at the time were shuttered since March 16th and required to adjust to distance learning, would remain closed for the remainder of the 2019-2020 academic year, while also proposing that businesses could potentially open in May 2020.[258] However, Governor Cuomo soon thereafter stated that no decision had been made regarding closing schools or opening businesses in New York City or the State.[259] As previously noted, the Governor believes in the deep interconnection between business and school operations, and thus determines that they must open in concert.[260] On May 7, 2020, Governor Cuomo signed an Executive Order extending the closure of schools statewide for the remainder of the school year.[261] School districts are required to continue established alternative instructional options, distribution of meals, and child care, while prioritizing services for children of essential workers.[262] This symbiotic relationship contributes to various public health and social services related issues which must be closely analyzed and ultimately rectified going forward in the interest of future economic and social stability and most importantly, social justice. In an effort to address some of these challenges in a targeted fashion, the Governor has partnered with the Gates Foundation to develop a blueprint to reimagine education in the "new normal"[263] and has established New York's Reimagine Council[264] to prepare for reopening. Key considerations include:[265]

- How can we use technology to provide more opportunities to students no matter where they are;
- How can we provide shared education among schools and colleges using technology;
- How can technology reduce educational inequality, including English as a new language student;
- How can we use technology to meet educational needs of students with disabilities;
- How can we provide educators more tools to use technology;
- How can technology break down barriers to K-12 and Colleges and University to provide greater access to high quality education no matter where the student lives; and

---

[257] Eliza Shapiro, *N.Y.C. Closes Schools for Academic Year, but Cuomo Says it's His Decision*, N.Y. Times, Apr. 11, 2020, https://www.nytimes.com/2020/04/11/nyregion/nyc-schools-closed.html.

[258] *Id*.; Governor Cuomo Press Conference, Apr. 18, 2020, https://www.rev.com/blog/transcripts/andrew-cuomo-new-york-COVID-19-briefing-transcript-april-18 (last accessed 04/20/2020).

[259] Jesse McKinley, Eliza Shapiro and Jeffery C. Mays, *De Blasio Used Last-Minute Text to Tell Cuomo Schools Would Stay Shut*, N.Y. TIMES, Apr. 12, 2020, https://www.nytimes.com/2020/04/12/nyregion/schools-cuomo-de-blasio-nyc-coronavirus.html (last accessed Apr. 20, 2020).

[260] Governor Cuomo Press Conference, Apr. 18, 2020, https://www.rev.com/blog/transcripts/andrew-cuomo-new-york-COVID-19-briefing-transcript-april-18 (last accessed Apr. 20, 2020).

[261] N.Y. Exec. Order No. 202.28, https://www.governor.ny.gov/news/no-20228-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency (last accessed May 8, 2020).

[262] *Id.*

[263] Governor Cuomo Press Conference, Video, *Audio, Photos & Rush Transcript: Amid Ongoing COVID-19 Pandemic, Governor Cuomo Announces Collaboration with Gates Foundation to Develop a Blueprint to Reimagine Education in the New Normal*, May 5, 2020, https://www.governor.ny.gov/news/video-audio-photos-rush-transcript-amid-ongoing-covid-19-pandemic-governor-cuomo-announces-19 (last accessed May 8, 2020).

[264] Governor Cuomo Press Conference, *Amid Ongoing COVID-19 Pandemic, Governor Cuomo Announces Members of the Reimagine Education Advisory Council*, May 8, 2020, https://www.governor.ny.gov/news/amid-ongoing-covid-19-pandemic-governor-cuomo-announces-members-reimagine-education-advisory (last accessed May 8, 2020).

[265] Governor Cuomo Press Conference, Video, *Audio, Photos & Rush Transcript: Amid Ongoing COVID-19 Pandemic, Governor Cuomo Announces Collaboration with Gates Foundation to Develop a Blueprint to Reimagine Education in the New Normal*, May 5, 2020, https://www.governor.ny.gov/news/video-audio-photos-rush-transcript-amid-ongoing-covid-19-pandemic-governor-cuomo-announces-19 (last accessed May 8, 2020).

- Given ongoing social distancing rule, how can we delay classroom technology, like immersive cloud virtual classrooms learning, to recreate larger class or lecture hall environments in different locations?

As the Gates Foundation collaboration and New York's Reimagine Council progress forward toward a revitalized and stronger New York, it is essential that health care practitioners and public health experts are proactively integrated in future discussions in light of the significant impact health has on positive education outcomes.

New York State has the largest comprehensive public university system in the United States, the State University of New York (SUNY) system, with a total enrollment of over 400,000 students across 64 campuses and over 2 million continuing education enrollments.[266] Additionally, the City School District of the City of New York (the New York City public schools) is the largest school district in the United States with over 1.1 million students.[267] Almost 1.5 million children receive free or reduced lunch through the public school system.[268] In regards to child care, there are approximately 17,000 day care centers throughout New York State.[269] Despite having a total capacity of over 630,000 children across centers, child care shortages are an ongoing issue throughout the state.[270] Bearing in mind that these statistics fail to include all public and private institutions and entities throughout the State, it is evident that New York State manages one of the most robust, coordinated educational and social services systems nationally. New York families heavily rely on these systems, in addition to supplemental after school programs, extra-curricular opportunities, day and residential camps, and other child and youth-directed programming, to supervise and provide care for their minor children while at work. Deprived of these resources, in-person business operations throughout the state effectively deteriorate with a markedly disparate impact on women, minorities, and economically vulnerable populations.

Child Care

Child care is undeniably one of the most fundamental, critical and coveted social services in New York State under the oversight of Office for Children and Family Services (OCFS) and the New York City Department of Health (NYC DOH).[271] Such services are offered in varied forms, including day care centers, small day care centers, family day care homes, group family day care homes, and school-aged child care programs.[272] Over the years and in recent past, associations and advocacy groups throughout New York State, such as the Empire State Campaign for Child Care, Winning Beginning NY, and Business Council of New York State, have highlighted the fact that child care services offerings throughout the State are woefully inadequate and prohibitively costly due to inadequate funding, limited staff[273] and a stringent

[266] State Univ. of New York, Fast Facts, Jan. 2019, https://www.suny.edu/about/fast-facts/ (last visited Apr. 19, 2020).
[267] NEW YORK CITY DEP'T OF EDUC., DOE Data at a Glance, https://www.schools.nyc.gov/about-us/reports/doe-data-at-a-glance (last accessed Apr. 19, 2020).
[268] Council On Children & Families: Kids' Well-Being Indicators Clearinghouse, KWIC Indicator: Children Receiving Free of Reduced-Price School Lunch – Public Schools, Apr. 19, 2020, https://www.nyskwic.org/get_data/indicator_profile.cfm?subIndicatorID=52.
[269] OFFICE OF CHILDREN AND FAMILY SERV., New York State 2017 Child Care Demographics (2017).
[270] *Id.*; Childcare Careers, Addressing the Childcare Shortage: An Analysis of the Potential Benefits Offered by the Temporary Childcare Worker Industry 2 (Nov. 2018) (citing an estimated 60 percent of New York residents live in "childcare deserts," described as a location with inadequate child care facilities).
[271] Find Child Care Providers New York State, Guidelines, https://www.ny.gov/services/find-child-care-providers-new-york-state, (last accessed Apr. 19, 2020).
[272] *See* 18 N.Y.C.R.R. § 413.2.
[273] Saima Akhta et al., Empire Justice Center, Joint Legislative Public Hearings on 2020-2021 Executive Budget Proposal 10-20, Jan. 30, 2020; The Business Council, Support of S.5811-A, Jun. 4 2019; Winning Beginning NY, Testimony of Winning Beginning NY 2-3, Jan. 30, 2020; Timothy Denton, *Nassau County is Child Care Desert, Comptroller finds COVID-19 Lockdown Highlights High Cost to Families*, Li Herald.com, Apr. 19, 2020, https://www.liherald.com/stories/nassau-county-is-childcare-desert-comptroller-finds,124247.

regulatory framework related to adult-child ratios, training and experience, inspections, and employee eligibility requirements.[274]

Though childcare policies may vary, a significant number of childcare centers operate on a schedule that aligns with the school districts. In February 2020, OCFS began releasing COVID-19 pandemic updates to child care providers with public health and operations related updates.[275] To date, OCFS has been collecting information from licensed and registered providers via surveys to determine "whether they have openings in their child care program, and if they have the capacity and desire to serve more children than their established capacity.[276] Furthermore, surveys were distributed to determine parent or caregiver need.[277] OCFS advises that child care *may* be available based on the responding party's "job, employer, number of children, and financial need."[278] Simultaneously, school leaders, special education directors, and charter school leaders were directed by Governor Cuomo to "establish and submit plans for the care of children of essential health care workers and first responders and to address other identified student needs" in preparation for school closures across the state.[279] Since then various stakeholders have started initiatives to ensure that health care workers, first responders and font-line workers have access to child care.[280] In recognition of the shortage of child care workers and the significant impact potential infection could have on maintaining sufficient manpower, Governor Cuomo also altered background check requirements for child care workers.[281]

Now that in-person operations for all non-essential business are closed, many parents at home are forced to work remotely, if able to do so, and care for their children while many work productivity and performance expectations not only remain unchanged, but potentially increase in light of such dire economic circumstances.[282] Additionally, it is uncertain whether all frontline workers in need of child care have sufficient and convenient access to it. The New York City Administration for Children's Services (ACS) has also issued guidelines to facilitate the identification of a child or children whose parent or primary caregiver is impacted by COVID-19 resulting in hospitalization.[283] The issue is whether there is a sufficient number of healthy, trained, and experienced child care workers available to support the workforce as the

---

[274] *Id*.
[275] Letter from Office of Children and Family Serv. to Child Care Providers, Feb. 6, 2020, (online at https://ocfs.ny.gov/main/childcare/letterstoproviders/2020/Dear-Provider-2020Feb-Corona-Virus.pdf).
[276] OFFICE OF CHILDREN AND FAMILY SERV., Coronavirus Information (COVID-19) News and Updates, Survey on Child Care Program Openings, Mar. 25, 2020, https://ocfs.ny.gov/main/news/COVID-19/#t1-Letters-to-Child-Care-Providers (last accessed Apr. 20, 2020).
[277] *Id*.
[278] *Id.*
[279] Letter from New York State Ed. Dep't, Mar. 17, 2020; N.Y. EXEC. ORDER No. 202.4, Mar. 17, 2020.
[280] *See* NEW YORK CITY DEP'T OF ED., Regional Enrichment Centers, https://www.schools.nyc.gov/enrollment/enrollment-help/regional-enrichment-centers (last accessed Apr. 21, 2020); *NBC New York: New York Giants Fund Childcare for First Responders During COVID-19*, NBC Television Broadcast, Mar. 23, 2020, https://www.nbcnewyork.com/news/coronavirus/new-york-giants-fund-childcare-for-first-responders-during-COVID-19-crisis/2340883/ (last accessed Apr. 21, 2020); Press Release, Westchester County, Westchester County to Offer Child Care Opportunities for the Children of Healthcare Workers and First Responders, Mar. 25, 2020, https://www.westchestergov.com/home/all-press-releases/8343-westchester-county-to-offer-child-care-opportunities-for-the-children-of-healthcare-workers-and-first-responders (last accessed Apr. 21,2020); Public Notice, Ichabod Crane Central Sch. Dist., Childcare for Essential Emergency Workforce Personal, Mar. 20, 2020, https://www.ichabodcrane.org/2020/03/20/emergency-responder-health-worker-child-care/ (last accessed Apr. 21, 2020).
[281] N.Y. EXEC. ORDER No. 202.13, Mar. 29, 2020.
[282] Adam Golick, *The Productivity Pitfalls of Working From Home in the Age of COVID-19*, STANFORD NEWS, Mar. 30, 2020, https://news.stanford.edu/2020/03/30/productivity-pitfalls-working-home-age-COVID-19/ (last accessed Apr. 21, 2020).
[283] Identifying Caregivers for Children Unaccompanied and/or Unsupervised Due to the Hospitalization of their Primary Care Giver, NYC Children Emergency Guidelines, Apr. 9, 2020.

State's battle against the pandemic continues, and we begin phasing in the workforce.[284] Such weaknesses in our social and workforce structure must be resolved.

