To boost or not to boost, that is the question?

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Summary

High-income countries are progressing rapidly with vaccination and are starting to consider the use of booster shots where many low-income countries are struggling to vaccinate significant numbers of people. Given excess availability of vaccines in many high-income countries this article aims to answer the question about what whether to use these vaccines as booster shots.

It concludes that excess vaccines may save potentially 11 times the number of lives in a low-income country that has not administered any 1st doses as yet compared to being used as a booster in a high-income country. Furthermore, ensuring sufficient vaccination world-wide may reduce the risk of further variants emerging.

Introduction

One question that seems to be coming to the forefront is that of booster vaccines. In this bulletin we consider these and what the implications may be.

It has long been thought that vaccine booster shots may be required to supplement immunity produced by current vaccines. A booster vaccine would be an additional vaccine dose provided some time after fully completing the doses required of a regular vaccination regimen (be that 2-dose such as Pfizer or AstraZeneca or 1-dose such as Johnson & Johnson vaccines).

The reasons for a booster dose could be:

- Waning immunity over time since the initial vaccination that could be improved by an additional vaccine dose.
- Emergence of variants that may lead to vaccine escape and thus vaccine efficacy could be impacted.

Types of booster

There are at least three types of booster vaccine that could be considered:

1. The simplest form of boosting is using the same vaccine again as a booster. This AstraZeneca media release reports on a study of exactly this and claims "a third dose of Vaxzevria given at least 6 months after a second dose, boosted antibody levels sixfold and maintained T cell response. A third dose also resulted in higher neutralising activity against the Alpha (B.1.1.7, 'Kent'), Beta (B.1.351, 'South African') and Delta (B.1.617.2, 'Indian') variants."
2. Using vaccine combinations. The COV-BOOST study is in progress in the UK trialling various combinations of vaccines used as a 3rd booster dose after completing the full regimen of an initial vaccine.

3. Booster shots could also be developed as variations of the original vaccine that are updated to better target new variants. This AstraZeneca trial is studying a new AstraZeneca vaccine targeted at the Beta variant and Pfizer is also investigating a vaccine targeted at Delta.

It is not clear whether or to what degree waning antibody levels over time actually translate into reduced vaccine efficacy. Also, it is not clear to what degree an increase in antibody levels due to a booster shot will increase vaccine efficacy. This article provides a good overview on some of the points to consider.

Recently, Pfizer has indicated that it believes a booster may be required. The CDC responded to this stating a booster is not needed at this time, whereas the WHO indicated it is not clear whether a booster would be needed.

To boost or not?

Countries with surplus existing vaccines may be motivated to distribute these as boosters to their own populations to reduce the risk of severe COVID-19 outcomes. But this may be sub-optimal when considered from a global perspective.

We illustrate this using a simple model, with assumptions that err a little on the side of favouring boosting.

Let us consider a vaccine that is 80% effective in single-dose and 95% effective in a two-dose regimen in preventing death. And let us assume that an additional (third) booster dose of the vaccine changes that to 97.5% effective.

We will also assume that our virus follows the infection fatality rate as predicted by Levin et al. (2020). We will assume prior infection with the virus is 99% effective at preventing death from reinfection.

We will model the decision-making process of a hypothetical high-income country with age distribution as per high income countries' age distribution for 2021 in World Population Prospects. We assume a total population of 50m.

This country has achieved 80% vaccine take-up rates across all ages. The remaining 20% cannot or will not ever get vaccinated. The country has seen 20% of its population infected by the virus to date (independent of vaccine status). However, over time the vaccine efficacy has dropped to 90%.

The decision-makers in this country need to decide how to use an extra 1m vaccines available and have 3 options:

1. Make it available to those aged 70 or older in their own country as a booster.
2. Make it available to a low-income country as a second dose for those aged 60 and older. This country has only administered first doses covering 5% of their population in descending age order with maximum vaccination rate up to 70% in each age group.
3. Provide it as a 1st dose to a low-income country that has not vaccinated any people and will be able to administer the vaccine as a first dose in descending age order, achieving a maximum of 70% take-up in any age group.

The low-income countries follow the age distribution as per the World Population Prospects 2021 and have populations of 50m each. The low-income countries have had 50% of their populations infected to date.

Following these vaccinations, a further wave sweeps all countries causing everyone to be infected (or reinfected) and deaths occur according to the assumptions above.

The Results

The results of different usage of these 1m spare doses are as follows:

1. Boosting as a 3rd dose in the high-income country saves 6 200 lives in that country.
2. Making the doses available as a 2nd dose in a low-income country with some vaccination saves 2 500 lives.
3. Making the doses available as a 1st dose in a country with no vaccinations saves 20 500 lives.

The high efficacy of a 1st dose results in a 2nd dose having lower impact in a low-income country than boosting a far older population in a high-income country (assuming the vaccine efficacy has indeed reduced).

