# CDC/IDSA Clinician Call

May 4, 2023

## Welcome & Introductions

**Dana Wollins, DrPH, MGC**
Vice President
Clinical Affairs & Practice Guidelines
Infectious Diseases Society of America

- 97th in a series of calls, initiated in 2020 as a forum for information sharing among frontline clinicians caring for patients with COVID-19.
- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.
- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.

# CDC/IDSA Clinician Call: The Latest on COVID-19 Vaccination; Plus Update on Avian Influenza

## 1. FDA Update

**Simplification of mRNA Vaccination Regimens and Plans for Possible Vaccine Strain Update**
**Peter Marks, MD, PhD**
Director, Center for Biologics Evaluation & Research, FDA

## 2. CDC Update

**Bivalent mRNA COVID-19 Vaccine Safety Update**
**Karen R. Broder, MD**
Captain, U.S. Public Health Service
Chief Medical Officer, Immunization Safety Office
Division of Healthcare Quality Promotion, CDC

**Updates to Policy and Recommendations**
**Sara Oliver, MD, MSPH**
LCDR, U.S. Public Health Service
Co-Lead, COVID-19 Work Group of the Advisory Committee on Immunization Practices (ACIP), CDC

## 3. Q&A - All Speakers Plus Additional Experts

**Steven Pergam, MD, MPH**
Professor, Vaccine & Infectious Disease Division
Professor Clinical Research Division
Fred Hutchinson Cancer Center

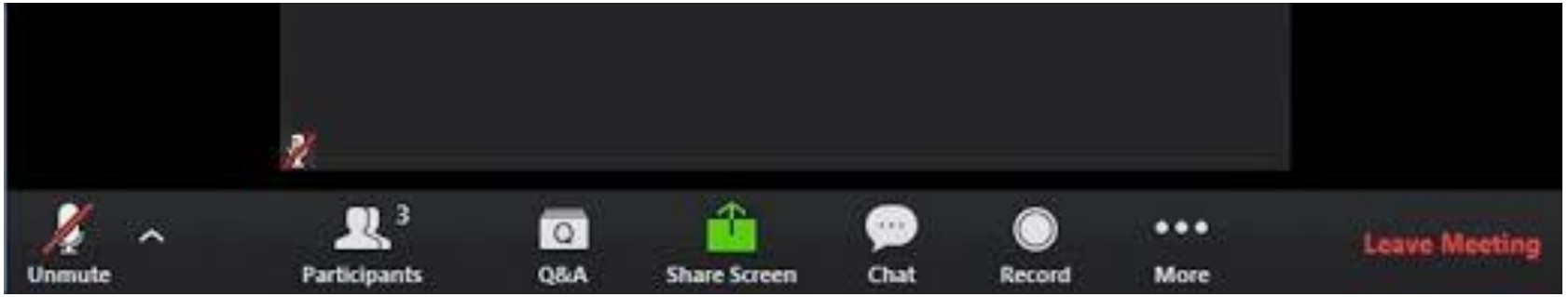
**Cameron R. Wolfe, MD, MBBS(Hons), MPH, FIDSA, FAST**
Professor of Medicine
Transplant Infectious Disease
Duke University Medical Center

## 4. Update on Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

**Tim Uyeki, MD, MPH, MPP**
Chief Medical Officer, Influenza Division
CDC

Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button



# FDA Update – Simplification of mRNA Vaccination Regimens and Plans for Possible Vaccine Strain Update

**Peter Marks, MD, PhD**
FDA

# FDA Vaccine Update

Peter Marks, MD, PhD

CDC/IDSA Clinician Call

May 4, 2023

# Two Topics

- Simplification of mRNA vaccination regimens
- Plans for possible vaccine strain update

# Simplification of the COVID-19 Vaccination Regimen Is Desirable

- Multiple COVID-19 vaccine compositions (e.g., different primary series and booster compositions) and immunization schedules complicate vaccine administration, communication, and uptake
- Simplification would contribute to easier vaccine deployment, better communication and may improve vaccine coverage

# Simplification of the COVID-19 Vaccination Regimen Is Desirable

- Significant simplification of the COVID-19 vaccination regimen can be achieved by adopting:
  - Same COVID-19 vaccine composition for primary series and booster vaccination
  - A simplified immunization schedule that applies to all COVID-19 vaccines
  - The same vaccine strain composition for all Spike-based COVID-19 vaccines

# Simplification of the COVID-19 Vaccination Regimen Is Feasible

- Monovalent BA.4/BA.5 vaccines have been found to be as effective in neutralizing prior COVID-19 variants (Original, Beta, Delta, Omicron BA.1) as well as the BA.4/BA.5 variants, so that the Original monovalent vaccines are no longer clinically relevant

# Simplification of the COVID-19 Vaccination Regimen Is Feasible

- Most children over three years of age and nearly all adults have either received at least one COVID-19 vaccine or have had natural SARS-CoV-2 infection
- Data indicate that natural infection plus vaccination, even with a single dose, produces immunity comparable to that which was previously provided by a primary vaccination series

# COVID-19 Vaccination Going Forward for Most Individuals 6 to 65 Years of Age*

- One dose when the vaccine composition is updated to stay up to date
  - Next update is anticipated to be available in September 2023

*Exception: those with significant immunocompromise

# COVID-19 Vaccination Going Forward for Most Individuals Under 6 Years of Age*

- For previously unvaccinated children, a multidose vaccination regimen is appropriate
  - 2 doses of Moderna for age 6 months through 5 years
  - 3 doses of Pfizer-BioNTech for age 6 months through 4 years
  - 1 dose of Pfizer-BioNTech for age 5 years

*Exception: those with significant immunocompromise

# COVID-19 Vaccination Going Forward for Most Individuals 65 Years of Age and Older*

- One dose when the vaccine composition is updated to stay up to date
- A second dose may be administered at least 4 months after the first dose
  - Helps address waning immunity in older individuals

*Exception: those with significant immunocompromise

# COVID-19 Vaccination Going Forward for Individuals with Immunocompromise

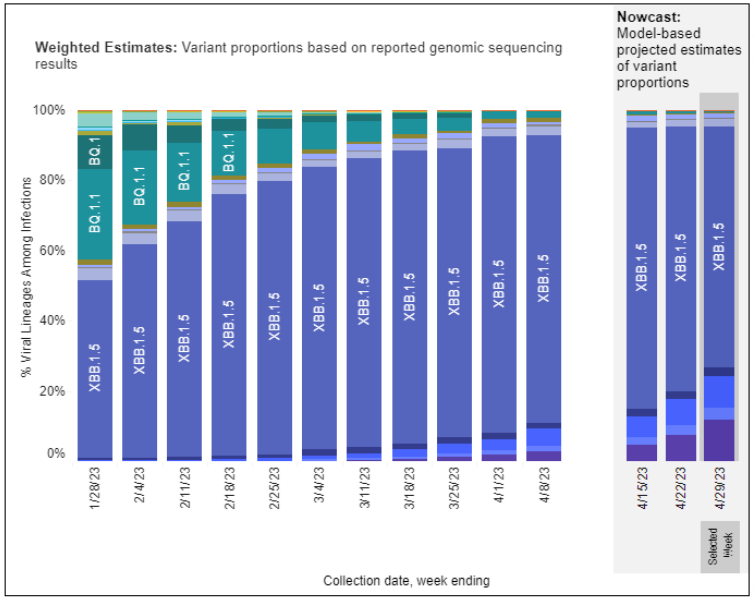
- Additional vaccine doses may be administered initially and then at the discretion of the provider
  - At least 1 month after first series of doses for those under age 4 (Pfizer-BioNTech) or age 5 (Moderna)
  - At least 2 months after the last dose for older individuals and then at the discretion of the provider

# Recent Evolution of SARS-CoV-2

**Weighted and Nowcast Estimates in United States for Weeks of 1/22/2023 – 4/29/2023**

**Nowcast Estimates in United States for 4/23/2023 – 4/29/2023**

**Hover over (or tap in mobile) any lineage of interest** to see the amount of uncertainty in that lineage's estimate.




USA

| WHO label | Lineage # | US Class | %Total | 95%PI |
|---|---|---|---|---|
| Omicron | XBB.1.5 | VOC | 68.8% | 65.3-72.2% |
| | XBB.1.16 | VOC | 11.7% | 9.2-14.6% |
| | XBB.1.9.1 | VOC | 9.0% | 7.3-10.9% |
| | XBB.1.9.2 | VOC | 3.7% | 2.8-4.9% |
| | XBB | VOC | 2.4% | 1.4-4.0% |
| | XBB.1.5.1 | VOC | 2.2% | 1.7-2.8% |
| | FD.2 | VOC | 1.3% | 0.7-2.4% |
| | BQ.1.1 | VOC | 0.4% | 0.3-0.7% |
| | CH.1.1 | VOC | 0.3% | 0.2-0.4% |
| | BQ.1 | VOC | 0.1% | 0.0-0.1% |
| | BN.1 | VOC | 0.0% | 0.0-0.0% |
| | BA.5 | VOC | 0.0% | 0.0-0.0% |
| | BA.1.1 | VOC | 0.0% | 0.0-0.1% |
| | BA.2 | VOC | 0.0% | 0.0-0.0% |
| | BA.2.75 | VOC | 0.0% | 0.0-0.0% |
| | BA.2.12.1 | VOC | 0.0% | 0.0-0.0% |
| | BA.2.75.2 | VOC | 0.0% | 0.0-0.0% |
| | BF.7 | VOC | 0.0% | 0.0-0.0% |
| | BA.5.2.6 | VOC | 0.0% | 0.0-0.0% |
| | BF.11 | VOC | 0.0% | 0.0-0.0% |
| | BA.4.6 | VOC | 0.0% | 0.0-0.0% |
| Other | Other* | | 0.1% | 0.0-0.1% |

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.2.75.2, CH.1.1 and BN.1, BA.2.75 sublineages are aggregated with BA.2.75. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except the lineages shown and their sublineages, sublineages of XBB are aggregated to XBB. Except XBB.1.5.1 and FD.2, sublineages of XBB.1.5 are aggregated to XBB.1.5. For all the other lineages listed, their sublineages are aggregated to the listed parental lineages respectively. Previously, XBB.1.9.2 and XBB.1.16 were aggregated to XBB; FD.2 was aggregated to XBB.1.5. Lineages BA.2.75.2, XBB, XBB.1.5, XBB.1.5.1, FD.2, XBB.1.9.1, XBB.1.9.2, XBB.1.16, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

