Global/WHO perspective on booster doses in the context of global vaccine supply

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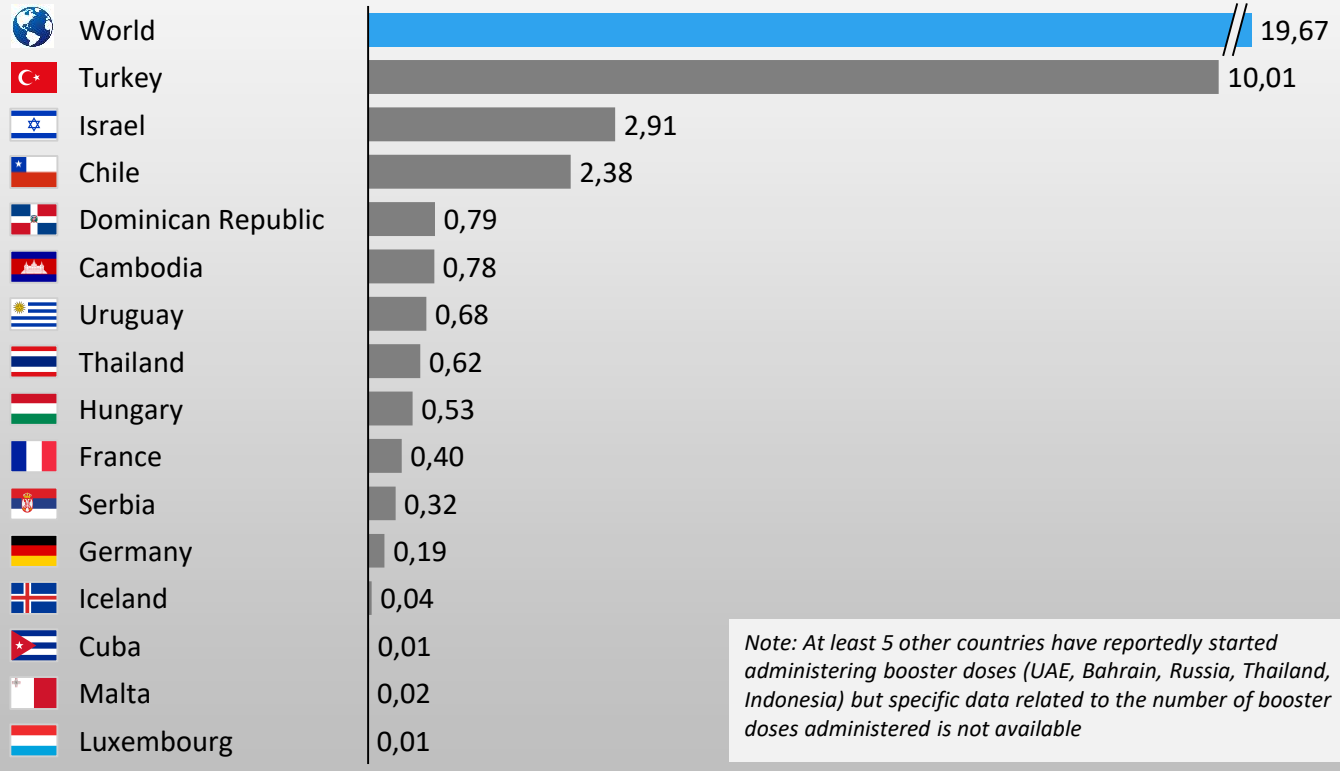
World Health Organization | EPI•WiN | infodemic MANAGEMENT

At least 20mn booster doses have been administered globally (data at 14 Sept.)

NON EXHAUSTIVE

Total number of booster doses administered Million of doses



Note: At least 5 other countries have reportedly started administering booster doses (UAE, Bahrain, Russia, Thailand, Indonesia) but specific data related to the number of booster doses administered is not available

Source: Our World in data (data extracted on Sept. 14; latest data available for each country)

- **At least 15 countries have started administering booster doses**
- **~20mn booster doses have been administered globally incl. 10mn in Turkey only**
- **Booster doses represent 0.3% of the total number of doses administered** (20mn doses out of 5,760mn)

Outline

- Definition of Booster
- Rationale for a Booster
- Boosters in the context of global vaccine shortage and inequity
- Evidence required before recommending boosters
- Available evidence
- Next Steps

Primary series v Booster

- **Primary series:** **a series of vaccine doses administrated to achieve an initial protective immune response in the target *population* for a defined period (ideally measured as a seroprotection rate with a target of >95%)**

- **Booster dose:** **a subsequent dose of vaccine administered when the initial (or subsequent) sufficient immune response to a primary vaccine series (or previous booster) has likely waned in the target *population* below a protective immune response upon subsequent infection.**
  - Typically, a booster dose elicits an immune response that increases faster, reaches higher absolute titres, results in higher avidity antibodies, and remains more durable (i.e., decays slower) than that of the primary series

Loosely adapted from https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/03-COVID-Goswami-508.pdf

Roles of an Additional Dose

There are two distinct potential uses for an additional vaccine dose:

