Optimal dosing of vaccines

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Revised autumn 2026

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1 About

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

This is the first draft of a shallow investigation report commissioned by Open Philanthropy. If you have access to it, I'll be very grateful for comments and suggestions, which you can make directly in this doc.

This is a public document (although I have not posted it anywhere) and you're welcome to cite it.

The purpose of this doc is to serve as a general introduction of the topic of optimal dosing/schedules of vaccines. It is not a research proposal or a policy document, but rather a tool for those who are exploring this as a cause area.

It is structured as follows: first, I start with a short overview: what it sets out to do and why, what I've learned, and what my tentative recommendations are. I tried to keep the executive summary very non-technical.

I then flesh out the factual claims and analysis throughout this document in a dozen separate chapters. I wrote each of them as a separate note, so you can read them as needed and in no particular order. In fact, the chapters were written in parallel and only merged afterwatds. I aimed to keep each chapter to 3,000 words.

I am very grateful to Open Philanthropy for commissioning this investigation. It's been a fantastic experience to set aside enough time to finally read and write about this topic, as well as to interview experts. On a more meta level, I discovered over and over that optimisation (especially of dose) is really understudied relative to other topics in vaccines.

Special thanks to my research assistants Danny Toomey and Josh Muthu, who helped on case studies and some of the early chapters. I am not naming any of my interviewees in this first draft, as I have not sought their approval or comments on this text, but most of the good ideas in this report come from them.

Lastly, an important statement of ignorance: in case you're not familiar with my work, my academic background is in statistics and infectious disease modelling. I thought it important for this report to look at the optimisation issue holistically, all the way from biology to decision making. However, I am not an immunologist or a clinical researcher or a public health expert and I do not want to claim expertise on these topics. I am very thankful for all corrections.

Witold Więcek

June 2024

1.1 Using and citing this report

Most of this report was written in 2023–2024. It is not fully up to date and is being revised.

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Cite as Więcek, W. (2026). Optimal dosing of vaccines. https://witold.xyz/vaccines/

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2 Executive summary

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

2.1 Introducing the problem

These are the problems we want to solve:

1. For many vaccines against infectious diseases that are in routine use, the existing supply is often not enough to vaccinate everyone (e.g. inactivated polio vaccine).[1]
2. In outbreaks of diseases such as cholera, yellow fever, mpox, we have the stockpiles, but they are not sufficient and/or they do not reach people quickly enough.
3. These shortages are starker for new vaccines: when the global production and distribution start from scratch, no matter how quickly we can manufacture the vaccine, there will never be enough early on (e.g. ongoing rollout of malaria vaccine).
4. Shortages are even worse in pandemics, when a speedy rollout of vaccine could play an essential role in slowing down or stopping the exponential growth of epidemics (e.g. COVID).

Timely production, delivery, and administration of all vaccines is constrained by manufacturing capacity and available budgets. Both of these are often fixed in the short term. Even in wealthy countries certain vaccines face prioritisation decisions due to high costs.

There are some solutions that can work well without expanding supply. For many vaccines we know about ways to optimise coverage and quality of protection by targeting them appropriately, timing their delivery, choosing appropriate doses or gaps between doses. In this document, I set out to investigate these last two aspects of vaccine optimisation.[2]

In this report I explain how optimisation works in biological, practical and policy sense, with a few specific case studies. I attempt to chart in generic terms the difficulties and benefits of optimising vaccines and then tentatively discuss the future prospects for it. I will link to particular sections of the document as I summarise their contents. (As a reminder, you can read them in any order as they were written as hyperlinked, stand-alone notes.)

[1] I am only concerned with vaccines against infectious diseases; henceforth it's just "vaccines". Also, I tend to use a lot of footnotes, I invite the readers to treat them as wholly optional.

[2] There are a few more technical terms used when discussing the problem of optimising doses or their timing, e.g. vaccine developers like to talk about optimal regimen (how many doses), optimal schedule (when to give them) or fractionation, whereas in public health and epidemiology we talk about dose sparing or dose stretching. (Also, I think people usually use "regimen" to also mean schedule and dosage.) I will use these terms often, but in general in this report I often opt for bland "optimisation" as a shorthand finding optimal dosing and regimens.