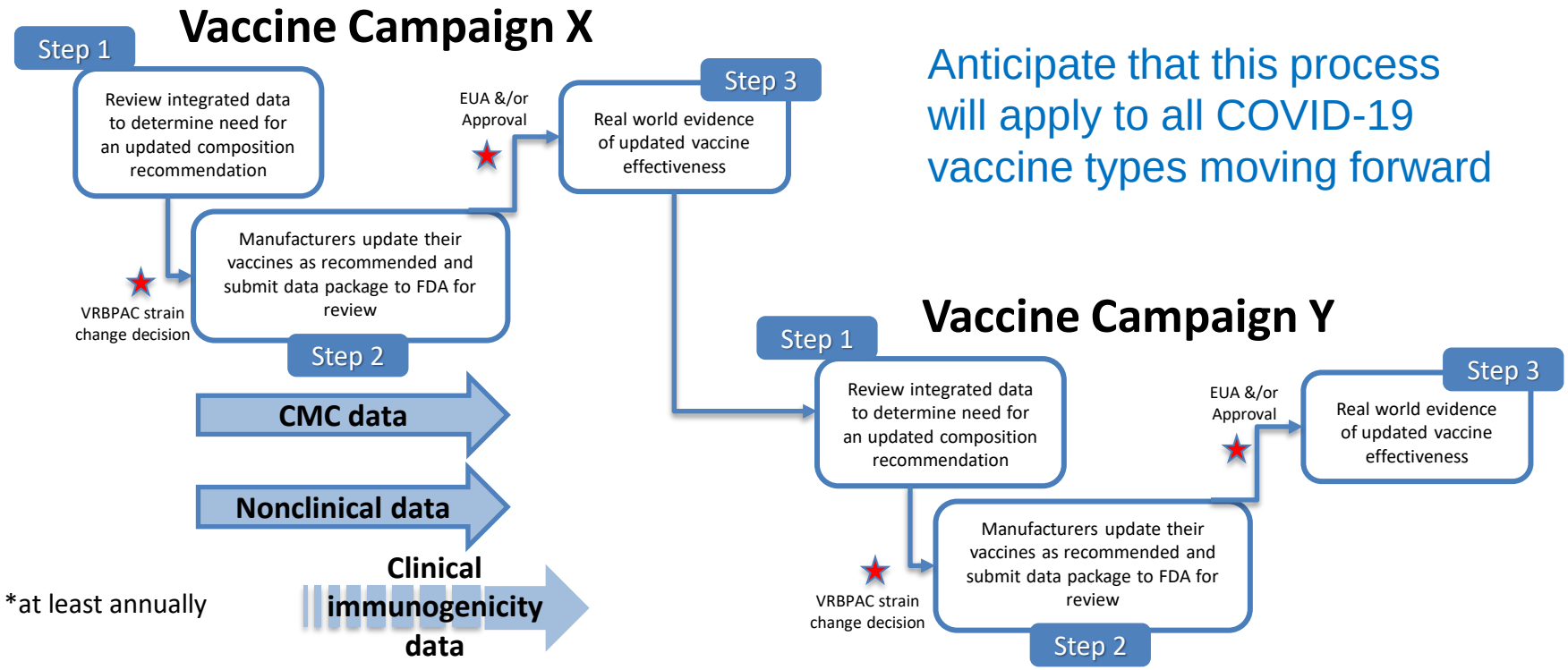
# XBB.1.9.1 (Hyperion)

- XBB.1.9.1 was the first variant to receive a nickname using the new system: "Hyperion", after a moon of Saturn. XBB.1.9.1 (Hyperion)
  - 1st descendant of the 9th descendant of the first descendant of XBB
  - It is not descended from XBB.1.5 (Kraken)
- XBB.1.9.1 is the first variant to have a clear increased transmission advantage over XBB.1.5
- First detected in Southeast Asia in January 2023. By late January it was circulating globally at over 1% and by mid-February over 4% globally.
  - First appeared on CDC Nowcast on February 27th. It has also been increasing in the United Kingdom and Europe

# XBB.1.16 (Arcturus)

- XBB.1.16 is a recombinant of BA.2.10.1 and BA.2.75
- Additional mutations in the spike protein compared with XBB.1.5
  - Contains T478R and E180V mutations in the receptor binding domain (RBD)
  - ORF9b I5T mutation provides growth advantage
- The mutations of this variant have been associated with signs of increased transmissibility and a higher degree of infection
- As of April 29, 2023 represents about 12% of US viral isolates

# Approach to Updating Vaccine Composition: High-level Overview of a Continuous* Iterative 3-Step Process

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ADMINISTRATION

# Bivalent mRNA COVID-19 Vaccine Safety Update

**Karen Broder, MD**
CDC

# Bivalent mRNA COVID-19 Vaccine Safety Update

## CDC/IDSA Clinician Call

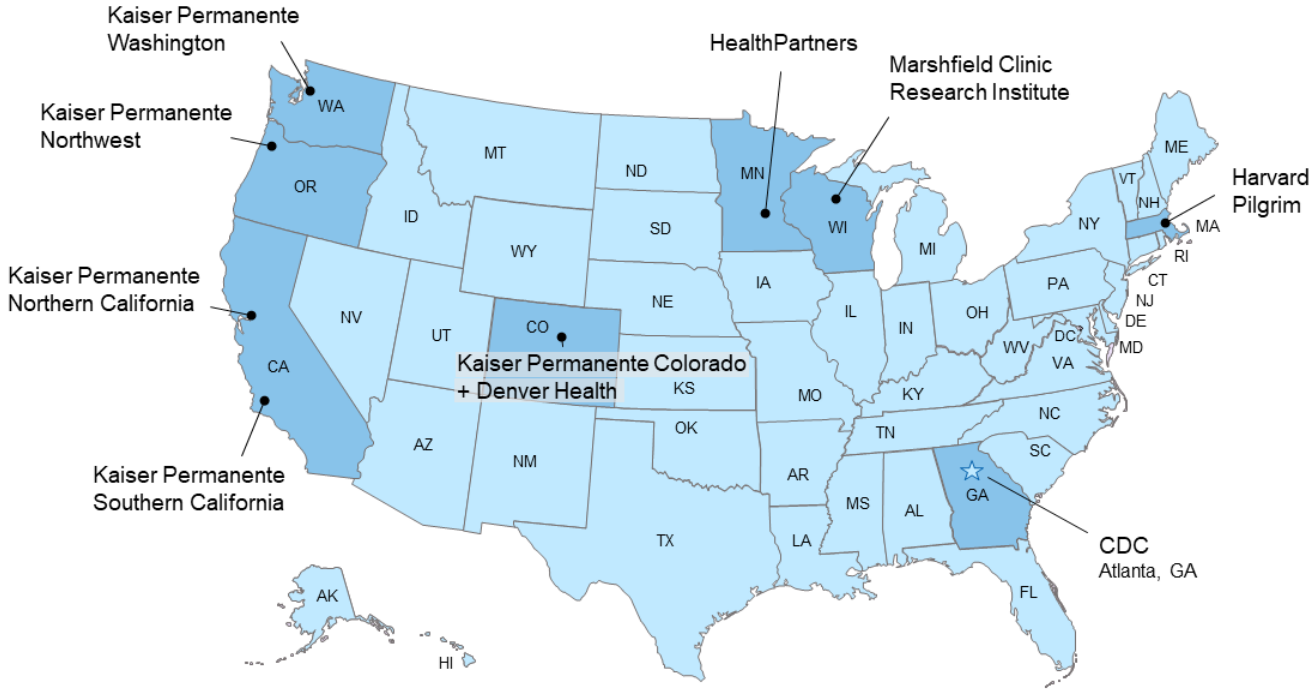
**May 4, 2023**

**Karen R. Broder, MD**
Captain, U.S. Public Health Service
Chief Medical Officer, Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention (CDC)

# Disclaimer and Disclosures

- The material was previously presented to the Advisory Committee on Immunization Practices (ACIP) meeting April 19, 2023 by Dr. Tom Shimabukuro (Advisory Committee on Immunization Practices (ACIP) | CDC)
- Dr. Nicola Klein prepared data from the Vaccine Safety Datalink (VSD) for this presentation; Dr. Klein reports research support from Pfizer for COVID-19 vaccine clinical trials and from Pfizer, GlaxoSmithKline, Merck and Sanofi Pasteur for unrelated studies
- The findings and conclusions in this presentation are those of the presenters and do not necessarily represent the official position of the CDC
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC

# Vaccine Safety Datalink (VSD)




- Established in 1990
- Collaborative project between CDC and 9 integrated healthcare organizations
- Includes electronic health record data on ~12.5 million individuals across all sites

# VSD Rapid Cycle Analysis (RCA)* for bivalent mRNA COVID-19 vaccine

- Pre-specified outcomes were assessed during weekly sequential monitoring after bivalent mRNA COVID-19 vaccination*
  - Risk of pre-specified outcomes 1–21 days following a bivalent vaccination compared with bivalent vaccinated individuals who were 22–42 days following the bivalent dose (vaccinated concurrent comparator method)
  - All analyses adjusted for age, sex, race/ethnicity, VSD site, calendar time (days) and seasonality (time)
  - Signal if p-value <0.01 (1-sided)

* Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink. Available at: Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink (cdc.gov)

# VSD COVID-19 vaccine RCA prespecified surveillance outcomes

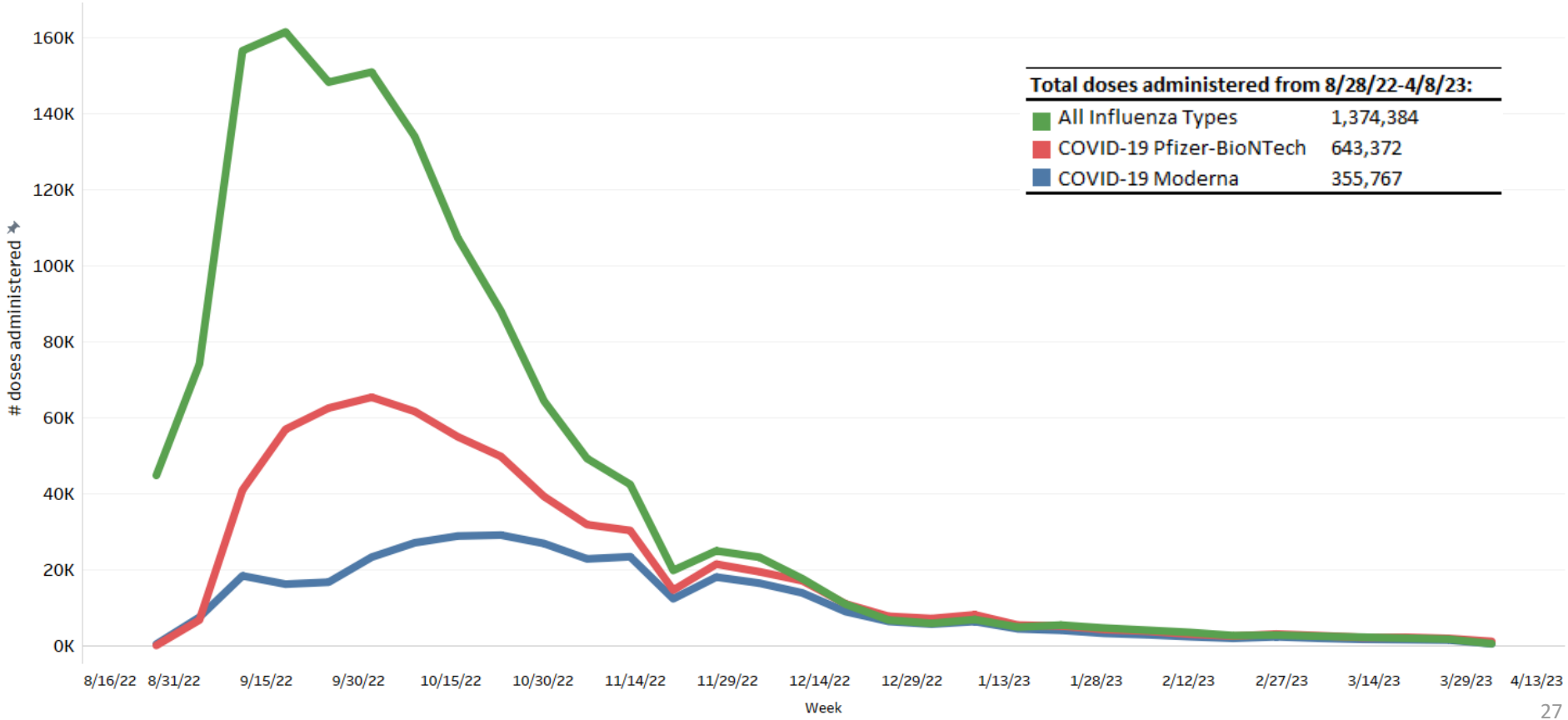
- In bivalent mRNA COVID-19 vaccine monitoring, VSD RCA detected a statistical signal for ischemic stroke after bivalent Pfizer-BioNTech vaccination in the age group 65 years and older
- No other VSD RCA pre-specified surveillance outcomes have signaled in any age groups for either of the bivalent mRNA COVID-19 vaccines or when data for the two mRNA vaccine types are combined/pooled

| Prespecified outcomes | Settings |
|---|---|
| Acute disseminated encephalomyelitis | Emergency dept, Inpatient |
| Acute myocardial infarction | Emergency dept, Inpatient |
| Acute respiratory distress syndrome | Emergency dept, Inpatient |
| Anaphylaxis* | Emergency dept, Inpatient |
| Appendicitis | Emergency dept, Inpatient |
| Bell's palsy | Emergency dept, Inpatient, Outpatient |
| Cerebral venous sinus thrombosis | Emergency dept, Inpatient |
| Disseminated intravascular coagulation | Emergency dept, Inpatient |
| Encephalitis / myelitis / encephalomyelitis | Emergency dept, Inpatient |
| Guillain-Barré syndrome | Emergency dept, Inpatient |
| Immune thrombocytopenia | Emergency dept, Inpatient, Outpatient |
| Kawasaki disease | Emergency dept, Inpatient |
| Multisystem inflammatory syndrome in children/adults (MIS-C/MIS-A) | Emergency dept, Inpatient |
| Myocarditis / pericarditis* | Emergency dept, Inpatient |
| Narcolepsy / cataplexy | Emergency dept, Inpatient, Outpatient |
| Pulmonary embolism | Emergency dept, Inpatient |
| Seizures/Convulsions (including 0-7 days for youngest ages) | Emergency dept, Inpatient |
| Stroke, hemorrhagic | Emergency dept, Inpatient |
| Stroke, ischemic | Emergency dept, Inpatient |
| Thrombosis with thrombocytopenia syndrome | Emergency dept, Inpatient |
| Thrombotic thrombocytopenic purpura | Emergency dept, Inpatient |
| Transverse myelitis | Emergency dept, Inpatient |
| Venous thromboembolism | Emergency dept, Inpatient, Outpatient |

