COVID-19 VACCINES:
UNC HEALTH PLANNING

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COVID-19 vaccines in human clinical trials – United States*

Candidate	Manufacturer	Type	Phase	Trial characteristics	Trial #	Recruiting
mRNA-1273	Moderna TX, Inc.	mRNA	III	• 2 doses (0, 28d) • IM administration • 18-55, 56+ years	NCT04470427	✓
mRNA-BNT162	Pfizer, Inc./BioNTech	mRNA	II/III	• Single or 2 doses • IM administration • 18-85 years	NCT04368728	✓
AZD1222	University of Oxford/AstraZeneca consortium**	Viral vector (NR)	III	• 2 doses (0, 28d) • IM administration • ≥18 years	NCT04516746	On Hold
Ad26COVS1	Janssen Pharmaceutical Companies	Viral vector (NR)	I/II	• Single or 2 doses (0,56d) • IM administration • 18-55, 65+	NCT04436276	✓
--	Sanofi/GSK	Protein Subunit	I/II	• Single or 2 doses • 18-49, 50+	NCT04537208	✓
NVX-CoV2373	Novavax	Protein Subunit	I/II		NCT04368988	✓
AV-COVID-19	Aivita	AuDendritic cell	I/II		NCT04386252	
INO-4800	Inovio Pharmaceuticals, Inc.	DNA plasmid	I	• 2 doses (0, 4w) • SC administration/ electroporation • ≥18 years	NCT04336410	

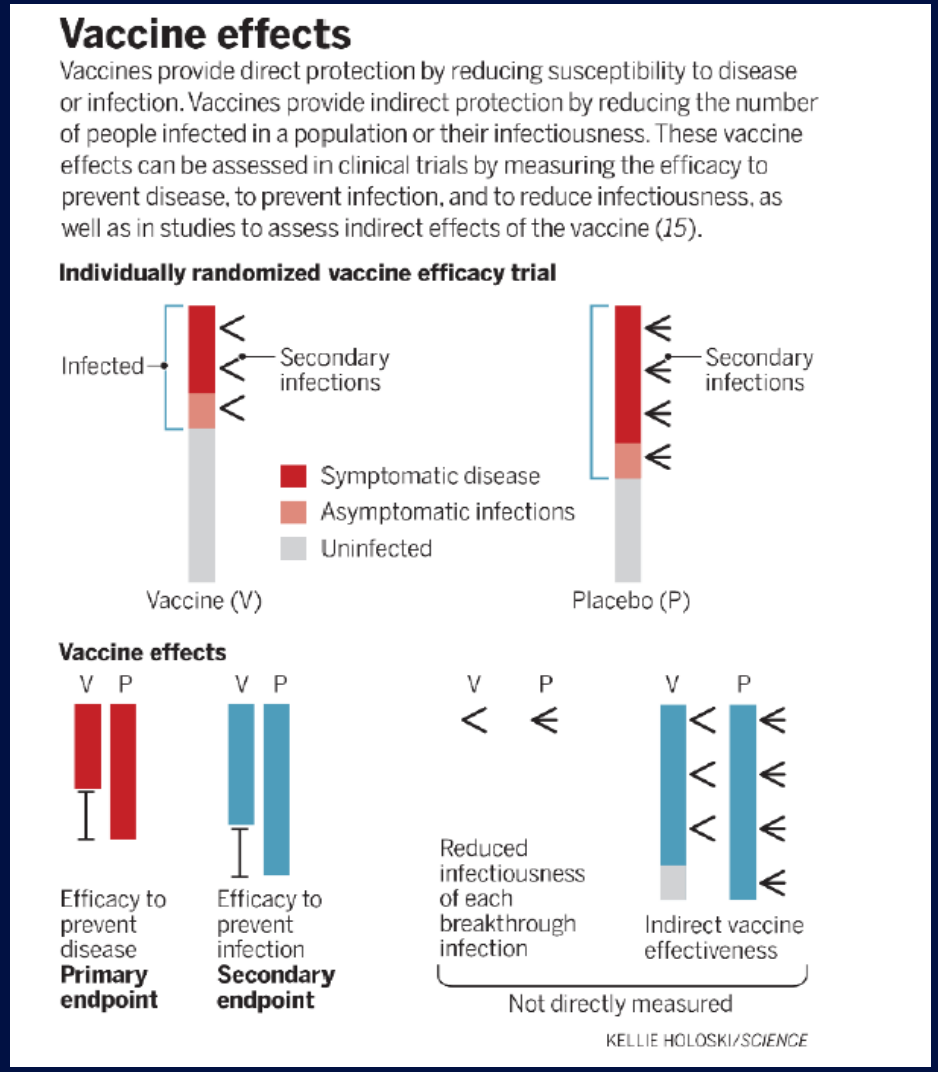
*As of September 14, 2020
**Currently on hold in US
Sources: https://milkeninstitute.org/covid-19-tracker; https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines; https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/ ; https://clinicaltrials.gov/; https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