2.2 How dose and schedule optimisation works

Section: Introducing four case studies (section 3)

Case study appendices:

- Case study: mpox vaccine (section 12)
- Case study: yellow fever (section 14)
- Case study: polio (section 13)
- Case study: COVID (section 11)

I start with four specific examples, addressing the problems I opened this summary with. In a pandemic context, for COVID vaccines, fractionation was discussed but not implemented. However, many countries decided to change gaps between doses. For yellow fever and mpox vaccines we saw rapid and successful switch to lower doses during outbreaks/ epidemics where the stockpiles were not sufficient. For inactivated polio vaccines (IPV), there was a persistent shortage of the vaccine and many countries rolled out partial doses.

An important common feature of these optimisation problems is that they may sometimes make trade-offs for immediate individual benefits, i.e. more protection, for public health benefits (smaller overall health burden). Prioritising access to first doses of vaccines to extend coverage to more people is an obvious example.[3]

Section: Biology of optimal dosing (section 4)

However, it is not all about trade-offs: sometimes dropping dose or extending gaps can *improve* immune response, something we know empirically. One mechanism that could explain success of lower doses and extended gaps is affinity maturation: less antigen may lead to selection of higher-affinity B cells and hence better long-term immune response. I explain this at length in the note. However, the mechanisms underlying dose optimization are disease- and platform-specific and often not fully understood. I offer a broad categorisation of vaccines into three groups based on character of protection and immune memory.

Section: Vaccine development perspective (section 5)

I also investigate the perspective of development of new vaccines. How do researchers make decisions about doses and their timing in the first place? Initially, the developers look for the optimal trade-off between immunogenicity and reactogenicity, testing a few human subjects at a time. Unlike in drug development the world of vaccines seems to be much more heuristics-driven and I try to contrast the two. De-escalation studies seem to be rare. It's also interesting to note that there is much less regulatory guidance on any of this than in drugs.

When moving to large scale trials, generally there seem to be strong commercial incentives to go with the highest tolerated dose. Lastly, I found some literature on using

[3] In other cases there are no individual-level trade-offs, e.g. when switching to intradermal (ID) delivery of a small dose of a vaccine which would normally be injected into the muscle may in fact improve protection. ID may however also increase side effects and the difficulty lies in additional complexity and cost or insufficient data.

mathematical and statistical models to improve development process, including dosing choices; this is promising, but right now their role in development is limited.

Section: Practical aspects of changing dose (section 6)

For fractionation, there are practical considerations around syringes, vial usage, administration techniques and training to deliver doses. Most crucially, precision dosing requires a particular type of syringe and/or needle. How many doses can be extracted depends on the size of vials. Intradermal (ID) delivery is often used for lower doses, because it can elicit strong immune responses with smaller amounts of antigen, but it's more difficult to carry out. Several technologies have been developed to address this, including adapters for regular syringes, new-generation jet injectors, but cost-effectiveness and feasibility of these needs to be investigated further.

Section: Health benefits from optimisation (section 7)

Solutions that can speed up access to vaccines have an obvious potential to save significant numbers of lives or infections and, by proxy, help avoid or shorten lockdowns and associated economic burden in pandemics. These conclusions are backed by an array of epidemiological models. I look at a range of modelling papers to get a general sense of the magnitude of benefits that different types of optimisation can yield.

There is often a very simple rule of thumb: for vaccines where protection from disease is all-or-nothing (you either get protection or you don't), it makes sense to use lower doses if fold reduction in dose exceeds fold reduction in protection in disease. In practice this has to be weighed against factors such as individual willingness to get vaccinated with a less potent vaccine on the one hand and epidemiological effects (vaccine may break transmission) on the other.

Section: How optimisation decisions are made (section 8)

However, in the real world this type of benefit modelling is often moot: rather than focusing on trade-offs, the regulators and public health decision makers demand no loss of individual efficacy and safety. This disconnect is more pronounced for fractionation and less for extending gaps. I try to discuss the factors driving decision makers by showing three examples. I make some tentative points on what more I think would be needed to change their mind.

2.3 Do we not do enough already?

An obvious suspicion to what I am describing here is that I use cherry-picked historical examples. Perhaps we have already picked all of the low-hanging fruit of optimisation? After all, we currently vaccinate against about 25 infectious diseases (with several more expected to arrive in the next decade) yet the examples I used so far span only several diseases. Does that mean we already use other vaccines optimally? Are there no more hypothetical candidates?