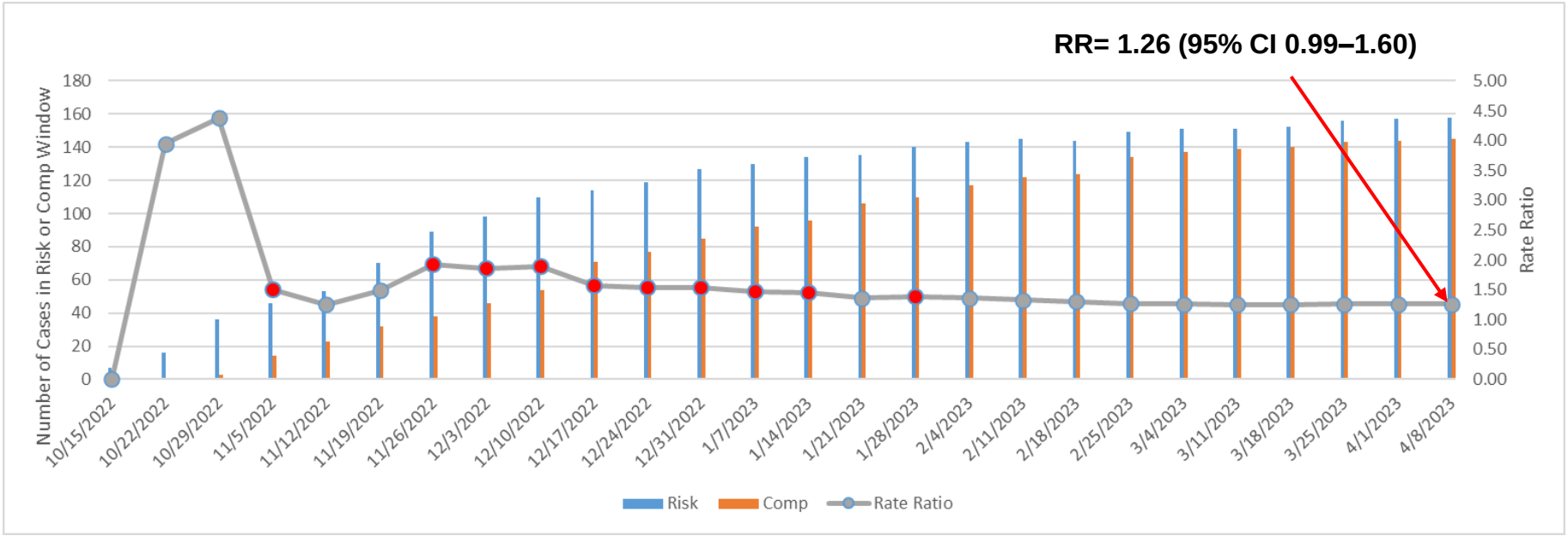
*All outcomes are first ever in the ICD-10 era, except anaphylaxis which is first in 7 days, and myocarditis/pericarditis which is first in 60 days

# VSD COVID-19 RCA Analyses: Ischemic stroke after bivalent Pfizer-BioNTech vaccine among persons aged ≥65 years

# Bivalent COVID-19 vaccine doses and influenza vaccine doses administered over time among persons aged ≥65 years, by vaccine type



# Ischemic stroke after bivalent Pfizer-BioNTech vaccine, aged ≥65 years, counts and adjusted rate ratios (Oct 16, 2022–April 8, 2023)




- Red dot represents sequential signal: p-value <0.01 (1-sided)

## Supplemental RCA analyses:
## Ischemic strokes during the *1–21*-day interval comparing *bivalent boosted vs. un-boosted* concurrent comparators (but eligible for bivalent booster)*

| Age group (years) | Interval (days) | Comparators | Vaccine | Risk events (N) | Comp events (N) | Adjusted Rate Ratio | 95% Confidence Interval | P-value (2-sided) |
|---|---|---|---|---|---|---|---|---|
| 65+ | 1–21 | Not bivalent boosted | Pfizer | 168 | 2536 | 1.01 | 0.86–1.19 | 0.907 |

* Analyses only included outcomes through April 8, 2023.

# Post-signal analyses*: Ischemic stroke incidence during days 1–21 compared with days 22–42, among persons aged ≥65 years with and without simultaneous influenza vaccination

| Analytic population | Cases in 1–21-day Risk Interval (N=139) | Cases in 22–42-day Comparison Interval (N=108) | Adjusted Rate Ratio** (95% CI) | P-value |
|---|---|---|---|---|
| Bivalent Pfizer + same-day high-dose or adjuvanted flu vaccine | 43 | 27 | 1.59 (0.99–2.61) | 0.06 |
| Bivalent Pfizer + same day standard dose flu vaccine | 8 | 11 | 0.73 (0.28–1.83) | 0.50 |
| Bivalent Pfizer without any same day flu vaccine | 107 | 99 | 1.08 (0.82– 1.42) | 0.58 |

* Analyses only include vaccination data through January 14, 2023, and stroke outcome data through Feb 25, 2023

** Adjusted by 5-year age groups

# Ischemic stroke following bivalent Pfizer-BioNTech mRNA COVID-19 vaccination in perons aged ≥65 years

- **Statistical signal**
  - The statistical signal persisted during the November 2022–January 2023 timeframe
  - The rate ratio has slowly attenuated from 1.92 to 1.26 and has not met signaling criteria during the past 10 weekly analyses
- **Additional signal investigation analyses**
  - Supplemental analyses using un-boosted concurrent comparators showed a rate ratio RR=1.01 (95% CI 0.86–1.19; p-value 0.907)
  - Analyses evaluating simultaneous high-dose or adjuvanted influenza vaccine showed a rate ratio RR=1.59 (95% CI 0.99–2.61; p-value 0.06)
    - Separate analyses did not detect an elevated RR for stroke after influenza vaccine alone (data not shown)
  - Supplemental analyses suggest comparison interval (22–42 days) rates were lower than expected (data previously presented to ACIP February 24, 2023*)

* ACIP Meeting COVID-19 mRNA bivalent booster vaccine safety--February 24, 2023 (cdc.gov)

# Summary

# Bivalent mRNA COVID-19 vaccination safety – data from other monitoring systems and programs*

- Vaccine Adverse Event Reporting System (VAERS) monitoring for bivalent mRNA COVID-19 vaccines found no evidence of a safety concern for ischemic stroke with either vaccine (Pfizer-BioNTech or Moderna)
- FDA monitoring in the CMS data and Department of Veterans Affairs monitoring in the VA system have not detected any safety signals for ischemic stroke following bivalent mRNA COVID-19 vaccines using historical comparator designs
- Surveillance conducted by international regulatory and public health partners has not detected a safety concern for ischemic stroke following bivalent mRNA COVID-19 vaccination
- No evidence of a safety signal for ischemic stroke in Pfizer's global monitoring of bivalent mRNA COVID-19 vaccination
- No safety signals were detected for ischemic stroke for ***primary series*** or ***monovalent boosters*** for Pfizer-BioNTech or Moderna COVID-19 vaccines in U.S. and global monitoring

* These surveillance activities did not include analyses to evaluate the effect of simultaneous influenza vaccination; different formulations of bivalent mRNA COVID-19 vaccinations were used globally

# Further evaluation and key next steps

## Further evaluation

- Consult with other surveillance systems to better understand:
  - Possible role of simultaneous high-dose or adjuvanted flu vaccination with COVID-19 vaccination
  - Possible decreased rate of stroke observed in VSD in the 3–6 weeks following vaccination
- In the process of chart reviewing a random sample of 100 cases across VSD sites
- Continue monitoring in VAERS

## Key next steps

- CDC continues to recommend that everyone eligible for a bivalent mRNA COVID-19 vaccine or an influenza vaccine get vaccinated*
- CDC and FDA are engaged in epidemiologic analyses regarding simultaneous vaccination with bivalent mRNA COVID-19 vaccine and influenza vaccine

* Interim Clinical Considerations for Use of COVID-19 Vaccines | CDC and Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season | MMWR (cdc.gov)

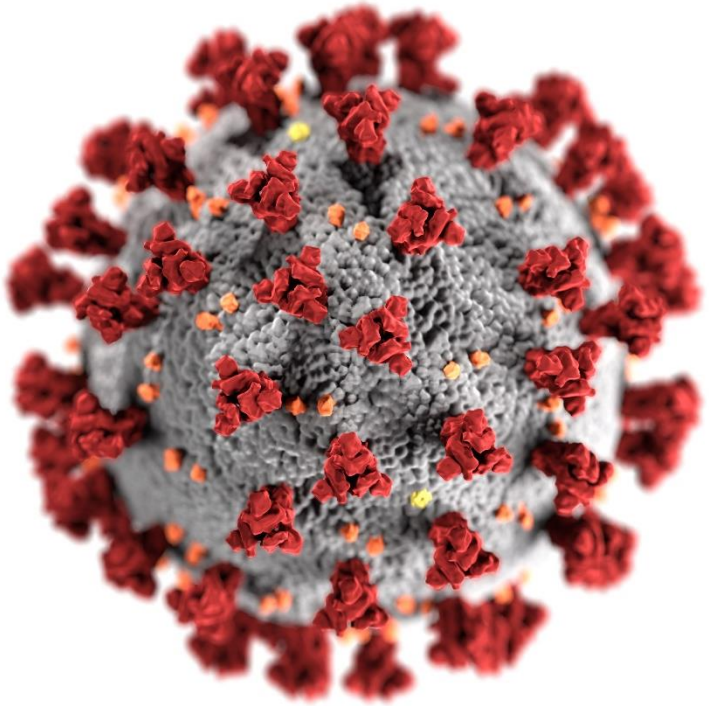
# Acknowledgements


- CDC Immunization Safety Office
  - VAERS Team
  - V-safe Team
  - Clinical Immunization Safety Assessment (CISA) Project
  - Vaccine Safety Datalink (VSD) Team
- COVID-19 Vaccine Task Force Data Monitoring and Reporting Group
- Kaiser Permanente Northern California (VSD)
- Marshfield Clinic Research Institute (VSD)
- VSD sites
  - HealthPartners Institute, Minneapolis, MN
  - Kaiser Permanente Colorado, Denver, CO
  - Kaiser Permanente Northwest, Portland, OR
  - Kaiser Permanente Southern California, Los Angeles, CA
  - Kaiser Permanente Washington, Seattle, WA
  - Denver Health, Denver, CO