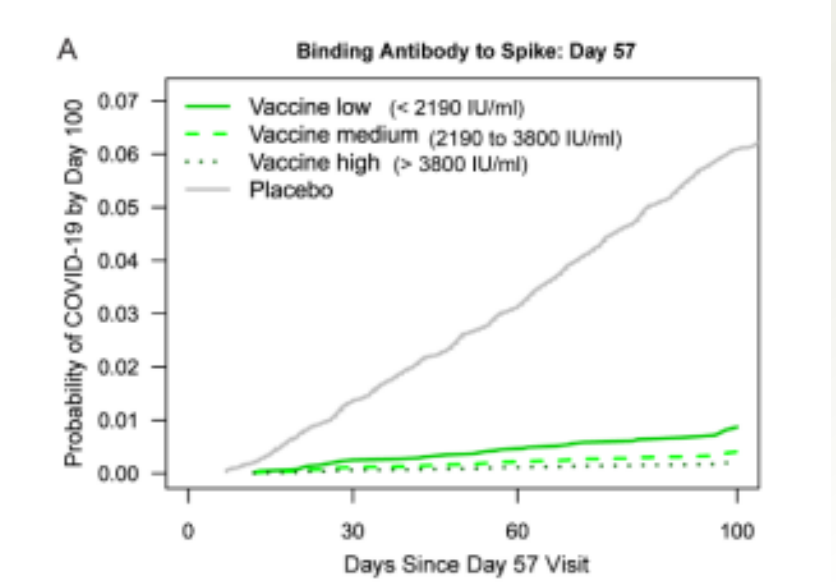
- **Additional dose after an initial primary vaccine series**: administration of an additional vaccine dose when the initial immune response following a primary vaccine series is likely to be insufficient.

- **Booster dose:** a dose of vaccine administered when the initial sufficient immune response to a primary vaccine series is likely to have waned over time. The need for and timing of a COVID-19 booster dose have not been established

Source: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-13/03-COVID-Goswami-508.pdf

Antibody based immunity after COVID-19 vaccination

- Neutralizing antibodies seem to correlate with protection from symptomatic SARS-CoV-2 infection[1,2.]
- Data suggest that antibodies against SARS-CoV-2 persist for at least 6 months after vaccination but neutralizing capacity is lowered with regards to certain variants of concern
- Vaccines do not provide sterilizing immunity, hence breakthrough infections are expected *regardless of waning*
- Waning of neutralizing antibodies has been reported[3.]
- At present, it is unknown what level of neutralizing antibodies or other immune markers are associated with a vaccine's protection of infection, severe disease and transmission
- Cellular immunity seems to be associated with protection against severe disease

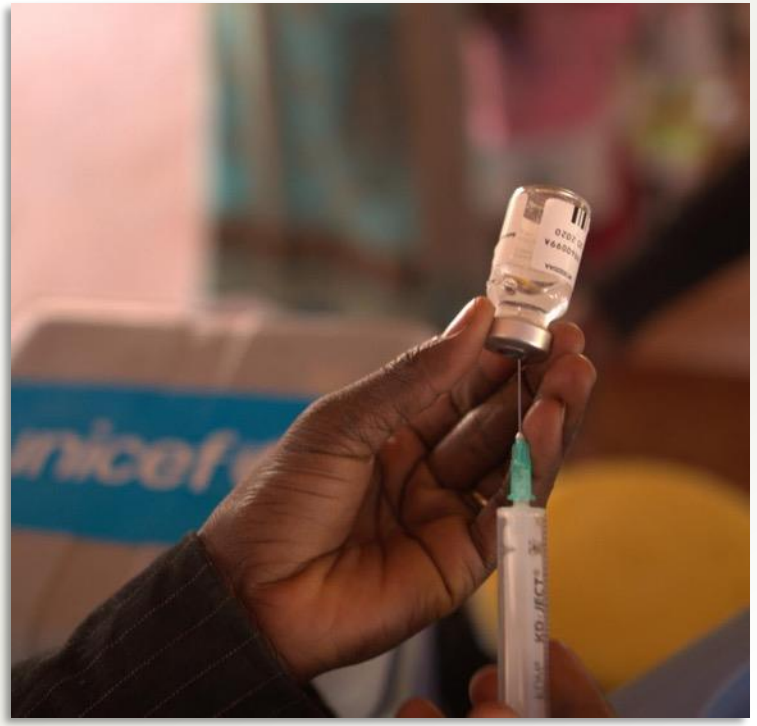


1.Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection | Nature Medicine
2. 2021.08.09.21261290v1.full.pdf (medrxiv.org)
3. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination (nih.gov)

Current COVID-19 vaccines prevent severe disease

- Vaccines have reported sustained effectiveness against severe COVID-19 after 6 months[1,2,3]
- While breakthrough infections are increasing, the vast majority are less severe than those seen in unvaccinated people[4]

We increasingly see an epidemic of the unvaccinated.



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1.https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm
2. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study | The BMJ
3. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/media-resources/science-in-5/episode-30---vaccines-when-and-why
4. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers - PubMed (nih.gov)

Rationale for a Booster

- **(1) Decline over time** in performance of vaccine primary series, may vary by clinical endpoints
- **(2) Insufficient response to primary series** for some risk groups (for example, immunocompromised). ("Additional dose")
- (3) **Variants** have evolved to a degree that protection by original vaccines becomes inadequate (original or variant vaccine boost). A **variant** may require a booster[1] because:
  i. Higher antibody levels need to be sustained
  ii. A new/modified vaccine is needed implicating 're-immunizing' vaccinated individuals