The CARES Act contains increased appropriations for childcare services to help mitigate the impact of the COVID-19 health emergency. Monies were appropriated for the Child Care and Development Block Grant Act (CCDBG) and to remain available through September 20, 2021 to "prevent, prepare for, and respond" to the COVID-19 health emergency.[285] The CARES Act also includes appropriations for Head Start, while reducing State cost-sharing contributions.[286] Although these appropriations do not direct funding towards increasing access to childcare services to frontline workers, they provide States with increased flexibility to develop child care programs for these workers if warranted.[287] Access to CCDBG grants typically require states to implement work plans that include background checks into State/local criminal databases, and the National Crime Information Center's National Sex Offender Registry. Currently, States that do not have access to the federal National Sex Offender Registry for various reasons, but the Office of Child Care has extended waivers for this provision which allow those States to continue to receive CCDBG grant funding.

On April 23, 2020, Governor Cuomo announced $30 million in childcare scholarships for essential workers and supplies for health care providers through federal funding under the CARES Act.[288] Such essential workers include, "first responders such as health care providers, pharmaceutical staff, law enforcement, firefighters, food delivery workers, grocery store employees and others who are needed to respond to the COVID-19 pandemic."[289] The income level for eligibility is less than 300 percent of the federal poverty level, which is $78,600 for a family of four.[290] The funding may be used to cover existing care arrangements or to establish a new one.[291] Funding will also provide child care providers critical resources, such as masks, gloves, diapers, baby wipes, baby formula and food, with child care resource and federal agencies receiving grants of approximately $600 per provider.[292] As child care resource and referral agencies, child care providers, and families persevere through this pandemic season and strategically prepare for the "new normal" that awaits, stakeholders must consider the resources, facility space, and manpower necessary to ensure the public health and safety of our children, their associated families and our child care workers, while still maintaining a welcoming and nurturing environment.

In regard to workforce, New York should consider granting staffing firms dedicated to childcare the provider status in the Statewide Central Register necessary to enable them to operate in the State and supplement our childcare workforce. In addition to the volunteers sought over the course of this pandemic, child care specific staffing firms could provide fully qualified and pre-screened teachers, assistant teachers and site directors for child care centers, preschools, and before & after school programs on an on-demand,

---

[284] Lillian Mongeau, *Coronavirus is Closing Day Cares; Child Care Providers Worry They Way Never Reopen,* USA TODAY, Apr. 5, 2020, https://www.usatoday.com/story/news/education/2020/04/05/coronavirus-daycare-child-care-center-essential-cares-act-unemployment/2946710001/ (last accessed Apr. 21, 2020).
[285] Coronavirus Aid, Relief, and Economic Security Act, Pub. L. No. 116-136, 134 Stat 281 (2020).
[286] *Id*.
[287] *See* 45 C.F.R. 98.16(aa) (incorporating use of block grant funding to be used to assist with childcare and safety during a state-emergency); *See also* OFFICE OF CHILD CARE, *CCDF Frequently Asked Questions in Response to COVID-19*, Mar. 13, 2020, https://www.acf.hhs.gov/occ/resource/ccdf-faqs-in-response-to-COVID-19 (last accessed Apr. 12, 2020).
[288] Press Release, Governor Cuomo, *Video, Audio, Photos & Rush Transcript: Amid Ongoing COVID-19 Pandemic, Governor Cuomo Announces State Health Department Will Partner with Attorney General James to Investigate Nursing Home Violations*, Apr. 23, 2020, https://www.governor.ny.gov/news/video-audio-photos-rush-transcript-amid-ongoing-COVID-19-pandemic-governor-cuomo-announces-12 (announcing $30 million in childcare scholarships for essential workers and supplies for childcare workers).
[289] *Id.*
[290] *Id.*
[291] *Id.*
[292] *Id*.

same day, short-term, long-term, or permanent basis.[293] Organizations such as this often employ a high percentage of graduate students and young adults seeking experience in pursuit of professional growth, parents seeking part-time work, and retired professionals to facilitate child care workforce stability within local communities on a routine and emergency basis, while also ensuring ensure the safety of one of our most treasured populations, our children. Furthermore, they have a significant impact on the school system, by alleviating the burdens that inevitably arise from sharing a limited pool of trained and fully vetted workforce members. Going forward, increased funding for existing centers supplemented by increased manpower must be prioritized to stabilize the existing childcare system and ultimately strengthen such system in anticipation of future emergencies such as this. Furthermore, we must ensure that the entire workforce is effectively supported by removing existing hurdles rooted in socioeconomic stratification.

Public and Private Schools, Colleges, and Universities

Once medical experts and government leaders realized that public and private academic institutions are high risk environments for the spread of the COVID-19 virus in light of the asymptomatic nature of the virus amongst children and young adults, such entities have faced numerous and diverse challenges which are not only ongoing, but also far-reaching beyond present day. Such challenges included the lack of regional uniformity and clarity regarding appropriate closure strategies and next steps upon recognition that the virus was a serious threat;[294] the significant reliance on schools for food security for a large population of students;[295] structural and economic disparities across academic institutions and students associated with home schooling and online learning;[296] disparities associated with alternative grading systems within institutions and the modification,[297] postponement and/or cancellation of institutional, state and/ or professional examinations;[298] the short-term and long-term impacts associated with the postponement and/or cancellation of graduation and other related ceremonies;[299] uncertainty regarding the timeline for reopening schools[300] and the overarching financial, psychological and emotional impact of all of the above on the communities, institutional leaders, workforce members, parents, and children implicated.

Operational Uniformity across Academic Institutions

In light of the proven significance of "social distancing" in New York State's effort to mitigate the spread of COVID-19, it is essential that key stakeholders, including local health, education, school, college and university leaders, whether public or private, be provided clear and timely guidance regarding operational expectations and best practices to ensure that such individuals and entities are empowered with the information necessary to make sound decisions in the best interest of their individual communities and public health within the State as a whole. Local leaders and leaders were disoriented and frustrated in the

---

[293] Child Care Careers, About Us, http://www.childcarecareers.net/about_us (last visited Apr. 23, 2020).

[294] Robyn Dixon, Karla Adam, Odysseus Patrick, *On Schools, No Global Consensus*, WASH. POST, Apr. 19, 2020, at A21 (discussing lack of consensus surrounding school closing/reopening policies).

[295] Council On Children & Families: Kids' Well-Being Indicators Clearinghouse, *Supra* at note. 7.

[296] Anna North, *The Shift to Online Learning Could Worsen Educational Inequality*, Vox (Apr. 9, 2020), https://www.vox.com/2020/4/9/21200159/coronavirus-school-digital-low-income-students-Covid-new-york.

[297] Shannon Doyne, Michael Gonchar, *Should Schools Change How They Grade Students During the Pandemic?*, N.Y. TIMES, Apr. 6, 2020, https://www.nytimes.com/2020/04/06/learning/coronavirus-schools-grading.html; Teresa Watanabe, *A's for all? Pass/fail? Colleges grapple with grading fairness during coronavirus*, L.A. TIMES, Mar. 27, 2020, https://www.latimes.com/california/story/2020-03-27/grades-vs-pass-fail-colleges-grapple-with-student-demands-to-change-grading-during-coronavirus.

[298] Court of Appeals (N.Y.), *New York Bar Exam Rescheduled for Fall 2020*, Mar. 27, 2020, https://www.nybarexam.org/Press/PressRelease_NY_BarExam.pdf (rescheduling of July Bar Exam to September); NEW YORK DEP'T OF CIVIL SERV., News and Notifications, https://www.cs.ny.gov/home/news.cfm (last visited Apr. 22, 2020) (indicating postponed state civil service exams).

[299] Elissa Nadworny*, No Caps, No Gowns: For Many In The Class Of 2020, Commencement Is Called Off*, NPR, Apr. 1, 2020, https://www.npr.org/2020/04/01/823866801/no-caps-no-gowns-for-many-in-the-class-of-2020-commencement-is-called-off.

[300] Dixon, et al, *supra*.

absence of strong direction from the State regarding school closures in the early phase of the pandemic.[301] Despite local leaders' appreciation for autonomy in many instances, emergency circumstances such as this where regional differences and conflicting priorities, such as public safety, food safety, and childcare, are at issue, strategic efforts to act in a staggered or unified fashion directed by the State helps mitigate anxiety and fear amongst interested parties, while strengthening public trust that local decision-makers are acting in their best interest.

Entanglement of the School System, Food Security, and Health Care

One of the most devastating issues from a logistical, public health and social equity standpoint beyond family reliance on schools for child care is the fact that so many children rely on the school system for food security, thus compromising New York State leaders' ability and willingness to close schools as early as they otherwise would have to mitigate the spread of the virus within schools and associated households.[302] Although the availability of such benefits for families and children in need is paramount, the State should closely assess the government entities, organizations, personnel, and strategies utilized over the course of the past several weeks during the school closure period to determine which programs can be maintained long term in an effort to purposefully transition the sole responsibility of food security for children in economically challenged households from schools to third-party entities. Furthermore, many schools have school-based health centers which offer primary health care services within the school environment.[303] Beyond providing first aid, emergency care and other services to individuals and students within the building, the center also provides diverse services, such as primary care and preventative health services (physical exams, required school health services, medical care for chronic illness and disease and referrals to specialty care), mental health services on site or by referral, health education, drug and alcohol abuse counseling, dental services, and age-appropriate teen reproductive health services.[304] Considering this, expanded partnerships with health care entities, such as federally qualified health centers, should be established to ensure access to such critical health services for children and youth. This proposal is not intended to suggest that school systems be excluded from providing such benefits entirely, but rather calls attention to the need for a more robust support system for children and families outside of the school system.

Different than the inherent nature of school as an indirect form of "child care" based on our society's operational structure, schools are otherwise designed and intended to be sources of academic and social development and support, while providing additional opportunities and resources as ancillary benefits. The mission and vision of the New York State Education Department is "to raise the knowledge, skill, and opportunity of all the people in New York" and "to provide leadership for a system that yields the best educated people in the world."[305] Considering this, schools should be funded and empowered as necessary to support its students when concerns such as food security are at issue. However, such institutions should act as collaborative partners with existing small business and nonprofit initiatives and programs, such as mobile food and produce projects, in the interest of public health and safety and social justice.

---

[301] Madina Toure and Sally Goldenberg, *Cuomo Defends Decision To Keep Schools Open, But Pressure Mounts*, POLITICO NEW YORK, Apr. 15, 2020, https://www.politico.com/states/new-york/albany/story/2020/03/15/cuomo-defends-decision-to-keep-schools-open-but-pressure-mounts-1267129 (last accessed Apr. 24, 2020).

[302] New York State Council on Children & Families, KWIC Indicator: Children Receiving Free or Reduced-price School Lunch - Public Schools, https://www.nyskwic.org/get_data/indicator_profile.cfm?subIndicatorID=52 (last accessed Apr. 24, 2020); Paul Berger and Lee Hawkins, *Gov. Cuomo Wants to Shut New York City's Public-School System*, WSJ, Mar. 15, 2020, https://www.wsj.com/articles/pressure-mounts-to-shut-new-york-citys-school-system-bars-and-restaurants-11584290883 (last accessed Apr. 24, 2020).

[303] NEW YORK STATE DEP'T OF ED., School-Based Health Centers, available at: https://www.schools.nyc.gov/school-life/health-and-wellness/school-based-health-centers (last accessed May 8, 2020)

[304] *Id.*

[305] NEW YORK STATE DEP'T OF ED., About NYSED, http://www.nysed.gov/about (last visited Apr. 24, 2020).

Disparities Associated with Home Schooling and Online Learning

The Governor's mandate across businesses and academic institutions to cease in-person operations and function remotely, including remote learning, has had a multifaceted impact on households and individuals throughout the State. Parents have been forced to assume a hands-on teaching role for courses of which they may not be well versed, using technologies with which they might be unfamiliar, while also working from home remotely with employer expectations of high productivity. For households led by front-line workers unable to work from home and single parent households, the burden can be unbearable logistically and emotionally. Considering the vastly diverse composition of our households today, caution must be taken to not discount or ignore the far-reaching implications of a fully technological and business framework. Caretakers and employees are required to not only have the necessary technological equipment to appropriately meet school and work requirements, but the technological and financial resources to support, such as internet. Many households positioned to operate remotely prior to the pandemic still experience the need to purchase necessary office supplies and develop home office and study spaces for work and student learning. We must remember that many others do not have that luxury.

