COVID-19
October 6, Update

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Durability of immune responses to the BNT162b2 mRNA vaccine

Methods

- Analysis of antibody responses to the homologous Wu strain as well as several variants of concern, including the emerging Mu (B.1.621) variant, and T cell responses at six months after the second dose.

Results

- Substantial waning of antibody responses and T cell immunity to SARS-CoV-2 and its variants
- A significant proportion of vaccinees have neutralizing titers below the detection limit,

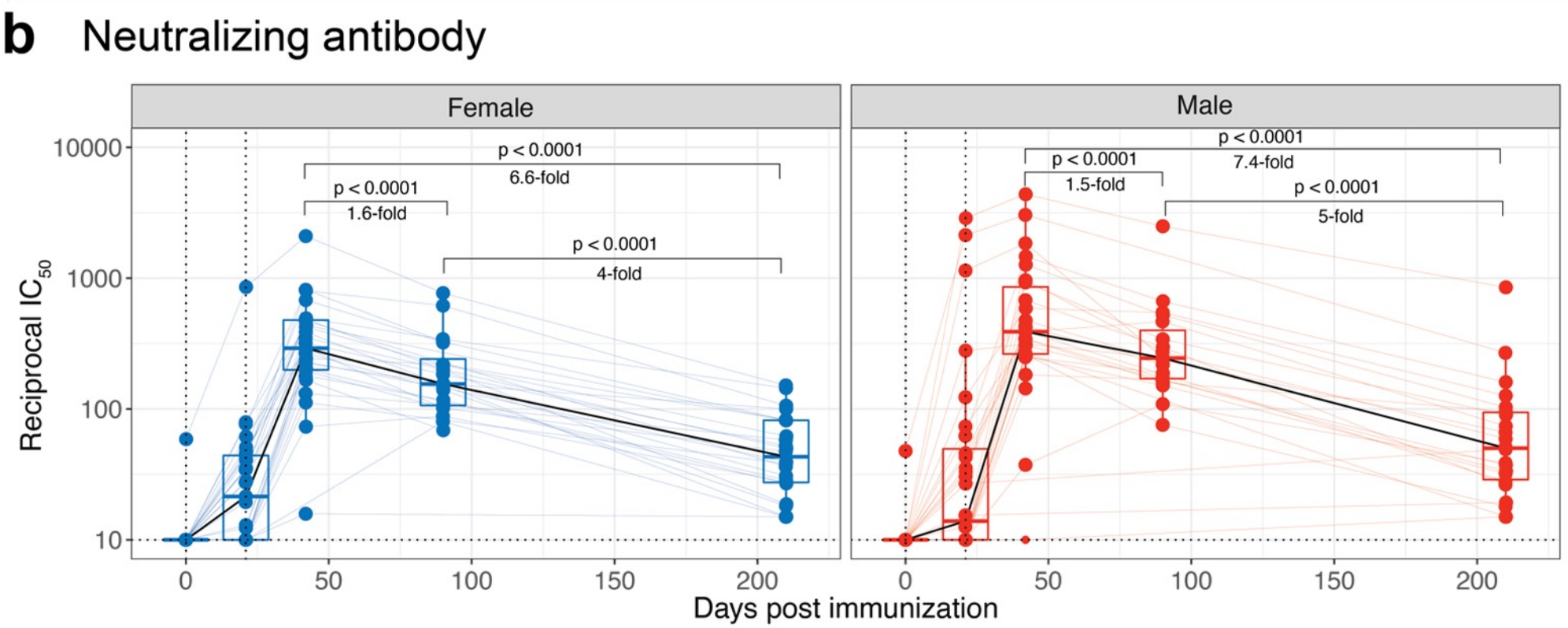
Conclusions

- This data suggest a 3rd booster immunization might be warranted to enhance the antibody titers and T cell responses.

Suthar1 MS, Arunachalam PS, Hu M, et al. doi: https://doi.org/10.1101/2021.09.30.462488This article is a preprint and has not been certified by peer review