# CDC Updates to Policy and Recommendations

**Sara Oliver, MD, MSPH**
**CDC**

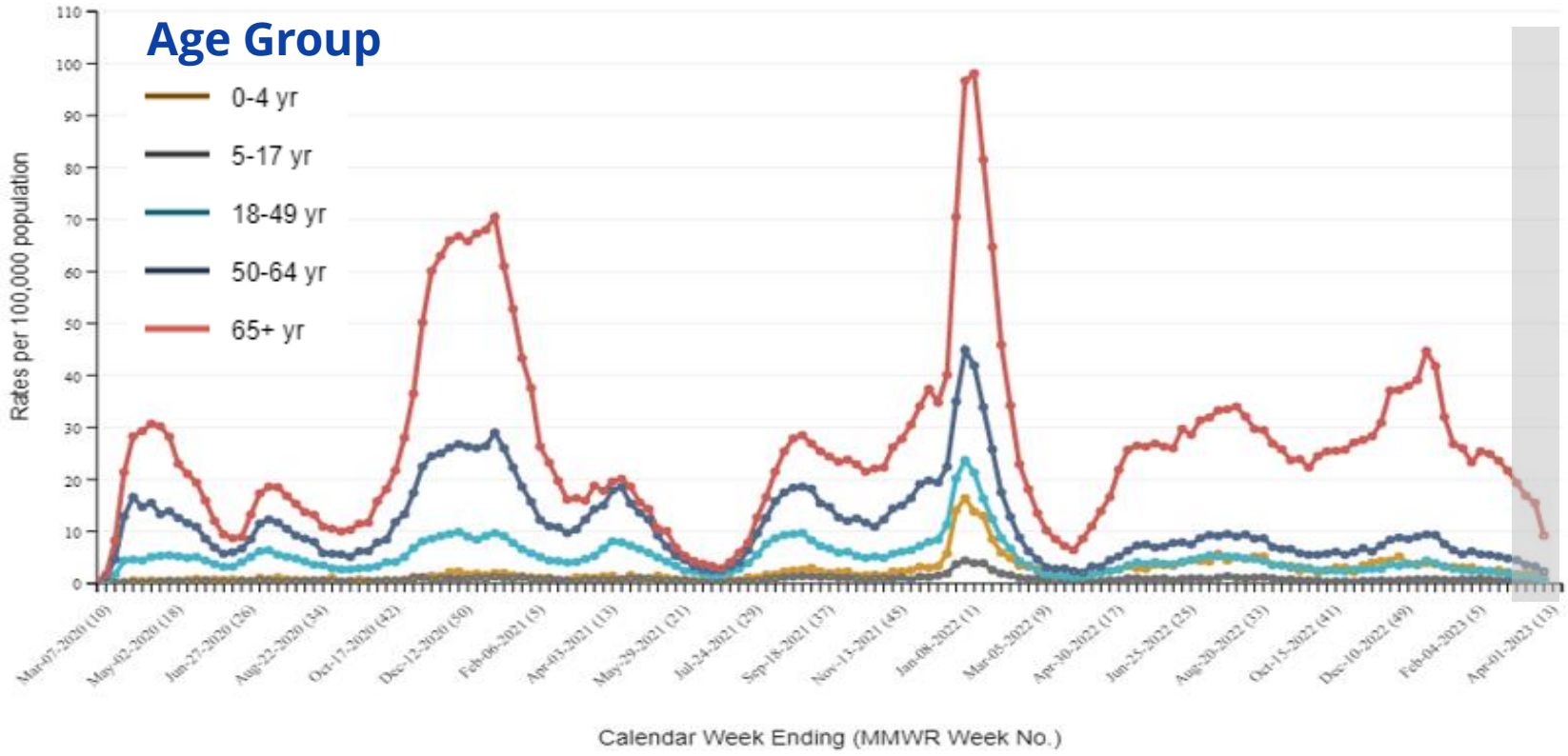
# COVID-19 Vaccines:
## Updates to Policy and Recommendations



Sara Oliver, MD, MSPH
NAIIS Meeting
May 9, 2023

cdc.gov/coronavirus

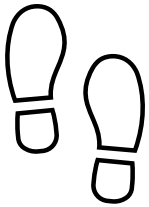
# **Weekly population-based rates of COVID-19-associated hospitalizations by age group—** COVID-NET, March 2020–April 2023




*Gray boxes indicate potential reporting delays. Interpretation of trends should be excluded from these weeks.*

https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network Accessed April 13, 2023

# Updates to COVID-19 vaccine policy



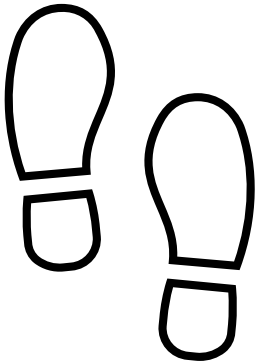
**Steps toward simple recommendations**:
Single formulation for mRNA COVID-19 vaccines
Single (possibly annual) dose for most individuals
Flexibility for vulnerable populations

COVID-19 vaccines: Where we are now

COVID-19 vaccines: Where we are going

**Goal: Simple recommendations**

# Updates to COVID-19 vaccine policy



**<u>Steps toward simple recommendations</u>**:

Single formulation for mRNA COVID-19 vaccines

Single (annual?) dose for most individuals

Flexibility for vulnerable populations

# Single formulation for mRNA COVID-19 vaccines

## Benefits and Harms: Summary from previous ACIP meetings

- Bivalent COVID-19 vaccines are able to **induce an immune response** when given either as a primary series or a booster dose
  - Immunogenicity data showed that a BA.1 bivalent vaccine given as a primary series induced antibody titers to BA.1 that were 25 times higher than the original monovalent vaccine
  - Percentage of patients reporting solicited local or systemic events was similar to or less than percentages seen after original vaccine, however this may be a result of the larger percent of seropositive participants in the bivalent vaccine group
- Limited data to directly compare COVID-19 outcomes after receipt of a monovalent or bivalent vaccine
  - Most studies show **improvement** in neutralizing antibodies for Omicron variants with a bivalent vaccine
  - Bivalent vaccines **expanded** the immune response and provided increased **diversity** in antibody response
  - While unable to directly compare clinical outcomes for monovalent and bivalent vaccines in the U.S., a study in the UK found ~**10% increase** in VE for COVID-19 infections

# Number of mRNA COVID-19 vaccine products

Moderna: 5 products

Pfizer-BioNTech: 6 products

**Previously:**
**11 TOTAL Products!**

Moderna: 2 products

Pfizer-BioNTech: 3 products

**Moving forward:**
**5 Products**

**Eliminates look-alike vials for Moderna and Pfizer-BioNTech**

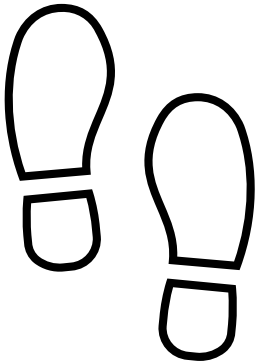
# Single formulation for mRNA COVID-19 vaccines

## CDC recommendations

- Transition to bivalent COVID-19 vaccines could **simplify** the presentations, reduce administration errors, and allow continued access to vaccines with expiration of monovalent products

Bivalent mRNA COVID-19 vaccines are now recommended for **all indications**

# Updates to COVID-19 vaccine policy



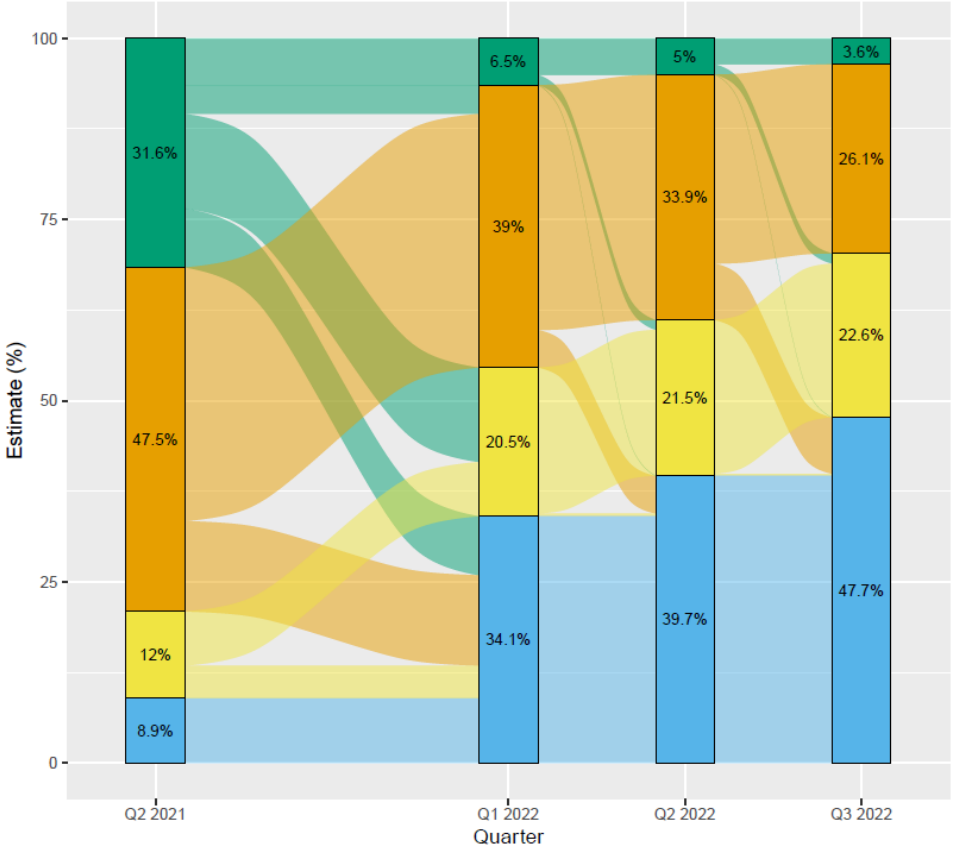
**Steps toward simple recommendations**:

Single formulation for mRNA COVID-19 vaccines

Single (annual?) dose for most individuals

Flexibility for vulnerable populations

# Shifts in vaccine-induced, infection-induced, and hybrid immunity against SARS-CoV-2 among people aged ≥16 years — United States, Quarter 2 2021– Quarter 3 2022




No infection or vaccination

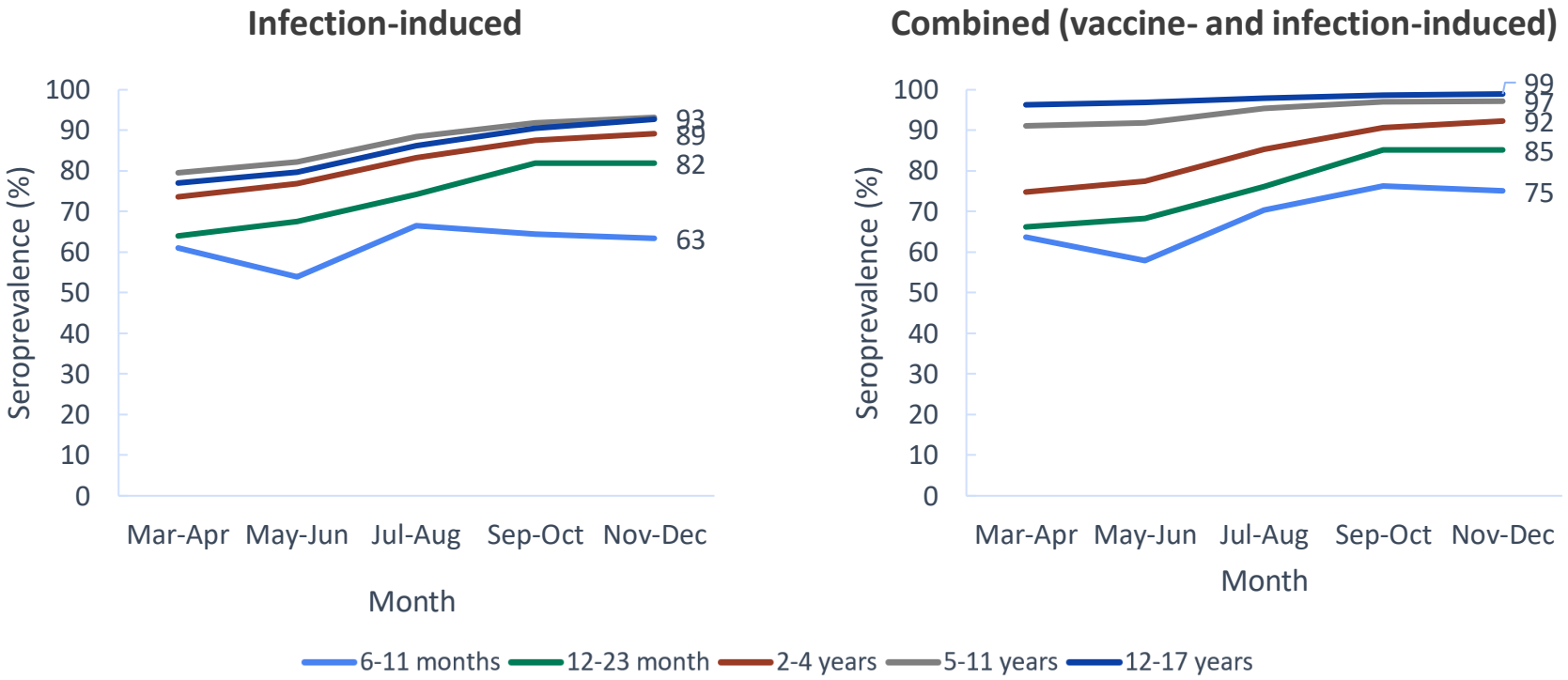
Vaccine only-induced antibodies

Infection only-induced antibodies

Both infection and vaccination-induced antibodies (hybrid immunity)