Such statement is hard to prove or disprove, but the notes support the following three statements:

1. **We do not test what is optimal. We then approve only what was tested.** What makes it to Phase 1-2 of clinical testing is based on heuristics. Testing

various permutations in large trials is expensive, therefore in Phase 3 developers focus on a single option, with focus on individual-level protection.

2. **It is uncommon to revisit dosing and schedules of existing vaccines**. Vaccine makers don't have strong incentives to go back to already approved vaccines and try to improve them: why research a less potent version of an already-approved vaccine? Especially considering that many/most vaccines are not large profit makers.
3. **Where evidence exists, there is a status quo bias.** Even when we know that there is an alternative that is potentially better, it is not likely that it will be adopted when appropriate. I hope the examples I compiled illustrate that.

I do not want to understate what a colossally difficult task all of the above is: I assume it is obvious to readers that vaccine research is an incredibly expensive enterprise with low probability of success. Moreover, a lot of required primary research that would enable dosing regimen/schedule optimisation is yet to happen: it is easier to hypothesise optimal dosing for COVID, where antibody counts proxy for protection from disease, than TB, where mechanism of protection is poorly understood. Lastly, global health governance and regulatory affairs are also incredibly complex and there are many good reasons not to tinker with existing vaccination practices.

2.4 What can be done?

It is obviously important to consider systemic changes and economic incentives. A lot of the problems could be avoided if running large trials was faster and cheaper or by using market design. However, the focus of this document is on what marginal changes can be made (e.g. generating better evidence for specific targets, better models, better decision making), since that is most appropriate from perspective of a single philanthropic funder.

What makes for a good target?

I briefly synthesise information from all earlier sections in Factors that make a vaccine worth optimising (section 9.2), which is copied here in a heavily abbreviated form.

Individual benefits	Population benefits	Feasible implementation
• Positive results already exist *or* limited testing was done before • Existing correlates of protection • Fast to generate more immunological data • Favourable immune memory profile	• Supply is limited in the short term • Need to quickly expand coverage • Promising modelling results	• Path to adoption (political/regulatory) • Programmatic and logistical feasibility • Possible to (quickly) measure effects of rollout

These are explained in the full table.

None of these are necessary conditions: they simply allow us to create rough rank ordering of vaccines to consider for optimisation, where several of these factors occur all at once. For example, a funder could focus on seeking out vaccines that have (1) limited supply, (2) no negative data on immunogenicity of lower doses.

Section: Short assessments for most common diseases (section 9.3)

Having summarised these general principles, I then provide two types of summaries. First, I run through a list of fifteen diseases/vaccines and make some tentative observations on the current value of optimisation and state of the research. Overall, I find that there are several important vaccines where optimisation has not been widely implemented, seems promising, and potentially has large benefits. In particular I'd suggest looking at cholera, pneumococcus, malaria, TB, and rotavirus.

Section: Conclusions and next steps (section 10.1)

To finish, I make some more general recommendations. I list four immediate follow-up projects, which are mainly secondary research and dissemination of ideas: not particularly exciting on the surface, but driven by the observation that optimisation is an underexplored area. My proposals include proof-of-concepts for better trials, connecting particular groups of experts, specific reviews of evidence aimed at making decision makers familiar and comfortable with these ideas, and sponsoring dose de-escalation research.

I also identify several larger areas for primary research, commercialisation, and "policy push": types of projects which would be aimed at gradual changes in the field, but which still feel feasible. Lastly, I note some of my own knowledge gaps and reasons why you should be sceptical of any of the proposed next steps.

3 Introducing four case studies

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

I include four recent case studies where optimal dosing has been implemented or seriously considered (focusing on fractionation). Reading the individual sections containing case studies first will be more informative and give you more background. However, it is not an essential place to start, so for now I just summarise them in very basic terms, so that readers who want to skip them can move to sections on biology, implementation, benefits etc.

It's best to categorise these case studies by use case. I focus on four diseases here to give enough context for what follows, but I will discuss about fifteen different diseases throughout this document.