Durability of antibody following the Pfizer-BioNTech mRNA vaccination

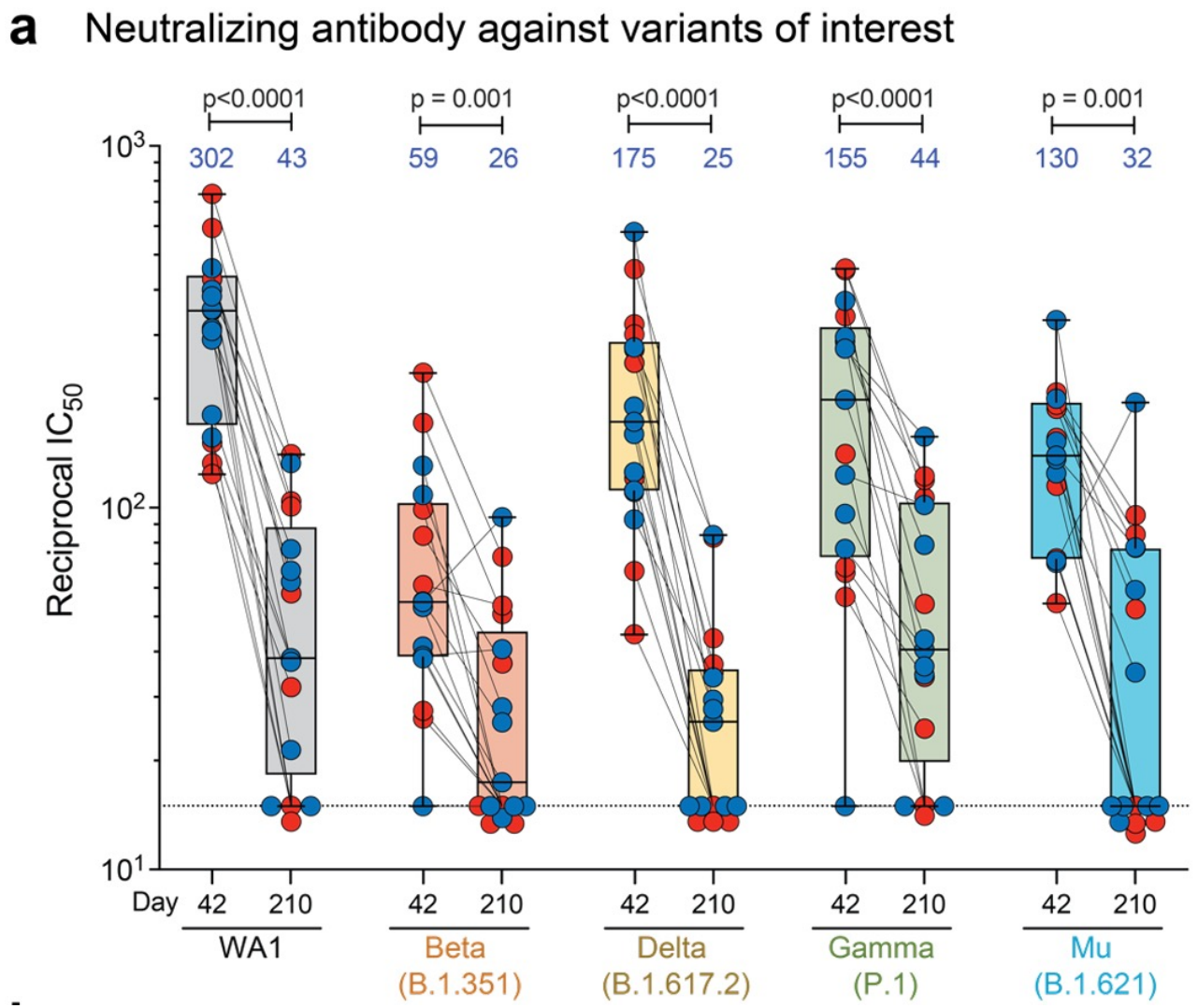
Kinetics of authentic live virus neutralizing antibody response against the homologous USA/WA1 strain (N = 46, 24 females and 22 males on day 210). Data of day 0, 21 and 90 were obtained from our previously published study6. Day 42 samples were re-assayed with day 210 samples by the FRNT assay.



Suthar1 MS, Arunachalam PS, Hu M, et al. doi: https://doi.org/10.1101/2021.09.30.462488This article is a preprint and has not been certified by peer review

Durability of antibody following the Pfizer-BioNTech mRNA vaccination

- Durability of cross-neutralizing antibody responses following the Pfizer-BioNTech mRNA vaccination. a, Authentic live virus neutralizing antibody responses against the homologous USA/WA1 strain and the variants of concerns B.1.351 (Beta), B.1.617.2 (Delta), P.1 (Gamma) and B.1.621 (Mu) (N=17). The numbers in blue indicate geometric mean titers.



Suthar1 MS, Arunachalam PS, Hu M, et al. doi: https://doi.org/10.1101/2021.09.30.462488This article is a preprint and has not been certified by peer review

Safety Monitoring of an Additional Dose of COVID-19 Vaccine – United States, August 12–September 19, 2021

What is already known about this topic?

- Among 306 Pfizer-BioNTech clinical trial participants, adverse reactions after dose 3 were similar to those after dose 2

What is added by this report?

- During August 12–September 19, 2021, among 12,591 v-safe registrants who completed a health check-in survey after all 3 doses of an mRNA COVID-19 vaccine:
- 79.4% and 74.1% reported local or systemic reactions, respectively, after the third dose;
- 77.6% and 76.5% reported local or systemic reactions after the second dose, respectively.

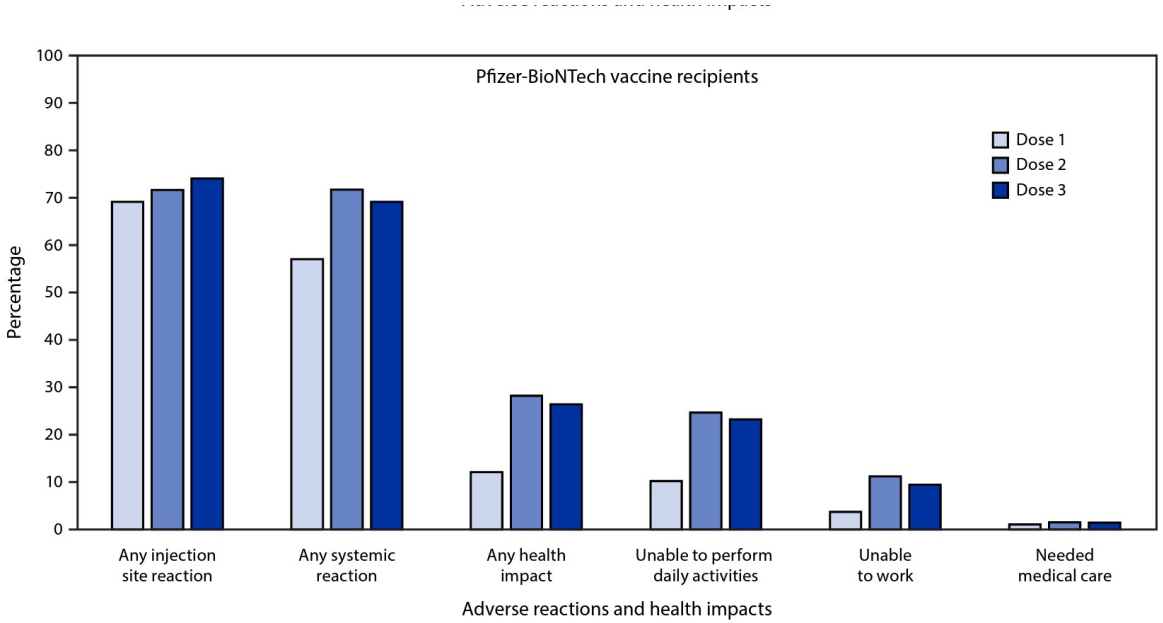
What are the implications for public health practice?