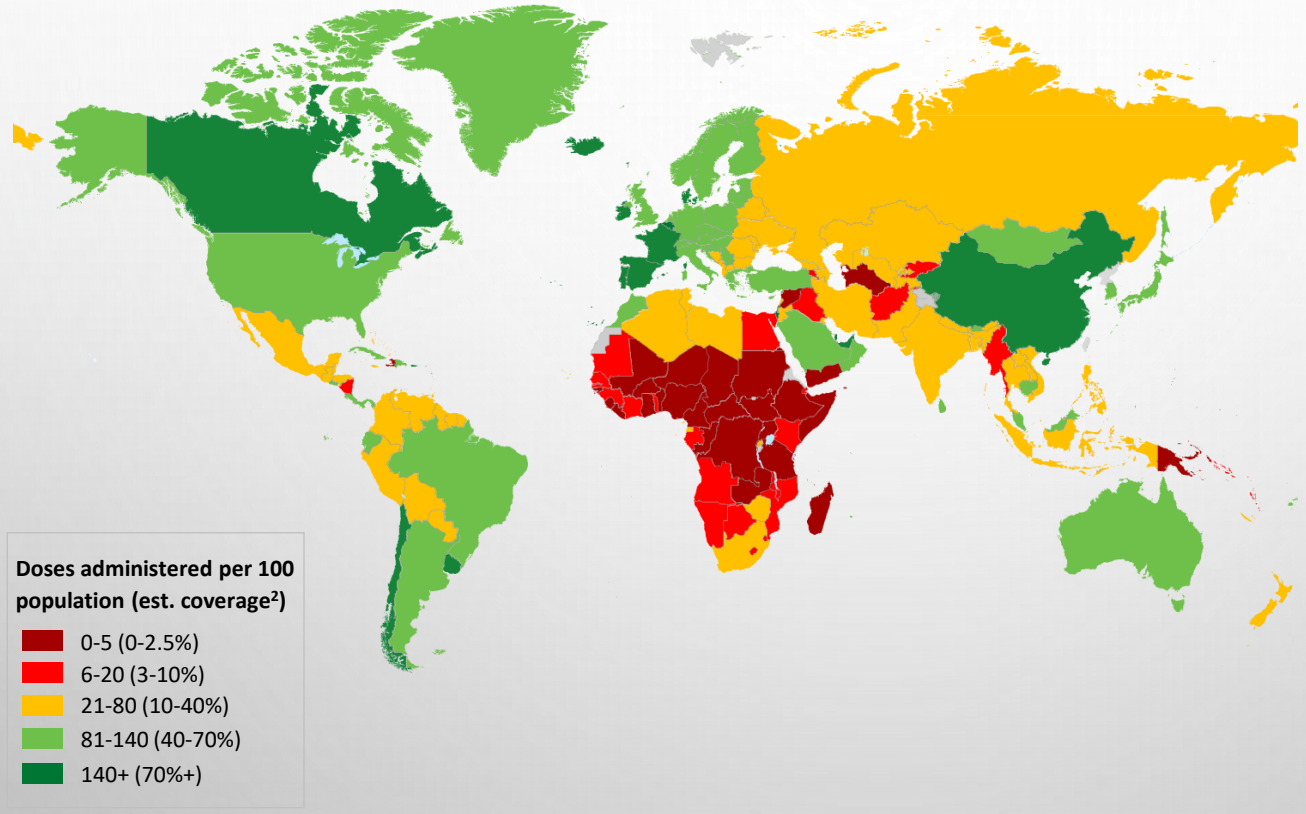
- Outcome of interest severe disease/hospitalization as reducing mortality and protecting health care systems remains the priority.

➢ *The need for booster doses may differ by vaccine product, epidemiological setting, risk group, and other factors*

Boosters in the context of global vaccine shortage and inequity

5,953M doses of COVID-19 vaccine have been administered globally, however 54 countries remain below 10% coverage

Total doses administered per 100 population



5,953M vaccine doses have been administered

COVAX has **shipped 286.8M** doses to **141** participants[1]

Immunization programmes **have not yet started in 3** countries, economies & territories

1. Including donations of doses through COVAX
2. Assuming 2 doses per fully vaccinated inhabitant

Note: The designations employed and the presentation of these materials do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Source: WHO COVID-19 Dashboard (map creation), Bloomberg (total # of doses administered), COVAX SCO tracker (UNICEF data) (COVAX shipments)

WHO calls for a pause to use booster vaccinations for equity reasons

High first dose coverage globally leads to a higher public health impact, compared to adding a third dose before high first dose coverage is achieved.

WHO is calling for a moratorium on Boosters until at least the end of September to enable at least 10% of the population of every country to be vaccinated.

https://www.youtube.com/watch?v=ST4MV0JwwKI

Equity first! **Emphasis remains on increasing first dose coverage.**

Potential downsides of using a booster dose for all at this time of the pandemic may include:

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- A threshold for true waning in VE needs to be established, otherwise a poor precedent is set to boost every 6 months for mild waning in hospitalization rates.
- If boosters that can have immune-mediated side effects (e.g., myocarditis after mRNA vaccines or Guillain-Barré syndrome with Janssen/J&J) are widely introduced too soon or too frequently, vaccine acceptance may be adversely affected in the future.
- **Higher income countries' pursuit of booster strategies further affects vaccine equity at a time when LICs and LMICs have not yet even administered 1st vaccine doses to priority groups:**
  - Booster strategies limit volumes available for dose-sharing with other countries
  - Demand for specific vaccines may increase significantly
  - Influences policy environment for other countries

Considerations in boosting COVID-19 vaccine immune responses

Philip R Krause, Thomas R Fleming, Richard Peto, Ira M Longini, J Peter Figueroa, Jonathan A C Sterne, Alejandro Cravioto, Helen Rees, Julian P T Higgins, Isabelle Boutron, Hongchao Pan, Marion F Gruber, Narendra Arora, Fatema Kazi, Rogerio Gaspar, Soumya Swaminathan, Michael J Ryan, Ana-Maria Henao-Restrepo

Evidence required for recommending boosters

- Definition of Booster
- Rationale for a Booster
- **Boosters in the context of global vaccine shortage and inequity**
- **Evidence required for boosters**
- Available evidence
- Next Steps

Evidence can come from RCTs and observational studies, stratified by risk group, variants, and product (incl. combinations)

1. Assessing the need for booster doses

- Immunologic assessments, over time of post-vaccine antibody and cellular responses
- RCT follow up studies of vaccine performance over time, by disease and infection outcomes, and by variants
- Post-introduction observational VE studies (real-world experience) to evaluate durability of vaccine performance over time, by disease and infection outcomes, and by variant

2. Assessing performance of booster doses

- RCTs on safety, immunogenicity, and disease outcomes
- Observational evaluations of immunogenicity
- VE, impact and safety of booster programmes
- Assessing heterologous vs homologous boosters
- Determining the optimal timing for booster doses

Why is it so difficult to determine waning VE over time?