3.1 For new pandemic vaccines

In a pandemic of a novel pathogen, a shortage of vaccines is virtually inevitable. In these cases fractional doses may yield better public health outcomes by increasing the number of people who can be vaccinated in the short term, even if the fractional doses are less efficacious. An obvious guiding example of this is fractional dosing of COVID vaccines (section 11):

COVID was an easy target for vaccination and fractionation: vaccines were highly effective and neutralising antibodies correlated with protection from disease. Extrapolating from avaialble data[4] suggested that the first highly effective vaccines, especially mRNA ones, would offer good protection from severe disease even at smaller doses. When this information was combined with epidemiological modeling (showing up to 50% reductions in mortality in some scenarios), fractionation appeared to be a highly effective public health solution: large increases in speed of vaccinations were worth trading off against small decreases in efficacy.

However, despite some positive evidence and interest from various groups, there was no coordinated push for fractional dosing for the initial two doses in 2021. Eventually, Moderna lowered doses for boosters of mRNA-1273 and considered lower dosing for the new mRNA-1283 vaccine. I return to these examples later in the report when discussing biology and implementation.

At the same time extending gaps between doses (from 3-4 weeks to about 3 months) was also considered and implemented in some countries. Immunological data showed that (1) first dose already led to some protection, (2) longer gaps between doses often led to more robust immune responses, although at the time these decisions were made, there was a lot of uncertainty. In retrospect, these trade-offs were worth it.

[4] Data were immunological data fromPhase 2 trials, but famously also from AstraZeneca Phase 3 trial, which accidentally administered lower doses to some patients.

3.2 In acute shortages in outbreaks and epidemics

There are two guiding examples for this category. First, fractional dosing of yellow fever vaccine (section 14). It's cheap and easy to make YF vaccine, but stockpile is not sufficient (or accessible enough) to quickly act against outbreaks, which have been occurring. Moreover, the supply was outstripped by demand due to use in routine vaccination in more and more countries. YF is a prime candidate for fractional dosing due to how well the vaccine works. 1/5 dose appears to be entirely sufficient. Fractional dosing was successfully used in outbreaks since 2016, but there is still a debate about what long-term effects of fully switching to fractional dosing would be.

Another example is fractional dosing of mpox vaccine (section 12). During 2022-23 emergency even wealthy countries only had enough stockpiles to vaccinate a third or quarter of those at risk. Fractionation of mpox vaccine was approved by the FDA (and then in Europe), rather than recommended by the WHO. The decision was made on the basis of a single Phase 2 study of intradermal vaccination. Use of two fractional doses does appear to have been the right choice and this case is also very interesting due to how quickly the decision was reached.

3.3 When there are intermittent/prolonged global shortages and cost considerations

Not all shortages are due to outbreaks, as we can see in the case study of fractional dosing of polio vaccine (section 13). Polio has almost been eradicated, yet the ongoing effort requires hundreds of millions of vaccinations per year. Including inactivated polio vaccine (IPV) in routine immunisation, done to avoid vaccine-derived polio, has increased costs and led to shortages in supply. Two 20% IPV doses have been shown to be sufficient. Fractionation was recommended and adopted by many countries at scale while waiting for extra capacity and new vaccines. It also offered some cost savings (e.g. 40% reductions in overall cost of IPV vaccination).

3.4 Optimising to improve vaccination

The examples above are about dose sparing: increasing public health benefits and cost-effectiveness. However, we also want to optimise vaccines to improve individual-level protection. Here we don't really have great recent examples: usually vaccines improve when a better alternative is developed, rather than by improving how an existing one is used. As we will see, this is not because there isn't a lot of potential for improvement. One example for this is work being done on malaria vaccines, but that is still ongoing. Therefore I discuss it in the section on biology.

4 Biology of optimal dosing

Why can a lower dose prove just as effective?

These notes were originally drafted in 2023 and revised in autumn 2026. I am a biostatistician, not an immunologist, so treat this as only a very basic introduction to a very complex topic.

4.1 Basic rationale

There are five groups of factors that determine the vaccine's effect. The first and most obvious to focus on is the antigen. Then there are (2) the mode of delivery, i.e. how the antigen is "packaged", but also where it is delivered[5], (3) vaccination regimen/schedule, (4) adjuvants, (5) host factors (e.g. age). I will focus on lowering the amount of antigen and then touch on points 2-5 as we go.[6]

That the lower doses are sometimes found to be non-inferior should not be surprising. In vaccine development perspective (section 5) chapter I discuss the reasons why vaccine makers are incentivised to test high doses. If that feels counter-intuitive to you, you may want to read that first. Here I will try to cover the basics of biological mechanisms. Let's start by getting a bit more precise about the terms. Let's talk about response curves and types of response.