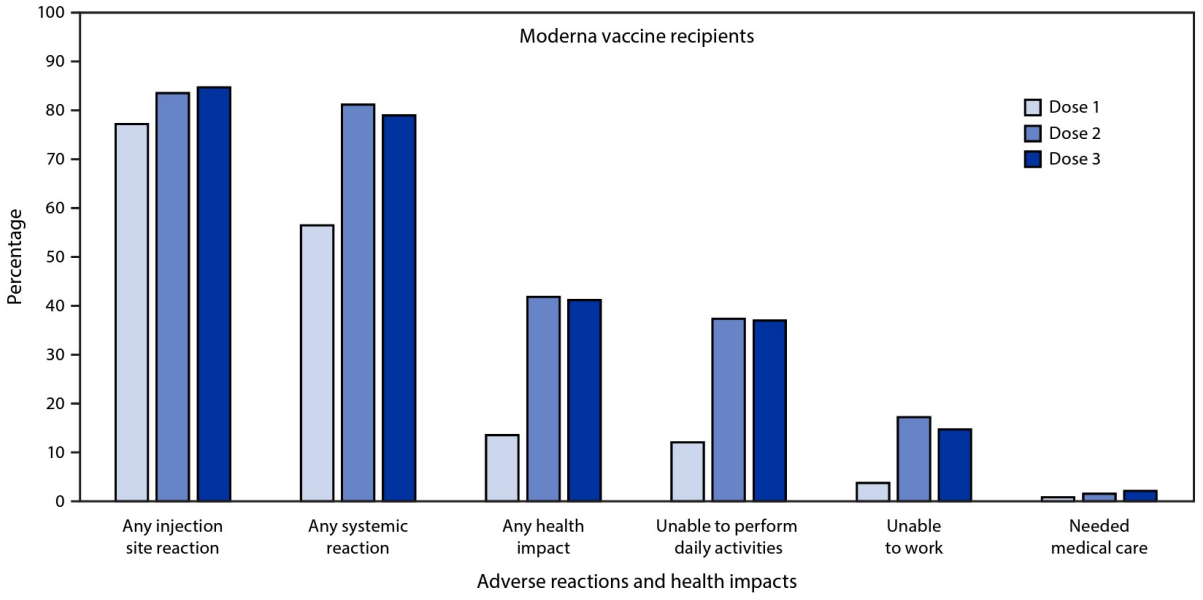
- Voluntary reports to v-safe found no unexpected patterns of adverse reactions after an additional dose of COVID-19 vaccine.
- CDC will continue to monitor vaccine safety, including for additional COVID-19 doses.

MMWR September 2021

Adverse reactions and health impacts reported by persons who received 3 doses* of Moderna (N = 6,283) or Pfizer-BioNTech (N = 6,308) COVID-19 vaccine and completed at least one v-safe health check-in survey on days 0–7 after each dose, by dose number – United States, August 12–September 19, 2021

- The odds of reporting an event after dose 2 and 3 were compared using a multivariable generalized estimating equations model that accounted for the correlation between registrants and adjusted for demographic variables (receipt of care was not adjusted because of small numbers); p-values <0.05 were considered statistically significant. For Moderna recipients, all differences except any health impact and inability to perform daily activities were statistically significant. For Pfizer-BioNTech, all differences except the need for medical care were statistically significant.





MMWR September 2021

COVID-19 Messenger RNA Vaccination and Myocarditis
A Rare and Mostly Mild Adverse Effect

Several recent case series have described acute myocarditis after COVID-19 messenger RNA (mRNA) vaccination.[1]

- This study examined the incidence and outcomes of acute myocarditis following COVID-19 mRNA vaccination in a large community health system.
- The study population was 54.0% women and 31.2% White, 6.7% Black, 37.8% Hispanic, and 14.3% Asian individuals.

During the 6 months of follow-up, there were 15 cases of myocarditis among the 2 392 924 Kaiser Permanente Southern California members who received at least 1 dose of the Pfizer and Moderna vaccines

- 1 case per 172 414 fully vaccinated individuals
- This represents a relative ratio of 2.7 compared with unvaccinated individuals.
- Affected patients were all men younger than 40 years with no prior cardiac history and were discharged within a week of conservative management.

Overall, vaccination-related myocarditis:

- Are rare and mostly mild adverse event.
- Data from the Vaccine Adverse Event Reporting System indicate that it is not unique to just the COVID-19 mRNA
- Up to 28% of patients with COVID-19 infection showed signs of myocardial injury.

Randomized clinical trials show that COVID-19 mRNA vaccines represent a safe and effective method of preventing infection

- The identification of rare myocarditis does not change clinical decision-making.

