

# Preventing Respiratory Diseases: Tennessee Immunization Summit

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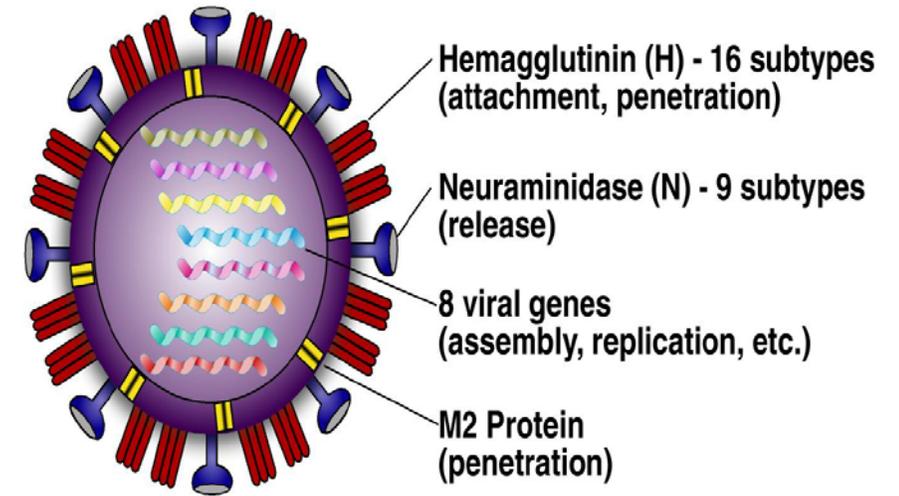
Vanderbilt University Medical Center

# Objectives

- Describe the unique challenges of influenza virus and influenza vaccines
- Review new vaccines for influenza prevention
- Describe approaches being used to develop vaccines against SARS Cov2
- Review how vaccines against SARS Cov2 will be licensed and implemented

# Influenza : Basics

- Influenza A viruses
  - Subtypes based on surface glycoproteins
    - Hemagglutinin (HA) and Neuraminidase (NA)
    - Current human influenza A virus subtypes: H1N1, H3N2
  - Infect multiple species
  - Epidemics and pandemics
- Influenza B
  - Humans only reservoir
  - Less mortality than influenza A
  - Associated with epidemics, not pandemics
  - Two circulating lineages (Yamagata and Victoria), resulting in expansion of influenza vaccine to include 4 antigens (2 A and 2 B)



# Human Influenza - Clinical

- Acute febrile respiratory illness
  - “Influenza-like illness”
    - Fever or feverish
    - Cough and/or sore throat or other manifestations (otitis)
  - More serious pulmonary manifestations
    - Primary or secondary pneumonia, croup, bronchiolitis
- Non-specific febrile illness
- Extra-pulmonary manifestations
  - Neurologic – Encephalitis, seizures
  - Myositis
  - Cardiac

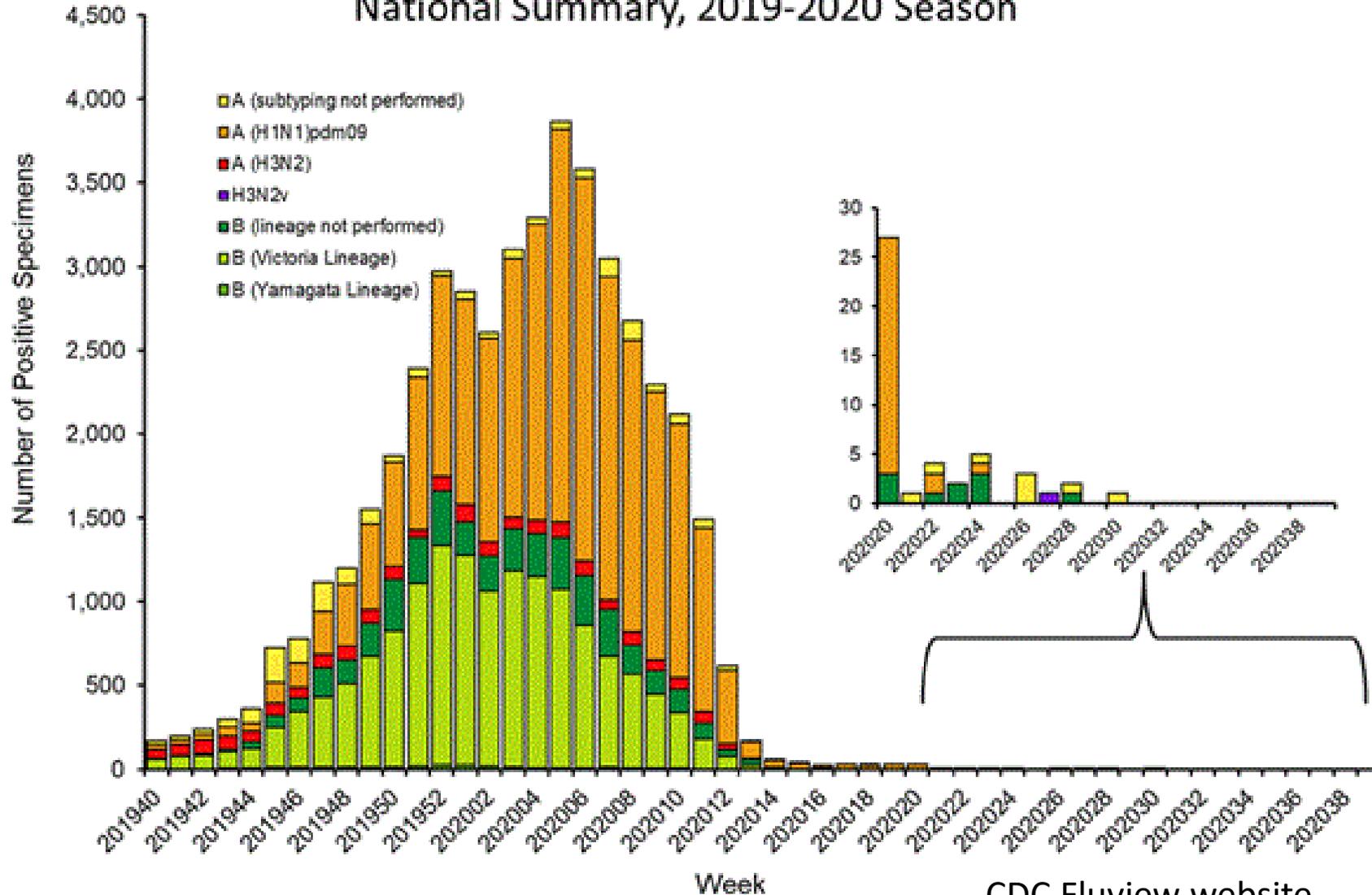


Absence of data does not  
equal absence of influenza!

# Seasonal Influenza: What do we know?

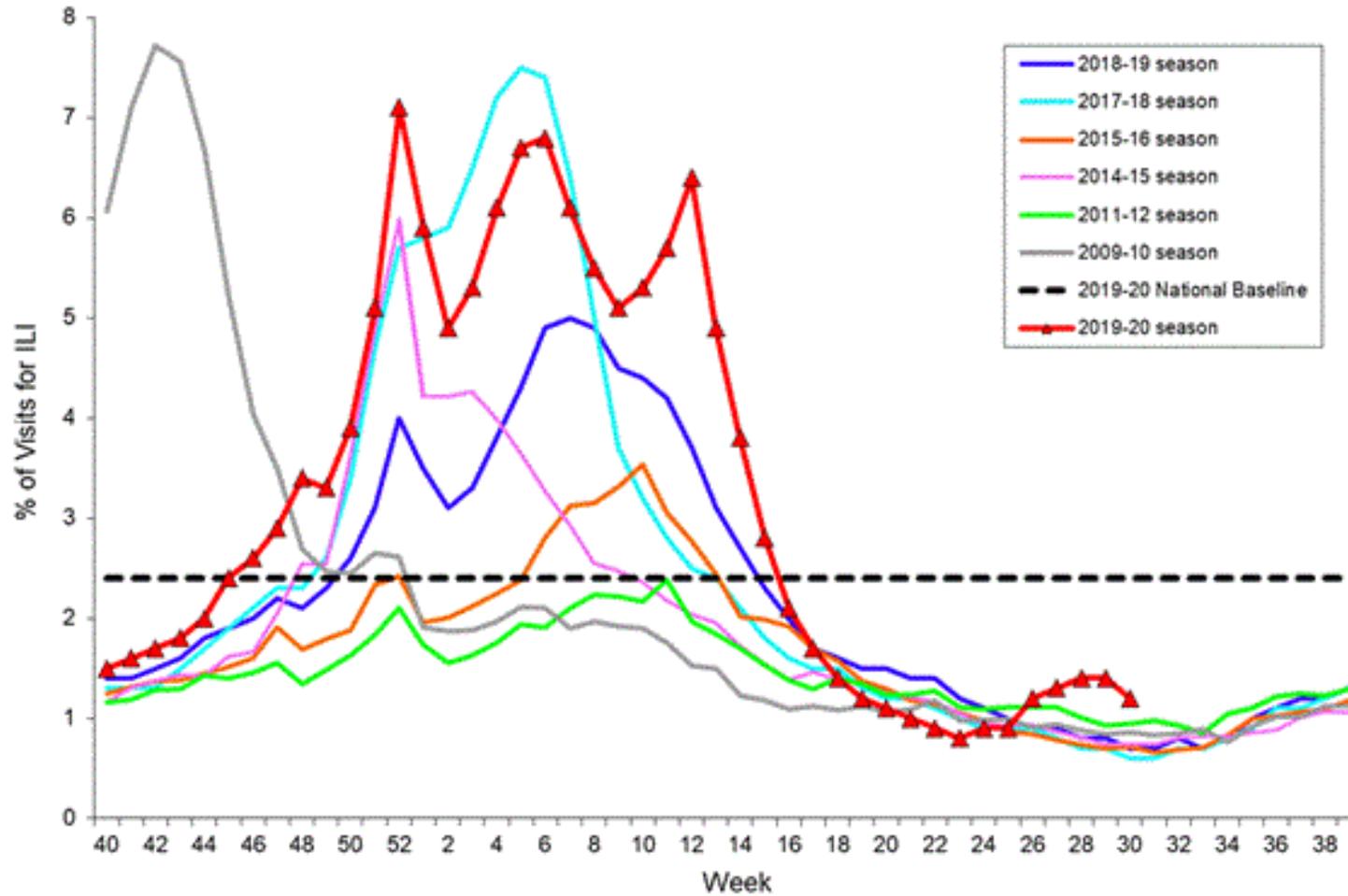
- Recent estimates of US influenza burden
  - CDC, 2019-2020 season Data
    - 39 million-56 million illnesses
    - 410,000-740,000 hospitalizations
    - 24,000-62,000 deaths
  - Highly variable from year-to-year
- Infection rates highest among children and children play an important role in the spread of influenza
- Severe disease and death most common at extremes of age, pregnant women are also at risk and those with underlying chronic conditions
- Most data on burden are from high resource settings

## Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, 2019-2020 Season

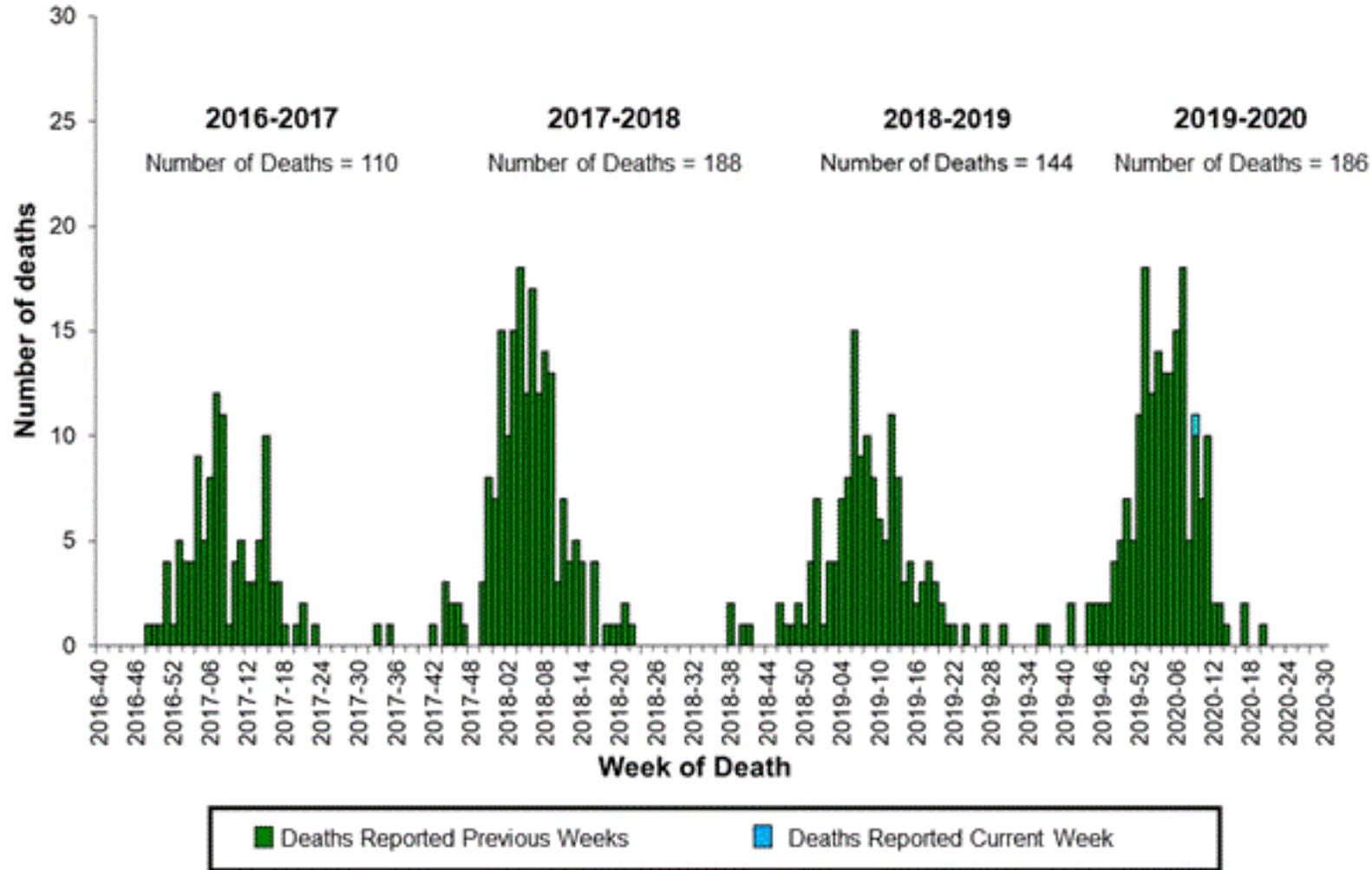


CDC Fluview website

Percentage of Visits for Influenza-like Illness (ILI) Reported by the U.S. Outpatient Influenza-like Illness Surveillance Network (ILINet), Weekly National Summary, 2019-2020 and Selected Previous Seasons



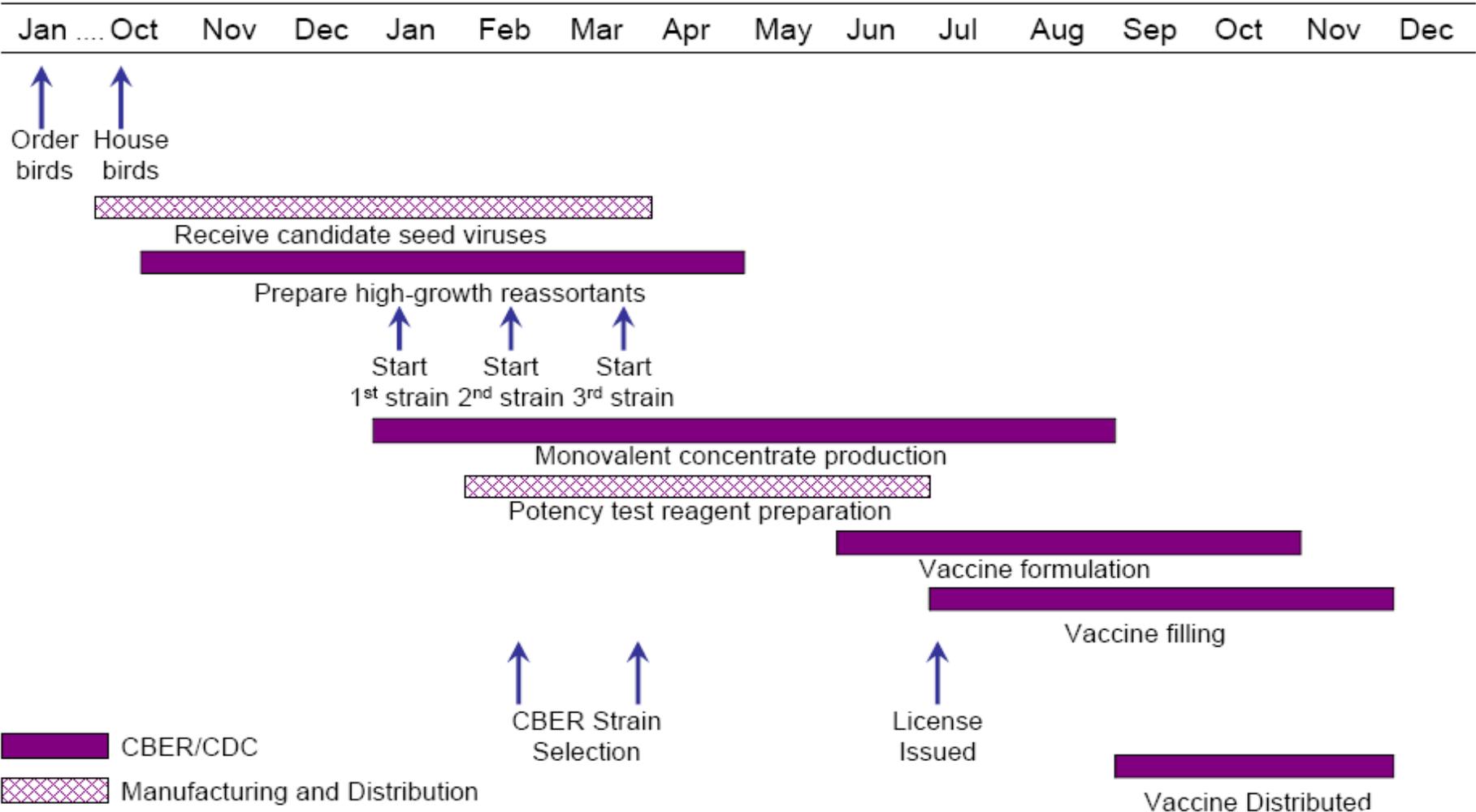
## Influenza-Associated Pediatric Deaths by Week of Death, 2016-2017 season to 2019-2020 season



# Influenza: Challenges

- Constantly changing virus
- Non-specific clinical manifestations
- Influenza burden variable from year-to-year
- Influenza vaccine must be changed frequently to capture the circulating strain

# Conventional Influenza Vaccine Manufacture and Distribution is a Year-Round Process



**Prevention and Control of Seasonal Influenza  
with Vaccines: Recommendations of the  
Advisory Committee on Immunization Practices —  
United States, 2019–20 Influenza Season**

**Routine annual influenza vaccination of all persons aged  
≥6 months continues to be recommended.**

TABLE 1. Influenza vaccines — United States, 2019–20 influenza season\*

Trade name (Manufacturer)	Presentation	Age indication	HA (IIVs and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route
<b><u>IIV4—Standard Dose—Egg based†</u></b>				
Afluria Quadrivalent (Seqirus)	0.25-mL PFS <sup>§</sup>	6 through 35 mos	7.5 µg/0.25 mL <sup>§</sup>	IM <sup>¶</sup>
	0.5-mL PFS <sup>§</sup>	≥3 yrs	15 µg/0.5 mL <sup>§</sup>	
	5.0-mL MDV <sup>§</sup>	≥6 mos (needle/syringe) 18 through 64 yrs (jet injector)		
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM <sup>¶</sup>
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM <sup>¶</sup>
	5.0-mL MDV	≥6 mos		
Fluzone Quadrivalent (Sanofi Pasteur)	0.25-mL PFS <sup>**</sup>	6 through 35 mos	7.5 µg/0.25 mL <sup>**</sup>	IM <sup>¶</sup>
	0.5-mL PFS <sup>**</sup>	≥6 mos	15 µg/0.5 mL <sup>**</sup>	
	0.5-mL SDV <sup>**</sup>	≥6 mos		
	5.0-mL MDV <sup>**</sup>	≥6 mos		
<b><u>IIV4—Standard Dose—Cell culture based (ccIIV4)</u></b>				
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	≥4 yrs	15 µg/0.5 mL	IM <sup>¶</sup>
	5.0-mL MDV	≥4 yrs		
<b><u>IIV3—High Dose—Egg based† (HD-IIV3)</u></b>				
Fluzone High-Dose (Sanofi Pasteur)	0.5-mL PFS	≥65 yrs	60 µg/0.5 mL	IM <sup>¶</sup>
<b><u>IIV3—Standard Dose—Egg based† with MF59 adjuvant (aIIV3)</u></b>				
Fluad (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM <sup>¶</sup>
<b><u>RIV4—Recombinant HA</u></b>				
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM <sup>¶</sup>
<b><u>LAIV4—Egg based†</u></b>				
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	10 <sup>6.5–7.5</sup> fluorescent focus units/0.2 mL	NAS

# Contraindications/Precautions

- Contraindications:
  - History of severe allergic reaction to the vaccine or any of its components
    - ACIP recommends that persons with egg allergy of any severity receive influenza vaccine
- Precautions:
  - Moderate or severe acute illness with or without fever.
  - Guillain–Barré syndrome within 6 weeks following a previous dose of influenza vaccine.