> **What is an immune response to vaccine?**
>
> *Vaccines mostly induce **adaptive immune responses**. Within adaptive immunity, we distinguish two mechanisms: **humoral** and **cellular**. Humoral is antibody-mediated, involves B cells, plasma cells, and antibodies they produce. T cells do not produce antibodies, but can attack infected cells or help other immune cells; this is cellular immunity.*[7]
>
> *Antibodies allow for neutralising pathogens before they enter cells (that could lead to **sterilising immunity**). They are the key mechanism in vaccination and also easier to measure, hence vaccine developers often focus on them. Typically vaccines rely primarily on antibody-induced protection. Many vaccines also induce a T-cell response; however, it is harder to measure and we understand it less well.*
>
> *We should also differentiate between sites of immunity. Typically we will be talking about measurement of antibodies in blood, but for a respiratory

[5] This category also includes additional factors such as stabilisation of the structure of the antigen (to make it persist longer) and the number of epitopes (valency), which is beyond my simple understanding of immune responses, so I won't cover it.

[6] I talk a bit about the route of administration in another chapter. It is well-established that using intradermal (ID) delivery may produce comparable immune responses at lower doses than the deeper IM/SC injections. In this section I am talking about an apple-to-apple comparison, i.e. what happens when vaccines are administered using the same route. You can find more examples of increased immunogenicity from switching to ID delivery in case studies, e.g. fractional dosing of polio or mpox vaccines.

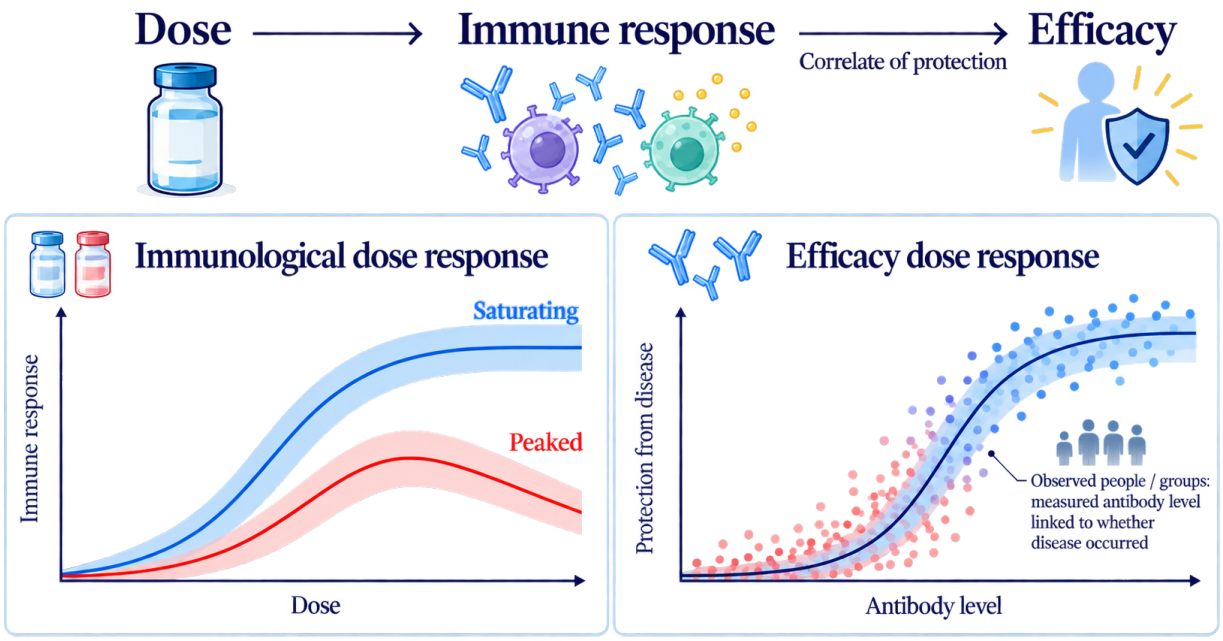
[7] First, however, the immune system needs an **antigen**; the way it is "presented" is specfic to a vaccine platform. E.g. in mRNA cells are instructed to produce antigen. Lipid nanoparticles that mRNA uses play role in both delivery and stimulation of immune system. The relationship between administered dose, antigen exposure and immune response is therefore more complicated.

infection like Covid or flu **mucosal immunity** in airways may prevent infection altogether. For oral cholera and polio vaccines intestinal mucosa is the target.