JAMA Intern Med. Published online October 4, 2021. doi:10.1001/jamainternmed.2021.5634

Booster Dose of BNT162b2 (Pfizer COVID-19 Vaccine)

In the United States, the US Food and Drug Administration has authorized and the Centers for Disease Control (CDC) recommends a booster dose of BNT162b2 (Pfizer COVID-19 vaccine),

- To be given six months after the last dose of the primary BNT162b2 series
- For certain high-risk adults, including adults ≥65 years
- Adults ≥50 years who have comorbidities that increase the risk of severe COVID-19
- Adults <50 years with such comorbidities
- Adults who are at risk for exposure because of occupation or congregate living situations are also eligible for a booster dose.

Booster doses for individuals who received other COVID-19 vaccines have not yet been authorized

CDC.gov

Established, probable, and possible risk factors

(comorbidities that have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review in observational studies, or in case series)

- Cancer
- Neurologic conditions, including dementia
- Obesity* (BMI ≥30 kg/m^2) and overweight (BMI 25 to 29 kg/m^2)
- Pregnancy
- Smoking* (current and former)
- Sickle cell disease or thalassemia
- Solid organ or blood stem cell transplantation
- Substance use disorders
- Use of corticosteroids or other immunosuppressive medications
- HIV
- Cerebrovascular disease
- Children with certain underlying conditions
- Chronic kidney disease
- COPD* and other lung disease (including interstitial lung disease, pulmonary fibrosis, pulmonary hypertension, cystic fibrosis)
- Diabetes mellitus, type 1* and type 2
- Down syndrome
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)

Possible risk factors but evidence is mixed

(comorbidities have been associated with severe COVID-19 in at least 1 meta-analysis or systematic review, but other studies had reached different conclusions)

- Asthma
- Hypertension
- Immune deficiencies
- Liver disease

TO BOOST OR NOT TO BOOST

THAT IS THE QUESTION

Considerations in boosting COVID-19 vaccine immune responses

What is the Problem?

- Delta variant has led to consideration of the potential need for booster doses for vaccinated populations.

The Idea

- Reducing the number of COVID-19 cases by enhancing immunity in vaccinated people

What should be done

- The decision should be evidence-based and consider the benefits and risks for individuals and society.
- These decisions should be informed by reliable science more than by politics.

What do we know:

- COVID-19 vaccines continue to be effective against severe disease, including that caused by the delta variant.
- Most of the observational studies on which this is based are, preliminary and difficult to interpret
- Even if boosting were eventually shown to decrease the medium-term risk of serious disease, current vaccine supplies could save more lives if used in previously unvaccinated populations than if used as boosters in vaccinated populations.

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine immune responses

PROs

Boosting May be Needed

For individuals in whom the primary vaccination might not have induced adequate protection

- Low efficacy vaccines
- I immunocompromised individuals
- Age

In the general population

- Because of waning immunity to the primary vaccination
- Because the original vaccine no longer protects adequately against currently circulating viruses.

CONs

Boosting May be a Problem

People who did not respond robustly to the primary vaccination

- Might also not respond well to a booster

It is not known what is more beneficial

- An additional dose of the same vaccine or a different vaccine

Even if humoral immunity appears to wane

- Reductions in neutralizing antibody titer do not necessarily predict reductions in vaccine efficacy over time

We don't know if benefits outweigh the risks for boosters

- Myocarditis, more common after the second dose of some mRNA vaccines
- Guillain-Barre syndrome, associated with adenovirus-vectored vaccines
- If unnecessary boosting causes significant adverse reactions, there could be implications for vaccine acceptance that go beyond COVID-19 vaccines.

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

The figure summarizes the reports that estimated vaccine efficacy separately for severe disease (variously defined) and for any confirmed SARS-CoV-2 infection, plotting one against the other