Technology has the ability to facilitate equality through increased access to otherwise inaccessible resources or further stratify us within society as a result of its potentially prohibitive costs for equipment and internet, in addition to the potential need for training.[306] Here, there is greater risk of stratification than the potential for equality that must be assessed and progressively resolved through collaborative public/private efforts. State, local and community leaders must ensure that vulnerable households needing economic or educational support are identified and supported to not only ensure that academic and professional requirements are able to be met, but academic and professional competency and growth are experienced and not hindered unfairly by this experience due socioeconomic status, disability, or any other factor. Individuals with disabilities must be provided the opportunity to receive ongoing education and services, whether via technological or in-person direct care services with sufficient protective measures, to safeguard them from being marginalized and ultimately harmed for the duration of this pandemic and going forward. The failure to provide appropriate evidence-based supports and services typically provided through schools could have long-term unintended consequences, such as regression. As New York seeks to become more technologically advanced in the area of education, the provision of technological hardware, software, communication devices, and other assistive technology which promote inclusive distant learning, while sheltering in place and beyond, could facilitate student access to the same educational opportunities as other students.

On April 4, 2020, the New York Times published an article entitled, "College Made Them Feel Equal. The Virus Exposed How Unequal Their Lives Are."[307] This speaks to the fact that these issues of inequality permeate all academic and professional levels, and thus must be pondered and remedied as we evaluate and adapt our societal framework to withstand the present pandemic and look ahead to the future. On April 20, 2020, SUNY's chancellor announced the distribution of over 8,800 laptops and chromebooks to students to ensure that they are able to complete their spring coursework.[308] Efforts such as this, with the provision of ancillary resources as needed, will help ensure the safety of our students at all levels and in all communities, while also enhancing their ability to more easily transition to remote learning and achieve academic regardless socioeconomic status.

---

[306] Suzanne Woolley, Nikitha Sattiraju, Scott Moritz, *U.S. Schools Trying to Teach Online Highlight a Digital Divide*, BLOOMBERG, Mar. 26, 2020, https://www.bloomberg.com/news/articles/2020-03-26/COVID-19-school-closures-reveal-disparity-in-access-to-internet.

[307] Nicholas Casey, *College Made Them Feel Equal. The Virus Exposed How Unequal Their Lives Are*, N.Y. TIMES, Apr. 4, 2020, https://www.nytimes.com/2020/04/04/us/politics/coronavirus-zoom-college-classes.html.

[308] Press Release, SUNY, Chancellor Johnson Announces Distribution of Over 8,800 Laptops and Chromebooks to Students in Need to Complete their Spring Semester Coursework, Apr. 20, 2020, https://www.suny.edu/suny-news/press-releases/04-2020/4-20-20/index.html.

Many of our students, especially those in colleges and professional institutions, are experiencing disappointment and fear as a result of separation from friends and loved ones; delayed special events and graduations; altered coursework and grading rubrics; postponed and cancelled state and national examinations; withdrawn opportunities and deteriorating job markets. Thus, every effort must be made to provide a strong foundation of resources, guidance and support from which our educational leaders, families and students can build and thrive despite the challenges faced, with social equity and justice in mind.

Essential Health Care Services Workers

Generally, health care services workers are deemed essential workers under Governor Cuomo's EOs.[309] However, not all health care services are deemed essential in a public health emergency crisis such as the coronavirus pandemic. For instance, routine dental care, elective joint replacements, non-emergent podiatric care are not deemed essential health care services during this crisis which demonstrates "a fundamental priority shift from routine, patient-centric health care services to providing the best care possible to the largest numbers of victims" of the virus.[310] As non-essential health care services are put on pause, many duly qualified health care services personnel become part of the scarce resources that are reallocated and reassigned to best protect the public's health as health care institutions and facilities assess their relative capacity to manage patient surges arising from a major public health crisis. Other health care providers may travel to different jurisdictions to assist where the incidence of COVID-19 is concentrated; they may be reassigned to roles and responsibilities not within their current contracts or delineation of privileges; or they may be asked to perform outside the boundaries of their traditional scope of practice. These contractual and regulatory frameworks within which and the laws governing the manner in which licensed health care workers practice must be relaxed to allow health care institutions and facilities to incrementally increase clinical staff and resources, establish stand-by pools of providers, and re-deploy non-essential clinical staff to address patient influx greater than current capacity. Likewise, individual health care providers must be assured that by accepting such reassignments they are not unduly exposed to personal professional liability otherwise applicable under normal patient-centric standards of care.

State Licensure

The New York State Education Law governs licensure requirements and scope of practice for licensed health care services providers.[311] Such laws restrict state licensed health care services providers from crossing state lines even in response to a public health emergency. Licensed providers risk investigation, prosecution, and discipline including, but not limited to, exclusion from participation in Medicare and Medicaid, for practicing in a state without a valid license. Likewise, even retirees who have allowed their license registrations to expire risk investigation, prosecution and discipline for professional misconduct for practicing in the state without a current registration.[312]

Recognizing state licensure as a significant barrier to interjurisdictional movement of health care service workers to meet the public health needs in areas of concentrated incidence of COVID-19, Governor

---

[309] *See* Essential Workers EO, Appendix F.

[310] James G. Hodge, Jr., Dan Hanfling, and Tia P. Powell, *Practical, Ethical, and Legal Challenges underlying Crisis Standards of Care*, J. L. MED. & ETHICS, Spring 2012, at 51 citing INSTITUTE OF MEDICINE, Crisis Standards of Care: A Systems Framework for Catastrophic Disaster Response (2012).

[311] Health care services providers include physicians, physician assistants, registered nurses, licensed practical nurses, and nurse practitioners, whose scope of practice is defined under New York State Education Law §§ 6524, 6542, 6905, 6906, and 6902, respectively.

[312] *See* N.Y. ED. LAW §§ 6530 and 6509 (defining "professional misconduct" with respect to licensed health care services providers); *(See also Chapter on Business Contracts, Insurance and Risk Management for additional discussion.)*.

Cuomo's EO 202.5 effectively waived these laws to permit such cross jurisdictional coverage.[313] More recently, EO 202.18 further relaxed these laws to allow physicians, physician assistants, registered nurses, licensed practical nurses, nurse practitioners, licensed master social workers, licensed clinical social workers and other similarly licensed or registered practitioners in good standing in any province or territory of Canada to practice in New York without civil or criminal penalty related to lack of licensure or registration. EO 202.18 further relaxed state laws governing laboratory and pharmacy practitioners to allow flexibility in the provision of those essential services for a designated time period during the pandemic.

Credentialing Requirements

Health care organizations and payors of health care services are required by federal and state law to assure that certain health care providers (e.g., physicians, dentists, podiatrists, physician assistants, nurse practitioners) undergo a robust clinical and economic credentialing process to verify licensure, character and competence to practice medicine and receive reimbursement.[314] Such processes typically take months to complete. Waivers of these laws coupled with organizations' expedited credentialing processes permit health care organizations to honor the credentialing processes of other health care institutions outside their jurisdictions or within the same health care system to facilitate the swift interjurisdictional movement of health care services workers to meet public health needs in a crisis and avoid unnecessary delays due to lengthy credentialing processes. The Centers for Medicare and Medicaid appropriately waived some applicable Conditions of Participation processes to allow for physicians whose privileges will expire to continue to practice and for new physicians to be able to practice before full medical staff/governing body review required by credentialing processes. Likewise, Governor Cuomo's EO 202.5 waives New York state laws requiring a robust credentialing process to permit hospital staff who are privileged and credentialed to work in a hospital or health care facility in any other state to practice in a hospital or health care facility in New York State. To further protect licensed health care providers from individual liability, many health care organizations and facilities are adopting disaster privileging policies to complement their existing medical staff disaster privileging processes established by their medical staff bylaws to address corresponding risk associated with such waivers.[315]

Scope of Practice Principles

The scope of practice for each type of health care services worker is governed by the New York State Education Law.[316] Licensed and registered practitioners are not permitted to practice outside their respective statutory and regulatory scope of practice. The Nurse Practice Act limits registered nurses' ability to practice independently outside the scope of physician-ordered treatment regimen or other pre-approved clinical protocols.[317] The scope of practice of certain licensed health care practitioners working in health care institutions and facilities is further defined by their respective delineation of clinical privileges. Allied health professionals, such as physician assistants, although permitted to diagnose, treat and prescribe independently, may not practice outside the scope of practice of their respective supervising physician who is required to provide certain oversight.[318] The incremental expansion of clinical staff, establishment of stand-by pools and intra-system cross coverage arrangements may require licensed practitioners to be assigned administrative and/or clinical duties and responsibilities beyond their regulatory or contractual

[313] *See* N.Y. EXEC. ORDER No. 202.5, Continuing Temporary Suspension and Modification of Laws Relating to the Disaster Emergency, Mar. 18, 2020. https://www.governor.ny.gov/news/no-2025-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency (accessed Apr. 16, 2020).

[314] 42 C.F.R.§ 482.22; PUB. H. LAW §§ 2805-j and 2805-k; 10 NYCRR 405.4, 405.5, 405.14, 405.19, and 405.22.

[315] *See* also discussion pertaining to negligent credentialing, *infra*, Section IV, Business Contracts, Insurance and Risk Management.

[316] N.Y. ED. LAW, Title VIII.

[317] *See* N.Y. ED. LAW § 6905 (requirements to qualify for a license as a registered professional nurse).

[318] *See* N.Y. ED. LAW §§ 6540-6548; N.Y. PUB. H. LAW §§ 3700-3704; 10 NYCRR 94.2 (relating to the licensure and scope of duties of physician assistants).

scope of services. Credentialed providers that typically provide elective medical care may be re-deployed to provide services beyond their delineation of privileges as Executive Orders "pause" elective and other non-essential health care services. EOs issued by Governor Cuomo in New York have waived certain limitations on scope of practice. For instance, EO 202.10 waived oversight requirements allowing physician assistants and advanced practice registered nurses with certain higher educational degrees to practice without otherwise necessary physician oversight during the public health crisis.[319] The relaxation of these oversight requirements makes it easier to reallocate essential providers as needs eb and flow during the crisis.

Education and Training to Crisis Standards of Care

During a PHE such as the coronavirus pandemic, as the standard of care shifts from traditional patient-centric standards to crisis standards of care, health care services workers must be educated and trained on the medical-legal implications of CSC. Consistent application of CSC is essential to give assurances to health care services providers who will be asked to exercise their professional clinical judgment to save as many lives as possible, sometimes to the detriment of individual patients where practitioners are taught "first, do no harm."[320] As the standard of care shifts, practitioners need to be assured that their decisions pertaining to triage, allocation of medical equipment, supplies and medications are consistent with generally accepted CSC adopted during a crisis. CSC will further require general practitioners, not often trained in palliative care, to offer palliative care interventions to manage symptoms and mitigate suffering in the face of shortages of vital health care equipment such as ventilators.

Employees' Rights

Even in the face of a pandemic, employees' rights must be balanced with those of the public health needs. The safety of society's workforce is vital to the public's health. Mandatory shelter-in-place and work from home policies are designed to keep non-essential employees and perhaps the most vulnerable workers out of harm's way during the PHE. Essential workers that must report to work to assure essential resources, services and goods remain available and accessible are being asked to put their own health and welfare at risk for the greater public good. Employers must assure that they implement enforceable pervasive safety measures to effectively protect their employees on the front lines. The Occupational Safety and Health Administration ("OSHA") and the Centers for Disease Control and Prevention ("CDC") have issued guidance for employers to their employees remain safe in the workplace during the current coronavirus pandemic. These measures are guidance only and do not necessarily have the effect of law. Notwithstanding, general OSHA requirements to provide a safe workplace remain in full force and effect. Governor Cuomo's EO 202.16 similarly requires all essential business employers to provide masks to employees in the workplace who have direct contact with customers or the general public. Such directive is enforceable by local governments or law enforcement pursuant to Public Health Law, section 12 or 12-b.