*I also talk about **correlates of protection** in this chapter. That is a marker that* statistically * predicts protection against infection/disease. Correlates can be identified with different stringency, as the name implies. Typically we first test a promising vaccine for efficacy and establish CoP's based on the trial results.

4.2 Immune response vs efficacy; shapes of response

I use the term "response" freely, but in vaccine development we establish two responses: first immunological and then protection from disease. We need to measure both of them to know how a given dose will translate to efficacy. A very simplified scheme looks like this
(I asked AI to generate this):



As I suggest on my mock inforgraphic, dose-response curves can take different shapes. Typically we could consider three types:

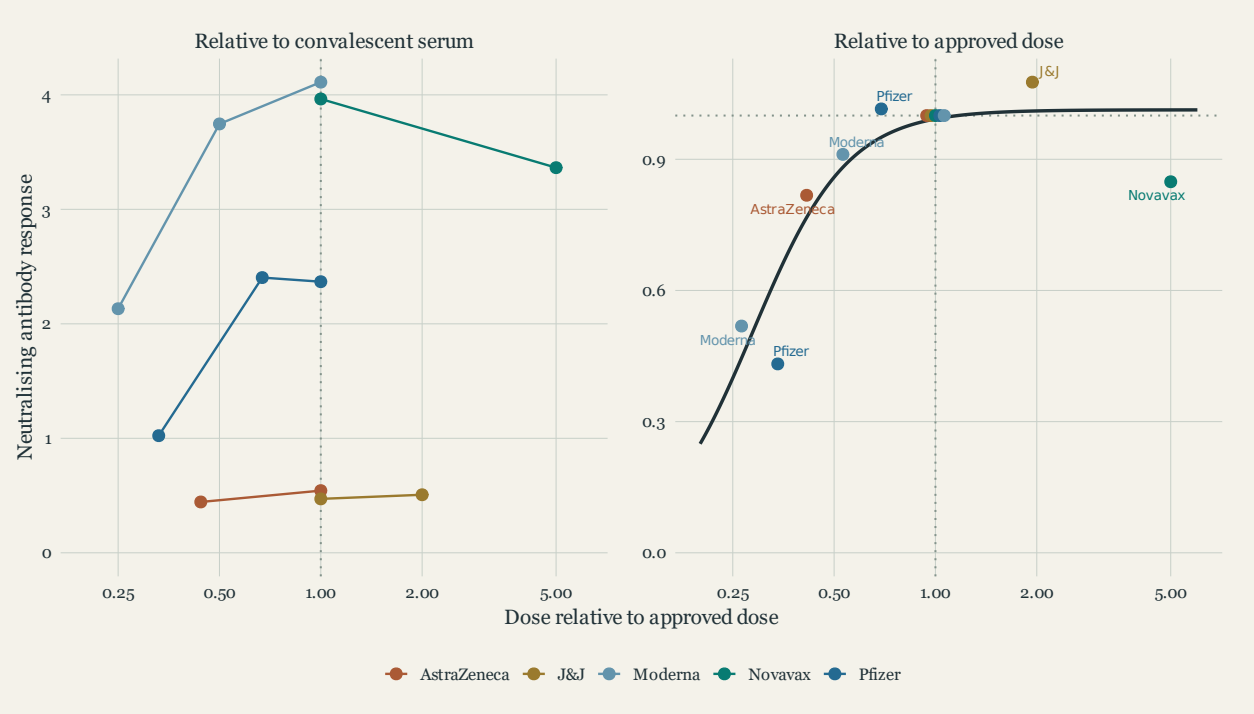
- concave,
- S-shaped,
- peaked.