But clearly 1m vaccines doses save more lives in the country that has had no vaccinations to date. It saves more than 3 times as many lives.

How are these results wrong?

Firstly, the assumed infection fatality rate could be wrong. Due to tighter healthcare capacity constraints, and higher prevalence of co-morbidities , it is likely that the infection fatality rate is higher in the developing world (standardised by age). Thus, the deaths saved in low-income countries are likely under-estimated, and due to advances in treatment of COVID-19, the deaths saved in a high-income country may be over-estimated.

The model also assumes that everyone will be infected. This seems unlikely as, at some point, herd immunity will occur. However, we have to note this is far more likely to occur in a country where 80% of the population is vaccinated. Thus, we are probably over-estimating infections in the high-income country compared to the country with minimal vaccinations and only 50% infected to date. The ability to apply non-pharmaceutical interventions in the high-income country would likely also be higher.

It is not clear if vaccine efficacy will indeed reduce over time, even if antibody levels reduce over time. If they do not reduce, we are over-estimating the number of lives saved in the high-income country.

It may also be that past infection may not be as good at preventing deaths from reinfection as was assumed here. This would further increase the lives saved in the low-income countries if vaccines were more effective than past infection. There are some sources that indicate that vaccines provide better immune responses to the virus than prior infection.

This model considers only death as an outcome. A model that considers serious illness and hospitalisation may reach different conclusions.

The analysis focusses on age-based prioritisation and thus ignores the benefits of vaccinating and protecting health care workers in a low-income country that may at least stabilise the health system and save more lives indirectly. Again, something likely to be of higher marginal benefit in a low-income country with limited vaccinations.

There may be a smaller subset of people who are immunocompromised. In this article the CDC is quoted as saying that 2.7% of the US population is immunocompromised. It goes on to note that Israel has started providing boosters to people who are immunocompromised. Given the smaller size of this group of people, we are not considering them here and, should the need be there, it may be relatively easy to provide boosters to this smaller group of people.

Alternative assumptions

Given the above comments we could update the assumptions in the model as follows:

- The infection fatality rate is doubled in the low-income countries.
- Prior infection is only 95% effective at avoiding fatal reinfection instead of 99%.
- Infections in the high-income country can be limited to 90% of the population.
- Booster efficacy is 95% instead of 97.5%.

The results of different usage of these 1m spare doses are then as follows:

1. Boosting as a 3rd dose in the high-income country saves 3 700 lives in that country.
2. Making the doses available as a 2nd dose in a low-income country with some vaccination saves 4 900 lives.
3. Making the doses available as a 1st dose in a country with no vaccinations saves 40 800 lives.

The reduction in lives saved in the high-income country reflects the reduced efficacy of the booster jab and the country being able to limit infections to 90% of the population. The increase in lives saved in the low-income countries is mainly due to the higher infection fatality rates in those countries. The result is a saving of 11 times as many lives in the low-income country where the extra vaccines are used as a first dose.

New Variants

This model has not allowed for new variants. A new variant may result in reinfections in both high-income countries and low-income countries and may also increase the infection fatality rates in both places. Health system capacity and benefits of vaccines delivered to date are likely to dampen these adverse effects in the high-income country.

Decision time

This simple model shows that administering vaccines in a low-income country as a first dose is clearly beneficial in terms of lives saved in aggregate. In the two scenarios considered, it saved between 3 and 11 times as many lives.

However, this assumes a rational, decision-maker, motivated by the greater good for all countries. A decision-maker focussed only on outcomes in their own country would also need to take pause and consider where variants come from for a virus that actually mutates rather slowly. Clearly the more people that become infected, the greater the opportunity for the virus to mutate. In a scenario where low-income countries are left with limited vaccines, such variants are likely to emerge (as happened with Beta, Gamma and Delta). Borders have proven porous to the original SARS-CoV-2 virus and its variants, and it seems likely that most of the world is likely to remain exposed to the emergence of variants for this reason.

The emergence of a variant, that escapes vaccines and/or previous immunity will worsen this disastrous pandemic in a low-income country but could also undo the benefits of high vaccination rates in the high-income country. It may partially or fully escape immunity from previous vaccinations. This could lead to higher deaths in high-income countries which typically have a higher proportion of older people. In an extreme scenario, a variant might start a new faster spreading SARS-CoV-3 pandemic.

Even if the 1m vaccines were not available, enabling the low- and middle-income countries to produce these vaccines may be a good decision too, especially when the pharmaceutical companies are not producing vaccines at a high enough rate for the world.

The benefit of boosters in a fully vaccinated society seems to be outweighed by lives saved globally and reducing the risk of a vaccine-evading variant. We should consider prioritising vaccinating low-income countries with first doses, over booster shots for high-income countries to fight the pandemic.

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