Bell D. ACIP 22 September 2020

UNDERSTANDING COVID-19 VACCINE EFFICACY

- Primary vaccine endpoints:
  - Virologically confirmed, symptomatic disease
- Secondary endpoints
  - Infection or viral shedding
  - Vaccine efficacy in subgroups (trials not powered to assess this endpoint)
- Indirect protection
  - Via preventing infection or reducing contagiousness
- Improving ability to assess efficacy in subgroups
  - Increasing enrollment goals for these groups
  - Post-approval observational studies (test negative design: persons testing negative compared to controls testing positive; vaccine status is compared, adjusting for selected confounders)

Lipsitch M, Dean NE. Science 10.1126.science.abe5938 (2020)



ASSESSING COVID-19 VACCINE EFFICACY

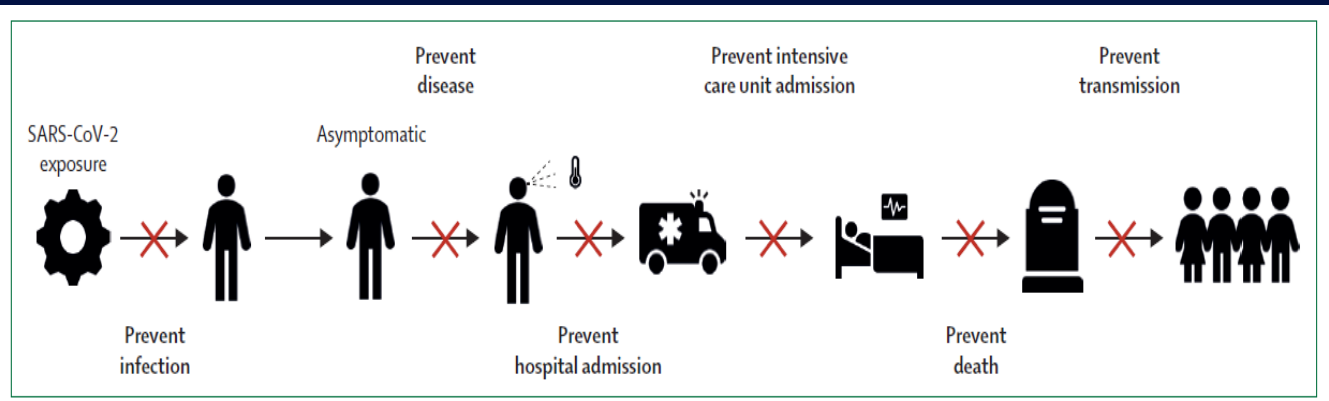


Figure 1: Potential endpoints of an efficacious COVID-19 vaccine
An efficacious COVID-19 vaccine could reduce the likelihood of infection of an individual, severity of disease in an individual, or degree of transmission within a population.

	Infection	Symptomatic infection	Hospital admission	Death
0·12 infections per 1000 people per day over 6 months*				
20–29 years	1880	3154	183 930	619 130
>80 years	1880	3154	10 364	24 494
0·013 infections per 1000 people per day over 6 months†				
20–29 years	17 876	29 816	1722 106	5 796 166
>80 years	17 876	29 816	97 304	229 584

Table 1: Illustrative sample size calculations for a randomised controlled trial to assess efficacy of a SARS-CoV-2 vaccine candidate, calculated according to incidence of SARS-CoV-2 infection and age of participants