Since we are talking about potential benefits from decreasing doses, the most important distinction to us is between peaked and the other two. Must the dose-response curve be *non-decreasing* in dose? What if past a certain point increasing the dose led

to a *weaker* immune response?[8]

4.3 Covid example: from dose to immune reponse to efficacy

Let's see this relationship on an example that will be familiar to us all. Below is a heavily simplified illustration of doses vs antibody responses in early Covid-19 vaccines, where the y axis has been standardised by comparing it to antibody level in people with natural Covid-19 infections.[9] It's hard to compare against vaccines, so in the right panel I normalise the graph so that the dose used in Phase 3 trials has efficacy of 1. I draw a hypothtetical S-shape there, just for illustration.



Early in the pandemic researchers understood that neutralising antibodies were a good correlate of protection against Covid. This meant we could use statistical models of the two relationships in my earlier graph: between dose, antibody responses, and efficacy measured in clinical trials. I won't recap these models here, but here is part of a figure from Yang et al 2022 which I think tells the most relevant part of the story:

[8]Thinking about dose response as a single 2D curve, like in my examples, is useful for intuitions, but also simplifies things too much. The most important is that we should imagine evolution of the curves **over time**. For example, imagine two levels of antibodies initially giving 100% efficacy, but only the higher dose giving lifetime protection against disease. Remember as well that we are dealing with statistical relationships. Moreover, the pathogens themselves evolve over time, so we have to consider many curves specific to many different variants. Lastly, there is going to be considerable variability across people, and sometimes also considerable variability in the amount of antigen in a set quantity of vaccine.

[9]Three publications that are relevant to this mini-example are Khoury et al 2021, Yang et al 2022 and Rhodes et al 2022.

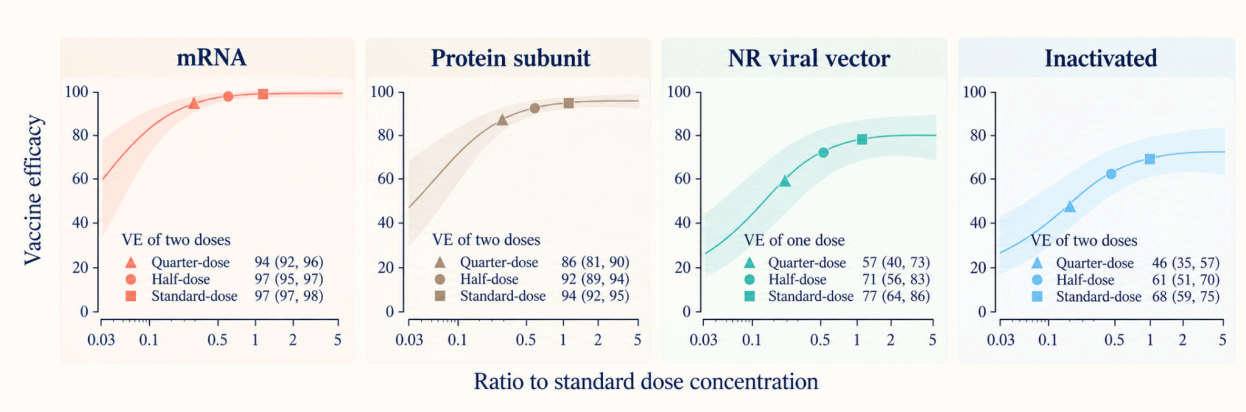


Figure. *An illustration of an uncertain, model-derived relationship between dose and efficacy for COVID-19 vaccines.*

We see here an example of the general principle that for a given vaccine many doses tested in trials can lie either on "top" of the S or close to it. Remember, however, that these are merely model predictions and that this figure focuses on the magnitude of short-term efficacy, not durability of protection.[10]

4.3.1 Are peaked immune response curves possible?

Earlier I mentioned peaked curves: ones where giving more dose leads to lower immune response. Such a claim may sound counterintuitive but we can find some evidence for it.

- In **adenoviral-vector vaccines** review by Benest et al (2020) 191 immune-response sets were analysed. Its usually hard to tell saturating and peaked responses apart, but where it is possible, "evidence towards a peaked adenoviral dose-response curve occurred five times more frequently than for a saturating curve".[11]
- In **Covid-19** Rhodes et al (2022) did similar modeling of 30 immune response datasets and found a mix of peaked and saturating curves.
- In **TB vaccines** early human trials and animal data, Billeskov et al. (2018), Rhodes et al (2016) and Luabeya et al. (2015) have shown worsening of immune response with higher dose. The first of the three actually showed worsening of *protection* with higher dose, albeit in mice. This was for candidate vaccines which were discontinued, not for the ones currently in development.