**TABLE 3. Dose volumes for inactivated influenza vaccines licensed for children aged 6 through 35 months\*— United States, 2019–20 influenza season**

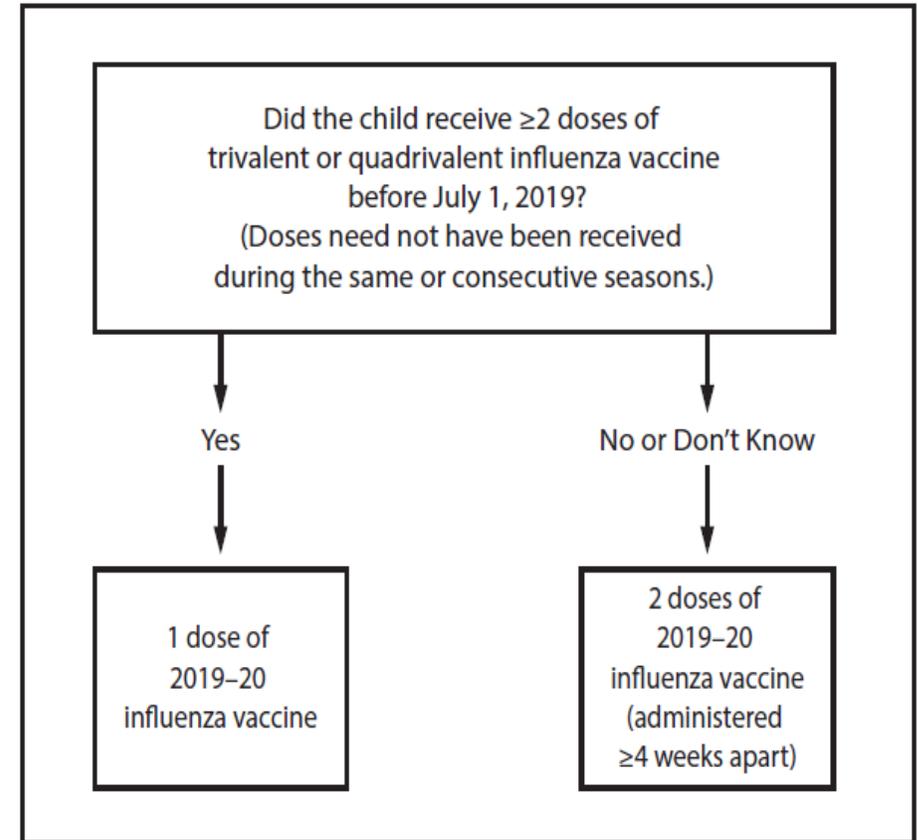
Trade name (Manufacturer)	Dose volume for children aged 6 through 35 mos ( $\mu\text{g}$ HA per vaccine virus)
Afluria Quadrivalent (Seqirus)	0.25 mL (7.5 $\mu\text{g}$ )
Fluarix Quadrivalent (GlaxoSmithKline)	0.5 mL (15 $\mu\text{g}$ )
FluLaval Quadrivalent (GlaxoSmithKline)	0.5 mL (15 $\mu\text{g}$ )
Fluzone Quadrivalent <sup>†</sup> (Sanofi Pasteur)	0.25 mL (7.5 $\mu\text{g}$ ) or 0.5 mL (15 $\mu\text{g}$ )

**Abbreviation:** HA = hemagglutinin.

\* For persons aged  $\geq 36$  months ( $\geq 3$  years), the dose volume is 0.5 mL for all inactivated influenza vaccines.

<sup>†</sup> Fluzone Quadrivalent may be administered as either 0.25 mL or 0.5 mL per dose (with no preference expressed for one volume over the other) for children aged 6 through 35 months.

**FIGURE. Influenza vaccine dosing algorithm for children aged 6 months through 8 years\* — Advisory Committee on Immunization Practices, United States, 2019–20 influenza season**



\* For children aged 8 years who require 2 doses of vaccine, both doses should be administered even if the child turns age 9 years between receipt of dose 1 and dose 2.

## Interim Estimates of 2019–20 Seasonal Influenza Vaccine Effectiveness — United States, February 2020

Influenza type/Age group	Influenza-positive		Influenza-negative		Vaccine effectiveness	
	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	Unadjusted % (95% CI)	Adjusted <sup>†</sup> % (95% CI)
<b>Influenza A and B</b>						
Overall	1,060	390 (37)	3,052	1,682 (55)	53 (45 to 59)	45 (36 to 53)
<b>Age group</b>						
6 mos–17 yrs	462	142 (31)	934	492 (53)	60 (50 to 69)	55 (42 to 65)
18–49 yrs	413	143 (35)	1,084	452 (42)	26 (6 to 42)	25 (3 to 41)
≥50 yrs	185	105 (57)	1,034	738 (71)	47 (27 to 62)	43 (19 to 60)
<b>Influenza B/Victoria</b>						
Overall	634	211 (33)	2,968	1,641 (55)	60 (52 to 66)	50 (39 to 59)
<b>Age group</b>						
6 mos–17 yrs	353	104 (29)	934	492 (53)	62 (51 to 71)	56 (42 to 67)
≥18 yrs	317	117 (37)	2,118	1,190 (56)	54 (42 to 64)	32 (11 to 48)
<b>Influenza A(H1N1)pdm09</b>						
Overall	326	138 (42)	3,052	1,682 (55)	40 (25 to 53)	37 (19 to 52)
<b>Age group</b>						
6 mos–17 yrs	98	35 (36)	934	492 (53)	50 (23 to 68)	51 (22 to 69)
18–49 yrs	125	48 (38)	1,084	452 (42)	13 (-27 to 40)	5 (-45 to 37)
≥50 yrs	103	55 (53)	1,034	738 (71)	54 (31 to 69)	50 (20 to 68)

\* Vaccine effectiveness was estimated as 100% x (1 – odds ratio [ratio of odds of being vaccinated among outpatients with CDC’s real-time RT-PCR influenza-positive test results to the odds of being vaccinated among outpatients with influenza-negative test results]); odds ratios were estimated using logistic regression.

† Adjusted for study site, age group, sex, race/ethnicity, self-rated general health, number of days from illness onset to enrollment, and month of illness using logistic regression.

Original Investigation

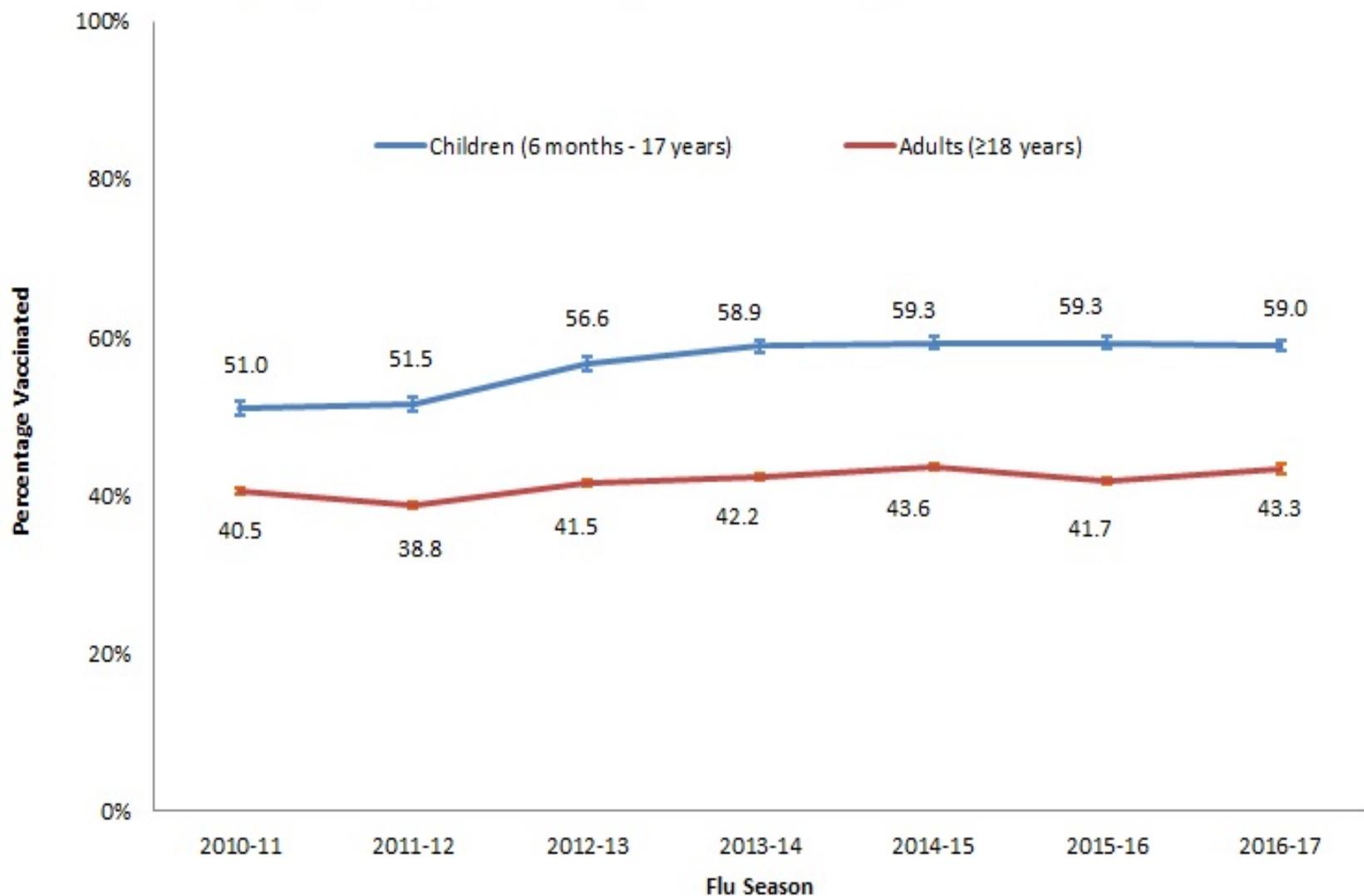
# Association Between Hospitalization With Community-Acquired Laboratory-Confirmed Influenza Pneumonia and Prior Receipt of Influenza Vaccination