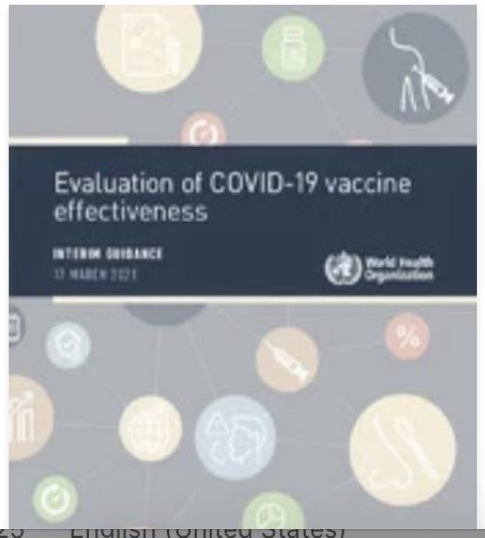
- **Phase 3 RCT were unblinded at the time of EUL for ethical reasons, hence we "lost" our control group. Only limited data from RCT exist on duration of vaccine efficacy beyond the phase 3 trial observation time, eg cross-over studies**
- **Hence we rely on post-introduction observational studies, which all have some confounding and risk of bias, eg:**
  - New Variants and changing incidence over time
  - VE estimates depend on the appropriate controls: High vaccine coverage rates make comparison against the diminishing cohort of unvaccinated "controls" less reliable
  - Controls increasingly get infected naturally and therefore the effect size of vaccine effectiveness estimates decreases
  - Earlier cohorts are different to the populations vaccinated later in the vaccine roll-out (older and vulnerable persons were vaccinated early in the outbreak), so VE since vaccination may differ because of the highly different cohorts

  - Nevertheless, post-introduction VE studies are crucial in understanding VE over time. Whilst acknowledging potential bias, they need to be carefully studied to inform policy decisions.

Evaluation of COVID-19 vaccine effectiveness

Interim Guidance

17 March 2021 | COVID-19: Vaccines



Overview

Vaccine effectiveness and impact document provides interim best practice guidance on how to assess COVID-19 vaccine effectiveness (VE) using observational study designs. It discusses critical considerations in the design, analysis and interpretation of COVID-19 VE evaluations, as biased results may be produced even in settings where data completeness and quality are high. This guidance is targeted mostly for evaluations undertaken in low- and middle-income countries but most of the concepts apply to VE evaluations in high-income settings as well.

Do boosters work?
Clinical trial data on booster vaccination

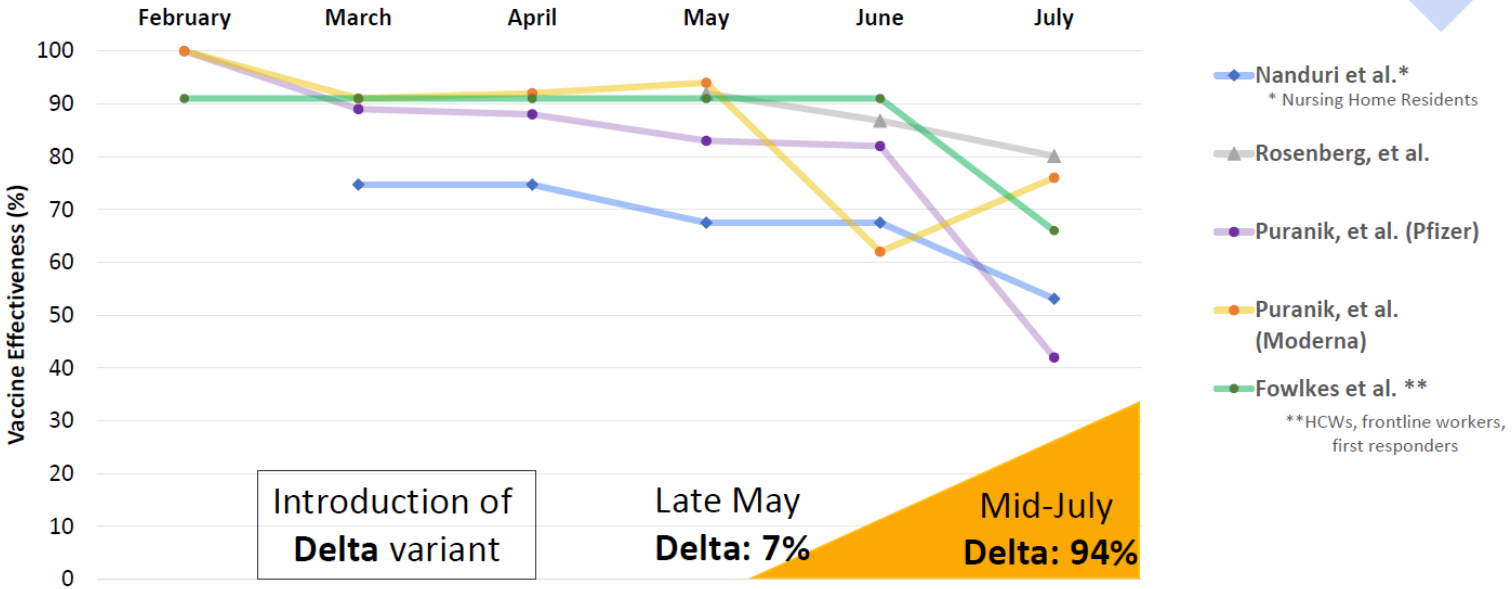
Vaccine	Data	Regulatory Status
Pfizer-BioNTech	30µg dose 6 months post primary	FDA 3rd dose ICP. VRBPAC: 65+, Health workers and Teachers
Moderna	50µg dose, 6 months+ post primary; homologous and variant vaccine; SAGE has not yet reviewed 100µg dose study	FDA 3rd dose (100µg) ICP
ChAdOx-1	28-38 weeks with regular dose, adults	
Janssen	Press communication this week; increased efficacy after 2nd dose	
SinoVac	8 months after 2nd dose, adults and >60y+	none
SinoPharm	Unknown	none
Bharat	6 months post dose 2, study ongoing	Study ongoing