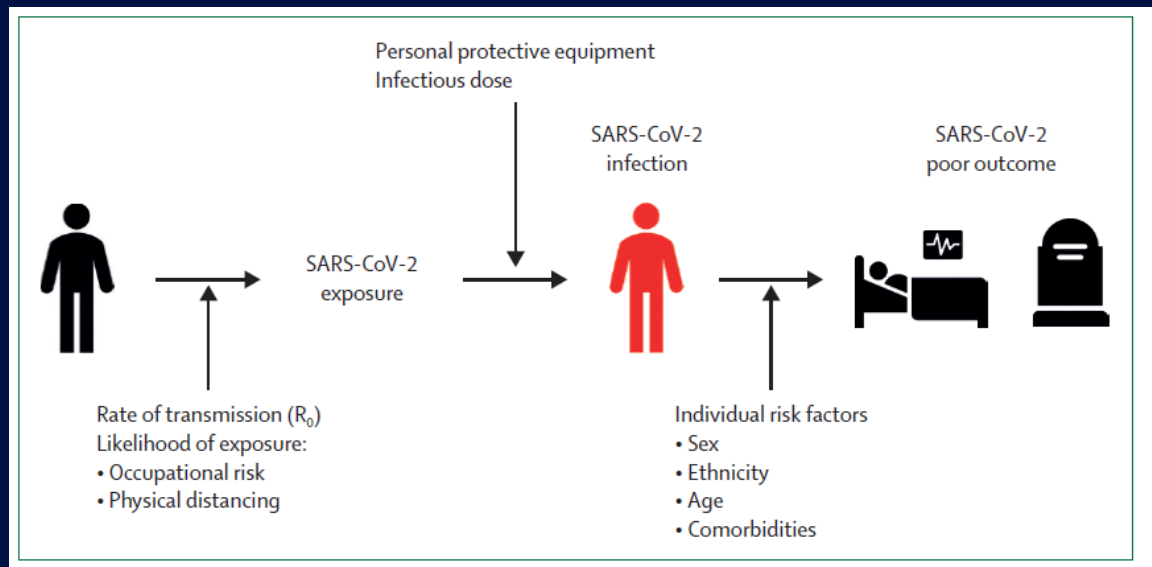


Figure 2: Key variables for SARS-CoV-2 exposure, infection, and poor outcome

Hodgson SH, et al. Lancet ID 2020;27 Oct

CLINICAL ENDPOINTS FOR EVALUATING EFFICACY IN COVID-19 VACCINE TRIALS

- Authors address the following issues study endpoints in COVID-19 vaccine efficacy trials.
  - First, we propose a general set of clinical endpoints to facilitate a harmonized evaluation and comparison of the efficacy of vaccine candidates, overall and across relevant subgroups.
  - Second, we consider the pros and cons of various endpoints for use as primary endpoints.
  - Third, we recommend adequate follow-up of all participants to enable enhanced sensitivity regarding effects on severe COVID-19 as well as assessment of the longer-term vaccine effect on the set of endpoints, including an assessment of durability of protection.
  - Fourth, we recommend including asymptomatic infection as a study endpoint, given that vaccine protection against COVID-19 could be accompanied by a shift toward more asymptomatic SARS-CoV-2 infections, a plausible outcome if the vaccine does not confer sterilizing immunity.
- The nesting of endpoints and their partitioning into mutually exclusive and exhaustive categories aid in the interpretation of results (Figure 1, top). Accordingly, for each of the core endpoints described in Figure 1, we advocate reporting point estimates and 95% CIs for vaccine efficacy for prespecified subgroups defined by factors that include sex assigned at birth; age; geographic location; race/ethnicity; and presence or absence of preexisting health problems, such as heart or lung conditions, severe obesity, or diabetes.

Mehrotra DV, et al. Ann Int Med, 22 Oct 2020

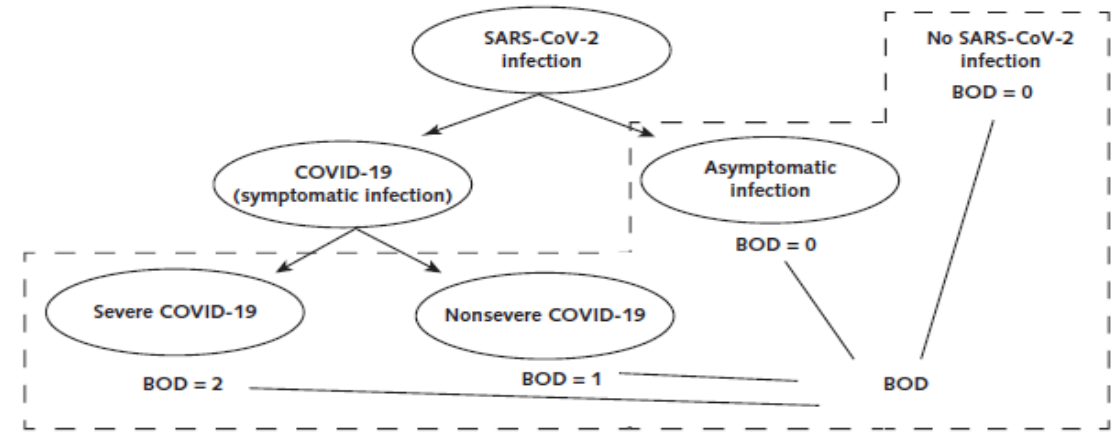
CLINICAL ENDPOINTS FOR EVALUATING EFFICACY IN COVID-19 VACCINE TRIALS

Pros and cons of different endpoints for use as the primary COVID-19 vaccine endpoints