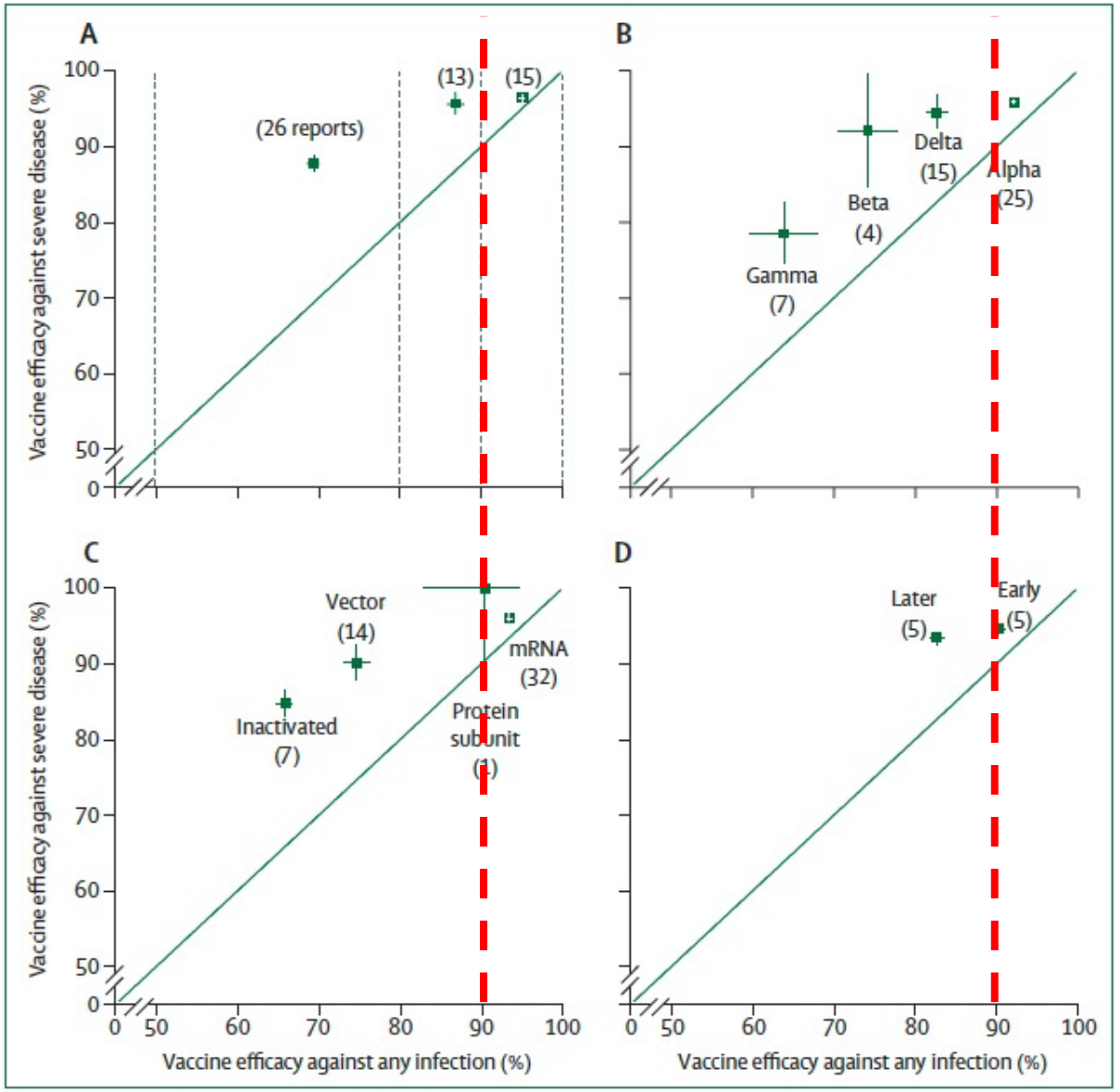
Review of published or informal reports of vaccine efficacy (with a 95% CI) in observational or in randomised studies (appendix pp 3–4) that gave results both for severe disease and for any infection. Plotted are inverse variance-weighted means (and 95% CIs) of the reported vaccine efficacy (giving the number of studies contributing to that mean), subdivided by

(A) Vaccine efficacy against any infection (50% to <80%, 80% to <90%, ≥90%).

(B) Viral variant.

(C) Type of vaccine (viral vector, inactivated SARS-CoV-2, adjuvanted protein subunit, or mRNA).

(D) Studies reporting vaccine efficacy early (more recently relative to vaccination) or later (less recently relative to vaccination) during the follow-up of the same observational study.



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Considerations in boosting COVID-19 vaccine immune responses: What do we know?

Findings from randomized trials

- Have reliably shown the high initial efficacy of several vaccines

Observational studies have attempted to assess the effects on variants or the durability of vaccine efficacy

- Some are peer-reviewed publications, but some are not, and there is a risk of unduly selective emphasis on particular results.

What have these studies shown:

- Vaccine efficacy is substantially greater against severe disease than against any infection
- Vaccination appears to be substantially protective against severe disease from all the main viral variants.
- There is still high vaccine efficacy against both symptomatic and severe disease due to the delta variant.

Current evidence does not appear to show a need for boosting in the general population

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine immune responses

Reductions in vaccine efficacy against mild disease do not necessarily predict reductions in the (typically higher) efficacy against severe disease.

- Protection against severe disease is mediated not only by antibody responses, but also by memory responses and cell-mediated immunity, which are generally longer lived

Vaccine efficacy Randomized trials are relatively easy to interpret reliably, but there are substantial challenges in estimating it from observational studies

- Estimates may be confounded both by patient characteristics at the start of vaccine roll-out and by time-varying factors that are missed by electronic health records.
- Those classified as unvaccinated might include some who were vaccinated, or who are protected because of previous infection, or some whose vaccination was deferred because of COVID-19 symptoms.

Apparently reduced efficacy among people immunised at the beginning of the pandemic could also arise because individuals at high risk of exposure (or of complications) were prioritised for early immunisation.

- Among vaccinated people, more of the severe disease could be in immunocompromised individuals, who are plausibly more likely to be offered and seek vaccination even though its efficacy is lower

The probability that individuals with asymptomatic or mild COVID-19 infection will seek testing might be influenced by whether they are vaccinated.

- In addition, outcomes may be affected over time by varying stress on health-care facilities.

However, careful observational studies that examine efficacy against severe disease remain useful and are less likely to be affected by diagnosis-dependent biases

- To date, none of these studies has provided credible evidence of substantially declining protection against severe disease, even when there appear to be declines over time in vaccine efficacy against symptomatic disease

Krause PP, Fleming TR, Peto Ret al. www.thelancet.com Published online September 13, 2021 https://doi.org/10.1016/S0140-6736(21)02046-8

Considerations in boosting COVID-19 vaccine immune responses

In a study in Minnesota, efficacy of mRNA vaccines against hospitalization appeared lower in July, 2021, than in the previous 6 months

- But these estimates had wide confidence intervals .

Reported effectiveness against severe disease in Israel was lower among people vaccinated either in January or April than in those vaccinated in February or March

- Exemplifying the difficulty of interpreting such data.

A report from Israel during August 2021, just after booster doses deployed widely, has suggested efficacy of a third dose (relative to two doses).