Safe Workplace

As essential businesses continue to operate in the face of a public health crisis, employers must continue to assure a safe workplace for their employees. The most relevant OSHA requirements applicable to the prevention of occupational exposure to COVID-19 are as follows:

- The General Duty Clause requires employers to furnish to each worker "employment and a place of employment, which are free from recognized hazards that are causing or are likely to cause death or

[319] *See* N.Y. EXEC. ORDER No. 202.10, Continuing Suspension and Modification of Laws Relating to the Disaster Emergency, 23 Mar. 2020. https://www.governor.ny.gov/news/no-20210-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency (last accessed Apr. 16, 2020).

[320] *See* discussion in Ethics Issues in the Management of COVID-19, *infra*.

serious physical harm."[321] COVID-19 presents a threat where persons gather together. Employers need to assure adequate social distancing in the workplace as essential workers interact with each other, customers and the general public. Meetings should be conducted virtually using appropriate video/audio conferencing mechanisms when available or in large conference rooms that permit adequate distance between and among attendees.

- OSHA's Personal Protective Equipment (PPE) standards for general industry require employees to "use gloves, eye and face protection, and respirators when necessary. When respirators are necessary, employers must implement a comprehensive respiratory protection program in accordance with the Respiratory Protection standard."[322]

- OSHA's Bloodborne Pathogens standard applies to "occupational exposure to human blood and other potentially infectious materials that typically do not include respiratory secretions."[323] However, they offer guidance for the control of infectious disease such as COVID-19.

Compliance with these standards can prove to be difficult during a public health emergency such as the coronavirus pandemic due to scarce resources such as hand sanitizer, masks and other cleansing products. The health care services workforce is accustomed to using universal precautions which are the set of infection control practices used for all patient care to protect healthcare workers from infection and prevent the spread of infection from patient to patient.[324] Universal precautions include proper hand hygiene, use of PPE, respiratory hygiene including cough etiquette principles, proper cleaning and disinfecting the environment, equipment, devices and laundry. Non-health care essential services workers are not necessarily educated, trained or otherwise familiar with such extensive precautions. As a result, essential workers outside the health industry and their respective constituents may be faced with unnecessary risk of exposure or general fear despite good faith efforts to adopt applicable precautions.

Despite good faith efforts of employers of health care services employees and other essential services employees to educate their workforce on the implementation of CSC and the use of appropriate PPE consistent with CDC and OSHA guidance, there are members of the essential workforce that fear coming to work or interacting with customers or the public during the coronavirus pandemic. Do essential business employees and essential health care services employees have a right to choose to stay home and/or self-quarantine or refuse to provide health care to patients who have not been tested for the virus? If so, under what circumstances do or should they have that right?[325] Such tension between employees' rights and their role in assuring essential goods and services remain available and accessible during the public health crisis inevitably arise. Employers engaged in providing essential goods and services to the public in times of such public health crises must be prepared to have an abundance of PPE available and examine their operational processes to minimize risk to their workforce and demonstrate genuine concern for their welfare such as limiting the number of employees within the workplace, hypervigilant efforts to keep surfaces clean and disinfected, social distancing protocols when dealing with co-workers and constituents, and temperature checks to assure the workforce remains symptom-free while on at the worksite. In addition, employers may

[321] Occupational Safety and Health (OSH) Act of 1970, 29 U.S.C. 654(a)(1).
[322] 29 C.F.R.1910.134.
[323] 29 C.F.R.1910.1030.
[324] Standard Precautions for All Patient Care, CDC, Jan. 26, 2016, https://www cdc.gov/infection control/basics/standard-precautions.html.
[325] Health care providers treating patients in hospitals or other places of public accommodation where there is adequate availability of PPE must be cognizant of their risk of violating federal and state anti-discrimination laws and licensure requirements not to abandon patients when refusing to treat patients, especially those patients requiring emergency care and treatment for conditions other than COVID-19. *See* chapter discussing Contracts, Liability and Risk Management.

consider offering incentives to come to work such as hazard pay and alternative housing to protect families of health care services workers who may be putting their families at risk if they return home.

Protection against Retaliation

Health care services workers are keenly aware of the need for adequate PPE and other operational adjustments necessary to minimize unnecessary employee exposure during the coronavirus pandemic. In the event of a shortage of PPE, given the prevalence of social media communications, employers should be careful not to curtail employees' rights to free speech as employees voice concerns over equipment shortages and other weaknesses in our societal response to the pandemic. Health care services workers are accustomed to reporting their concerns as part of continuous performance improvement programs as mandated by New York State laws.[326] Employers must be receptive to employees' concerns, especially in times of crisis to demonstrate the mutual care and concern for those individuals who are putting their own safety at risk to care for the public's health. The Public Health Law affords confidentiality and immunity for those who report and/or participate in any investigation of an incident or other concerns.[327] Similarly, OSHA prohibits employers from retaliating against workers for raising concerns about safety and health conditions.[328] Additionally, "OSHA's Whistleblower Protection Program enforces the provisions of more than 20 industry-specific federal laws protecting employees from retaliation for raising or reporting concerns about hazards or violations."[329]

Discrimination

The Americans with Disabilities Act of 1990 ("ADA")[330] is a civil rights law that prohibits discrimination based upon disability. Among other provisions, it prohibits employers from making disability-related inquiries and requiring medical examinations of employees, except under limited circumstances. A "medical examination" is a procedure or test that seeks information about an individual's physical or mental impairment or health.[331] Whether a procedure is a medical examination under the ADA is determined by considering factors such as whether the procedure or test involves the use of medical equipment; whether it is invasive; whether it is designed to reveal the existence of a physical or mental impairment; and whether is it given or interpreted by a medical professional. During employment, the ADA prohibits employee disability-related inquiries or medical examinations unless they are job-related and consistent with business necessity where an employer has a reasonable belief, based upon objective evidence, that an employee will pose a direct threat due to a medical condition. Objective evidence under CSC principles would require that public health authorities set forth those objective parameters for such employee testing to assure a safe work environment for all workers. For instance, health care workers may be required by their employers to submit to a temperature check prior to entering the workplace to assure they do not present a direct threat to patients and staff.[332] "Direct Threat" is an important concept during the COVID-19 pandemic where individual's rights often cede to that of the public's health. During a pandemic, employers should rely on the latest CDC and state or local public health standards. While the EEOC recognizes that public health recommendations may change during a crisis and differ between states, employers are expected to make their best efforts to obtain public health advice that is contemporaneous and appropriate for their location, and to make reasonable assessments of conditions in their workplace based on this information.[333]

---

[326] *See* N.Y. PUB. H. LAW § 2805-l.
[327] *See* N.Y. Pub. H. Law § 2805-m.
[328] Occupational Safety and Health Act of 1970, 29 U.S.C. 660(c).
[329] OCCUPATIONAL HEALTH & SAFETY ADMINISTRATION, Safety and Health Topics/COVID-19, U.S. DEP'T OF LABOR, http://www.osha.gov/SLTC/COVID-19/standards.html.
[330] 42 U.S.C. § 12101 et. Seq.
[331] 42 U.S.C. § 12112 (d).
[332] *Id.*
[333] *See* Guidance of the CDC and public health authorities as of March 2020, the COVID-19 pandemic meets the direct threat standard**.** http://www.eeoc.gov/facts/pandemic_flu.html.

Further, employers should be mindful of their obligation to assess on a case by case basis employees' requests for leave as a reasonable accommodation under the ADA. Employees suffering from certain medical conditions may have a legitimate basis to support a request for leave or an extension of leave until the risk(s) associated with COVID-19 subsides. Employers who neglect to conduct such case by case analyses may risk exposure to allegations of unlawful discrimination or wrongful termination and the protracted litigation that may ensue long after the crisis abates.[334]

VI. Vaccination

When a vaccine becomes available, there will be a majority of Americans who want the vaccination.[335] However, some Americans may push back on the COVID-19 vaccination for religious, philosophical or personal reasons.[336] Nonetheless, for the sake of public health, mandatory vaccinations for COVID-19 should be required in the United States as soon as it is available. Mandatory vaccinations are supported by the authority of the state police power when the vaccinations are necessary to protect the health of the community.[337] Constitutional challenges under the religious freedom clause under the First Amendment and under the substantive due process clause of the Fourteenth Amendment have failed, when the individual interests are not strong enough to outweigh the public benefit.[338]

In New York State, the courts have found that religious, personal or "unsupported…medical literature"[339] arguments persuasive.[340] Healthcare workers[341] and parents of unvaccinated children[342] have unsuccessfully challenged compulsory vaccination on administrative law grounds – questioning the NYS and NYC Department of Health's authority in mandating flu and measles vaccinations, as well as challenging the regulations as arbitrary and capricious**.** The courts found the policies mandating that healthcare workers be vaccinated for influenza, and children vaccinated for measles during an outbreak, were not arbitrary and capricious and the regulations were promulgated under proper authority.[343] Further, on June 13, 2019, the religious exemption for vaccinating school-attending children was repealed.[344] The gravity of COVID-19 presents compelling justification for State legislatures and Congress to mandate a COVID-19 vaccination.

---

[334] *See* Arnold v. Pfizer, Inc., 970 F.Supp.2d 1106, Oregon Dist. Ct. (Sept. 9, 2013).
[335] CENTERS FOR DISEASE CONTROL AND PREVENTION, *National Center for Health Statistics: Immunization* (2018) https://www.cdc.gov/nchs/fastats/immunize.htm (70.4% of children aged 19-35 months receiving all 7 major vaccines).
[336] *Prince v. Massachusetts*, 321 U.S. 158, 167 (1944); *Cruzan by Cruzan v. Director Missouri Dept. of Health*, 497 U.S. 261, 262 (1990); *Phillips v. City of New York*, 775 F.3d 538, 542 (2d. Cir. 2015); *Caviezel v. Great Neck Public Schools*, 739 F.Supp.2d 273, 274-75 (E.D.N.Y. 2010) (*affm'd by Caviezel v. Great Neck Public Schools* 500 Fed.Appx. 16 (2d Cir. 2012).
[337] *See generally Jacobson v. Massachusetts*, 197 U.S. 11 (1905).
[338] *See Cruzan by Cruzan*, 497 U.S. at 278 (*citing Jacobson*, 197 U.S. at 24-30). *Prince*, 321 U.S. at 167. *Phillips*, 775 F.3d at 542. *Cavizel*, 739 F.Supp.2d at 274-75.
[339] *C.F. v. New York City Dept. of Health and Mental Hygiene*, 2019 NY Slip Op. 31047, at 4-6 (Apr. 18, 2019) (administrative ruling) (NYC Dept. of Health and Mental Hygiene regulation requiring any person who lives or works in "designated zip codes" to be vaccinate for MMR (measles)).
[340] *See Cruzan by Cruzan*, 497 U.S. at 262. *Prince*, 321 U.S. at 167. *Phillips*, 775 F.3d at 542. *Cavizel*, 739 F.Supp.2d at 274-75. *C.F.*, 2019 NY Slip. Op. 31047, at 4-6.
[341] *Spence v. Shah*, 136 A.D.3d 1242, 1246 (App. Div. 3d 2016) (NYS Department of Health did not exceed their power and the regulation requiring healthcare workers to receive an influenza vaccination or wear a face mask was not "arbitrary, capricious, irrational or contrary to law").
[342] *Garcia v. New York City Dept. of Health and Mental Hygiene*, 31 N.Y.3d 601, 621 (N.Y. 2018) (NYC Dept. of Health and Mental Hygiene was acting "…pursuant to its legislatively-delegated and long-exercised authority to regulate vaccinations" of children for influenza).
[343] *See Garcia*, 31 N.Y.3d at 621, *Spence*, 136 A.D.3d at 1246, *C.F.*, 2019 NY Slip. Op. 31047, at 4-6.
[344] PUB. H. LAW § 2164(9) (repealed Jun.13, 2019).