Source: CDC (unpublished)

# Pediatric infection-induced and combined (vaccine- and infection-induced) Seroprevalence from U.S. commercial laboratories — March–December 2022




Source: https://covid.cdc.gov/covid-data-tracker/#pediatric-seroprevalence and unpublished data (CDC)

# Single (possibly annual) COVID-19 vaccine dose

## CDC recommendations

- A COVID-19 vaccine framework for a single dose could be easy for COVID-19 vaccine providers to implement, and for the public to understand
- The current recommendations for a single dose may evolve over time, and could move to an annual recommendation

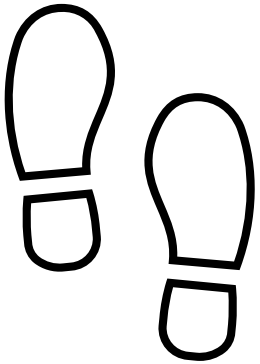
A **single bivalent dose** is now recommended for everyone ages 6 years and older

- For most people, this is not a change: if someone has not received a bivalent vaccine dose yet, they are recommended to receive one, regardless of their previous vaccine history

Children 6 months through 5 years receive **at least two** COVID-19 vaccine doses, including **at least one bivalent** COVID-19 vaccine

- Table and detailed guidance published in **Interim Clinical Considerations**

# Updates to COVID-19 vaccine policy



**Steps toward simple recommendations**:

Single formulation for mRNA COVID-19 vaccines

Single (annual?) dose for most individuals

Flexibility for vulnerable populations

# Flexibility for vulnerable populations

## CDC recommendations

- The bivalent COVID-19 vaccine continues to provide protection against severe COVID-19 disease, and rates of hospitalization or death among older adults who have received a bivalent booster continue to be low
- However, some older adults may benefit from an additional updated COVID-19 vaccine dose prior to possible future recommendations for updated vaccines this fall

Adults ages 65 years and older may now **choose to receive** another updated COVID-19 vaccine dose

# Flexibility for vulnerable populations

## CDC recommendations

- For people who are immunocompromised, additional doses have been recommended previously and current updates continue to allow additional protection to a vulnerable population
- Updates also allow **flexibility** to adjust to individual's specific circumstances, including timing of immunosuppression as well as the possible need for re-vaccination after particular events (e.g. stem cell transplant)

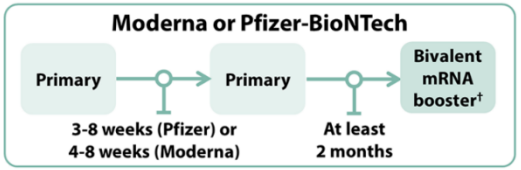
People who are immunocompromised may now **choose to receive** another updated COVID-19 vaccine dose -and-

Have the **flexibility** to receive **additional doses** based on their clinical circumstances

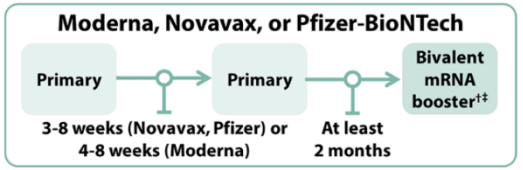
# Overview of recommendations

# Previous recommendations for people aged ≥6 years without immunocompromise

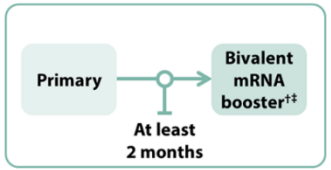
### People ages 6 through 11 years




### People ages 12 years and older




### People ages 18 years and older who previously received Janssen primary series dose§

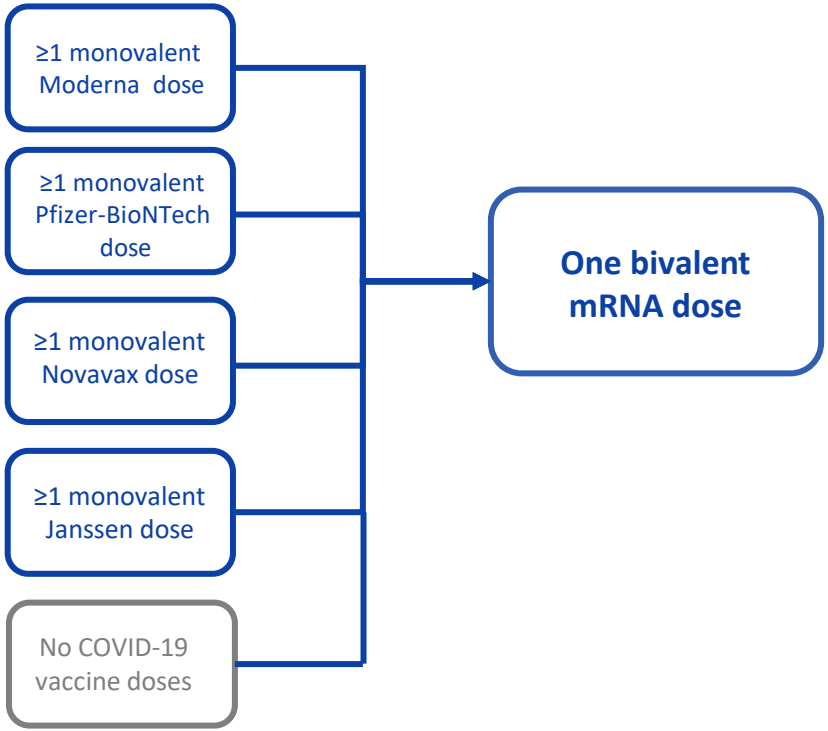



* People ages 6 months–4 years who previously completed a 3-dose monovalent Pfizer-BioNTech primary series are authorized to receive 1 bivalent Pfizer-BioNTech booster dose at least 2 months after completion of the monovalent primary series.
† For people who previously received a monovalent booster dose(s), the bivalent booster dose is administered at least 2 months after the last monovalent booster dose.
‡ A monovalent Novavax booster dose may be used in limited situations in people ages 18 years and older who completed a primary series using any COVID-19 vaccine, have not received any previous booster dose(s), and are unable or unwilling to receive an mRNA vaccine. The monovalent Novavax booster dose is administered **at least 6 months** after completion of a primary series.
§ Janssen COVID-19 Vaccine should only be used in certain limited situations. See: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us-appendix.html#appendix-a

# New recommendations for people aged ≥6 years without immunocompromise who have not yet received a bivalent mRNA dose

One bivalent mRNA dose

# New recommendations for people aged ≥6 years without immunocompromise who have not yet received a bivalent mRNA dose, regardless of COVID-19 vaccination history



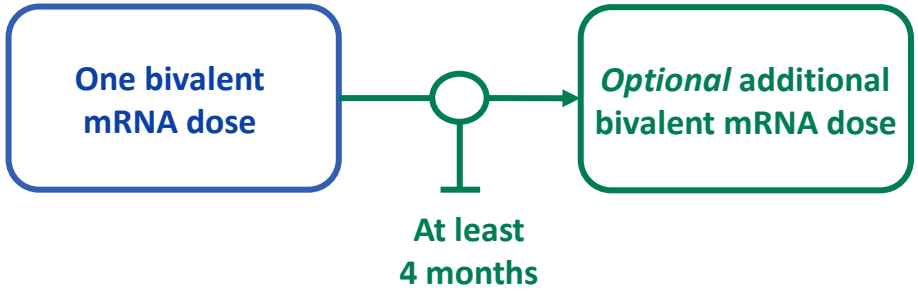
# New recommendations for aged ≥6 years without immunocompromise who have already received a bivalent mRNA dose


Vaccination is complete.
No doses are indicated at this time.

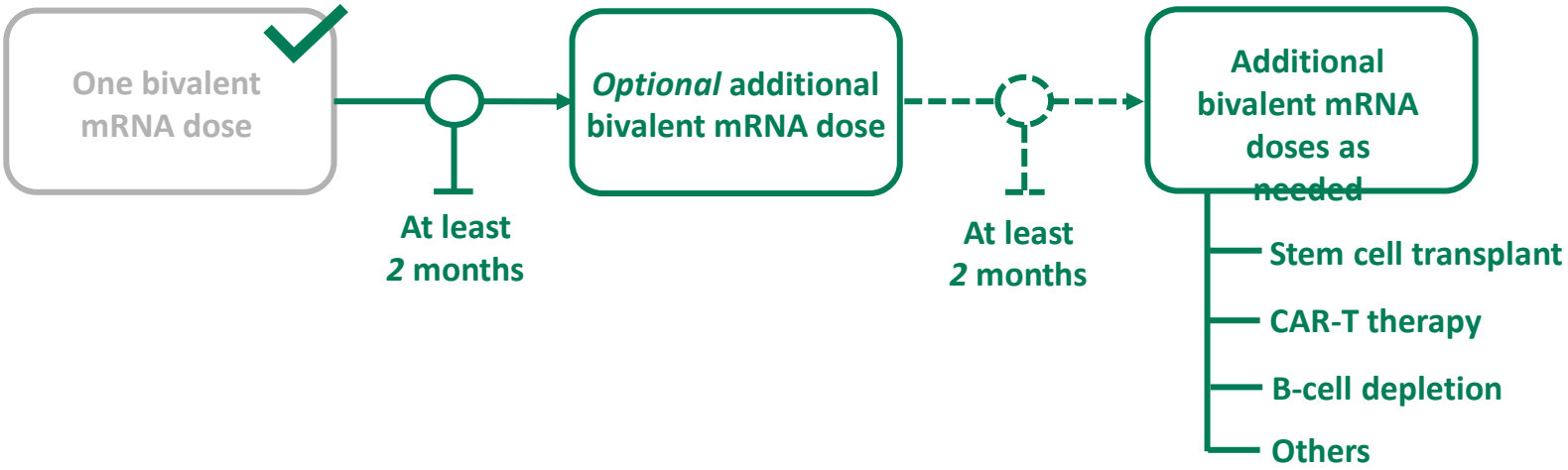
# Implications of the new recommendations

- Simple and singular for most
- **Flexible for people at higher risk**
- Customized recommendations for young children

# Flexible for people at higher risk of severe COVID-19: People aged ≥65 years who have not yet received a bivalent mRNA dose



# New flexibility for people at higher risk of severe COVID-19: People aged ≥6 years *with immunocompromise** who have already received a bivalent mRNA dose




*Including those with imminent immunocompromise (e.g., prior to organ transplant; other causes.)