Table 4. Subgroup Analyses Within Study of Influenza Vaccination and Influenza Pneumonia

Subgroups	Cases Who Were Vaccinated, No./Total No. (%)	Controls Who Were Vaccinated, No./Total No. (%)	Adjusted Odds Ratio (95% CI)	Estimated Vaccine Effectiveness, % (95% CI) <sup>a</sup>
Overall estimate	28/162 (17)	766/2605 (29)	0.43 (0.28 to 0.68)	56.7 (31.9 to 72.5)
Groups				
Children	7/68 (10)	376/1309 (29)	0.25 (0.11 to 0.58)	74.6 (42.5 to 88.8)
Adults	21/94 (22)	390/1296 (30)	0.59 (0.34 to 1.02)	41.5 (-2.2 to 66.5)

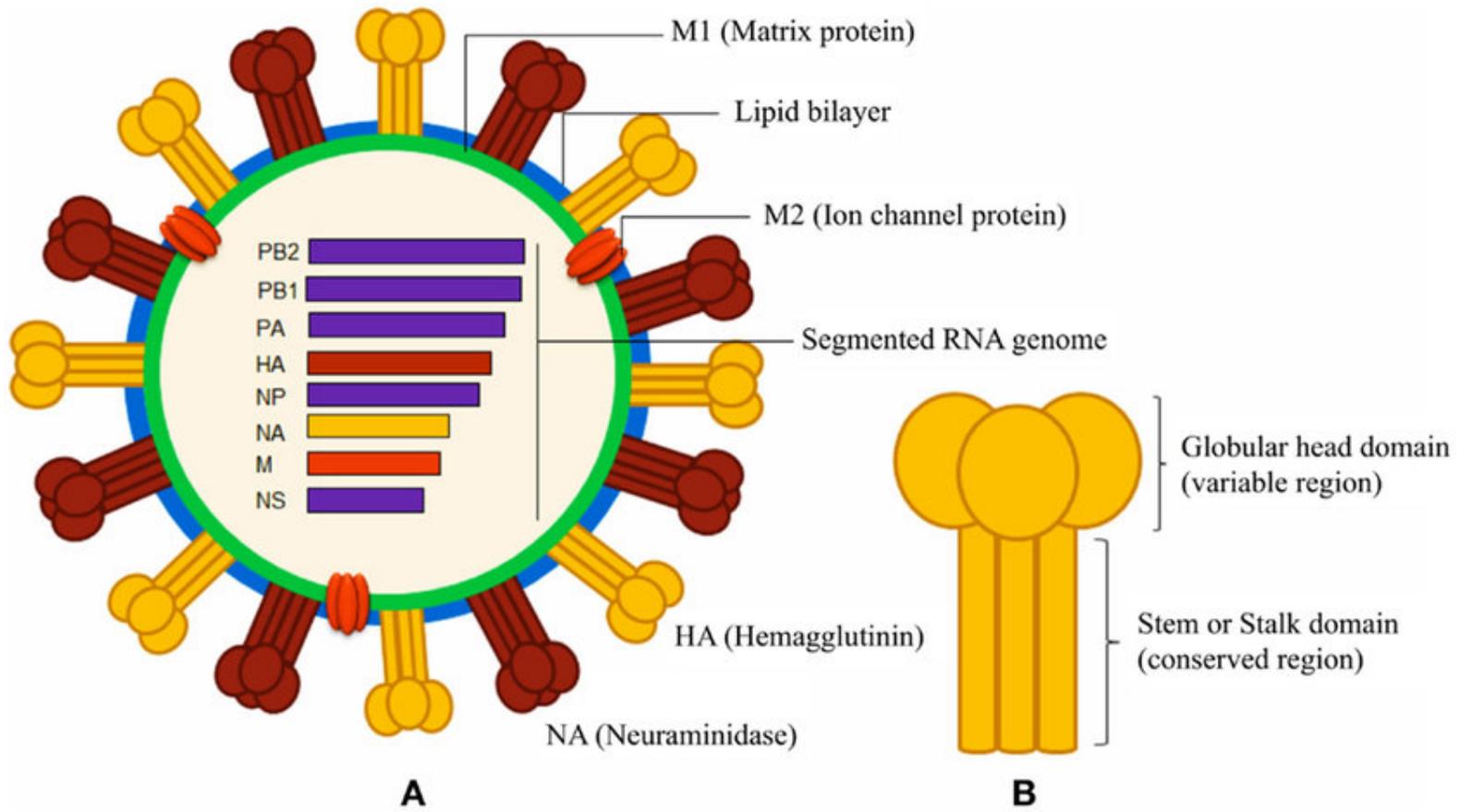
JAMA. 2015;314(14):1488-1497.

**Figure 1. Seasonal Flu Vaccination Coverage, by Age Group and Season, United States, 2010-2017**



Error bars represent 95% confidence intervals around the estimates.

Starting with the 2011-12 season, adult estimates reflect changes in BRFSS survey methods: the addition of cellular telephone samples and a new weighting method.

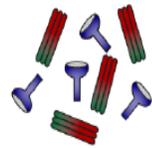


# Pathway to a Universal Influenza Vaccine

June 28-29, 2017 • 5601 Fishers Lane Conference Center, Rockville, MD, USA

## New Platforms for Seasonal and Pandemic Influenza Vaccines

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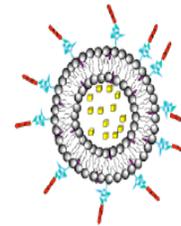
Recombinant subunit



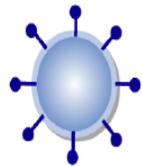
Synthetic peptide



Microbial vector



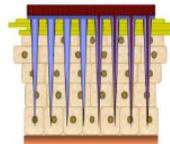
Nanoparticle-based



Virus-like particles  
(VLPs)



DNA-based



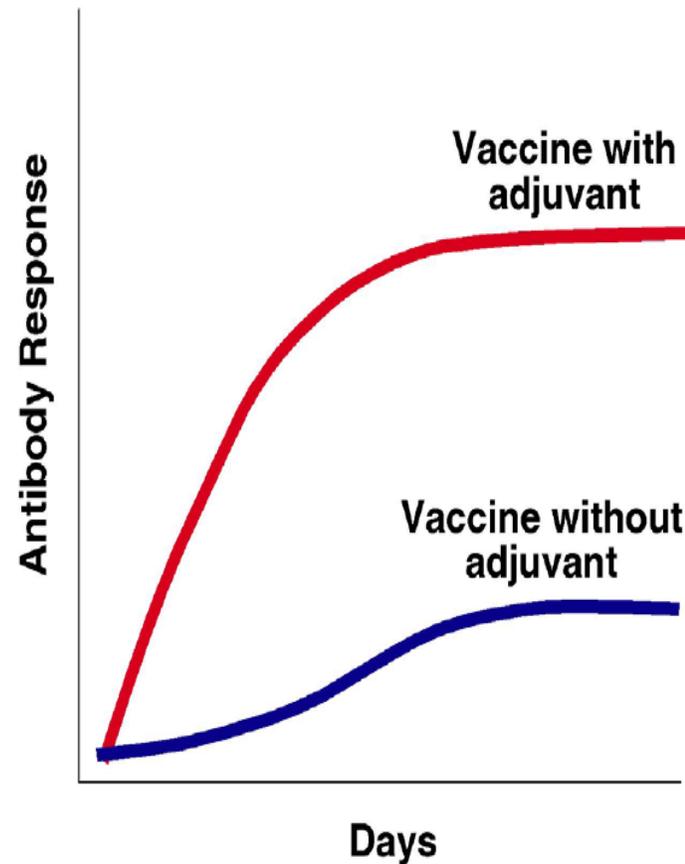
Novel delivery systems  
(e.g., microneedles)

# New Approaches to Influenza Vaccine

## Vaccine Adjuvants

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- Reduce amount of antigen needed
- Promote earlier, stronger, more durable immune responses
- May increase cross-protective immune response



**For 2020-2021, trivalent (three-component) egg-based vaccines are recommended to contain:**

- A/Guangdong-Maonan/SWL1536/2019 (H1N1)pdm09-like virus (updated)
- A/Hong Kong/2671/2019 (H3N2)-like virus (updated)
- B/Washington/02/2019 (B/Victoria lineage)-like virus (updated)

**Quadrivalent (four-component) egg-based vaccines, which protect against a second lineage of B viruses, are recommended to contain:**

- the three recommended viruses above, plus B/Phuket/3073/2013-like (Yamagata lineage) virus.