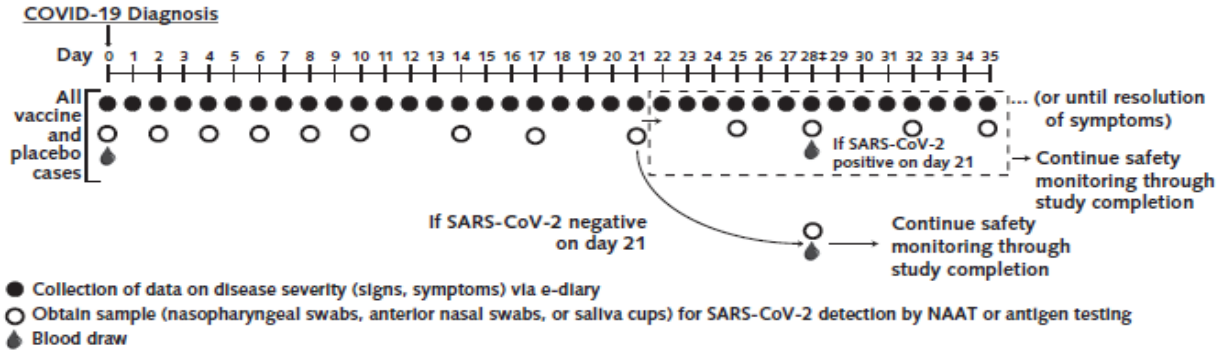
- From both a public health perspective and an individual perspective, prevention of severe COVID-19 is perhaps the most important clinical benefit expected from an effective vaccine. There is precedent (for example, dengue, influenza, pertussis, pneumococcal bacteremia, rotavirus, and varicella) that many vaccines confer greater efficacy against severe disease than milder disease. However, severe COVID-19 constitutes a relatively small portion of COVID-19 cases, and incidence varies widely by age, underlying risk, and ethnicity, implying that statistical power to demonstrate adequate vaccine efficacy against the severe COVID-19 endpoint may be lower than that for an endpoint that includes reduction in non-severe COVID-19. For that reason, the broader-encompassing endpoint of COVID-19 symptomatic disease is deemed an appropriate primary endpoint and has been selected as such for all 6 ongoing phase 3 trials and for the Solidarity Vaccines Trial. Moreover, there is consensus to assess severe COVID-19 as a key secondary endpoint.
- Given that detection of safety problems with vaccines is critically important, the statistical analysis plans of the trials use 2-sided 95% CIs for vaccine efficacy for each study endpoint, so the data analyses can detect evidence for a higher rate of any endpoint in the vaccine versus the placebo group.

Mehrotra DV, et al. Ann Int Med, 22 Oct 2020

Figure 1. Clinical endpoint relationships, definitions, and example sampling scheme for diagnosed COVID-19 cases.



Clinical Endpoint	Definition
SARS-CoV-2 infection	Positive RNA PCR result or SARS-CoV-2 seroconversion*, whichever occurs first
COVID-19 (symptomatic infection)	Meeting a protocol-specified list of COVID-19 symptoms with virologic confirmation of SARS-CoV-2 infection (symptom triggered)
Asymptomatic infection	SARS-CoV-2 seroconversion* without prior diagnosis of the COVID-19 endpoint†
Severe COVID-19	COVID-19 endpoint with at least 1 protocol-specified severe disease event
Nonsevere COVID-19	COVID-19 endpoint with 0 protocol-specified severe disease events
BOD	Composite endpoint score of 0 for no COVID-19, 1 for nonsevere COVID-19, and 2 for severe COVID-19

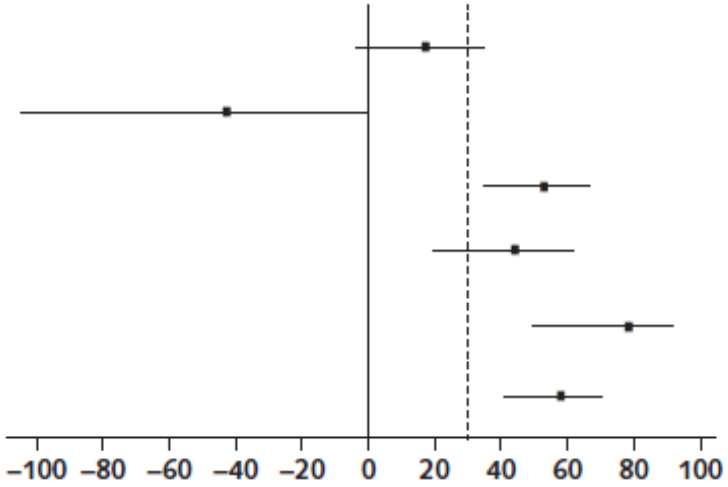


Mehrotra DV, et al. Ann Int Med, 22 Oct 2020

Figure 2. Hypothetical example of results of a COVID-19 vaccine efficacy trial with 2:1 (vaccine–placebo ratio) randomization, with the analysis done for 147 total COVID-19 cases.