# Implications of the new recommendations

- Simple and singular for most
- Flexible for people at higher risk
- **Customized recommendations for young children**

# Transitioning from the monovalent to the bivalent era for children without immunocompromise aged 6 months – 4 years

## Doses previously recommended:

**Moderna:**

- **2 monovalent** primary series doses
  +
- **1 bivalent** booster dose

**Pfizer:**

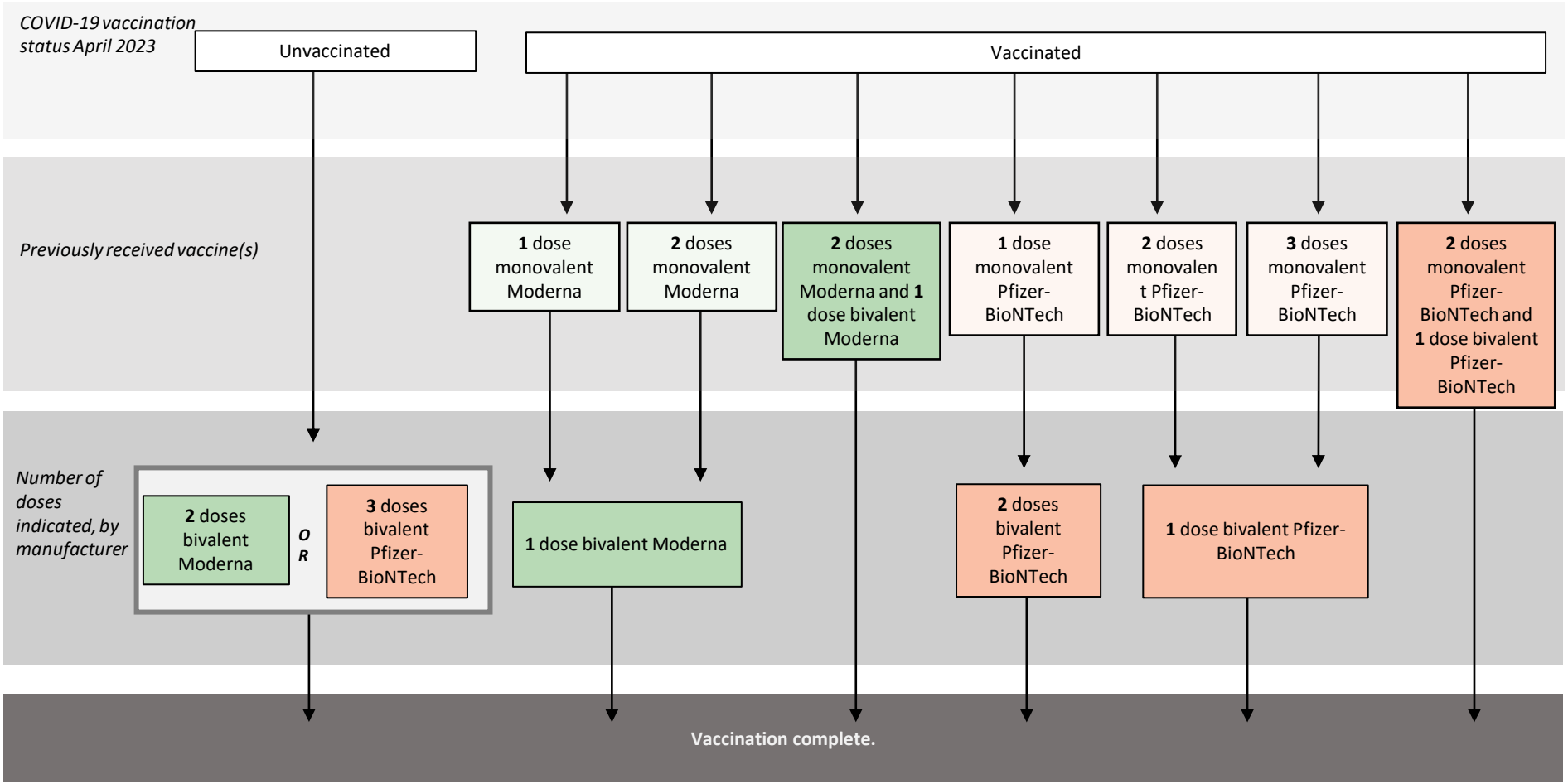
- **2** or **3 monovalent** primary series doses +
- **1 bivalent** primary series dose

## Doses now recommended:

**Customized** by COVID-19 vaccination history such that all children receive:

- At least 2 vaccine doses in total *including*
- At least **1 bivalent** dose

**COVID-19 vaccination algorithm for people without immunocompromise, ages 6 months–4 years, mRNA vaccines April 2023***




*To see product-specific doses and intervals of administration, see Table 1 and 2 forthcoming in Interim Clinical Considerations, forthcoming.

# Transitioning from the monovalent to the bivalent era for children without immunocompromise aged 5 years

## Doses previously recommended:

**Moderna:**

- **2 monovalent** primary series doses
  +
- **1 bivalent** booster dose

**Pfizer:**

- **2** or **3 monovalent** primary series doses +
- **1 bivalent** primary series dose

## Doses now recommended:

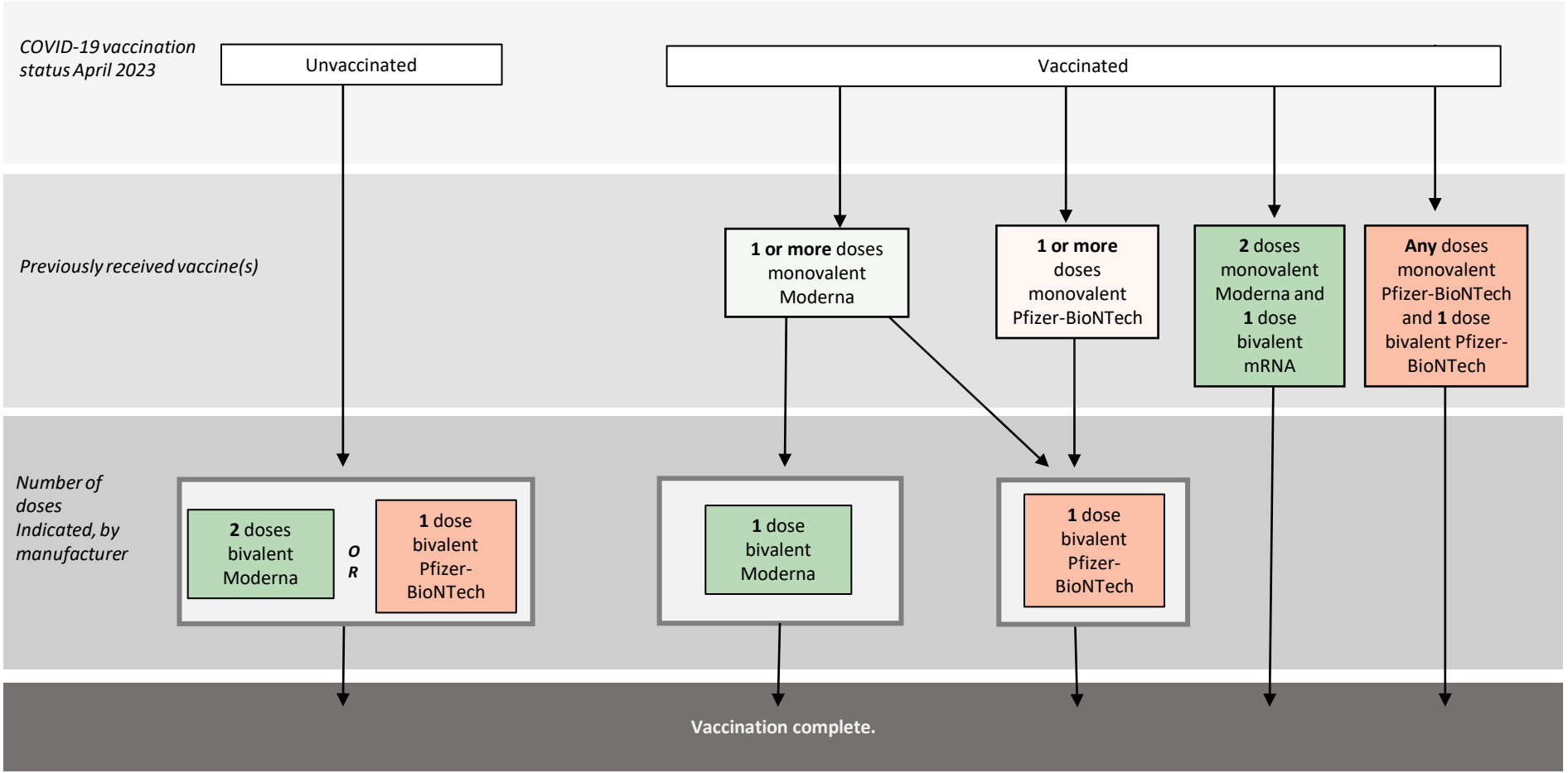
**Customized** so that **Moderna** recipients receive:

- At least 2 vaccine doses in total *including*
- At least **1 bivalent** dose

And **Pfizer** recipients receive:

- At least **1 bivalent** dose

**COVID-19 vaccination algorithm for people without immunocompromise, age 5 years, mRNA vaccines April 2023***

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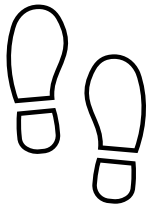
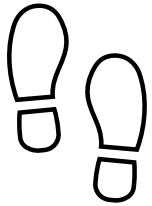
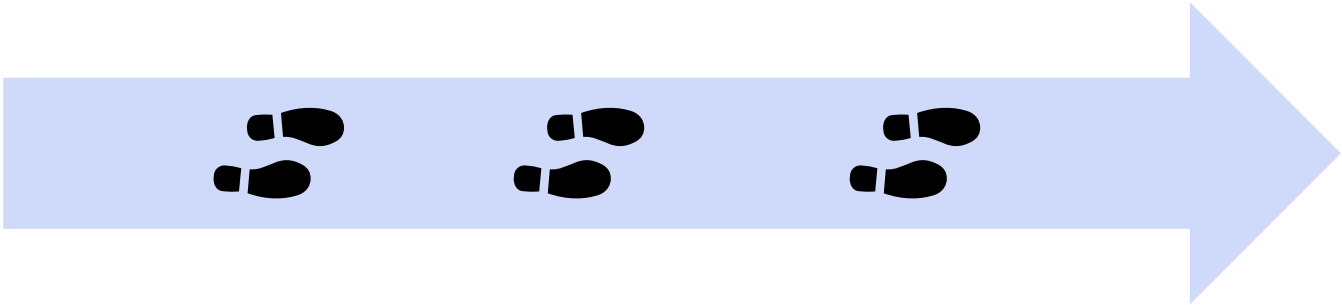
# Updates to COVID-19 vaccine policy



**Steps toward simple recommendations**:
Single formulation for mRNA COVID-19 vaccines
Single (possibly annual) dose for most individuals
Flexibility for vulnerable populations



**Future additional steps may be possible** :
Simplifications for all COVID-19 vaccines
Possible updated vaccines this fall
Continue to evaluate data-driven ways to simplify pediatric program
Flexibility and simple guidance



**Goal**:
**Simple recommendations**

# Updates to COVID-19 vaccine policy

## Steps toward simple recommendations

- COVID-19 vaccines continue to be the **most effective tool** we have to prevent serious illness, hospitalization and death from COVID-19
- **Simple recommendations** are easier to communicate, which may improve uptake
- Anticipate that an updated fall vaccine could be available
- Based on available data, anticipate benefits of COVID-19 vaccines given this fall
  - Updates to COVID-19 vaccine policy can also acknowledge possible future recommendations
- For most people, the **current doses needed** remain **unchanged**: a single bivalent vaccine is recommended and there could be an updated vaccine/recommendation this fall
  - **Flexibility** for vulnerable populations
  - Young children continue to be recommended for multiple doses to prime/boost immune response, and will continue to review additional data