The U.S. Department of Health and Human Services developed the National Vaccine Program, to assist with vaccination production, distribution and education.[345] It also annually issues a National Vaccine Plan.[346] The National Vaccine Program addressed the development of a COVID-19 vaccine in its February 2020 meeting.[347]

Before the COVID-19 outbreak, a bill was introduced to federally mandate vaccination for school children.[348] Since the COVID-19 outbreak began, additional bills and resolutions have been introduced by the 116th Congress regarding vaccination and immunization.[349] They include resolutions by the House and Senate, supporting the GAVI Alliance, which supports vaccines and immunizations in developing countries.[350]

Some of the remaining pending federal bills and resolutions provide immediate insurance coverage for treatment of COVID-19, including a vaccination when one becomes available.[351] Others support wide-

[345] 42 U.S.C. §300aa-1 (2020).
[346] 42 U.S.C. §300aa-1 (2020). U.S. Dept. of Health & Human Services National Vaccine Program, The National Vaccine Program Office Mid-Course Review of the 2010 National Vaccine Plan, https://www.hhs.gov/sites/default/files/nvpo-midcourse-review-final.pdf.
[347] U.S. Dept. of Health & Human Services National Vaccine Program, *February 13-14, 2020 NVAC Meeting, Agenda* https://www.hhs.gov/vaccines/nvac/meetings/2020/02-13/index.html (in the 1:15pm slot, Dr. Alan Embry presented the Coronavirus Vaccine Development: Opportunities and Potential Pitfalls https://www.hhs.gov/sites/default/files/nvac_feb2020_day1_panel2.pdf).
[348] Recognizing the importance of vaccinations and immunizations in the United States, H.Res.179, 116th Cong. (introduced by Rep. Adam Schiff on Mar. 5, 2019); A resolution recognizing the importance of vaccinations and immunizations in the United States, S.Res.165, 116th Cong. (agreed to in the Senate on Apr. 11, 2019); Vaccinate All Children Act of 2019, H.R. 2527, 116th Cong. (introduced on May 3, 2019 by Rep. Frederica Wilson); VACCINES Act of 2019, H.R.2862, 116th Cong. (introduced by Rep. Kim Schrier on May 21, 2019); Vaccine Awareness Campaign to Champion Immunization Nationally and Enhance Safety Act of 2019, S.1619, 116th Cong. (introduced by Sen. Gary C. Peters on May 22, 2019); Protecting Seniors Through Immunization Act of 2019, S.1872, 116th Cong. (introduced by Sen. Mazie K. Hirono on Jun. 13, 2019); Pandemic and All-Hazards Preparedness and Advancing Innovation Act of 2019, S.1379, 116th Cong. (became law on June 24, 2019 as Public Law 116-22); Supporting Older Americans Act of 2020, H.R.4334, 116th Cong. (introduced by Rep. Suzanne Bonamici on Sept. 16, 2019); Protecting Seniors Through Immunization Act of 2019, H.R. 5076, 116th Cong. (introduced by Rep. Donna Shalala on Nov. 13, 2019).
[349] *See, e.g.*, Take Responsibility for Workers and Families Act, H.R. 6379, 116th Cong. (introduced Mar. 23, 2020 by Rep. Nita Lowey). Ensuring Coverage in Public Health Emergencies Act of 2020, H.R. 6317, 116th Cong. (introduced by Rep. Lloyd Doggett on Mar. 23, 2020). Ensuring Treatment for Covid Act, S.3564, 116th Cong. (introduced by Sen. Robert P. Casey, Jr. on Mar 22, 2020). Care for COVID-19 Act, H.R.6311, 116th Cong. (introduced by Rep. Raul Ruiz on Mar. 19, 2020). Rapid Coverage of COVID-19 Vaccine Act of 2020, H.R. 6299, 116th Cong. (introduced Mar. 19, 2020 by Rep. Joe Courtney). Ensuring Coverage in Public Health Emergencies Act of 2020, S.3536, 116th Cong. (introduced by Sen. Robert P. Casey, Jr. on Mar. 19, 2020). Rapid Coverage for Coronavirus Vaccines Act, S.3505, 116th Cong. (introduced by Sen. Doug Jones on Mar. 17, 2020). Ensuring Access to COVID-19 Preventive Care Act of 2020, H.R. 6231, 116th Cong. (introduced by Rep. Larry Bucshon on Mar. 12, 2020). Ensuring Affordable COVID-19 Preventive Care Act of 2020, H.R. 6222, 116th Cong. (introduced by Rep. Janice Schakowsky on Mar. 12, 2020). Care for COVID-19 Act, S.3442, 116th Cong. (introduced by Sen. Cory A. Booker on Mar. 11, 2020). Coronavirus Vaccine Act, S.3370, 116th Cong. (introduced by Sen. Edward Markey on Mar. 2, 2020). Protecting Americans from Seasonal Influenza Act of 2020, H.R.5729, 116th Cong. (introduced by Rep. Rick Larsen on Jan. 30, 2020).
[350] A resolution supporting the role of the United States in helping save the lives of children and protecting the health of people in developing countries with vaccines and immunization through GAVI, the Vaccine Alliance, S.Res.511, 116th Cong. (introduced by Sen. Marco Rubio on Feb. 27, 2020); Supporting the role of the United States in helping save the lives of children and protecting the health of people in poor countries with vaccines and immunization through the GAVI Alliance, H.Res.861, 116th Cong. (introduced by Rep. Betty McCollum on Feb. 21, 2020).
[351] Ensuring Coverage in Public Health Emergencies Act of 2020, H.R. 6317, 116th Cong. (introduced by Rep. Lloyd Doggett on Mar. 23, 2020); Ensuring Treatment for Covid Act, S.3564, 116th Cong. (introduced by Sen. Robert P. Casey, Jr. on Mar 22, 2020); Care for COVID-19 Act, H.R.6311, 116th Cong. (introduced by Rep. Raul Ruiz on Mar. 19, 2020); Ensuring Coverage in Public Health Emergencies Act of 2020, S.3536, 116th Cong. (introduced by Sen. Robert P. Casey, Jr. on Mar. 19, 2020); Rapid Coverage of COVID-19 Vaccine Act of 2020, H.R. 6299, 116th Cong. (introduced Mar. 19, 2020 by Rep. Joe Courtney); Rapid Coverage for Coronavirus Vaccines Act, S.3505, 116th Cong. (introduced by Sen. Doug Jones on Mar. 17,

spread vaccination across the United States.[352] These include bills offering wide-spread vaccination programs that are subsidized by the federal government for seniors and children.[353] In the "Protecting Seniors Through Immunization Act of 2019," the Medicare program will encourage and provide free vaccinations to seniors already covered.[354] The "Vaccinate All Children Act of 2019" will require vaccinations for every student at a public elementary and secondary school to be vaccinated in order to receive federal grants, with only medical exemptions allowed.[355] Given these proposals, vaccination distribution and funding will likely be heavily influenced by Congress.

The devasting impact of COVID-19 has led to the call for solutions that will help return our society to normalcy, elevating the importance of ensuring scientists and legislators move cautiously but quickly to provide vaccines and treatments. The history of unsuccessful attempts to challenge mandatory vaccinations may reduce the extent of opposition. As Hastings Center scholars have said, to avoid, "COVID-19 interventions [joining] the list of others that entered the clinic on the basis of limited or contested evidence of effectiveness and then harmed patients or proved to be ineffective[, strategies] can be developed to minimize this from happening, but they will only work with commitment from scientists, physicians, policymakers, patients, and the general public."[356] Deliberate, reasoned attention to such strategies is imperative.

VII. Vulnerable Populations and Issues of Equity and Discrimination: A Call for Social Justice

An often overlooked set of legal and ethical issues in the context of the COVID-19 crisis and crisis conditions concerns the impact of the crisis on vulnerable populations, especially with respect to the heightened precarity of such populations as a result of the present crisis and the serious threats the crisis poses to health and mental health, well-being, and post-crisis recovery and resilience.

The public health law perspective is well suited to the examination of issues of equity across diverse populations and communities in New York during the crisis, assessing the responsiveness of the law to the needs of all persons and communities across settings, including communities of color, vulnerable persons such as older adults and persons with disabilities, and all those who are isolated, home-bound or living in residential, correctional or detention facility settings, as well as vulnerable health care workers in under-resourced communities.

2020); Ensuring Affordable COVID-19 Preventive Care Act of 2020, H.R. 6222, 116th Cong. (introduced by Rep. Janice Schakowsky on Mar. 12, 2020); Ensuring Access to COVID-19 Preventive Care Act of 2020, H.R. 6231, 116th Cong. (introduced by Rep. Larry Bucshon on Mar. 12, 2020); Care for COVID-19 Act, S.3442, 116th Cong. (introduced by Sen. Cory A. Booker on Mar. 11, 2020).

[352] Recognizing the importance of vaccinations and immunizations in the United States, H.Res.179, 116th Cong. (introduced by Rep. Adam Schiff on Mar. 5, 2019); A resolution recognizing the importance of vaccinations and immunizations in the United States, S.Res.165, 116th Cong. (agreed to in the Senate on Apr. 11, 2019).

[353] Vaccinate All Children Act of 2019, H.R. 2527, 116th Cong. (introduced on May 3, 2019 by Rep. Frederica Wilson); Protecting Seniors Through Immunization Act of 2019, S.1872, 116th Cong. (introduced by Sen. Mazie K. Hirono on Jun. 13, 2019); Protecting Seniors Through Immunization Act of 2019, H.R. 5076, 116th Cong. (introduced by Rep. Donna Shalala on Nov. 13, 2019).

[354] Protecting Seniors Through Immunization Act of 2019, S.1872, 116th Cong. (introduced by Sen. Mazie K. Hirono on Jun. 13, 2019); Protecting Seniors Through Immunization Act of 2019, H.R. 5076, 116th Cong. (introduced by Rep. Donna Shalala on Nov. 13, 2019).

[355] Vaccinate All Children Act of 2019, H.R. 2527, 116th Cong. (introduced on May 3, 2019 by Rep. Frederica Wilson).

[356] Karen J. Maschke & Michael K. Gusmano, *Ethics and Evidence in the Search for a Vaccine and Treatments for COVID-19*, The Hastings Center, Bioethics Forum, Apr. 16, 2020, https://www.thehastingscenter.org/ethics-and-evidence-in-the-search-for-a-vaccine-and-treatments-for-COVID-19/.

As framed in Part I of the report, public health law effects a shift from person-centered clinical care to community and population health, and the social and economic determinants of health, such as education, neighborhood, income, race and ethnicity, food insecurity, and access to health and mental health services.

COVID-19 has tragically resulted in the heightening of precarity among those who are already vulnerable and marginalized, such as older persons, members of communities of color or low-income communities, inmates, immigrants, nursing home and assisted living facility residents, persons who are homeless, persons with disabilities, and rural-dwelling community members. Health disparities across these groups, including among health care workers who are members of such groups, are well documented.[357] Data reported during the current crisis document higher numbers of COVID-19 positive cases and higher mortality rates among Black/African Americans and other marginalized and socioeconomically disadvantaged groups.[358] New York City Department of Health data show rates of cases, hospitalizations and deaths by race/ethnicity group, reflecting stark disparities across Black/African American, Hispanic/Latino, White and Asian groups,[359] as well as across the five boroughs.[360] Crisis conditions of scarce resources, such as PPE, dialysis machines, and ventilators, also heighten the precarity of vulnerable individuals who are more likely to have advanced illness, and therefore less likely to access life-saving measures based on certain crisis standard of care plans that use allocation criteria risking discrimination.[361] While federal law bars such discrimination,[362] forms of persistent discrimination and racism that remain embedded in our social structures, and less visible in non-emergency circumstances, are more prominently foregrounded in the crisis conditions of the COVID-19 emergency.

Health Care Workers and Essential Services

Strategic initiatives and efforts are desperately needed, in addition to increased access to protective equipment and testing to protect immuno-compromised or otherwise high-risk populations who work on the front lines. Statistically, a disproportionate number of older, minority and immigrant populations with limited access to quality health care work in low-paying front-line jobs deemed "essential" in the midst of the crisis, including direct service workers.[363] As we plan to reopen the economy, we must consider a way to protect individuals on the front lines identified by health care providers as very high-risk individuals based on their health status and underlying health conditions in the interest of the health of the individual, public health as a state and local community, and mitigating fatalities nationally.