Group	Participants, *n*	Uninfected, *n*	Infected, *n* (%)	Among the Infected Trial Participants, *n* (%)		
				Asymptomatic (No COVID-19)	Symptomatic Nonsevere COVID-19	Symptomatic Severe COVID-19
Placebo	10 000	9879	121 (1.21)	45 (37.2)	57 (47.1)	19 (15.7)
Vaccine	20 000	19 801	199 (1.00)	128 (64.3)	63 (31.7)	8 (4.0)

Endpoint	Vaccine Efficacy (95% CI), %
SARS-CoV-2 infection	17.8 (–4.0 to 34.7)
Asymptomatic infection	–42.2 (–104.5 to –0.5)
COVID-19 (symptomatic infection)	53.3 (34.6 to 66.7)
Nonsevere COVID-19	44.7 (19.5 to 62.0)
Severe COVID-19	78.9 (49.6 to 92.0)
BOD	58.4 (41.2 to 70.2)



BOD = burden of disease; COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2. **Top.** Number of uninfected and infected participants in each group, along with breakdown by endpoint for infected trial participants. **Bottom.** Vaccine efficacy point estimates and 95% CIs against 6 clinical endpoints. The black, dashed vertical line in the forest plot marks the lower 95% confidence bound of 30% given in guidance from the U.S. Food and Drug Administration.

Mehrotra DV, et al. Ann Int Med, 22 Oct 2020

CLINICAL ENDPOINTS FOR EVALUATING EFFICACY IN COVID-19 VACCINE TRIALS

Table 1. Comparison of Statistical Power for Different Efficacy Endpoints*

Assumed VE, %		Determined VE for	Statistical Power, %		
COVID-19	Severe COVID-19	Nonsevere COVID-19, %†	Severe COVID-19	COVID-19	BOD
55	0	69	0	74	29
55	30	61	2	74	50
55	60	54	26	74	75
55	70	51	47	74	82
55	80	49	73	74	87
55	90	46	94	74	92
60	0	75	0	91	47
60	30	68	2	91	70
60	60	60	27	91	89
60	70	57	50	91	93
60	80	55	76	91	96
60	90	52	95	91	98

BOD = burden of disease; COVID-19 = coronavirus disease 2019; VE = vaccine efficacy.

* Simulated design with 2:1 (vaccine to placebo) randomization and analysis after 147 COVID-19 cases have occurred.

† Assuming that 20% of COVID-19 cases in the placebo group will be severe (21), VE(COVID-19) = 0.2 × VE(severe COVID-19) + 0.8 × VE(nonsevere COVID-19). Hence, if the first 2 VE values in this equation are fixed, the third one is determined after invoking the aforementioned assumption. Power for a given efficacy endpoint is based on statistical success defined as a VE point estimate of at least 50%, with the lower bound of the corresponding 95% CI greater than 30% (5). Coronavirus disease 2019 endpoint scoring is 0 = no COVID-19 and 1 = COVID-19, and BOD endpoint scoring is 0 = no COVID-19, 1 = nonsevere COVID-19, and 2 = severe COVID-19. Vaccine efficacy is the relative reduction (vs. placebo) in the mean endpoint score, which is equivalent to a relative reduction in incidence for the COVID-19 endpoint.

Table 2. Interconnection Among VE Against SARS-CoV-2 Infection, Symptomatic SARS-CoV-2 Infection (COVID-19), and Asymptomatic SARS-CoV-2 Infection