**For 2020-2021, cell- or recombinant-based vaccines are recommended to contain:**

- A/Hawaii/70/2019 (H1N1)pdm09-like virus (updated)
- A/Hong Kong/45/2019 (H3N2)-like virus (updated)
- B/Washington/02/2019 (B/Victoria lineage)-like virus (updated)
- B/Phuket/3073/2013-like (Yamagata lineage) virus

# Summary

- Influenza is a common respiratory illness accounting for substantial morbidity and some mortality annually
- Influenza vaccines are safe and effective
  - Absolute efficacy varies by year and influenced by circulating virus, vaccine administered, host characteristics and previous influenza experience
- New influenza vaccines are being developed

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in China — Key Questions for  
Impact Assessment



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ORIGINAL ARTICLE BRIEF REPORT

# A Novel Coronavirus from Patients with Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xinwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., et al., for the China Novel Coronavirus Investigating and Research Team

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Article Figures/Media

Metrics

January 24, 2020  
DOI: 10.1056/NEJMoa2001017

17 References 1 Citing Article

## Summary

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used to isolate a novel coronavirus, named 2019-nCoV, which formed another clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily. Different from both MERS-CoV and SARS-CoV, 2019-nCoV is the seventh member of the family of coronaviruses that infect humans. Enhanced surveillance and further investigation are ongoing. (Funded by the National Key Research and Development Program of China and the National Major Project for Control and Prevention of Infectious Disease in China.)

### Related Articles

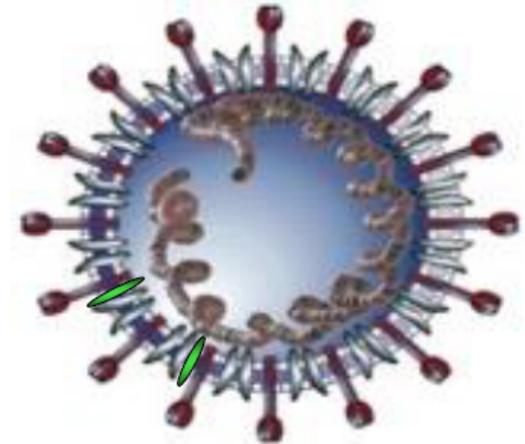
EDITORIAL JAN 24, 2020  
Another Decade, Another Coronavirus  
S. Perlman

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# Emerging Coronaviruses

- **SARS-CoV (2002-2004). – Severe Acute Respiratory Syndrome**
  - >8000 cases, 10% mortality, 32 countries in 3 months.
  - Bats –Civet Cats / Raccoon Dogs / Humans
- **MERS-CoV (2012-Present) (Middle East Respiratory Syndrome)**
  - > 2500 cases, ~35% mortality, 27 countries
  - Bats – Camels – Humans
- **COVID-19, SARS-CoV-2 (2019-present)**
  - **13,378,853 global cases; 580,045 deaths**
  - Bat most likely



## Two ways to become immune to a virus



One way is being infected and **surviving a viral infection**. For many viruses like measles and chickenpox, the infection will make you immune to that virus for the rest of your life. For other viruses, like influenza, infection will make you immune for a shorter period and only against a specific virus type.



The safest way to become immune is to **receive a vaccine** that protects you against the infection without making you sick. The best way to ensure that a lot of people become immune in a population is with a vaccine that can be given to everyone. Vaccines help the body learn how to fight off a disease before it strikes the body.

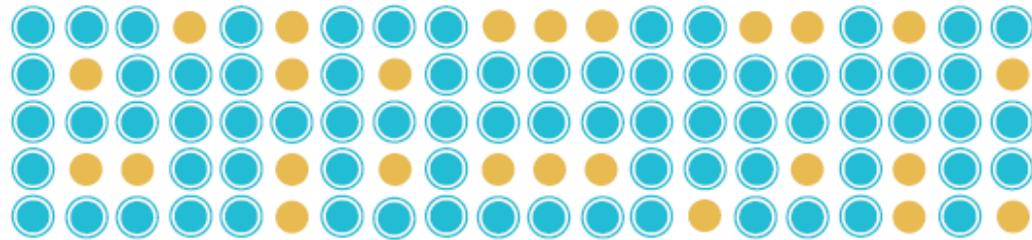
## How Herd Immunity Would Look Without a Vaccine

**1** Generally, the fraction of a population that needs to be immune before the population is protected from a virus by community immunity depends on how contagious the pathogen is; for example, for SARS-CoV-2, the the virus that causes COVID-19, the fraction of the population that needs to be immune is estimated between 60-75%.

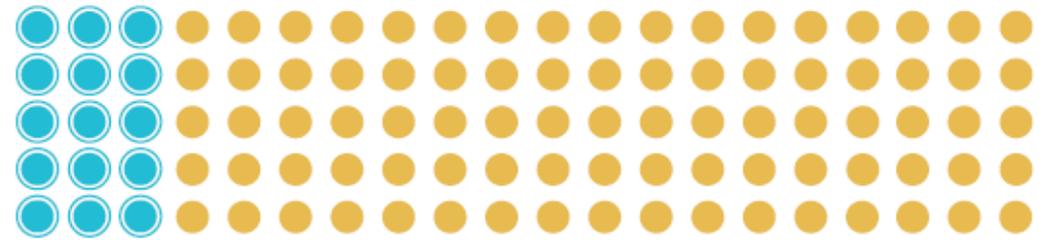
**2** The scientific evidence is not yet in about how much immunity having COVID-19 provides us, or for how long. Furthermore, in our models of local COVID-19 spread, less than 15% of the population may be infected at the peak, leaving us far below the 60-75% needed to achieve community immunity.

Each dot represents 1% of the population:  Immune  Susceptible

**60-75% needed for herd immunity**



**Less than 15% infected and now immune, following peak disease**

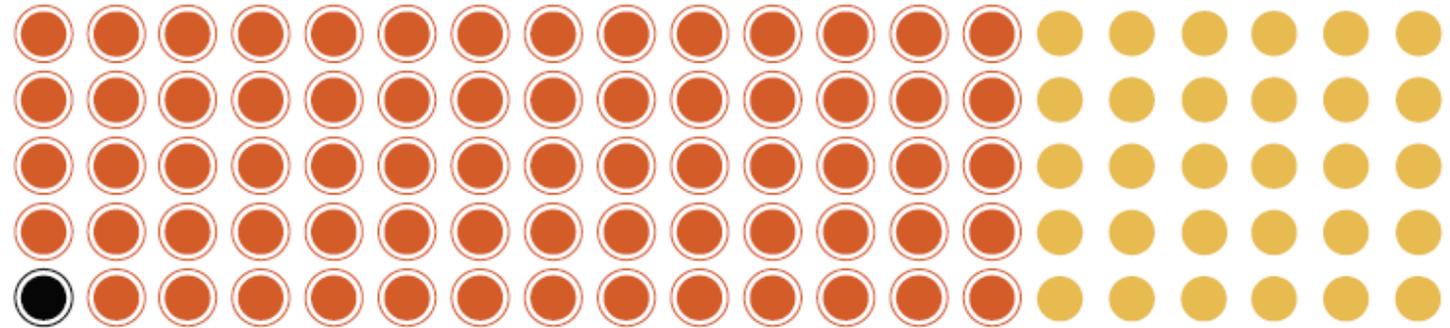


Having more people become infected to achieve this level of immunity would be costly since the rate of hospitalization with COVID-19 is very high and the estimated case fatality for COVID-19 is 10 times higher than for the average seasonal influenza infection. Those rates are even higher in vulnerable populations like the elderly.

Each dot represents 1% of the population:

● Infected ● Susceptible ● Deceased

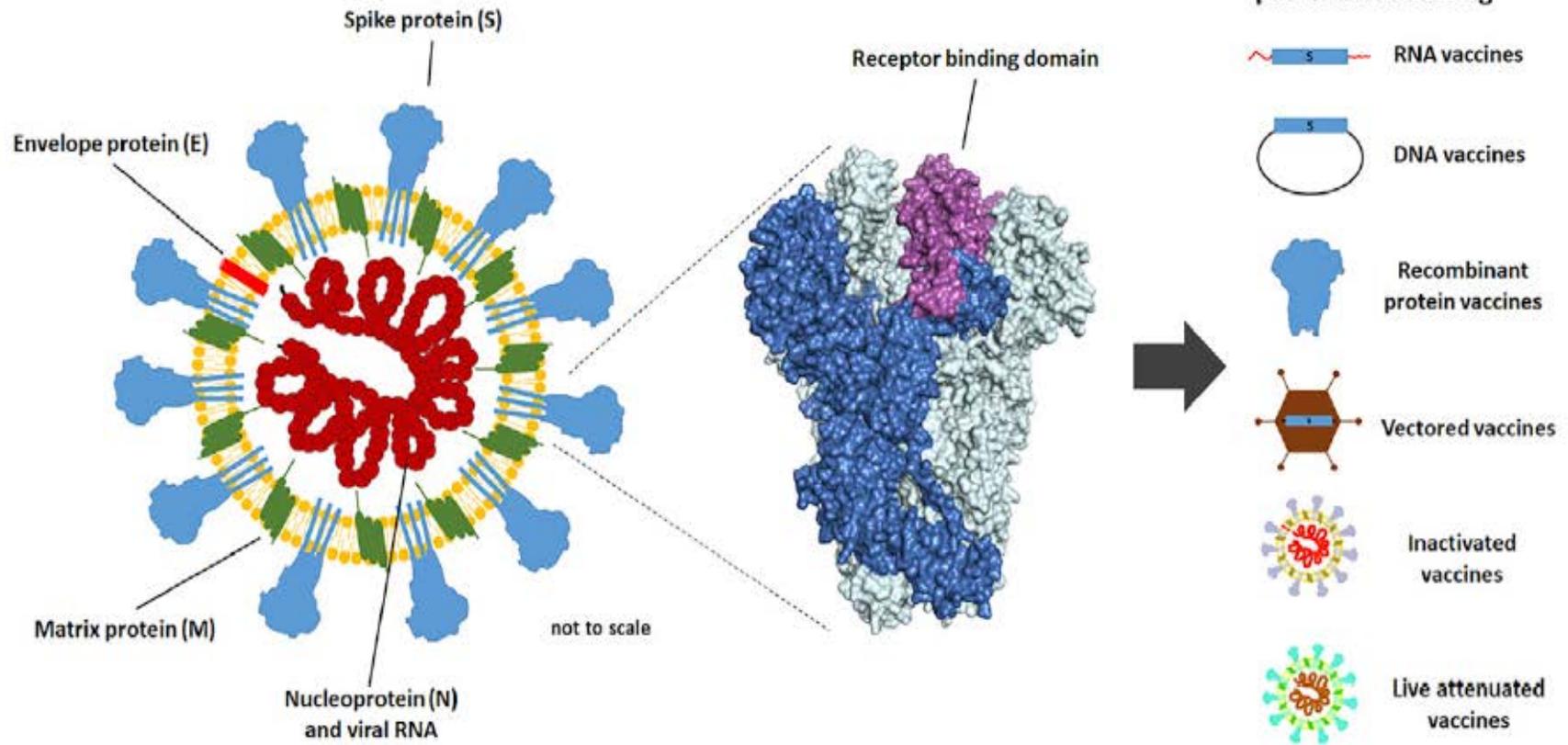
**3** For example, if 70% of Tennesseans were infected with COVID-19, **about 50,000 would die**, given a case fatality rate of about 1%.