- *All studies (mostly small scale) have shown characteristics of an anamnestic response*
- *To the extent data are available, studies show robust crossneutralization of Delta variant*
- *Effectiveness and large scale safety data are yet missing*
- *Limited data exist on heterologous boosting (≠ heterologous priming)*

Do we need booster doses? (mRNA)

Booster doses of COVID-19 vaccines:
Vaccine effectiveness against **infection**

Public Health Problem



Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021.
Nanduri S. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morbidity and Mortality Weekly Report. 2021 2021;70.
Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 24 August 2021.
Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv 2021.08.06.21261707.

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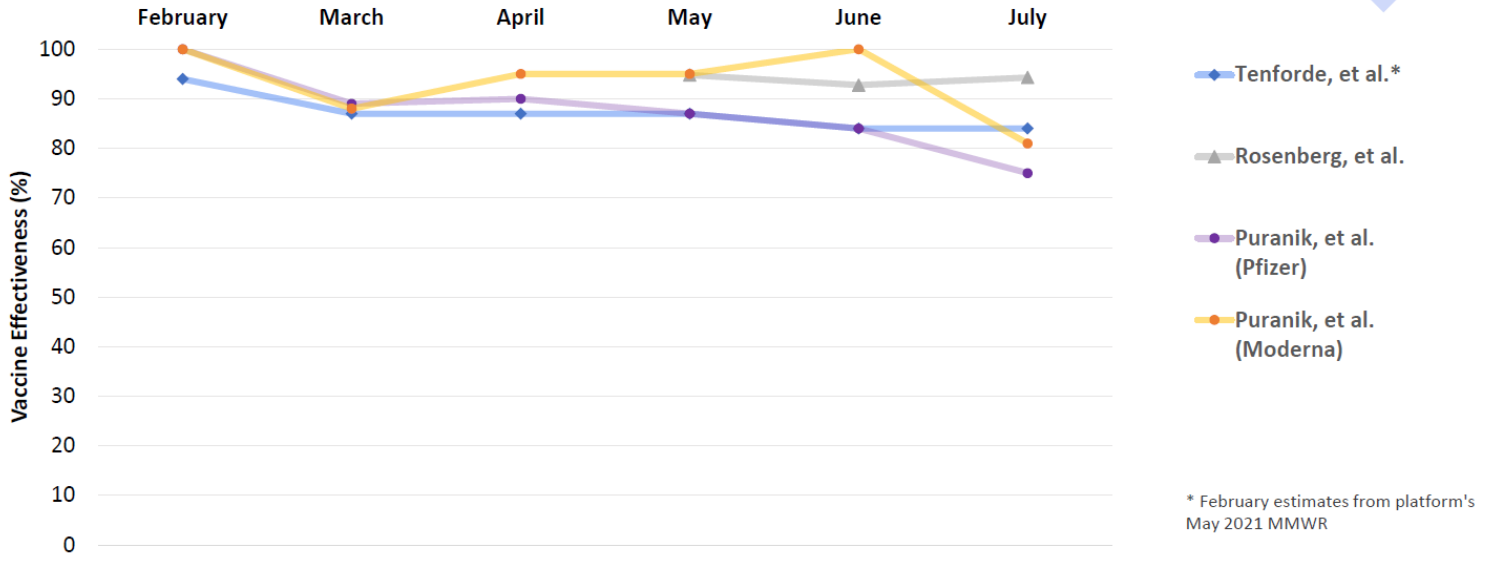
Do we need booster doses? (mRNA)

Booster doses of COVID-19 vaccines:

Vaccine effectiveness against **hospitalization**

Public Health Problem



* February estimates from platform's May 2021 MMWR

Tenforde MW, Self WH, Naioti EA, et al. Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults — United States, March–July 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021.

Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years — United States, January–March 2021. MMWR Morb Mortal Wkly Rep 2021;70:674–679.

Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021.

Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv 2021.08.06.21261707.

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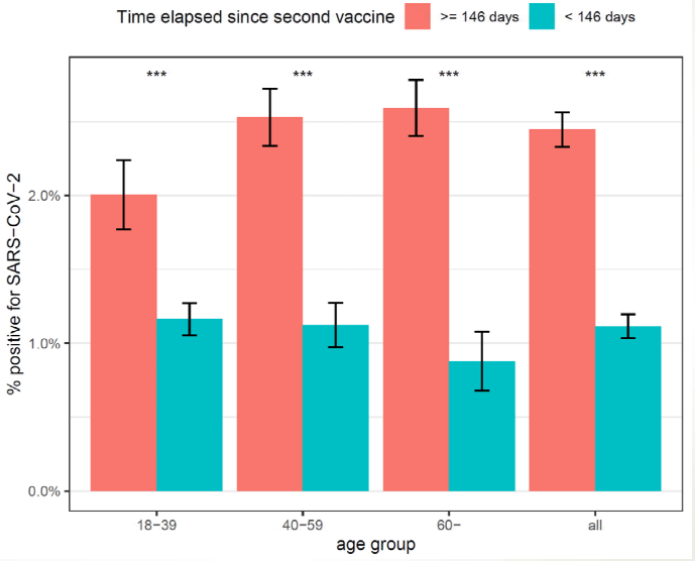
VE by age

