



World Health
Organization

Synthesis of the evidence and next steps

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R&DBlueprint

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to prevent epidemics

Situations where additional doses of a COVID vaccine in previously vaccinated individuals would likely be beneficial

There is evidence that primary vaccination never induced enough immunity to be protective, e.g.,

- Immunocompromised
- Recipients of vaccines with low or unproven efficacy

Individuals at high risk of severe disease are also at high risk of exposure to the virus, primarily due to uncontrolled transmission in the unvaccinated

Vaccine induced immunity wanes to the point that previous vaccination is no longer believed to be adequately protective

New variants arise that escape vaccine induced immunity, such that previous vaccination is no longer believed to be adequately protective

Vaccine benefit and risk

It is generally agreed that vaccine benefits need to exceed the risks

Risks of “boosting” may include immediate safety concerns for vaccinees, unknown long-term consequences of boosting, and **adverse public health outcomes**

Thus, benefits of boosting should be clear in order to make a benefit:risk assessment

Due to risk of confounding, it is better to look at data in the aggregate rather than to focus on individual studies

Vaccination records are incomplete in many locations

“Unvaccinated” individuals might have already had COVID or vaccine, making it appear that immunity could be waning as the control group progressively becomes smaller and more protected itself.

Reduction in size of the control group may also accentuate the impact of other differences between people to get vaccinated and those who choose not to

It's difficult to separate the effect of prioritization for early vaccination (due to higher risks) from those associated with time since vaccination

Especially in a pandemic, test-negative case control studies usually do not adequately control for health-seeking behaviors

COVID infection records, especially for milder disease, are incomplete in many locations. Records of severe disease are likely to be more accurate, and likelihood of presenting to hospital with illness is less likely to be associated with factors that may have also influenced likelihood of vaccination.

What vaccine efficacy outcomes are most critical?

Severe disease?

- Most would agree that primary protection against severe disease is most important
- Long COVID and other complications occur most frequently in those with severe disease

Mild disease?

- Mild disease is tolerated for many other illnesses, and may even confer long term protection advantages

Transmission?

- Transmission is driven by the unvaccinated
- Long term protection against transmission may be impossible to achieve with current vaccines
- Often difficult to assess in clinical trials
- We don't have direct evidence about impact on transmission for most vaccines in use today

What vaccine efficacy outcomes are most critical? (2)

Infection?

- Preventing infection would protect against mild disease, severe disease, and transmission
- Most vaccines are not successful in completely preventing infection
- Often difficult to assess in clinical trials

Loss of antibodies?

- Even if antibody responses were unambiguously predictive of short-term protection, because vaccines induce strong memory responses and cell-mediated responses, long-term effectiveness is unlikely to be well-predicted by circulating antibody levels
- Protection against severe disease is thought to be mediated by cellular immune responses, not antibodies

Studies of severe disease endpoints

- Some risks of confounding are reduced when severe disease endpoints are used
- Since severe disease endpoints are closely aligned with the goals of vaccination and are also more accurately assessed in observational studies, they provide the most reliable assessments of possible waning of protection
- Taken together, the least biased studies of severe disease endpoints do not suggest substantial waning of vaccine-induced protection

How are regulators evaluating boosters?

In some countries, benefit-risk evaluation is based on perceived need for boosters in specific subgroups

To evaluate efficacy:

- Immune responses after boosting are bridged to responses shortly after the primary vaccination series that were shown to be protective in clinical trials
- This provides a basis for believing that effectiveness post-boost will be similar to that after the primary series
- If immune responses post-boost are higher than after the primary series, this suggests a good response, but does not provide assurance that protection will be higher
- Duration of any additional protection observed after boosters may be transient

Benefits of focusing vaccination efforts on the unvaccinated

- Strong endorsement of boosters can reduce confidence in the primary series, making it more difficult to vaccinate the people who are still driving the pandemic
- Even without waning of protection, the major risk of disease in vaccinated individuals comes via exposure to infected unvaccinated people. Vaccinating the unvaccinated will indirectly protect vaccinated people
- Uncontrolled transmission will increase the likelihood that new variants develop. This risk can be reduced by vaccinating the unvaccinated
- Each dose of vaccine will save more lives if provided to the unvaccinated vs. being used as a booster in the general population

Booster math: Cases averted by using vaccine as primary series vs. as booster, using conservative assumptions

Primary series effectiveness	Wanes to	Effectiveness after booster	Relative benefit of primary series
90%	90%	99%	5-fold
	80%	98%	2.5-fold
	70%	97%	1.7-fold
	60%	96%	1.3-fold
80%	80%	98%	2.2-fold
	70%	97%	1.5-fold
	60%	96%	1.1-fold

Assumptions

- Primary series is 2 doses
- Booster reduces risk 10-fold
- Similar risks of exposure/disease

Conclusions

There will always be reasons why rich countries will see possible advantages to jumping to the head of the line for additional vaccines or vaccine doses, further delaying worldwide control of the pandemic

In a pandemic, perception of some of these advantages may be driven by fear, not fact

The available evidence still does not support the need for widespread deployment of boosters in any country

There is now still an opportunity to obtain important additional data, including what to (ultimately) boost with, what are appropriate booster dose levels, variant-specific information, more safety information

Decisions should be based on data and a transparent scientific process

Final thoughts

We have effective vaccines, and so far they are doing what they need to do.

There is no reason to panic, or to allow fear to drive policy decisions.

We need to find ways to vaccinate more people in all countries, regardless of wealth.