## **Staying the Course With Social Distancing**

It is much safer, then, to continue with some level of appropriate social distancing and hygiene, along with public health measures like increased testing and contact tracing while scientists develop a vaccine. When a safe and effective vaccine becomes available, we can then vaccinate the population and achieve herd or community immunity.

# Overview of Potential SARS-CoV-2 Vaccine Platforms



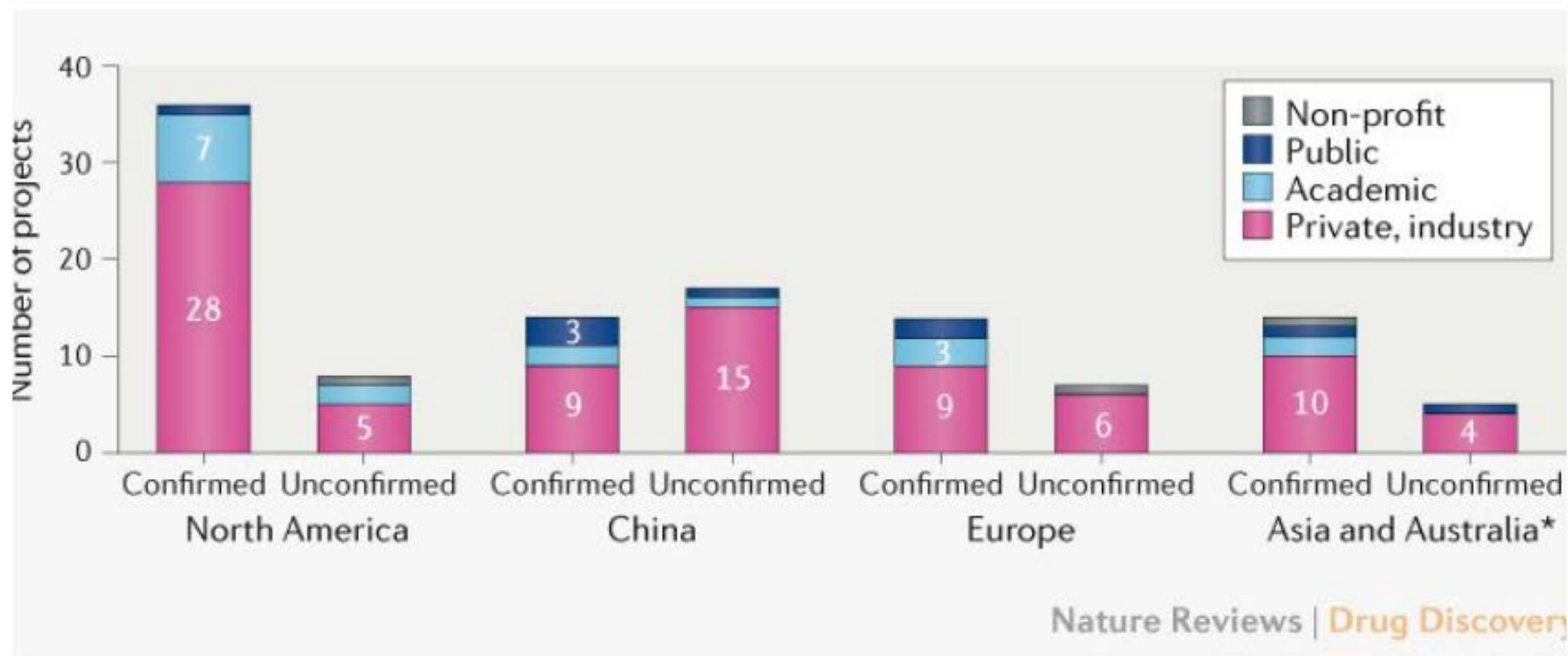
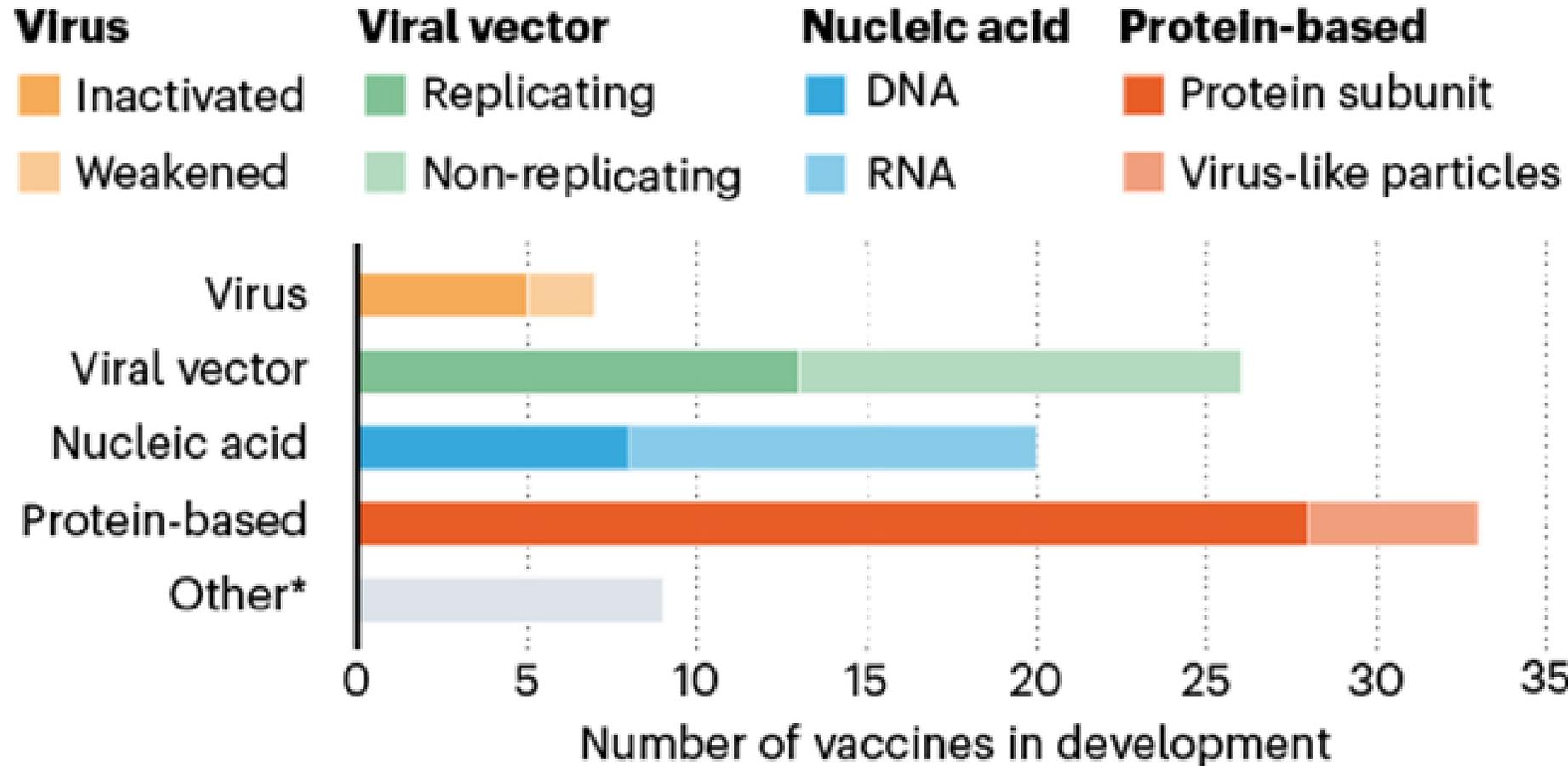


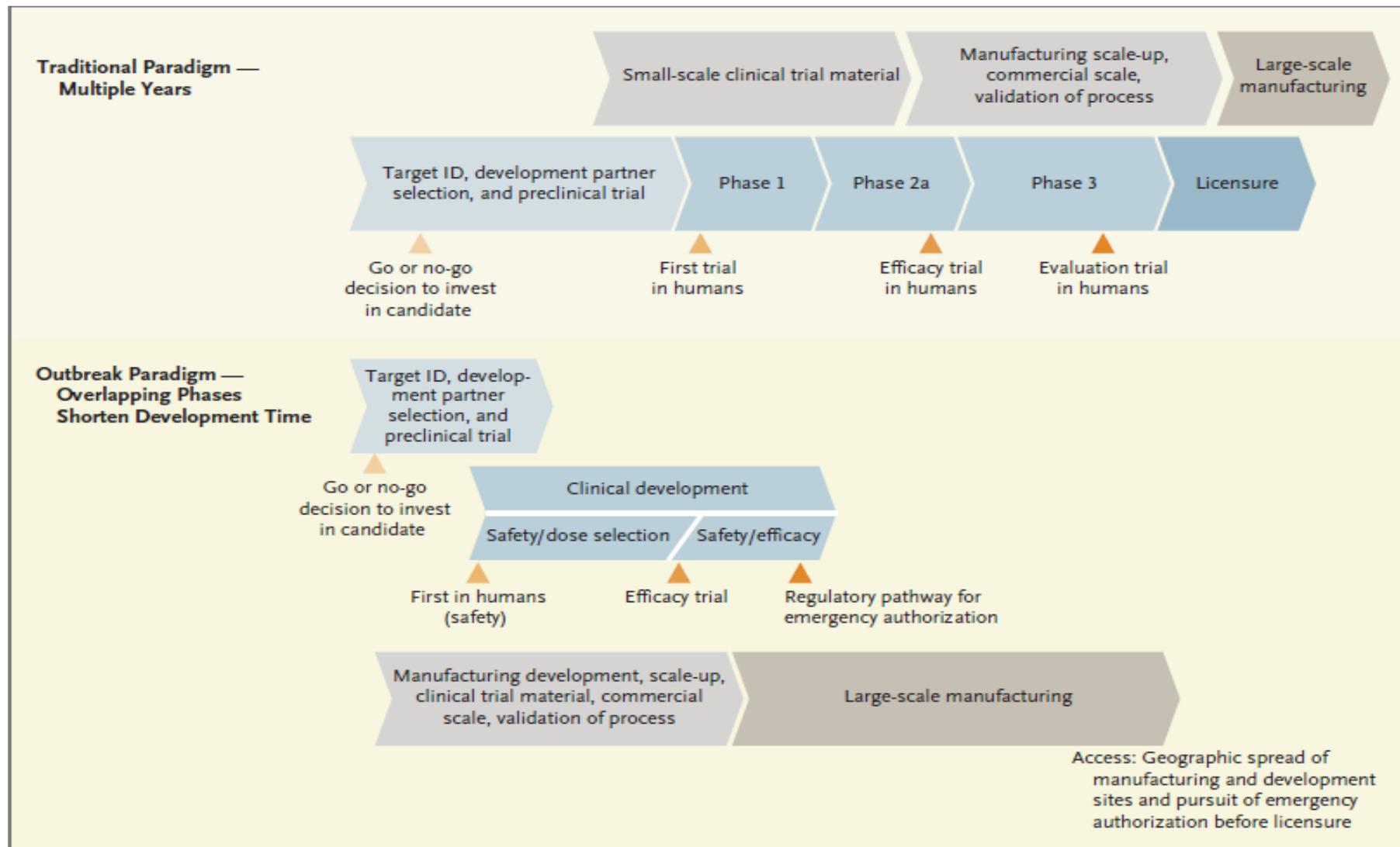
Fig. 2 | **Profile of COVID-19 vaccine developers by type and geographic location.** For partnerships, the location is that of the lead developer. \*Excluding China.