- **Israel et al,** **Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort.:**
  - Retrospective analysis of data from Israel, adjusted for confounders
  - Compared rate of breakthrough infections during May-July, (delta dominant @ 93%) among those who received vaccine < to ≥146 days.
  - Persons with vaccination ≥146 days before infection had an adjusted odds ratio for infection :
    - ≥ 60 years: 2.76 (95% CI 1.62-3.08)
    - 40-59 years: 2.22 (95% CI 1.62-3.08)
    - 18-39 years: 1.67 (95% CI 1.21-2.29)

Figure 2: Comparison of the percentage of positive results among fully vaccinated individuals, according to time elapsed since the second vaccine dose



Israel, A., Merzon, E., Schäffer, A. A., Shenhar, Y., Green, I., Golan-Cohen, A., Ruppin, E., Magen, E., & Vinker, S. (2021). Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection in a large cohort. *MedRxiv*, 2021.08.03.21261496. https://doi.org/10.1101/2021.08.03.21261496

Mild infections in HCW in the US

N Engl J Med 2021 Sep 1.
doi: 10.1056/NEJMc2112981. Online ahead of print.
Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce
Keehner et al.

Table 1. Symptomatic SARS-CoV-2 Infection and mRNA Vaccine Effectiveness among UCSDH Health Workers, March through July 2021.*

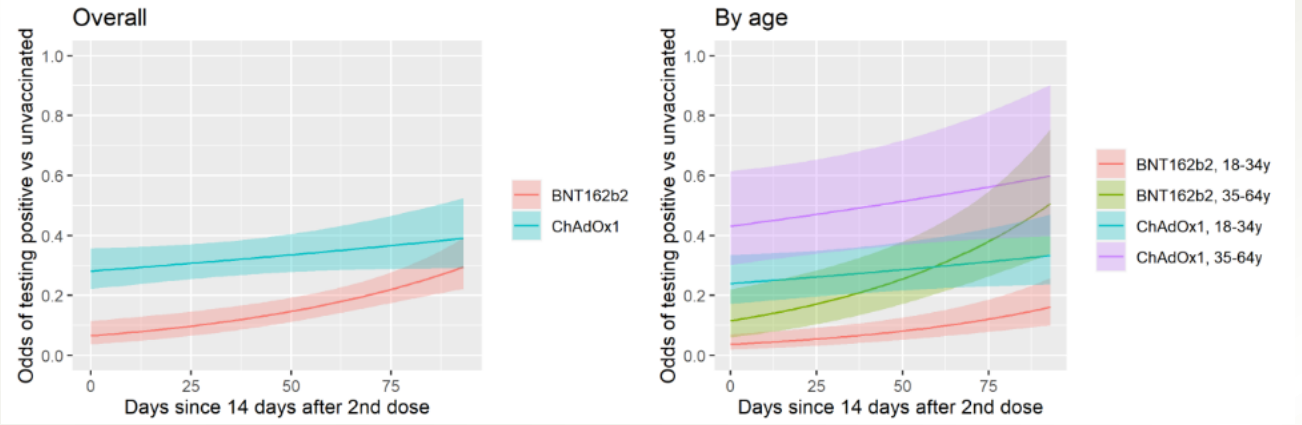
	March	April	May	June	July
Symptomatic Covid-19					
Fully vaccinated workers	3	4	3	5	94
Unvaccinated workers	11	17	10	10	31
Percentage of cases in fully vaccinated workers	21.4	19.0	23.1	33.3	75.2
Attack rate per 1000 (95% CI)					
Fully vaccinated workers	0.21 (0.21–0.47)	0.26 (0.26–0.50)	0.19 (0.21–0.40)	0.30 (0.31–0.53)	5.7 (5.4–6.2)
Unvaccinated workers	3.4 (2.1–5.9)	6.8 (4.5–10.6)	4.6 (2.6–8.2)	4.9 (2.9–8.7)	16.4 (11.8–22.9)
Vaccine effectiveness — % (95% CI)	93.9 (78.2–97.9)	96.2 (88.7–98.3)	95.9 (85.3–98.9)	94.3 (83.7–98.0)	65.5 (48.9–76.9)

* UCSDH denotes University of California San Diego Health.
† Data are the total number of workers who had received two doses of an mRNA vaccine as of the last day of the month.

UK: Pfizer and AZ duration of protection VE during delta dominant period

- Household longitudinal survey among 18-64
- Waning of Pfizer > waning of AZ against infection
  - VE of BNT162b2 against infection reduced by 22% (95% CI 6% to 41%) for every 30 days from second vaccination.
  - VE of ChAdOx1 reduced by 7% (95% CI -2 to 18%) per 30 days
  - No difference in waning by those </≥9 weeks dosing interval

Figure S4 Protection against all new PCR-positive episodes with reported symptoms over time from second dose, overall and by potential subgroups in those 18-64 years in the Delta-dominant period. Note: lthc=self-reporting a long term health condition. See **Figure 2** for effects on all PCR-positive episodes. See **Table S3** for estimates of VE within subgroups 14 days after second vaccination (intercept on panels below).