- Mean follow-up was, however, only about 7 person-days (less than expected based on the apparent study design
- A very short-term protective effect would not necessarily imply worthwhile long-term benefit

In the USA reports of large studies (US CDC's COVID-NET13 and two from major health maintenance organization)

- Demonstrate the continued high efficacy of full vaccination against severe disease or hospitalization.

Although vaccines are less effective against asymptomatic disease or against transmission than against severe disease

- The unvaccinated are still the major drivers of transmission and are themselves at the highest risk of serious disease.

If new variants that can escape the current vaccines are going to evolve then :

- They are most likely to do so from strains that had already become widely prevalent.
- The effectiveness of boosting against the main variants now circulating and against even newer variants could be greater and longer lived if the booster vaccine antigen is devised to match the main circulating variants
- There is an opportunity now to study variant-based boosters before there is widespread need for them.
- A similar strategy is used for influenza vaccines, for which each annual vaccine is based on the most current data about circulating strains

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Considerations in boosting COVID-19 vaccine immune responses

The message that boosting might soon be needed, if not justified by robust data and analysis, could adversely affect confidence in vaccines and undermine messaging about the value of primary vaccination.

Public health authorities should also carefully consider the consequences for primary vaccination campaigns of endorsing boosters only for selected vaccines.

- Booster programmes that affect some but not all vaccinees may be difficult to implement
- It will be important to base recommendations on complete data about all vaccines available in a country, to consider the logistics of vaccination, and to develop clear public health messaging before boosting is widely recommended.

If boosters (whether expressing original or variant antigens) are ultimately to be used, there will be a need to identify specific circumstances in which the direct and indirect benefits of doing so are, on balance, clearly beneficial.

- Additional research could help to define such circumstances.
- Given the robust booster responses reported for some vaccines, adequate booster responses might be achieved at lower doses, maybe with reduced safety concerns.

The vaccines that are currently available are safe, effective, and save lives.

- The limited supply of these vaccines will save the most lives if made available to people who are at appreciable risk of serious disease and have not yet received any vaccine.
- Even if some gain can ultimately be obtained from boosting, it will not outweigh the benefits of providing initial protection to the unvaccinated.
- If vaccines are deployed where they would do the most good, they could hasten the end of the pandemic by inhibiting further evolution of variants.

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TO BOOST OR NOT TO BOOST

THAT IS THE QUESTION

Viral Respiratory Illnesses in American Indian Communities: *A Longstanding History of Worsened Outcomes*

Mortality among American Indian/Alaska Native populations, compared to White persons

Seasonal Influenza
2.7x higher

2009 H1N1 Pandemic
4x higher

COVID-19 Pandemic
2.4x higher

Case-control study of risk factors for death from H1N1 across 5 states (N = 381)	
Risk factor	**OR (CI) for mortality**
Age ≥ 45 years	3.22 (1.02 – 8.62)
Pre-existing medical conditions	7.10 (3.20 – 15.78)
Smoking	3.03 (1.01 – 9.23)
Antiviral ≥ 3 days after symptom onset	6.46 (2.24 – 18.62)
Barrier to healthcare access	5.34 (1.45 – 19.68)
AI/AN race was not significantly associated with death	

Modifiable risk factors, immunization, and prompt medical attention are key areas to prevent influenza deaths

OR = Odds Ratio; CI = Confidence Interval. **Doxey M, et al. *J Public Health Manag Pract*. 2019;25(S5):S7-10; Castodale L, et al. CDC MMWR. 2009;58(48):1341-1344. Available at https://www-cdc-gov.lp.hscl.ufl.edu/mmwr/preview/mmwrhtml/mm5848a1.htm. Accessed 6/30/2021; Hennessy TW, et al. *Epidemiol Infect*. 2016;144(2):315-324; CDC. Risk for COVID-19 Infection, Hospitalization, and Death by Race/Ethnicity. Available at https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html. Accessed 6/30/2021.**

Persons at High Risk of Complications from Influenza

- Children aged < 5 years, especially < 2 years
- Adults aged ≥ 65 years
- Immunosuppression
- Pregnancy & within 2 weeks postpartum
- Children and adolescents taking aspirin or other salicylates
- American Indian/Alaskan Native people
- Extreme obesity (BMI ≥ 40kg/m^2)
- Long-term care/nursing home residents
- Chronic conditions:
  - Pulmonary (including asthma)
  - Cardiovascular (excluding isolated hypertension)
  - Renal disorders
  - Hepatic disorders
  - Hematological (including sickle cell disease)
  - Intellectual disability/developmental delay
  - Metabolic disorders (including diabetes mellitus)
  - Neurological/neurodevelopmental conditions

BMI = Body Mass Index

Uyeki T, et al. *Clin Infect Dis*. 2019;68(6):895-902.

Signs and Symptoms of Influenza and COVID-19

	Influenza	COVID-19
Typical symptoms	• Fever with cough • Headache • Myalgia • Fatigue	• Fever with cough • **Shortness of breath** • Headache – **frontal more common** • Myalgia • Fatigue
Atypical symptoms	• Sore throat • Sputum production • **Conjunctival hyperemia and tearing** • Rhinorrhea/nasal congestion **(children)** • Vomiting and diarrhea **(children)**	• Sore throat • Rhinorrhea/nasal congestion **(all ages)** • Nausea and diarrhea **(all ages)** • **Anosmia** • **Dysgeusia** • **Lymphopenia** • **Bilateral opacities on chest radiographs**

Typical and atypical symptoms can aid in differentiating between influenza and COVID-19

Uyeki T, et al. *Clin Infect Dis*. 2019;68(6):895-902; CDC. Flu symptoms and complications. https://www.cdc.gov/flu/symptoms/symptoms.htm. Accessed 7/16/2020; Kimball A, et al. *MMWR Morb Mortal Wkly Rep*. 2020; 69:377-381; Zayet S, et al. *Microbes Infect*. 2020. [Epub].