We are confronted too with the social and ethical problem of access to health care and education for some of our most vulnerable populations, such as individuals with disabilities, especially as related to direct care services. The Office for People with Disabilities (OPWDD) has issued guidance stating that Direct Support Professionals (DSPs) are "essential and integral employees to OPWDD's provision of services" which is

---

[357] Aaron van Dorn, Rebecca E. Cooney & Mariam L. Sabin, *COVID-19 exacerbating inequalities in the US*, 395.
[358] *Id*.; COVID-19 exacerbating inequalities in the US, LANCET, Vol. 395, Apr. 18, 2020; Yancy CW, COVID-19 and African Americans, JAMA, Published online Apr. 15, 2020, doi:10.1001/jama.2020.6548.
[359] Age-adjusted rates of lab confirmed COVID-19 nonhospitalized cases, estimated non-fatal hospitalized cases, and patients known to have died 100,000 by race/ethnicity group as of Apr. 16, 2020, https://www1.nyc.gov/assets/doh/downloads/pdf/imm/COVID-19-deaths-race-ethnicity-04162020-1.pdf.
[360] NEW YORK CITY DEPARTMENT OF HEALTH, Rates by Borough of positive cases per 100,000 people in each borough, https://www1.nyc.gov/site/doh/Covid/COVID-19-data.page#download,
[361] Ari Ne'eman & Sam Bagenstos, Evaluation Framework for Crisis Standard of Care Plans, Apr. 8, 2020, http://thearc.org/wp-content/uploads/2020/04/Evaluation-framework-for-crisis-standards-of-care-plans-4.9.20-final_4-14-20.pdf.
[362] 42 U.S.C. §§ 2000 *et. seq.*; HHS Office for Civil Rights in Action, Bulletin: *Civil Rights, HIPAA, and the Coronavirus Disease 2019 (COVID-19)*, Mar. 28, 2020, https://www.hhs.gov/sites/default/files/ocr-bulletin-3-28-20.pdf.
[363] NEW YORK STATE OFFICE FOR PEOPLE WITH DEVELOPMENTAL DISABILITIES, *Direct Support Professionals Defined As Essential Employees*, Mar. 18, 2020; *See also* Dorn, *supra* note 1.

"especially true during this public health emergency,"[364] which echoes that of the New York State Department of Education.[365] The Department further clarified that agencies which provide services to individuals with developmental disabilities and are operated, certified, authorized or funded by OPWDD are exempt and "should remain in operation to the extent necessary to provide those services."[366] The failure to do such could potentially result in the suspension or limitation of a provider's operating certificate.[367] However, some patients and students who receive therapies in their homes and schools are not receiving such critical direct care services, despite them being prescribed by a physician and covered by health insurance. Moreover, the temporary expansion of Title 1 of the Family and Medical Leave Act (FMLA)[368] and adoption of "The Emergency Paid Sick Leave Act" under The Families First Coronavirus Response Act[369], do not provide relief for families who must care for vulnerable adult children who are unable to attend adult day care facilities due to government shut-downs.

Thus, anecdotal evidence suggests lack of uniformity in access to services, such as therapeutic interventions for individuals with autism, in response to the implementation of "New York State on Pause," enacted by Governor Cuomo, which are designed to minimize the transmission of the COVID-19 virus through social distancing and business closures.[370] Some providers may be unsure as to whether the OPWDD exemption applies to them, especially if the provider serves the disabled community but is not a licensed OPWDD provider, while others may opt to not provide services in light of the pandemic. Whichever is the case, interruption of such services for even short periods of time, let alone the duration of the pandemic's "PAUSE" period, significantly increases the risk of adverse outcomes when such services are necessary to maintain physiological and emotional stability, while facilitating health and social progress.[371]

The scope of this issue is expansive as it also impacts our young and adult patients and minor students residing in schools for the developmentally disabled or other TBI programs where they would otherwise receive physical and occupational therapy, and other services essential to their unique physical and mental needs. Considering this, it is imperative that any clarification necessary to ensure that exempt providers are operating in accordance with OPWDD guidance be published. Furthermore, providers not regulated by the OPWDD, but are otherwise exempt, should be advised to continue to serve any patients with which a treatment relationship has been established, if able, or refer the patient elsewhere to prevent patient abandonment.[372] This is critical from not only a professional but ethical standpoint, and in the best interest of public health.

---

[364] NEW YORK STATE OFFICE FOR PEOPLE WITH DEVELOPMENTAL DISABILITIES, *supra* note 4.
[365] THE STATE EDUCATION DEPARTMENT, *Additional Guidance on Statewide School Closures Due to Novel Coronavirus (COVID-19) Outbreak in New York State*, Mar. 17, 2020.
[366] NEW YORK STATE OFFICE FOR PEOPLE WITH DEVELOPMENTAL DISABILITIES, *COVID-19 Guidance for Providers on Essential Business*, Mar. 20, 2020.
[367] N.Y. EXEC. ORDER No. 202.5, Mar. 18, 2020.
[368] 29 U.S.C. § 2601 *et. seq.*
[369] Families First Coronavirus Response Act, Public Law No. 116-127 (Mar. 18, 2020) (*to be added as* 29 U.S.C. §§ 2601 *et. seq.*). Paid Leave Under the Families First Coronavirus Response Act, 85 Fed. Reg. 19,326 (Apr. 6, 2020).
[370] N.Y. EXEC. ORDER No. 202.8, Mar. 20, 2020, https://www.governor.ny.gov/news/no-2028-continuing-temporary-suspension-and-modification-laws-relating-disaster-emergency. *See also* NEW YORK STATE, *Governor Cuomo Signs the 'New York State on PAUSE' Executive Order*, Mar. 20, 2020, https://www.governor.ny.gov/news/governor-cuomo-signs-new-york-state-pause-executive-order.
[371] *See generally* Mary Beth Walsh, *The Top 10 Reasons Children With Autism Deserve ABA*, 1 BEHAVIOR ANALYSIS PRACTICE 72-79 (2011).
[372] *See generally* Valerie Blake, J.D., M.A., *When Is a Patient-Physician Relationship Established?*, AMERICAN MEDICAL ASSOCIATION JOURNAL OF ETHICS (May 2012).

Action Steps

In sum, the COVID-19 crisis has illuminated the social structural inequities in the health systems and put the most vulnerable populations and communities of color, including vulnerable health care workers, at the highest risk. The Task Force urges action steps, including appropriate regulatory oversight, to ensure:

- adequate and non-discriminatory allocation of resources to vulnerable populations and communities of color;
- equitable access of vulnerable populations to health and mental health services, including palliative care as an ethical minimum to mitigate suffering among those vulnerable persons who remain in residence or institutionalized in nursing homes, assisted or independent living facilities or group homes, or are hospitalized during the COVID-19 crisis, especially when desired equipment or other resources are not available;
- provision of PPE to essential health care workers at highest risk in delivering essential services to vulnerable populations; and
- monitoring conformity with federal laws barring discrimination.

We call for urgent attention to these issues both in the context of the current crisis, as well as through long-term health policy planning. In the words of our esteemed colleague and public health law scholar Lawrence O. Gostin, we must settle for no less than a fully unburdened, "global health with justice."[373]

VIII. Conclusion

The preceding Sections of this Report contain a number of specific recommendations which may be found in summary form in Appendix F. The following observations present overarching recommendations to further strengthen both New York State's emergency preparedness capabilities and its general delivery of health care.

Improving Preparation for Next Public Health Emergency

COVID-19 has proven that city, state and federal emergency preparedness efforts, which were enhanced after 9/11, are insufficient for an extreme public health crisis. The Task Force recommends that Governor Cuomo keep a core team of experts in place to review the MSEHPA, the Columbia University Center for Health Policy Gap Analysis, [374] IOM's Crisis Standards of Care, as applicable, equipment allocation guidelines,[375] and each of the emergency orders needed to manage COVID-19. This team could be charged with drafting legislation to combine the essential provisions of these useful resources.

Legislation in New York, and other states which have not yet adopted the MSEHPA and the CSC, would facilitate the immediate activation of most if not all of the emergency orders which have been needed to manage COVID-19.

Further, Governor Cuomo will soon become the Chair of the National Governors Association.[376] In that role, New York will be well placed to facilitate a coordination of efforts across the states. Effective state coordination will place each state in a position to be less vulnerable to inadequate federal action.

---

[373] LAWRENCE O. GOSTIN, GLOBAL HEALTH LAW 72 (Har. Univ. Press 2014).

[374] Benjamin Mason Meier & Jocelyn Getgen, *Gap Analysis: Comparing the Model State Emergency Health Powers Act with Corresponding New York State And New York City Statutory Authority*, CENTER FOR HEALTH POLICY, Columbia University (2008).

[375] *See* discussion *infra,* Section II of this Report, Ethical Issues in the Management of COVID-19.

[376] National Governors Association, Executive Committee, *https://www.nga.org/governors/ngaleadership/.*

Evaluation of Laws and Regulations Post-Pandemic

For the purposes of assuring a post-pandemic legal environment that serves the public well, we also call for evaluation of the state and federal laws and regulations that have been waived during the pandemic. CMS has provided a convenient list of the federal and state COVID-19 waivers.[377] In the post-COVID 19 world, both government and health care providers will face enormous financial pressure. Before being automatically reinstated, laws and regulations that have been waived during the pandemic should be critically re-evaluated in terms of benefit to the public, as well as the costs and administrative and enforcement burdens to government. For instance, emergency waivers relating to EMTALA, HIPAA and 42 CFR Part 2, and federal fraud and abuse laws have elements that could be continued in the post-COVID-19 world. At the New York State level, some scope of practice requirements, CON requirements and directives to managed care organizations should be reviewed before waivers and directives are lifted. In short, this emergency provides an opportunity to re-test waived regulations for new circumstances.

It is evident through the progress in "flattening the curve" achieved to date that employers, employees, and community members at large in the State of New York are committed to working hard to maintain and ultimately re-strengthen our economy while keeping public health, safety and community values at the forefront of their efforts. If we continue to commit ourselves to pressing forward in a united fashion and reaching beyond the racial, socioeconomic, geographic and political barriers that often seek to divide us, our communities and the State of New York can not only heal, but be transformed and strengthened in a fashion beyond our comprehension.

[377] CMS, CMS list of Coronavirus Waivers & Flexibilities, available at: https://www.cms.gov/about-cms/emergency-preparedness-response-operations/current-emergencies/coronavirus-waivers.

APPENDIX A

New York State Bar Association Health Law Section Letter to Governor Cuomo, March 26, 2020

COVID-19 New York Public Health Emergency and Disaster Conditions: Call for Essential Crisis Standards in New York

APPENDIX B

University of Rochester Medical Center Decision Algorithms (2015 NYSTFLL Guidelines)

2015 Ventilator Allocation Guidelines, NYS Task Force

University of Rochester 2015 Updated Ventilator Allocation Flow Diagrams

APPENDIX C
Health Law Section Proxy Law Memo

TO: Howard Zucker, MD, Commissioner, NYSDOH
Megan Baldwin, Assistant Secretary, Executive Chamber

FROM: NYSBA Health Law Section
RE: **Health Care Proxy Barriers and Solutions**

The New York State Bar Association (NYSBA) Health Law Section was pleased to learn about Executive Order 202.14, which should make it much easier for most people to complete a health care proxy when two witnesses are not physically present. However, it is not enough to help the most vulnerable, those who have no one to witness or have only one person, or those who don't have access to, cannot use, or cannot be taught to use technology.

Therefore, the NYSBA Health Law Section supports additional urgently needed reforms to ensure that people are able to complete valid health care proxies.

In the midst of the coronavirus pandemic, we have learned that many patients want to complete health care proxies, but cannot as there are no available witnesses given the social distancing and quarantine requirements. We have also heard from clinicians that many patients have no advance directives, especially as hospitals continue to become overwhelmed. There is little doubt that similar problems must exist in other facilities, such as nursing homes.

It is critically important that patients have the ability to complete health care proxies, but existing legal barriers will still prevent some people, despite EO 202.14, from doing so.

Urgent measures are needed, either legislatively or through Executive Order, to address this concern, including:

- Removing the two-witness requirement and requiring only one witness.
- If no witnesses are available, provide the option of requiring only a notary public signature.
- If a notary is used, allowing an audio-visual notarization as the Governor's Executive Order 202.7 now allows for other notary services.
- Allowing for individuals who do not have access to the technology which enables them to accomplish video conference witnessing, to have a valid health care proxy if the patient communicates auditorily to two witnesses the name of their health care agent and possible alternate(s). The communication to the witnesses does not need to be simultaneous and can happen at separate times. Such witnesses' contact information shall be stated in the document and such witnesses shall be willing to confirm they heard the principal express their wishes if contacted by a health care facility.
- All the above would include the I/DD population, but required capacity determination should remain in effect.
- Accelerating the effective date regarding the amendments to PHL 29-CCC on physician assistants (currently June 17, 2020) regarding MOLST forms which it is possible, but unclear, that Executive Order 202.10 now does.