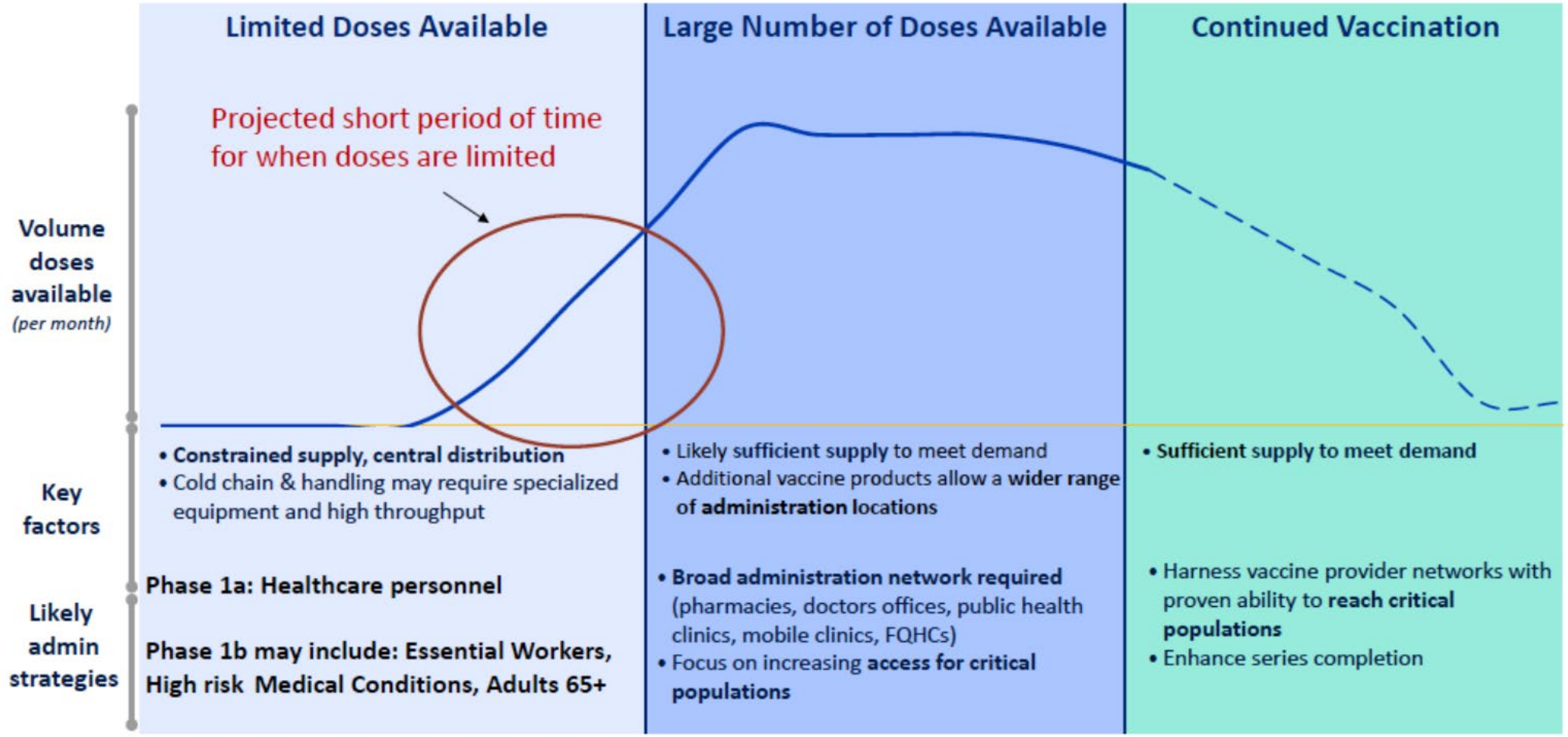
Assumed VE, %		Determined VE for Asymptomatic SARS-CoV-2 Infection, %*
SARS-CoV-2 Infection	Symptomatic SARS-CoV-2 Infection (COVID-19)	
20	60	−40
20	70	−55
40	60	10
40	70	−5
60	60	60
60	70	45

COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VE = vaccine efficacy.

* Assuming that 40% of SARS-CoV-2 infections in the placebo group will be asymptomatic (21), VE(infection) = 0.6 × VE(symptomatic infection) + 0.4 × VE(asymptomatic infection). Hence, if the first 2 VE values are fixed, the third one is determined after invoking the aforementioned assumption. Negative VE implies a higher incidence of endpoint cases for vaccine vs. placebo.