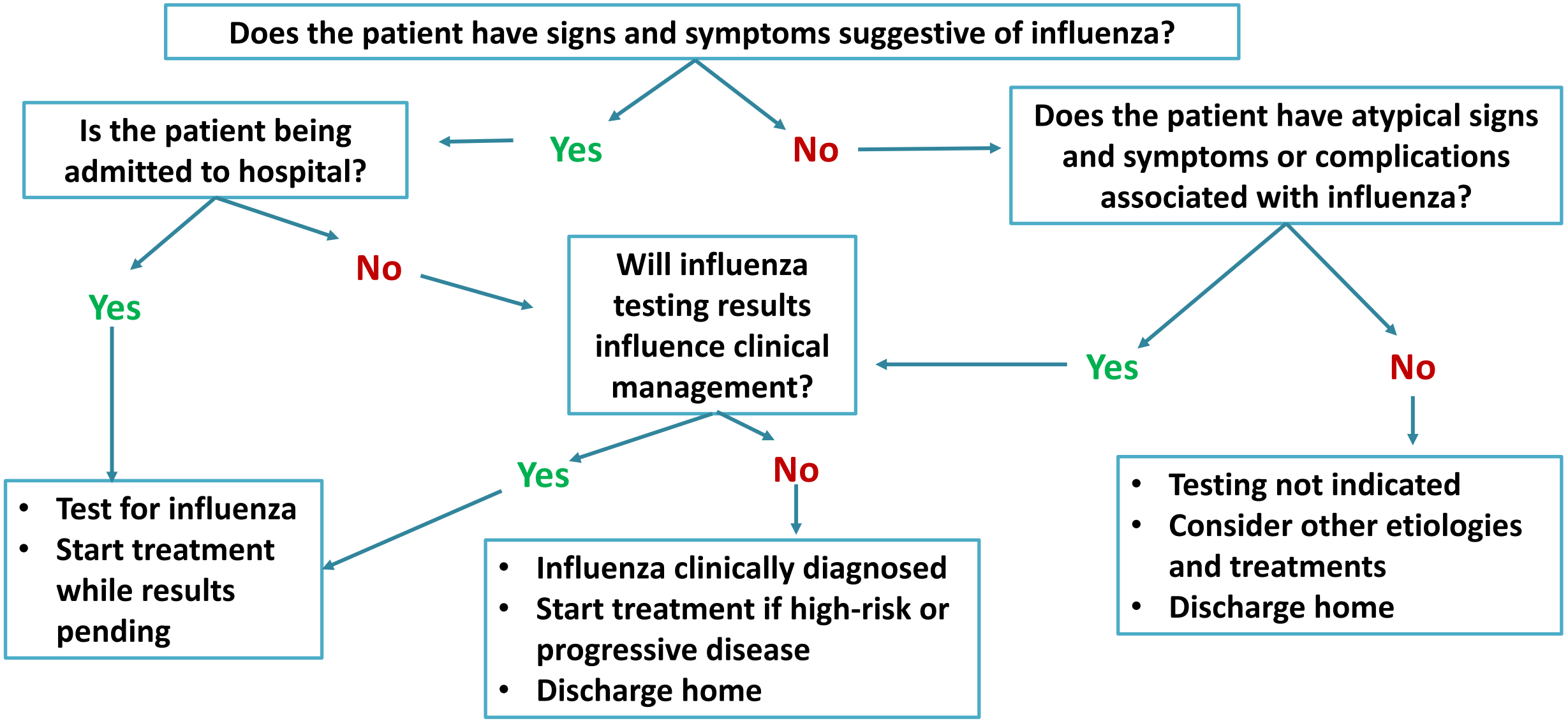
Influenza Diagnostic Tests for Respiratory Specimens

Method	Testing Category	Detects	Distinguishes Influenza A Subtypes	Time to Results	Sensitivity	Specificity
Antigen Detection Assays	Rapid influenza diagnostic test	Influenza virus antigens	No	10-15 min	Low to moderate (↑ with analyzer)	High
	Direct and indirect immunofluorescence assays	Influenza virus antigens	No	1-4 h	Moderate	High
Molecular Assays	Rapid molecular assay	Influenza viral RNA	No	15-30 min	High	High
	Conventional RT-PCR	Influenza viral RNA	Yes (subtype primers)	1-8 h	High	High
	Multiplex molecular assays	Influenza viral RNA, other viral/bacterial targets (RNA or DNA)	Yes (subtype primers)	1-2 h	High	High
Virus isolation	Rapid cell culture (shell vial and cell mixtures)	Influenza virus	Yes	1-3 days	High	High
	Viral culture (tissue cell culture)	Influenza virus	Yes	3-10 days	High	High

IDSA recommends rapid molecular assays over rapid influenza diagnostic tests in outpatients to improve detection of influenza virus infection

RT-PCR = Reverse Transcription Polymerase Chain Reaction; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; **Uyeki T, et al. *Clin Infect Dis.* 2019;68(6):895-902; CDC. CDC's diagnostic multiplex assay for flu and COVID-19 and supplies. https://www.cdc.gov/coronavirus/2019-ncov/lab/multiplex.html. Accessed 7/16/2020.**

IDSA Decision Tree for Testing and Treatment of Influenza



IDSA = Infectious Diseases Society of America; COPD = Chronic Obstructive Pulmonary Disease; HF = Heart Failure; **Uyeki T, et al. *Clin Infect Dis*. 2019;68(6):895-902.**

Indications for Treatment

Treatment should be provided:

- High risk of complications
- Hospitalization for influenza
- Severe or progressive illness

Treatment can be considered:

- Illness onset ≤ 2 days before presentation
- Household contacts or healthcare providers for high-risk persons, particularly immunocompromised

- ✓ Treatment should ideally start within 48 hours of symptom onset
- ✓ Treatment started > 48 hours after onset may still be beneficial in severe illness
- ✓ Treatment decisions should not wait until laboratory confirmation

Uyeki T, et al. *Clin Infect Dis.* 2019;68(6):895-90; CDC. Influenza antiviral medications: summary for clinicians. Available at: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 7/16/2020.