Implementing these measures will make it more likely that patients will get health care and treatment that they want and need, and make it easier for health care professionals to both know the health care wishes of their patients.

Others who are experts in the field, doctors, lawyers and organizations which work with people on advance care planning and specifically health care proxies, also support the urgent need for the reforms proposed. These include among others, those listed below.

Patricia A. Bomba, MD, MACP, FRCP
Vice President & Medical Director, Geriatrics, Excellus BlueCross BlueShield
Chair, MOLST Statewide Implementation Team
MOLST & eMOLST Program Director
Chair, National Healthcare Decisions Day NYS Coalition

Carla Braveman
President & CEO
Hospice and Palliative Care Association of New York State

Thomas V. Caprio, MD, MPH, MS
Director, Finger Lakes Geriatric Education Center
Chief Medical Officer, UR Medicine Home Care & Hospice
University of Rochester Medical Center

CaringKind

Maggie Carpenter, MD, HMDC
Nightingale Medical

Sarah Egan, MD
Hospice and Palliative Medicine
Brooklyn, NY

David N. Hoffman, Esq.
Compliance Officer
Carthage Area Hospital and Claxton-Hepburn Medical Center

Robert Milch, MD, FACS
Professor, Clinical Surgery
University at Buffalo
Jacobs School of Medicine

New York Legal Assistance Group (NYLAG)

Volunteers of Legal Service

APPENDIX D

New York State Bar Association Department of Health Proposed Rulemaking in Relation to the Release of Subject-Identified Research Findings

Proposed Rule by the NYSBA Health Law Section

Proposal in Relation to the Release of Subject-Identified Research Findings

APPENDIX E

State Society on Aging of New York Letter to Governor Cuomo, April 30, 2020

COVID-19 New York Public Health Emergency and Disaster Conditions: Call for Equitable Allocation of Scarce Resources to Older Adults and Non-Discriminatory Crisis Standards

APPENDIX F

GUIDANCE FOR DETERMINING WHETHER A BUSINESS ENTERPRISE IS SUBJECT TO A WORKFORCE REDUCTION UNDER RECENT EXECUTIVE ORDERS (enacted to address the COVID-19 Outbreak)[378]

ESSENTIAL BUSINESSES OR ENTITIES, including any for-profit or non-profit, regardless of the nature of the service, the function they perform, or its corporate or entity structure, are not subject to the in-person restriction. *Essential Businesses must continue to comply with the guidance and directives for maintaining a clean and safe work environment issued by the Department of Health (DOH) and every business, even if essential, is strongly urged to maintain social distancing measures to the extent possible.*

This guidance is issued by the New York State Department of Economic Development d/b/a Empire State Development (ESD) and applies to each business location individually and is intended to assist businesses in determining whether they are an essential business. With respect to business or entities that operate or provide both essential and non-essential services, supplies or support, only those lines and/or business operations that are necessary to support the essential services, supplies, or support are exempt from the workforce reduction restrictions.

State and local governments, including municipalities, authorities, and school districts, are exempt from these essential business reductions, but are subject to other provisions that restrict non-essential, in-person workforce and other operations under Executive Order 202.

For purposes of Executive Order 202.6, "Essential Business," shall mean businesses operating in or as:

1. **Essential health care operations including**
   - research and laboratory services
   - hospitals
   - walk-in-care health clinics and facilities
   - emergency veterinary, livestock medical services
   - senior/elder care
   - medical wholesale and distribution
   - home health care workers or aides for the elderly
   - doctor and emergency dental
   - nursing homes, residential health care facilities, or congregate care facilities
   - medical supplies and equipment manufacturers and providers
   - licensed mental health providers
   - licensed substance abuse treatment providers
   - medical billing support personnel
   - emergency chiropractic services
   - physical therapy, prescribed by medical professional
   - occupational therapy, prescribed by medical professional

2. **Essential infrastructure including**
   - public and private utilities including but not limited to power generation, fuel supply, and transmission

[378] Please note that the content below represents an abridged version of content noted on the following Empire State Development website, https://esd.ny.gov/guidance-executive-order-2026.

- public water and wastewater
- telecommunications and data centers
- airlines/airports
- commercial shipping vessels/ports and seaports
- transportation infrastructure such as bus, rail, for-hire vehicles, garages
- hotels, and other places of accommodation

3. **Essential manufacturing including**
   - food processing, manufacturing agents including all foods and beverages
   - chemicals
   - medical equipment/instruments
   - pharmaceuticals
   - sanitary products including personal care products regulated by the Food and Drug Administration (FDA)
   - telecommunications
   - microelectronics/semi-conductor
   - food-producing agriculture/farms
   - household paper products
   - defense industry and the transportation infrastructure
   - automobiles
   - any parts or components necessary for essential products that are referenced within this guidance

4. **Essential retail including**
   - grocery stores including all food and beverage stores
   - pharmacies
   - convenience stores
   - farmer's markets
   - gas stations
   - restaurants/bars (but only for take-out/delivery)
   - hardware, appliance, and building material stores
   - pet food
   - telecommunications to service existing customers and accounts
   - delivery for orders placed remotely via phone or online at non-essential retail establishments; provided, however, that only one employee is physically present at the business location to fulfill orders

5. **Essential services including**
   - trash and recycling collection, processing, and disposal
   - mail and shipping services
   - laundromats and other clothing/fabric cleaning services
   - building cleaning and maintenance
   - childcare services
   - bicycle repair
   - auto repair
   - automotive sales conducted remotely or electronically, with in-person vehicle return and delivery by appointment only
   - warehouse/distribution and fulfillment
   - funeral homes, crematoriums and cemeteries
   - storage for essential businesses

- maintenance for the infrastructure of the facility or to maintain or safeguard materials or products therein
- animal shelters and animal care including dog walking, animal boarding
- landscaping, but only for maintenance or pest control and not cosmetic purposes
- designing, printing, publishing and signage companies to the extent that they support essential businesses or services
- remote instruction or streaming of classes from public or private schools or health/fitness centers; provided, however, that no in-person congregate classes are permitted

6. News media

7. Financial Institutions including
- banks or lending institution
- insurance
- payroll
- accounting
- services related to financial markets, except debt collection

8. Providers of basic necessities to economically disadvantaged populations including
- homeless shelters and congregate care facilities
- food banks
- human services providers whose function includes the direct care of patients in state-licensed or funded voluntary programs; the care, protection, custody and oversight of individuals both in the community and in state-licensed residential facilities; those operating community shelters and other critical human services agencies providing direct care or support

9. Construction

All non-essential construction must safely shut down, except emergency construction, (e.g. a project necessary to protect health and safety of the occupants, or to continue a project if it would be unsafe to allow to remain undone, but only to the point that it is safe to suspend work).

Essential construction may proceed, to the extent that:
- construction is for, or your business supports, roads, bridges, transit facilities, utilities, hospitals or healthcare facilities, homeless shelters, or public or private schools;
- construction is for affordable housing
- construction is necessary to protect the health and safety of occupants of a structure;
- construction is necessary to continue a project if allowing the project to remain undone would be unsafe, provided that the construction must be shut down when it is safe to do so;
- construction is for projects in the energy industry
- construction is for existing (i.e. currently underway) projects of an essential business; or
- construction work is being completed by a single worker who is the sole employee/worker on the job site.

10. Defense
- defense and national security-related operations supporting the U.S. Government or a contractor to the US government

11. Essential services necessary to maintain the safety, sanitation and essential operations of residences or other businesses including

- law enforcement, including corrections and community supervision
- fire prevention and response
- building code enforcement
- security
- emergency management and response, EMS and 911 dispatch
- building cleaners or janitors
- general maintenance whether employed by the entity directly or a vendor
- automotive repair
- disinfection
- residential moving services

12. **Vendors that provide essential services or products, including logistics and technology support, child care and services including but not limited to:**
    - logistics
    - technology support for online services
    - childcare programs and services
    - government owned or leased buildings
    - essential government services
    - any personnel necessary for online or distance learning or classes delivered via remote means

13. **Recreation**
    - Parks and other open public spaces, except playgrounds and other areas of congregation where social distancing cannot be abided
    - However, golf courses are not essential and cannot have employees working on-premise; notwithstanding this restriction, essential services, such as groundskeeping to avoid hazardous conditions and security, provided by employees, contractors, or vendors are permitted and private operators may permit individuals access to the property so long as there are no gatherings of any kind and appropriate social distancing of six feet between individuals is strictly abided
    - Marinas, boatyards, and recreational marine manufacturers, for ongoing marina operations and boat repair/maintenance, where such facilities adhere to strict social distancing and sanitization protocols. Use of such sites for the purposes of personal use or operation of boats or other watercraft is permissible, provided that no establishment offer chartered watercraft services or rentals. Restaurant activity at such sites are limited to take-out or delivery only.

14. **Professional services with extensive restrictions**
    - Lawyers may continue to perform all work necessary for any service so long as it is performed remotely. Any in-person work presence shall be limited to work only in support of essential businesses or services; however, even work in support of an essential business or service should be conducted as remotely as possible.
    - Real estate services shall be conducted remotely for all transactions, including but not limited to title searches, appraisals, permitting, inspections, and the recordation, legal, financial and other services necessary to complete a transfer of real property; provided, however, that any services and parts therein may be conducted in-person only to the extent legally necessary and in accordance with appropriate social distancing and cleaning/disinfecting protocols; and nothing within this provision should be construed to allow brokerage and branch offices to remain open to the general public (i.e. not clients).

Restrictions on requesting designation as an essential business:

Pursuant to the Governor's Executive Orders, the following businesses are specifically enumerated as non-essential and are, therefore, unable to request a designation:

- Any large gathering or event venues, including but not limited to establishments that host concerts, conferences, or other in-person performances or presentations in front of an in-person audience;
- Any dine-in or on-premise restaurant or bar service, excluding take-out or delivery for off-premise consumption;
- Any facility authorized to conduct video lottery gaming or casino gaming;
- Any gym, fitness centers, or exercise classes, except the remote or streaming service noted above;
- Any movie theater;
- Any indoor common portions of retail shopping malls with 100,000 or more square feet of retail space available for lease;
- All places of public amusement, whether indoors or outdoors, including but not limited to, locations with amusement rides, carnivals, amusement parks, water parks, aquariums, zoos, arcades, fairs, children's play centers, funplexes, theme parks, bowling alleys, family and children's attractions; and
- Any barbershops, hair salons, tattoo or piercing parlors and related personal care services, including nail technicians, cosmetologists and estheticians, and the provision of electrolysis, laser hair removal services.

APPENDIX G
Task Force Recommendations

The Task Force acknowledges the leadership of New York State Governor Andrew M. Cuomo and Commissioner of Health Howard A. Zucker, M.D., J.D., during the State Disaster Emergency. Governor Cuomo and Commissioner Zucker *inter alia* rapidly and creatively adapted State policies to: **(1)** prevent the spread of the COVID-19 pandemic**, (2)** enhance the ability of health care providers to treat and care for persons suffering from COVID-19, and **(3)** protect health care workers in doing so.

The members of the Task Force recommend the following actions in order to build upon the Governor's and Commissioner's considerable accomplishments to date:

1. **Public Health Law Framework and Legal Reforms:**

   The Department of Health (or through it the Task Force on Life and the Law) to review and consider:

   (a) Enactment into New York Law of the Model State Emergency Health Powers Act (MSEHPA), which was developed by the Center for Law and Public Health and the Public Health at Georgetown and John Hopkins Universities in 2001, as informed by the Columbia University Center for Health Policy Gap Analysis and as otherwise updated; and

   (b) Adoption of the, "Crisis Standards of Care," developed by the Institute of Medicine in 2012, as is, or as otherwise updated and amended, by the New York State Department of Health (or through it The Task Force on Life and the Law).