Mehrotra DV, et al. Ann Int Med, 22 Oct 2020

Administration of COVID-19 vaccine will require a phased approach



Draft Prioritization Framework – Phase 1

Phase	Population	Population Details	Identification Approach
1A	Health Care Workers and COVID Responders *at High Risk for Exposure or Vital to the COVID Response*	• High risk of exposure/vital to initial COVID response is defined as those caring for COVID-19 patients, cleaning areas where COVID-19 patients are admitted, performing procedures at high risk of aerosolization (e.g., intubation, bronchoscopy, suctioning, invasive dental procedures, invasive specimen collection, CPR), handling decedents with COVID-19, administering vaccine in initial closed or targeted vaccination clinics. • Population includes: nurses, home health workers, personal care aides, physicians, respiratory techs, dentists, hygienists, nursing assistants, environmental services staff, EMT/paramedics, community health workers, pharmacists, public health nurses, public health and emergency preparedness workers and morticians/funeral home staff who meet the above definition of "high risk of exposure."	• List generated by employer based on classifications
	LTC Staff	• Staff in skilled nursing facilities, adult care homes, family care homes, group homes, and intermediate care facilities for individuals with IDD (ICF-DD).	• List generated by facilities
1B	LTC Residents	• Residents in skilled nursing facilities, adult care homes, family care homes, group homes, and ICF-IDDs.	• List generated by facilities
	Migrant Farm/Fisheries Workers in *Congregate Housing with 2+ Chronic Conditions* or ≥ age 65*	• Migrant farm and fisheries workers *in congregate living settings with 2+ chronic conditions* or ≥* age 65 *listed below*. (Note that migrant farm workers will enter NC on a staggered schedule based on harvesting calendar, with only a small proportion likely present in November and December)	• Self-identification
	Incarcerated individuals *with 2+ Chronic Conditions* or ≥ age 65* and jail/prison staff	• Incarcerated individuals in jails, prisons, and immigration detention centers *with 2+ chronic conditions*or ≥* age 65 and all jail, prison, and detention center staff	• List generated by facilities
	Homeless shelter residents *with 2+ Chronic Conditions** or ≥ age 65 and homeless shelter staff	• Homeless individuals (based on average number of homeless individuals in shelters per night) *with 2+ chronic conditions* or ≥* age 65 and all homeless shelter staff	• List generated by facilities
	Other individuals *with 2+ Chronic Conditions**	• Among adults with 2+ chronic conditions who are not in congregate setting; Sub-populations below priority for outreach, provider enrollment, allotment	• Self-identification
	Health Care Workers with 2+ Chronic Conditions and Not Included in Phase 1A	• *Health Care Workers with 2+ chronic conditions* who are not in Phase 1A* • *Population includes inpatient and outpatient staff who are not directly caring for COVID patients*	• List generated by employer based on classifications
	Other Frontline Workers with high risk of exposure and 2+ Chronic Conditions	• *Firefighters, police, meat packing plant workers, seafood/poultry workers not in congregate housing, food processing, preparation workers and servers, manufacturing, construction, funeral attendants and undertakers not included in Phase 1A, transportation workers, retail workers (including grocery store workers), membership associations/org staff (e.g., religious orgs),child care workers, and workers in government, public health, emergency management and public safety whose functioning is imperative to the COVID-19 response with 2+ chronic conditions**	• Self-identification
	*For all populations 2+ Chronic conditions means those defined by CDC as increased risk for COVID (Cancer, Chronic kidney disease, COPD, Immunosuppressed from organ transplant, Obesity, Serious heart condition, Sickle Cell disease, Type 2 Diabetes)		

NC DHHS COVIED-19 VACCINE PLAN, 16 OCTOBER

North Carolina's vaccine plan reflects five principles that guide the planning for and distribution of one or more COVID-19 vaccines in the state. The principles include:

- All North Carolinians have equitable access to vaccines.
- Vaccine planning and distribution is inclusive; actively engages state and local government, public and private partners; and draws upon the experience and expertise of leaders from historically marginalized populations.
- Transparent, accurate, and frequent public communications is essential to building trust.
- Data is used to promote equity, track progress and guide decision-making.
- Appropriate stewardship of resources and continuous evaluation and improvement drive successful implementation.

COVID-19 VACCINES: UNC HEALTH PLANNING ASSUMPTIONS

- A COVID-19 vaccine will be approved by the FDA within the next 6 months (potentially Nov-Dec, 2020)
  - An mRNA vaccine will likely be the first vaccine available under an FDA EUA – major problem is that mRNA vaccines require storage at very low temperature (i.e,, -70 ^{o}C $\pm$ 10 ^{o}C) – will be shipped on dry ice (stable for 10 days)
  - Multiple vaccines will be FDA approved within the next 12 months
- At the time of approval there will be insufficient supplies for the vaccine to provide to all persons desiring immunization. Hence, there will be prioritization algorithm developed by US DHSS & NC DHHS
  - The highest priority groups will be HCP (1a) and persons with co-morbidities (1b)
- At the time of approval the following will NOT be known: Duration of protection; Correlate of immunity; Long term safety; Effectiveness and safety in population subgroups (children, pregnant women, immuno-compromised persons); Effectiveness and safety with simultaneous administration other vaccines (e.g., influenza)
- Receipt of a COVID-19 vaccine will not alter the PPE worn by an immunized HCP and will not alter the isolation of a symptomatic SARS-CoV-2 positive patient