# Vaccine Approach: Strategies

## AN ARRAY OF VACCINES



\* Other efforts include testing whether existing vaccines against poliovirus or tuberculosis could help to fight SARS-CoV-2 by eliciting a general immune response (rather than specific adaptive immunity), or whether certain immune cells could be genetically modified to target the virus.



**Difference between Traditional Vaccine Development and Development Using a Pandemic Paradigm.**

The pandemic paradigm requires multiple activities to be conducted at financial risk to developers and manufacturers and without knowing whether the vaccine candidate will be safe and effective, including very early manufacturing scale-up to commercial scale before establishment of clinical proof of concept. ID denotes identification.

ORIGINAL ARTICLE

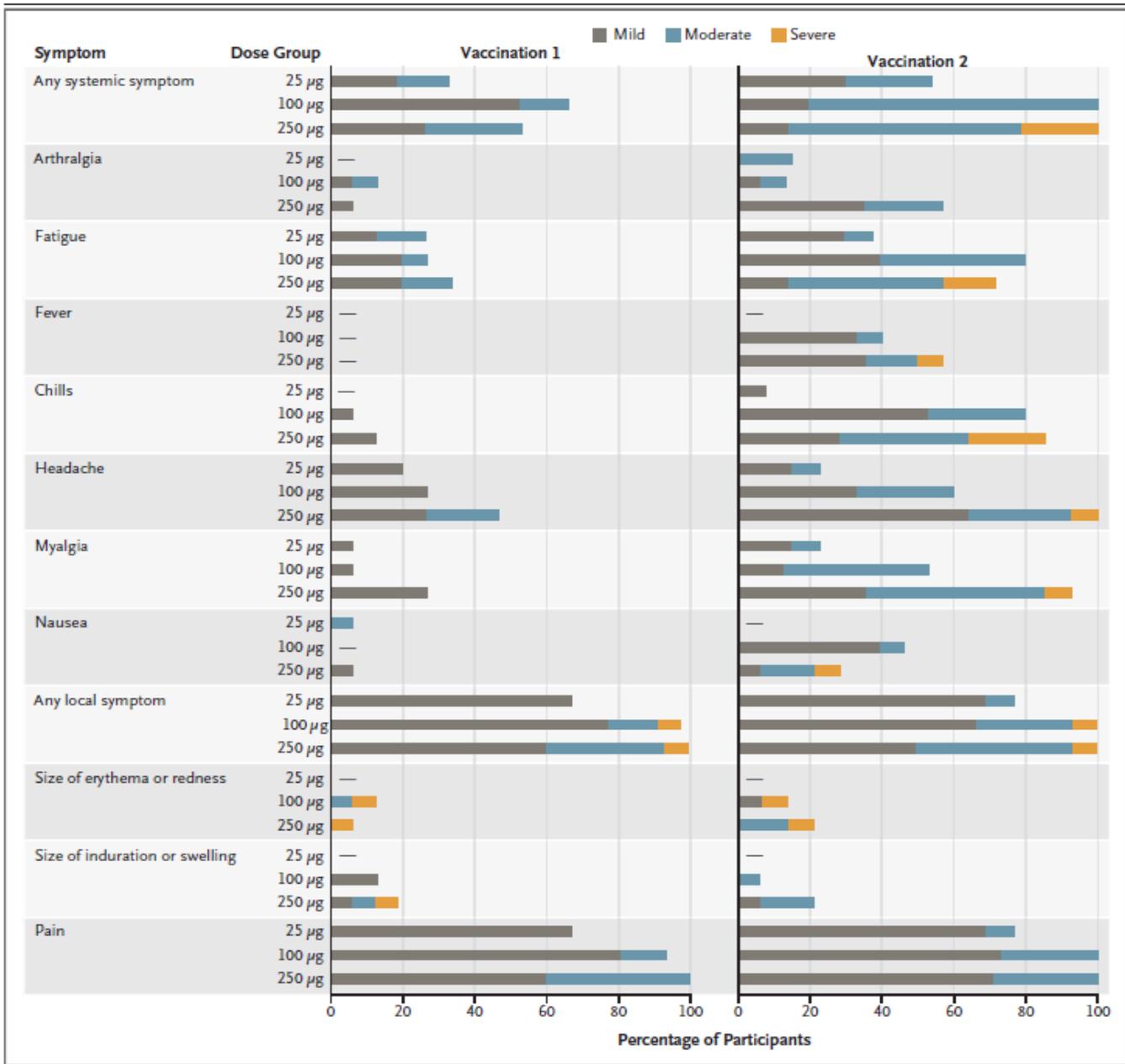
# An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene,  
R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens,  
A.J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett,  
K.M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson II, M. Padilla, J.R. Mascola,  
K.M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross,  
W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, and J.H. Beigel,  
for the mRNA-1273 Study Group\*

This article was published on July 14, 2020,  
at [NEJM.org](https://www.nejm.org).

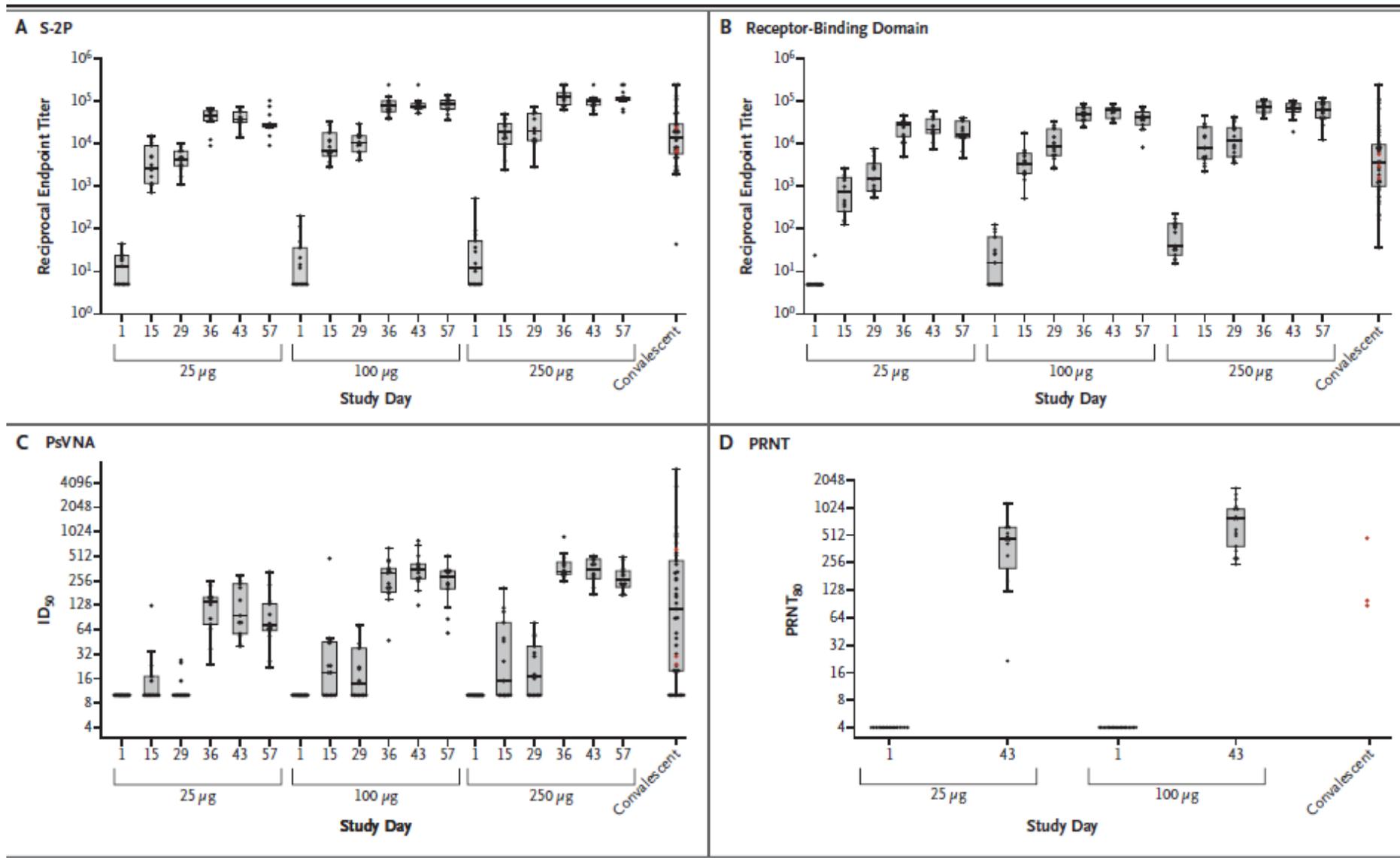
**Table 1.** Characteristics of the Participants in the mRNA-1273 Trial at Enrollment.\*