2. **Ethical Issues in the Management of COVID-19:**

   (a) Allocation of Life-Saving Equipment: The Task Force on Life and the Law (NYSTFLL) or New York State Department of Health or Governor to:

      i. Review and consider whether the 2015 Task Force Report entitled, "Ventilator Allocation Guidelines" requires updating and amendment, including without limitation whether the equipment to be allocated should include hemo-dialysis or other life-saving machines, and recommend that the New York State Department of Health adopt the policy as is, or as amended, and

      ii. DOH to issue emergency regulations mandating all providers and practitioners follow the ethics guidelines, and ensure: 1. the needs of vulnerable populations, including older adults, persons with disabilities, inmates and immigrants, are met in a non-discriminatory manner in the implementation of emergency regulations and guidelines; 2. provision of palliative care as an ethical minimum to mitigate suffering among those who are in institutional, facility, residential, or home care settings during the COVID-19 crisis, especially when access to life-saving measures, desired equipment or other resources are not available; 3. provision of education and training to physicians, health care practitioners, and institutional triage and ethics committees; and 4. provision of generalist-level palliative care education and training for all health care workers and health-related service workers in all settings who are providing supportive care.

iii. Governor to: 1. waive or suspend certain NYS laws to protect from civil and criminal liability exposure practitioners who follow the ethics guidelines; and 2. direct all state agencies to interpret and apply the law and regulations in a way to support compliance with the ethics/triage guidelines.

(b) Withdrawal, DNR and Futility: Amend the New York State Public Health Law:

i. Article 29-C "Health Care Proxy," to require in the case of a State Disaster Emergency Declaration: (i) at least one, rather than two, witnesses, or (ii) attestation by a notary public in person or remotely; and

ii. to provide criminal and civil immunity for physicians, nurses and other health care practitioners and Article 28 facilities, when the following steps are taken: (1) a practitioner, as defined in Public Health Law Section 2994-a, determines that a patient's resuscitation would be "medically futile" as defined in PHL 2961.12; (2) a second practitioner concurs with the determination; and (3) both practitioners document their determination in the medical record; and in connection therewith, revoke or amend all laws and regulations prohibiting or penalizing such determinations and actions, including without limitation, those set forth on page 12 of this Report.

(c) Virus Testing: New York State Department of Health or Governor to consider:

i. Establishing a coordinated statewide plan that ensures: frontline health care workers are prioritized in access to rapid diagnostic testing; and further, the most vulnerable individuals from health status and essential business/employee standpoint have equitable access to rapid diagnostic testing.

3. Provider Systems and Issues:

(a) Amend New York Law:

i. Purchasing Necessary Supplies:

1. Amend New York General Business Law Section 396-r to include prohibition from exorbitant pricing of all equipment and products of any kind used either in patient care or to protect health care workers from infection.

(b) Continue Waivers and Executive Orders:

i. Ability to Exceed Certified Bed Capacity for Acute Care Hospitals

1. Continue the waiver by the Governor's Executive Orders 202.1 and 202.10 of the DOH regulations governing certified bed restrictions for the pendency of the State Disaster Emergency.

ii. Limitation on Resident Hours Working in Acute Care Hospitals

1. Continue the Governor's Executive Order 202.10's waiver of NYCRR Article 10, Section 405, limiting resident work hours for the pendency of the State Disaster Emergency.

iii. Temporary Changes to Existing Hospital Facility Licenses Services and the Construction and Operation of Temporary Hospital Locations and Extensions

1. Continue the waiver provided in Executive Orders 202.1 and 202.10 of the State requirements that restrict the ability of Article 28 facilities to reconfigure and expand operations as necessary, for the pendency of the State Disaster Emergency.

iv. Anti-Kickback and Stark Law Compliance during the COVID-19 Emergency

1. New York State: Adopt the waivers provided by CMS and the OIG as to the Anti-Kickback and Stark Laws in substantially similar form for the state versions of the Stark Law and AKS during the State Disaster Emergency, each as tailored for the particular statute at issue

(c) Long Term Care, Residential and Home Care, and Correctional and Detention Facility Settings

i. Older Adults, Nursing Home Providers and Nursing Home Residents: Governor, Department of Health (DOH), DOH Bureau of Long Term Care and State Office for Aging to ensure:

1. Equitable allocation of scarce resources from the Public Health and Social Services Emergency Fund—established by the CARES Act—to older adults and their health care providers, prioritizing under-resourced long-term care providers;[379]
2. Adequate provision of PPE;
3. Adequate levels of staffing;
4. Adequate funding of employee testing, as required under Executive Order 202.30;
5. Consistent and timely tracking and reporting of case and death data;
6. Adoption of non-discriminatory crisis standards and ethics guidelines; and
7. Recognition and honoring of Older New Yorkers' right to health and human rights, as protected under international conventions: and
8. Adequate resources for the Office of the State Long Term Care Ombudsman, which provides advocacy for nursing home residents and families and helps residents understand and exercise their rights to quality care and quality of life.

ii. Persons with Disabilities in Residential Facilities or Group Homes: Governor and Department of Health to ensure:

1. Access of persons with disabilities to adequate COVID-19 testing and appropriate medical care, mental health and other supportive services, including appropriate day

[379] U.S. SENATE COMMITTEE ON FINANCE, Senator Charles E. Grassley, Chairman, Letter to HHS Secretary Alex Azar and CMS Administrator Verma, Apr. 17, 2020, (asking about the federal response to COVID-19 in nursing homes, group homes, and assisted living facilities, and expressing concerns about testing capacity, data tracking inconsistencies, lack of personal protective equipment (PPE) for nursing home staff, and federal spending transparency), https://www.finance.senate.gov/imo/media/doc/HHSCOVIDLetter17Apr2020Final.pdf.

services to substitute for community-based day programs that need to be discontinued during a pandemic;
2. Adequate and appropriate staffing, of residential facilities and group homes, for both day and evening shifts, and provision of appropriate funding for such staff and for appropriate COVID-19 staff training;
3. Access of residential facility and group home staff to adequate testing and appropriate medical care and mental health and other supportive services;
4. Oversight of residential facilities and group homes and programs to assure non-discriminatory management of persons with disabilities during the COVID-19 crisis conditions; and
5. Recognition and honoring of persons with disabilities' right to health and human rights, as protected under international conventions.

iii. Inmates and Correctional Facilities: Governor, NYS Department of Corrections and NYC Department of Corrections, to ensure:

1. Adequate access of inmates to COVID-19 testing, medical care and mental health and supportive services;
2. COVID-19 testing of correctional staff and adequate provision of gloves, masks and other protective equipment;
3. Release to the community of older inmates and inmates with advanced illness who do not pose a danger to the community;
4. Adequate funding of prison-to-community transitions including access to housing, meals, and supportive services, and non-discriminatory access to employment opportunities; and
5. Recognition and honoring of inmates' right to health and human rights, as protected under international conventions.

iv. Immigrants in Detention Facilities: In its exercise of its police powers in the COVID-19 public health emergency, New York State must take steps, similar to those outlined above, in cooperation with federal agencies to ensure:

1. Reduction of risk of the spread of COVID-19 among immigrants being held in detention centers.[380]

(d) Telehealth

i. Eliminate restrictions on the provision of care by telehealth and increase reimbursement for services provided via telehealth.

(e) Immunities

i. Adapt Executive Orders to be consistent with Sections of the Public Health Law and include criminal liability, as well as immunity to health care facilities.

4. Business/Contracts/Risk Management

[380] *See* Cole J.P Cole, *Federal and State Quarantine Isolation Authority*, CONGRESSIONAL RESEARCH SERVICE, Oct. 19, 2014, https://www.ncsl.org/documents/statefed/health/FedandStateQIAuth.pdf.

(a) Consider extending immunity under NY UCC section 2-615(a) to supply chain vendors where specific performance under a contract becomes impracticable due to unforeseen event or good faith compliance with governmental orders or regulations during crisis.

(b) Adopt CMS 1135 Waivers and afford civil and criminal immunity to permit health care and health care related organizations and individual providers to modify operations to control contagion and manage the public health crisis. Immunity afforded to individual practitioners should extend to treatment of all patients during the crisis, not just acts of omission or commission in the management of COVID-19 since other patients within the health care system are inevitably impacted by the decisions made by these practitioners on the front lines.

5. Workforce

(a) Provide clear, timely guidance and support to all non-health care businesses and academic institutions to coordinate effective implementation of universal precautions and other workplace safety best practices to facilitate public health and trust, while mitigating disparate conditions during the phase-in process and long-term.

i. Consider publicly posting essential/non-essential business operations decisions with an industry-wide impact on the Empire State Development (ESD) website in real time to mitigate confusion and enhance institutional compliance.

ii. Consider granting staffing firms dedicated to child care the provider status necessary to enable them to operate in New York State and supplement the childcare workforce in order to ensure the health and safety of our children, while enabling businesses to effectively reopen within sufficient childcare support.

iii. Consider education and training pertaining to crisis standards and civil and criminal immunity to assure all practitioners are supported as they exercise professional medical judgment in triage, treatment and services.

iv. Consider enhanced employee assistance and other mental health counseling programs to address and mitigate the moral distress suffered by front-line health care workers under crisis conditions.

6. Vaccination

(a) When the efficacy of a COVID-19 vaccine has been confirmed, enact legislation requiring vaccination of each person unless the person's physician deems vaccination for his or her patient to be clinically inappropriate.

7. Vulnerable Populations and Issues of Equity and Discrimination: A Call for Social Justice

(a) Enhance regulatory oversight, to ensure:

i. adequate and non-discriminatory allocation of resources to vulnerable populations and communities of color;

ii. equitable access of vulnerable populations to health and mental health services, including palliative care as an ethical minimum to mitigate suffering among those

vulnerable persons who remain in institutional, facility, residential or home or care settings, or are hospitalized during the COVID-19 crisis, especially when desired equipment or other resources are not available;

iii. provision of PPE to essential health care workers at highest risk in delivering essential services to vulnerable populations; and

iv. monitoring conformity with federal laws barring discrimination.

8. Emergency Preparedness

(a) Maintain a core team of emergency preparedness experts to review and draft legislation, drawing upon the following evidentiary sources:

i. MSEHPA;

ii. Columbia University Center for Health Policy Gap Analysis;

iii. IOM's Crisis Standards of Care;

iv. Allocation of scarce resource guidelines, and

v. Emergency orders needed to manage COVID-19.

(b) Re-evaluate the public benefit and costs of reinstating laws which have been waived during COVID-19.

APPENDIX H

New York State Bar Association Health Law Section Task Force Members, Advisors and Experts

Hermes Fernandez, *Health Law Section Chair*

Members of Task Force
Mary Beth Quaranta Morrissey, Esq., PhD, MPH, *Task Force Chair*
Jane Bello Burke, Esq.
Kathleen M. Burke, Esq.
Veda Collmer, Esq.
Karen Gallinari, Esq.
Edward S. Kornreich, Esq.
Anoush Koroghlian-Scott, Esq.
Thomas G. Merrill, Esq.
Brendan S. Parent, Esq.
Nathan G. Prystowsky, Esq.
Salvatore J. Russo, Esq.
Jennifer M. Schwartzott, Esq.
Mishka A. Woodley, JD, LLM

Advisors to the Task Force:
Thomas V. Caprio, MD, MPH, MS, CMD, HMDC, FACP, AGSF, FAAHPM
Christopher Comfort, MD
Larry Faulkner, Esq.
Allie Gold, Esq.
Roshni D. Persaud, Esq.
Donna Seminara, MD, MACP
Samuel J. Servello, JD, LLM

Attorney, law clerk and law student, and other volunteers:
Patrick Benjamin
John D. Clopper, Esq.
Marissa Cohen
Morgan Dowd
Michele Korkemaz-Christie
Martha Mahoney
Kerianne Morrissey
Matthew Pappalardo
Ivelina V. Popova, Esq.
Daniel S. Weinstein

We thank the following esteemed members of the bar, scholars and ethicists who served as experts and provided generous assistance and consultative support to the Task Force:
Linda Fentiman, JD, LLM
Joseph J. Fins**,** M.D., M.A.C.P., F.R.C.P.
Professor Lawrence O. Gostin
James Hodge**,** Jr., JD, LLM
Beth Roxland, JD, M.Bioethics
Robert Swidler, Esq.