NC DHHS COVID-19 VACCINE PRIORITY GROUPS

- HCP and COVID responders at high risk for exposure based on work duties or vital to initial COVID vaccine response (**1a**)
  - Providing care for COVID-19 patients or cleaning areas with COVID-19 patients are admitted
  - Performing procedures at high risk for aersolization
  - Handling decedents with COVID-19
  - Administering vaccine in initial closed or targeted vaccination clinics
  - LTC staff
- HCP and COVID responders at high risk for exposure based on work duties or vital to initial COVID vaccine response (**1b**)
  - LTC residents
  - Staff of congregate living settings
  - Adults with high risk of complications

NC DHHS COVID-19 VACCINE PRIORITY GROUPS:
Operationally Prioritize Settings Based On Risk of Exposure

Phase 1

- Migrant farm and fisheries workers in congregate housing with 2+ chronic conditions or ≥age 65
- Incarcerated individuals with 2+ chronic conditions or >age 65 and jail and prison staff
- Homeless shelter residents with 2+ chronic conditions or ≥age 65 and homeless shelter staff
- HCP not included in phase 1a with 2+ chronic conditions
- Frontline workers with 2+ chronic conditions at high risk of exposure (firefighters, police, workers in meat packing plants, seafood and poultry not in congregate housing, food processing, preparation workers and serves, manufacturing, construction, funeral attendants and undertakers not included in phase 1A, transportation workers (including grocery store workers), membership associations/org staff (e.g., religious orgs), child care workers, and workers in government, public health, emergency management and public safety whose function is imperative to the COVID-19 response)
- Other adults with 2+ chronic conditions: For all populations 2+ chronic conditions means those defined by CDC as increased risk for COVID (cancer, chronic kidney disease, COPD, immunosuppressed from organ transplant, obesity, serious heart condition, sickle cell disease, type 2 diabetes)

NC DHHS REQUIRED DATA ELEMENTS

IIS Data Elements: Required

Required Data Element	Standard or Mass Vaccination
Administrated at location: facility name/ID	Standard
Administered at location: type	Standard
Administration address (including county)	Standard
Administration date	Standard
CVX (product)	Standard
Dose number	Standard
IIS recipient ID	Standard
IIS vaccination event ID	Standard
Lot number: unit of use and/or unit of sale	Standard
MVX (manufacturer)	Standard
Recipient address*	Standard
Recipient date of birth*	Standard
Recipient name*	Standard
Recipient sex	Standard
Recipient ethnicity	Standard
Recipient race	Standard
Sending organization	Standard
Vaccine administering provider suffix	Standard
Vaccine administering site (on the body)	Standard
Vaccine expiration date	Standard
Vaccine route of administration	Standard
Vaccination series complete	Mass Vaccination

Mass Vaccination:
may require mass vaccination module or enhancement

Standard:
IIS core data element commonly collected during routine vaccination

Race and Ethnicity are key analytic metrics because of the disparities in COVID-19 outcomes in people from some racial and ethnic minority groups.

UNC HEALTH COVID-19 VACCINE IMPLEMENTATION

- UNC Shared Service Center Pharmacy has purchased a low temperature freezer capable of storing >30,000 doses
- UNC will adhere to EUA and DHHS priority algorithm (as required by law)
  - If vaccine supply is limited, UNC will provide vaccine per DHHS algorithm until supply exhausted; once UNC receives a resupply immunization of designated groups will be reinitiated
  - The EUA vaccine information sheet will need to be provide to each vaccinated person*
  - For non-UNC HCP or patients, we can except a self-report of meeting the priority requirements*
- Each UNC Health affiliate will receive its own vaccine supply from the State, and be responsible for administration and documentation*
  - Likely will need limited locations for vaccine administration (due to temperature requirements)
  - Ancillary vaccine administration kits will also be provided (needles, syringes, masks and face shields)
- Vaccine will be provided free. Ability to charge an administration fee is under consideration*
- DHHS will develop a vaccine "portal" – All HCP providing a COVID vaccine will be required to enter the portal and provide specific data on the person vaccinated (exact information required to be entered to be provided)*
- Vaccine administration to nursing homes (NHs) will be accomplished via retail pharmacies (NHs can sign up via CDC NHSN)*; does not include UNC Health pharmacies

*Per discussion with NC DHHS