# Updates to COVID-19 vaccine policy

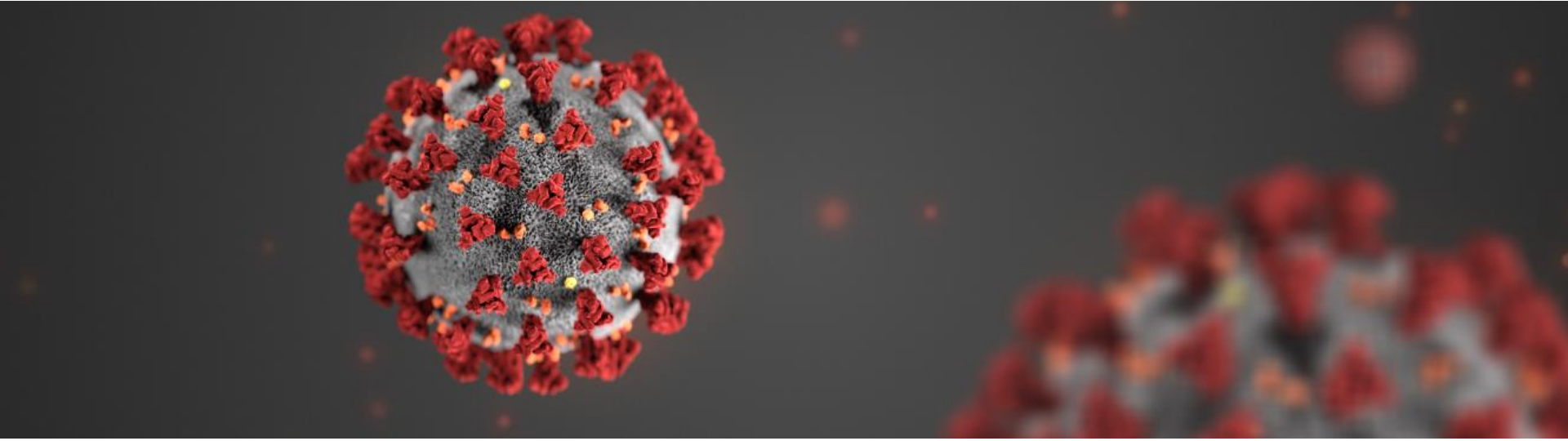
## Steps toward simple recommendations

- Continue to **review data** and **evaluate COVID-19 vaccine program** in context of evolving epidemiology
- Early COVID-19 vaccine recommendations made in light of a highly susceptible, immune naive population, with limited treatment options
- Increases in population-level immunity through both vaccine and infection, SARS-CoV-2 virus evolution, availability of anti-viral treatments, and review of COVID-19 epidemiology and hospitalization rates can lead to **evidence-based updates** in vaccine policy
- **Work is ongoing** to review additional data, continue efforts for simplification

# Additional help for providers is on the way

- CDC's **Interim Clinical Considerations for Use of Authorized COVID-19 Vaccines** is updated with comprehensive tables of vaccine doses and dosages indicated
  - For each age group
  - By history of COVID-19 vaccines received, for children ages 6 months through 5 years
- Revision of clinical guidance materials is underway
- COCA Call to be held May 11th, 2023*

*Please visit https://emergency.cdc.gov/coca/ for complete details
https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#covid-vaccines



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

# Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

# Stay Up to Date with COVID-19 Vaccines

- Adults and children aged 6 years and older are up to date with COVID-19 vaccines if they got a bivalent (updated) COVID-19 vaccine.
- Children 6 months through 5 years of age who received the Pfizer-BioNTech COVID-19 vaccine are up to date if:
  - They are 6 months to 4 years of age and got at least 3 COVID-19 vaccine doses, including at least one bivalent (updated) COVID-19 vaccine dose.
  - They are 5 years of age and got at least 1 bivalent (updated) COVID-19 vaccine dose.
- Children 6 months through 5 years of age who got the Moderna COVID-19 vaccine are up to date if they got at least two Moderna COVID-19 vaccine doses, including at least one bivalent (updated) COVID-19 vaccine dose.
- You may be eligible for additional COVID-19 vaccine doses if:
  - You are 65 years of age and older and got your first bivalent (updated) COVID-19 vaccine booster 4 or more months ago.
  - You are moderately or severely immunocompromised and received a bivalent (updated) COVID-19 vaccine booster 2 or more months ago.
- If you are unable or choose not to get a recommended bivalent mRNA vaccine, you will be up to date if you got the Novavax COVID-19 vaccine doses approved for your age group.

# Q&A/ Discussion

# Update on Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

**Tim Uyeki, MD, MPH, MPP**
**CDC**

# Update on Human Infections with Highly Pathogenic Avian Influenza A(H5N1) Virus

Tim Uyeki, MD, MPH, MPP

Influenza Division, CDC

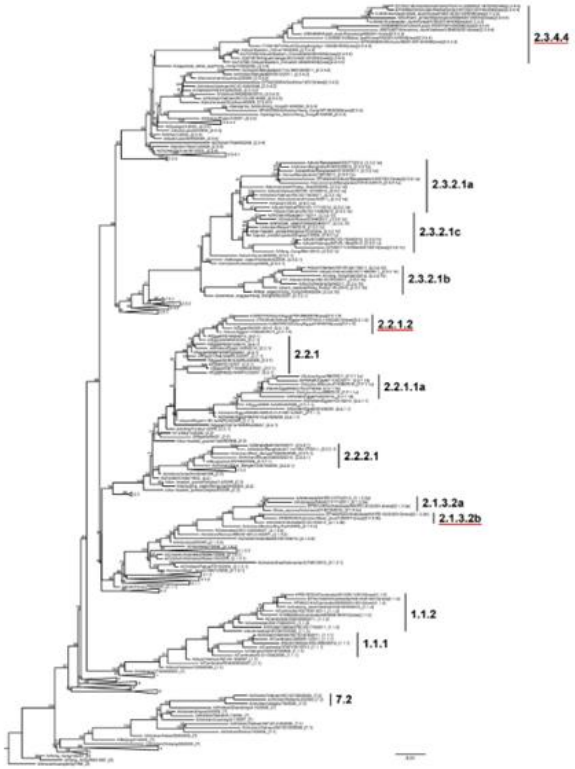
May 4, 2023

# Disclosures

- None

# Highly Pathogenic Avian Influenza A(H5N1) Virus

- First identified in 1959 during a poultry outbreak in Scotland
- Identified in a goose from southern China in 1996 (Guangdong Province)
- HPAI A(H5N1) virus evolution
  - Since 1996, H5N1 viruses have continued to evolve into distinct antigenic clades and subclades (including by genetic reassortment)
    - Spread in wild birds and poultry in Asia, and >60 countries during 2004-2007 (Europe, Africa, Middle East)
    - Endemic circulation (enzootic) among poultry in some countries




*Smith and Donis Influenza Other Resp Viruses*

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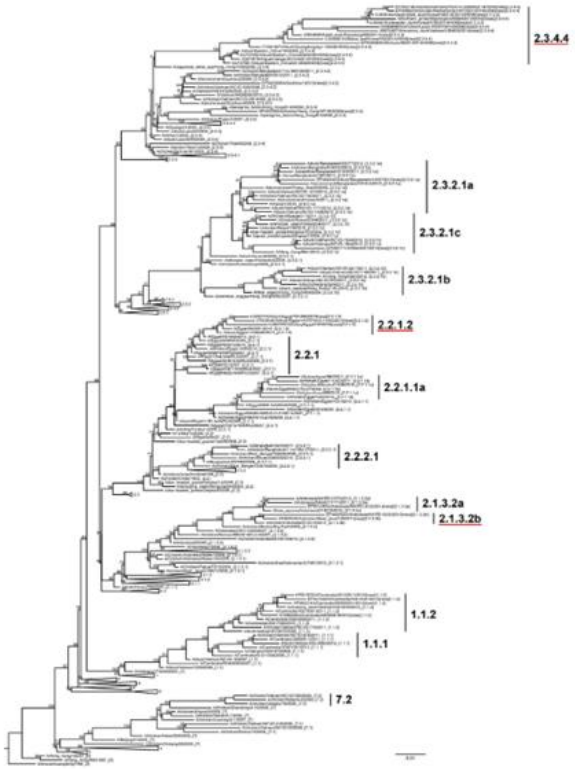
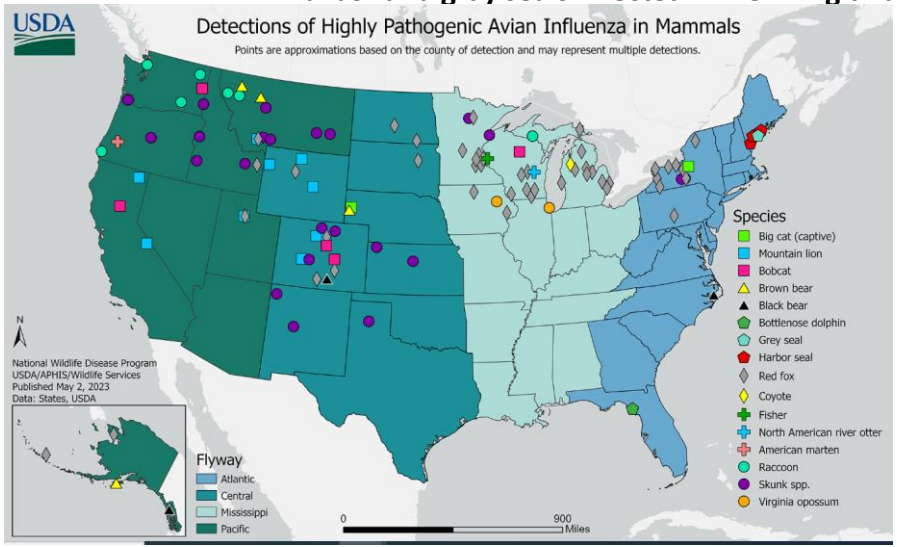
    - Endemic circulation (enzootic) among poultry in some countries
  - **Spread in recent years by wild birds**
    - **Since 2020: H5N1 clade 2.3.4.4b viruses have spread via migratory birds in Africa, Asia, and Europe**
    - **Late 2021-2022: spread to North America: poultry outbreaks, wild bird detections (hawks, eagles, owls, vultures, raven, crows, geese, ducks, grebes, pelicans, swans, shovelers, teal, cormorants, kestrels, gulls, etc.)**
    - **Late 2022-2023: spread to South America**
  - **Not all birds are equally susceptible to HPAI A(H5N1) viruses (e.g., some ducks do not show disease)**




*Smith and Donis Influenza Other Resp Viruses*

# Highly Pathogenic Avian Influenza A(H5N1) Virus

- **Transmission to mammals reported since 2003** (neurologic & respiratory disease, fatal outcomes)
  - **Terrestrial mammals** (tigers, leopards in a zoo; dogs, cats, other animals) during 2003-2004
    - **Recent infections:** (red fox, raccoon dog, coyote, otter, badger, polecat, ferret, farmed mink, lynx, mountain lion, bobcat, fisher cat, amur leopard, raccoon, skunk, black bear, brown bear, grizzly bear, opossum)
  - **Marine mammals** (seals, porpoise, dolphin)
    - Unclear if mammal-to-mammal transmission is occurring, some markers of mammalian adaptation reported
      - Harbor and gray seals infected in New England, 2022 (environment-to-seal transmission)




*Puryear EID 2023*

# Epidemiology of Human Cases of H5N1 Virus Infection

- First infections identified in Hong Kong, 1997 (18 cases, 6 deaths)
- Re-emergence in humans: 2003-2005 (China, Southeast Asia)
- Cases identified in other regions since 2006 (Middle East, Europe, Africa)
- 2003-2023: 876 cases with >50% mortality reported in 22 countries (severe pneumonia)
  - Few cases reported worldwide since 2016
  - Mostly sporadic avian-to-human transmission from poultry exposures
  - Small number of cases with unknown source of infection (e.g., Canada Dec. 2013)

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  - Mostly sporadic avian-to-human transmission from poultry exposures
  - Small number of cases with unknown source of infection (e.g., Canada Dec. 2013)
- **Some clusters of epidemiologically-linked cases**
  - **Most clusters represent common poultry exposures in family members**
  - **Two clusters of wild bird-to-human transmission (2006)**
  - **Small number of clusters: probable limited, non-sustained human-to-human transmission among blood-related family members**
  - **No cases of mammal-to-human transmission**
- **Risk factors for H5N1 virus infection**
  - **Direct/close unprotected exposure to sick/dead infected poultry, visiting a live poultry market**
  - **Prolonged, unprotected, close exposure to a symptomatic case (household or hospital exposures)**