Characteristic	25- $\mu$ g Group (N=15)	100- $\mu$ g Group (N=15)	250- $\mu$ g Group (N=15)	Overall (N=45)
Sex — no. (%)				
Male	9 (60)	7 (47)	6 (40)	22 (49)
Female	6 (40)	8 (53)	9 (60)	23 (51)
Age — yr	36.7 $\pm$ 7.9	31.3 $\pm$ 8.7	31.0 $\pm$ 8.0	33.0 $\pm$ 8.5
Race or ethnic group — no. (%) <sup>†</sup>				
American Indian or Alaska Native	0	1 (7)	0	1 (2)
Asian	0	0	1 (7)	1 (2)
Black	0	2 (13)	0	2 (4)
White	15 (100)	11 (73)	14 (93)	40 (89)
Unknown	0	1 (7)	0	1 (2)
Hispanic or Latino — no. (%)	1 (7)	3 (20)	2 (13) <sup>‡</sup>	6 (13)
Body-mass index <sup>§</sup>	24.6 $\pm$ 3.4	26.7 $\pm$ 2.6	24.7 $\pm$ 3.1	25.3 $\pm$ 3.2



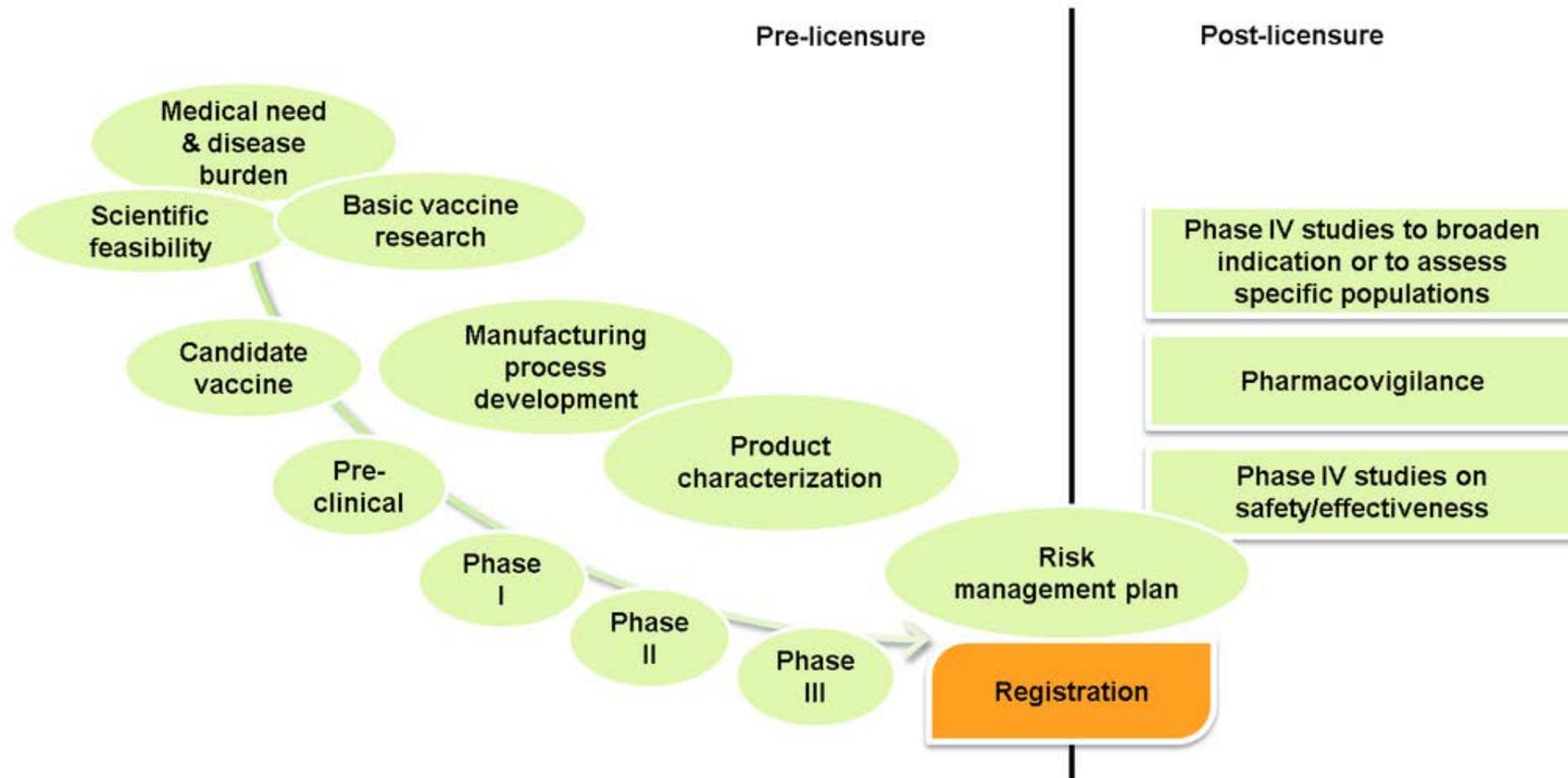
**Figure 1. Systemic and Local Adverse Events.**

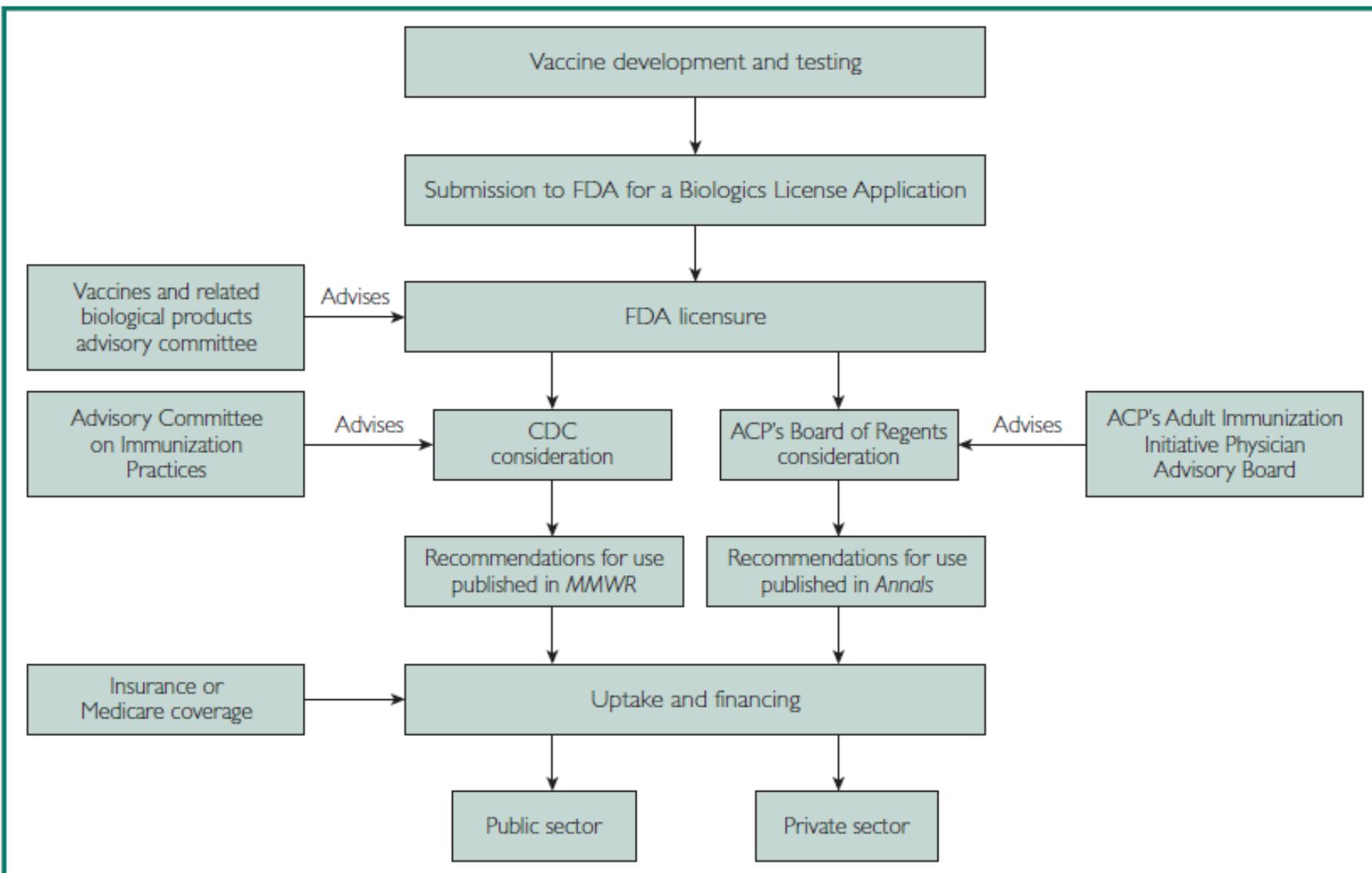
The severity of solicited adverse events was graded as mild, moderate, or severe (see Table S1).



This article was published on July 14, 2020,  
 at NEJM.org.

# The Vaccine Evaluation Process





**FIGURE 1.** Development and dissemination of vaccine recommendations and policies. ACP = American College of Physicians; *Annals* = *Annals of Internal Medicine*; CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; *MMWR* = *Morbidity and Mortality Weekly Report*. From *Ann Intern Med*.<sup>7</sup> Copyright © 2019 American College of Physicians. Used with permission.

# Prioritization of Vaccination

## PRIORITY POPULATIONS

- Native/Indigenous
- AA/Black
- Latinx
- Occupational Engagement
- People with pre-existing health conditions
- Communities experiencing health disparities
- Older Adults
  - Nursing Home
  - Assisted Living Facility residents

- All activities will be tailored for each of these vital priority populations
- Priority populations will require varying:
  - Outreach
  - Engagement
  - Recruitment approaches
- Building and maintaining relationships with experts working with these groups

# Summary

- Safe and effective vaccines are needed for COVID-19; must be accessible, affordable and globally available
- Vaccine development is a staged, deliberate and careful process
- Many challenges – New disease, poorly understood immunity, uncertain trajectory of outbreak
- Vaccine safety will be meticulously assessed