- Pouwels, K. B., Pritchard, E., Matthews, P. C., Stoesser, N., Eyre, D. W., Vihta, K.-D., House, T., Hay, J., Bell, J. I., Newton, J. N., Farrar, J., Crook, D., Cook, D., Rourke, E., Studley, R., Peto, T., Diamond, I., & Walker, A. S. (2021). *Impact of Delta on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK*. https://www.ndm.ox.ac.uk/files/coronavirus/covid-19-infection-survey/finalfinalcombinedve20210816.pdf

Inactivated vaccines:
Evidence from selected CoronaVac studies

Author	Study details	VE results	Comments
Jara et al	Prospective Cohort of 10 million from Feb-May to calculate VE (Chile)	66% against symptomatic, 88% hospitalization, 90% ICU admission, 86% death	Overall persistent protection against hospitalization and ICU/death; prevalent VoCs alpha, gamma, July 31 update pending (*some decline in VE observed - unpublished*)
Ranzani et al	TND in Sao Paulo of 43K ≥70 year olds January-April	33-59% against symptomatic, 39-78% hospitalization, 44-85% death (lowest in 80+)	*Lower effectiveness in older adults*, in particular above 80y; can be confounded by time since vaccination; No duration of protection information
Cerqueria-Silva et al	Retrospective cohort of 75 million vaccinated Brazilians January-July	53% for symptomatic, 73% hospitalization, 74% ICU, 74% death	Have data on hospitalization rate over time; Low hospitalization incidence up to 84 days in vaccinees up to 79 years, *some increase 80y+*; high VoC gamma prevalence*; little information on duration of protection; update requested*

- Observational studies confirm RCT data obtained in the region
- Robust effectiveness against hospitalization, less in older age
- Follow-up ongoing to monitor duration of protection (Jara et al., Cerqueria-Silva et al.)

➢ Possibility that inactivated vaccines need a 2+1 primary schedule

References:
Jara et al. : https://www.nejm.org/doi/10.1056/NEJMoa2107715
Ranzani et al.: https://www.bmj.com/content/374/bmj.n2015
Cerqueria-Silva et al.: https://www.medrxiv.org/content/10.1101/2021.08.21.21261501v2

Response to a third dose of CoronaVac (Sinovac) in healthy adults ≥60y

Design

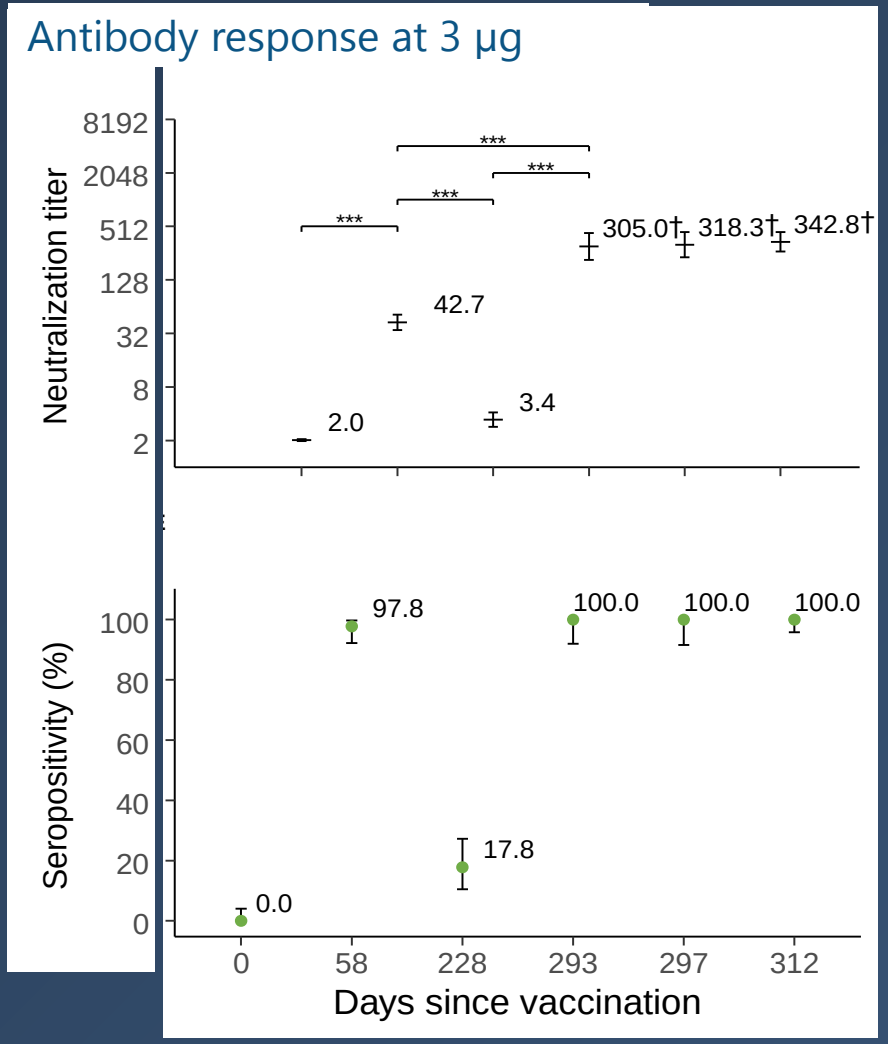
1.5 µg	X	X	X
3 µg*	X	X	X
6 µg	X	X	X
	0d	28d	+8m

* Licensed formulation

Overview

Study	Li et al; medRxiv
Trial ID	NCT04383574
Country	China
Vaccine	CoronaVac
Population	Healthy adults, ≥60y
N	303
D2–D3 interval	≥8m

Antibody response at 3 µg



- After 2 x CoronaVac at **3 µg**, seroprotection rate declined from 98% at D2+28d to 18% after D2+6m
- After 3rd dose at ~8m, GMTs **8-fold higher** on D3+28d vs D2+28d