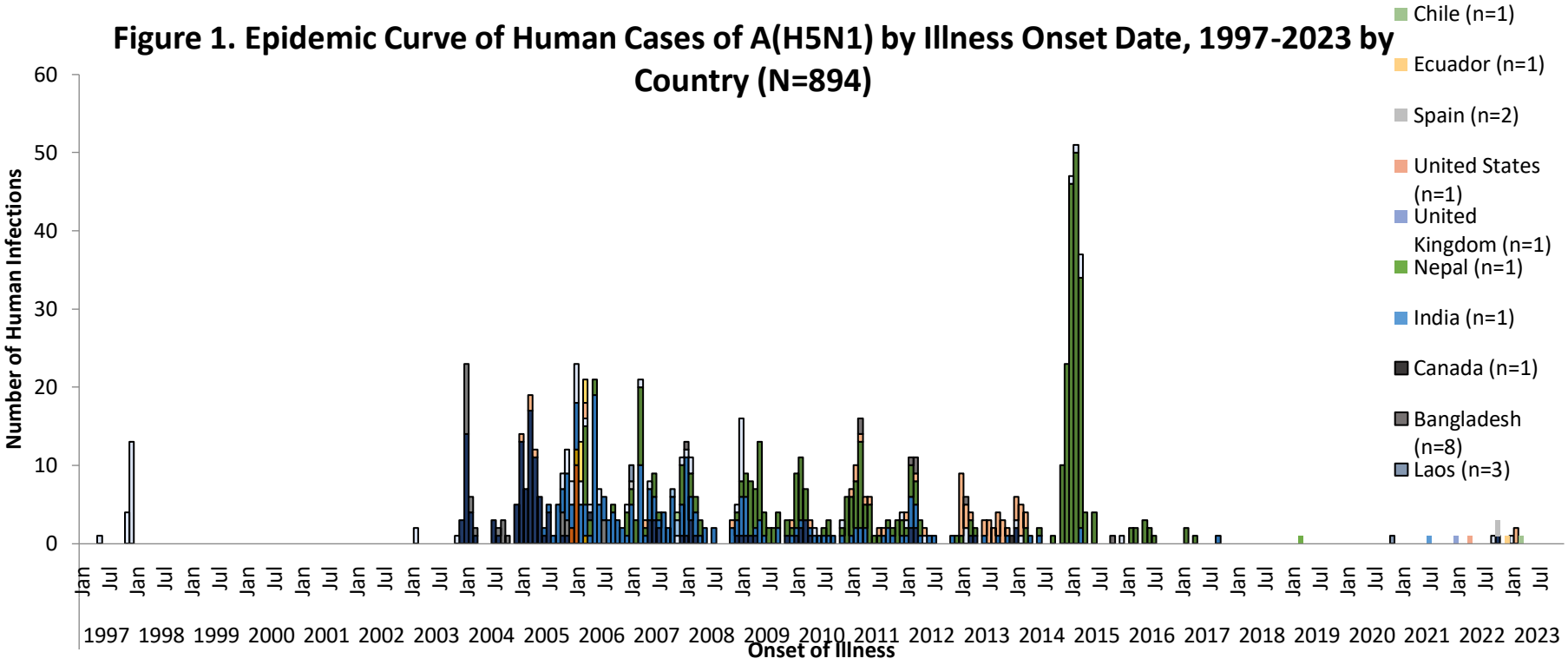
Figure 1. Epidemic Curve of Human Cases of A(H5N1) by Illness Onset Date, 1997-2023 by Country (N=894)
Number of Human Infections
0
10
20
30
40
50
60
Jan Jul
1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023
Onset of Illness
Chile (n=1)
Ecuador (n=1)
Spain (n=2)
United States (n=1)
United Kingdom (n=1)
Nepal (n=1)
India (n=1)
Canada (n=1)
Bangladesh (n=8)
Laos (n=3)

# H5N1 Virus Diagnostic Testing

- **Patients with mild respiratory disease:**
  - Collect NP swab and combined nasal & throat swabs for rRT-PCR testing for influenza A and B viruses at public health laboratories (CDC Flu rRT-PCR Dx Panel)
    - Influenza A positives are subtyped for H1 and H3; if A positive, H1 & H3 negative:
      - Test for H5 by CDC H5 primer/probe set; H5+ confirmed at CDC
    - Throat swabs have higher sensitivity to detect H5N1 virus >nasal >NP specimens
- **Patients with lower respiratory tract disease (pneumonia):**
  - Collect upper respiratory specimens and sputum for rRT-PCR testing for influenza A virus subtypes H1, H3, and H5 at public health laboratories
  - Intubated patients: Also collect endotracheal aspirate specimens (or BAL fluid)
  - ICU patients: influenza A positive results <u>without subtyping</u>: have subtyping done at public health laboratories
- **Commercially available influenza assays**
  - Cannot specifically identify H5N1 virus
    - Tests that identify influenza A virus do not distinguish seasonal influenza A viruses from novel influenza A viruses, including H5N1 virus

# Infection Prevention and Control Recommendations

- **Rationale: Potential for close range large droplet and small particle (aerosol) spread, and H5N1 virus infection with high mortality**

➢ **Place patient in airborne infection isolation room (AIIR)**

- **If not available, isolate in single-patient room, place facemask on patient, keep door closed; arrange transfer to facility with an AIIR (negative-pressure, HEPA filtration)**

➢ **Standard, contact, airborne precautions recommended**

  ➢ **PPE: single-use gown, gloves, eye protection, fit-tested N95 respirator**

# Clinical Management

- **Antiviral Treatment: Start oseltamivir or other neuraminidase inhibitor (zanamivir, peramivir) empirically as soon as possible for patients with suspected H5N1 virus infection (based on history of exposures)**
  - **Oseltamivir standard dosing: twice daily x 5 days (mild disease); longer duration for severe disease (optimal duration unknown)**
    - **Case reports of emergence of oseltamivir resistant H5N1 viruses during treatment**
  - **No clinical trials - Observational studies: earlier treatment associated with greater survival versus later treatment**
  - ***No markers of resistance to FDA-approved antivirals in clade 2.3.4.4b H5N1 viruses circulating in birds or detected in humans***

# Clinical Management

- Antiviral Treatment: Start oseltamivir or other neuraminidase inhibitor (zanamivir, peramivir) empirically as soon as possible for patients with suspected H5N1 virus infection (based on history of exposures)
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  - ➢ *No markers of resistance to FDA-approved antivirals in clade 2.3.4.4b H5N1 viruses circulating in birds or detected in humans*
- **Clinical management → supportive care of complications**
  - **Avoid high-dose corticosteroids**
  - **Respiratory support: may require invasive mechanical ventilation**
  - **Other advanced organ support:**
    - **ECMO has been used for H5N1 patients**
    - **Renal replacement therapy**

# Current Situation and Recent H5N1 Cases

- **Clade 2.3.4.4b H5N1 viruses are circulating in wild birds and poultry in most regions of the world, with sporadic spillover to mammals**
  - **U.S. 2022 to date: H5N1 viruses detected in *wild birds* in 49 states, *commercial or backyard poultry* in 47 states; @58.8 million poultry culled; *mammals* in 23 states**

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  - U.S. 2022 to date: H5N1 viruses detected in *wild birds* in 49 states, *commercial or backyard poultry* in 47 states; @58.8 million poultry culled; *mammals* in 23 states
- **Human H5N1 cases: 2022 to date (N = 11, 8 countries)** ***(most had recent poultry exposures)***
  - **Severe illness: 6 cases (2 deaths); Mild illness: 2 cases; Asymptomatic: 3 cases**
    - **UK (Dec. 2021):** Elderly asymptomatic man who raised ducks in England, clade 2.3.4.4b
    - ***US (April 2022): Adult involved in poultry culling, reported fatigue,** clade 2.3.4.4b
    - **Vietnam (October 2022): child developed critical illness, survived**
    - **China (September/October 2022): adult developed critical illness, died,** clade 2.3.4.4b
    - ***Spain (September): 2 asymptomatic adult poultry workers,** clade 2.3.4.4b
    - **Ecuador (Dec 2022/January 2023): child developed critical illness, survived,** clade 2.3.4.4b
    - **China (January 2023): adult developed severe illness,** clade 2.3.4.4b
    - **Cambodia (February 2023): 2 cases**, **girl (died)** and father (mild illness), poultry exposures: Clade 2.3.2.1c
    - **Chile (March 2023): adult developed critical illness**, clade 2.3.4.4B
      - Sequencing of viral RNA from a BAL specimen identified a few mutations in the PB2 gene associated with mammalian adaptation in animal models (e.g., enhanced replication, pathogenicity in inoculated mice)

***May not represent true infection**

*CDC H5N1 Technical Report March 17, 2023; Aznar et al. Euro Surveill. Feb. 23, 2023*

# Summary/Conclusions

- **Clade 2.3.4.4b H5N1 viruses are circulating in wild birds and poultry in most regions of the world, with sporadic spillover to mammals, and rare sporadic human infections; other clades of H5N1 viruses are in circulation in some countries**
  - **H5N1 viruses are well-adapted to infect and spread among wild birds and poultry**
  - **Sporadic spillover to mammals is not surprising; no evidence of sustained transmission among mammals, no instances of mammal-to-human transmission**
  - **Nearly all sporadic human cases reported since 2022 had exposure to poultry**
    - **No indication of human-to-human transmission**
  - **Expect additional sporadic human infections with H5N1 viruses**
  - **H5N1 viruses currently lack ability to bind well to receptors in the human upper respiratory tract and lack ability to spread efficiently among people**
  - **The public health risk is low, but because H5N1 viruses continue to evolve: vigilance and on-going monitoring is needed in animals and people**

# Resources

- Case definitions: https://www.cdc.gov/flu/avianflu/case-definitions.html
- Monitoring & post-exposure antiviral prophylaxis: https://www.cdc.gov/flu/avianflu/guidance-exposed-persons.htm
- Follow-up of close contacts: https://www.cdc.gov/flu/avianflu/novel-av-chemoprophylaxis-guidance.htm
- Summary for clinicians: https://www.cdc.gov/flu/avianflu/clinicians-evaluating-patients.htm
- Specimen collection & testing: https://www.cdc.gov/flu/avianflu/severe-potential.htm
- Infection prevention and control: https://www.cdc.gov/flu/avianflu/novel-flu-infection-control.htm
- Antiviral guidance: https://www.cdc.gov/flu/avianflu/novel-av-treatment-guidance.htm
- Current situation: https://www.cdc.gov/flu/avianflu/avian-flu-summary.htm
- de Jong et al. Fatal outcome of H5N1 associated with high viral load and hypercytokinemia. *Nat Med 2006;12:1203-7*
- Gambotto et al. Human infection with highly pathogenic H5N1 influenza virus. *Lancet 2007;371:1464-75*
- WHO Writing Committee Update on H5N1 virus infection in humans. *N Engl J Med 2008;358:261-273*
- Uyeki. Human infection with H5N1 virus: review of clinical issues. *Clin Infect Dis 2009;49:279-90*
- White et al. What is the optimal therapy for patients with H5N1 influenza? *PLoS Med 2009;6:e1000091.*
- CDC H5N1 Technical Report: https://www.cdc.gov/flu/avianflu/spotlights/2022-2023/h5n1-technical-report.htm

Selected Resources

**Dr. Broder**

- https://www.cdc.gov/vaccines/acip/index.html
- https://www.cdc.gov/vaccinesafety/pdf/COVID19-RCA-Protocol-1342-508.pdf
- https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-24/COVID-02-Shimabukuro-508.pdf
- https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#:~:text=The%20CDC%20Interim%20Clinical%20Considerations%20are%20informed%20by,currently%20approved%20or%20authorized%20in%20the%20United%20States.
- https://www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm
- https://vaers.hhs.gov/

**Dr. Oliver**

- https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network
- https://covid.cdc.gov/covid-data-tracker/#pediatric-seroprevalence
- https://emergency.cdc.gov/coca/
- https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html#covid-vaccines

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