Antivirals for the Treatment of Acute Uncomplicated Influenza

Antiviral	Administration	Approved age for pediatric use	Use in patients at high risk for complications		Prophylaxis
			FDA approved?	CDC recommended?	
Baloxavir marboxil	Oral Single dose	≥ 12 years*	Yes	No	Yes
Oseltamivir	Oral BID x 5 days	≥ 2 weeks	No	Yes	Yes (once daily)
Peramivir	Intravenous Single dose	≥ 2 years	No	No	No
Zanamivir	Inhaled BID x 5 days	≥ 7 years	No	No	Yes (once daily)

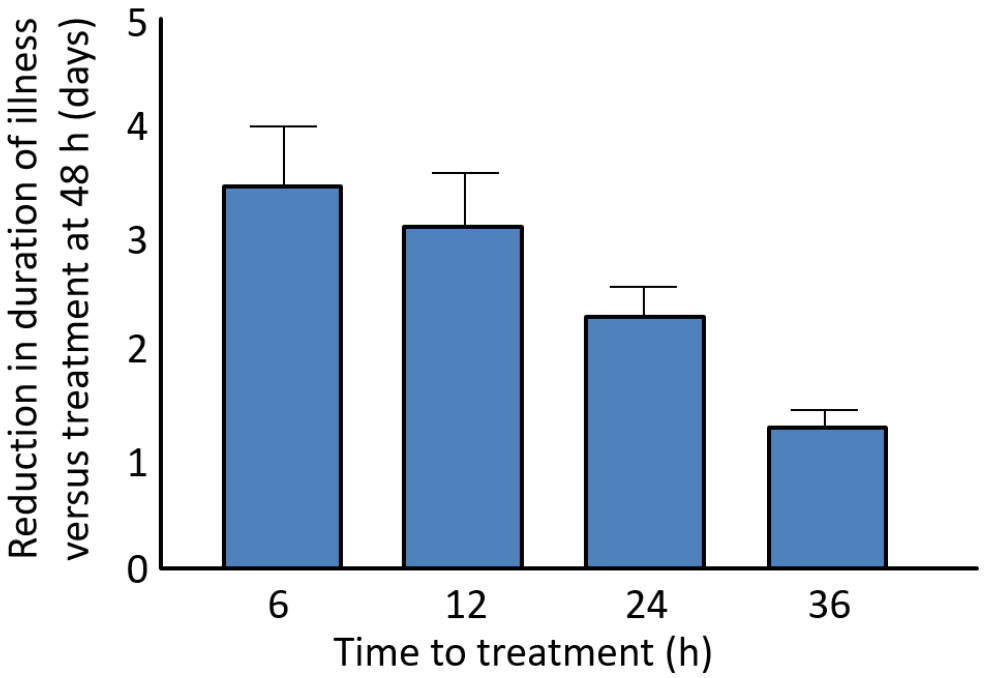
*NDA submitted for 1-12 years

TAMIFLU® (oseltamivir phosphate) [package insert]. Distributed by Genentech, Inc., San Francisco, CA. Licensor: Gilead Sciences, Inc., Foster City, CA. December 2018; RELENZA (zanamivir inhalation powder) [package insert]. GlaxoSmithKline, Research Triangle Park, NC. June 2018; RAPIVAB® (peramivir injection) [package insert]. BioCryst Pharmaceuticals, Inc., Durham, NC. April 2018; XOFLUZA™ (baloxavir marboxil) [package insert]. Distributed by Genentech USA, Inc., South San Francisco, CA. Manufactured by Shionogi & Co., Ltd., Osaka, Japan. October 2018; Duffy S. FDA to review baloxavir sNDA for patients at high risk for flu complications. Available at: https://www.infectiousdiseaseadvisor.com/home/topics/respiratory/influenza/fda-to-review-xofluza-snda-for-flu-treatment-in-patients-at-high-risk-for-complications. Accessed 7/6/2021.

Early Presentation, Diagnosis and Treatment Improves Outcomes: *The IMPACT Study*

Open-label, multicenter study of 1,426 patients presenting within 48 hours of influenza symptom onset

Reduction (days) of illness duration



Duration of illness in infected intent-to-treat population (n=955)

Duration of illness (h) between onset of symptoms and treatment start	Median duration, h (95% CI)
0-6 (n=140)	81.8 (70.7-105.5)
>6-12 (n=100)	110.2 (93.0-123.5)
>12-24 (n=332)	111.1 (98.5-122)
>24-36 (n=258)	127.8 (111.8-151.5)
>36-48 (n=125)	180.0 (146.7-202.85)

Earlier initiation of oseltamivir 75 mg twice daily is associated with shorter duration of illness from influenza

Aoki FY, et al. *J Antimicrob Chemother*. 2003;51:123-129.