Li et al; medRxiv 2021; doi 10.1101/2021.07.23.21261026

Target groups for COVID-19 booster doses

Waning immunity

- Third doses should be prioritized for the vulnerable: those most at-risk populations when there is evidence of waning immunity against severe disease and death. They are not for the fit and healthy[1]

Poor primary response to vaccination

- Immunocompromised people may not respond sufficiently to two doses of COVID-19 vaccine. For example, in a trial with organ transplant recipients only 4% of people generated SARS-CoV-2 antibodies after one dose, increasing to 40% after two doses and 68% after three doses[2].
- Emerging data shows that immunocompromised people should receive a third dose if they did not respond sufficiently to their initial doses or if they are no longer producing antibodies. Such groups would be exempt from the booster moratorium[2]

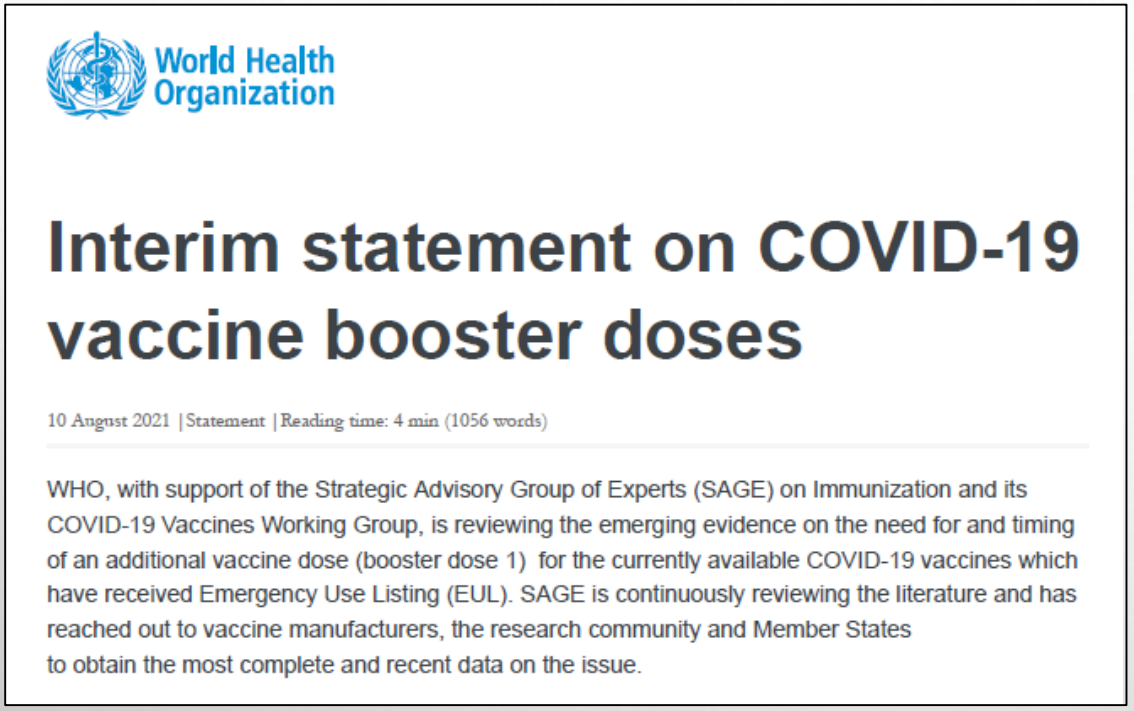
1. *WHO news updates*
2. *https://www.nejm.org/doi/full/10.1056/NEJMc2108861*
   Interim statement on COVID-19 vaccine booster doses (who.int)

Policy work … the way ahead

- **Continued review of data** on duration of protection/breakthrough cases with specific view on subpopulations and occurrence of hospitalization/severe disease
- Importance for **communication on breakthrough** infections/disease in times of increasing vaccination coverage
- Review the need for **additional dose** for populations not mounting a robust primary response (**immunocompromised**)
- Review the need for **adjusted primary immunization** schedules (2 plus 1) in select populations
- Insights from the interpretation of **immunological data** (R&D blueprint)
- **Mathematical modelling** on impact optimization of limited vaccine
- Plan for a discussion on booster doses at **an Extraordinary SAGE meeting in November 2021**

Conclusions

- WHO`s primary objective remains focused on **preventing hospitalizations and deaths globally**
- **Increasing first dose coverage globally will have a higher public health impact** of COVID-19 vaccination compared to increasing 3rd dose coverage in a small number of countries
- Robust evidence on waning VE against severe hospitalizations/deaths is still lacking. **Current data on well maintained VE against severe disease remains encouraging** while WHO notes waning VE against mild breakthrough infections
- WHO acknowledges the need for **ongoing evaluation of VE over time**
- WHO proposes a **moratorium** on the use of booster doses until global vaccine coverage targets have been reached and more robust data are available on the (1) public health need for a 3rd dose and (2) booster dose performance assessments been conducted
- WHO acknowledges that **special subpopulations** (immune compromised for example) will require special attention



World Health Organization

Interim statement on COVID-19 vaccine booster doses

10 August 2021 | Statement | Reading time: 4 min (1056 words)

WHO, with support of the Strategic Advisory Group of Experts (SAGE) on Immunization and its COVID-19 Vaccines Working Group, is reviewing the emerging evidence on the need for and timing of an additional vaccine dose (booster dose 1) for the currently available COVID-19 vaccines which have received Emergency Use Listing (EUL). SAGE is continuously reviewing the literature and has reached out to vaccine manufacturers, the research community and Member States to obtain the most complete and recent data on the issue.

- Rationale for boosters
- Factors to be considered
- Data needs for policy
- Current perspective
- *Not a policy position*

https://www.who.int/news/item/10-08-2021-interim-statement-on-covid-19-vaccine-booster-doses