I think this provides us with enough empirical evidence to at least question whether a higher dose is more effective at preventing disease. But what is the underlying reason for why this may occur? Before we talk about that, let's say a few things about multi-dose vaccines.

[10] Note as well that such a model is for antibody measurements in blood. These are the most useful predictors of protection in this context, but they do not capture mucosal or cellular immunity. So a dose may have high efficacy against symptomatic disease, but low protection against infection or transmission.

[11] Note that the publications I list largely come from the same group of researchers. You may want to discount the evidence slightly for that reason, but I personally think this demonstrates how underexplored the topic of dose-response shapes is.

4.4 Gaps between doses

Many vaccines require multiple prime and booster doses.[12] Continuing with our Covid-19 example, the Astrazeneca vaccine (two-dose) trials measured higher efficacy for patients who were given a lower dose and longer gap between two doses. (The consensus was that it was the gap rather than dose that drove higher efficacy.) This preference for longer gaps could also be seen in antibody response data. In general, many studies of different COVID vaccines have found that longer gaps (without change in dose) between 2 doses (not just of AZ vaccine) led to more robust responses; ditto for third dose.[13]

Unlike fractionation of a single dose, this mechanism of increased gaps leading to better response was not surprising to experts. Nor is it a mechanism limited to COVID; we will show a few more examples soon. In general terms, when a priming dose of a vaccine is administered, it triggers an initial immune response. Following this, immune responses continue developing over weeks/months. B cells undergo affinity maturation (more on that below) and memory B cells and plasma cells are generated. Following this stimulation of immune system it also enters a refractory period—this is to prevent excessive immune activation and potential harm to the host.

To maximize the benefit of a booster dose, it should be administered after the immune system has generated a pool of memory B and T cells, a period which is highly specific to each vaccine. Consequently, administering a booster dose too early may not elicit a robust secondary response. This also suggests that dosing of boosters will generally differ from dosing of the first dose. We will return to this in a moment.

4.5 Possible mechanism: B-cell selection

> What follows is definitely beyond my understanding of the immune system and is simply based on rather shallow exploration of existing literature. However, I believe it is fair to say that for many of these mechanisms there is no consensus among immunologists which would be grounded in hard empirical facts. Immunology is not only very difficult, but also many relevant mechanisms elude direct observation, so we have to rely on theory and computer modeling. Treat all of what follows as hypotheticals of varying quality.

Staying with the earlier Covid examples, a modeling study by Garg et al. (2021) suggests a possible explanation for the mechanism observed in the AZ study, which extends beyond delayed booster and also applies to lower doses. It can be most simply summarised as a quantity-quality trade-off that occurs in germinal centers, i.e. the locations where antigens are presented to B cells, which then leads to production of

[12] In the context of the Covid example here, "prime and boost" is used in reference to first and second dose, but it can also refer to priming with two doses and a later 3rd booster dose. Many multi-dose vaccines are given in childhood. In that context "prime" doses would typically be the ones given within the first 6 months of life. A single vaccine can have multiple priming doses (and no booster doses).

[13] Of course the trade-off is extending the period where the individuals are protected by only one dose. There are several factors to consider: individual protection, public health perspective from extending protection to more people ("First Doses First"), and risk of mutations. See the section on modeling health benefits of optimal dosing.

memory B cells and long-lived plasma cells (residing in bone marrow).

In that (generic, i.e. non-Covid-specific) process of affinity maturation, as B cells proliferate, they undergo somatic hypermutation and then clonal selection. This second step is crucial. When there is a lot of antigen, B cells with both moderate and high affinity will bind to it. Hypothetically, when the prime dose is lower, then fewer B cells are selected, but they are on average higher affinity, leading to a stronger immune response (higher quality antibodies) from those cells when antigen is encountered again.[14]

The length of this process is measured in (a few) weeks. Going back to the previous subsection, the value of delayed boost can also be explained through what happens in germinal centers. Since the process of selecting cells takes time (proliferate, mutate, be selected), the length of the gap will impact the quality of immune memory.

However, it's important to note that when such trade-off is cited for a specific vaccine, it is (usually? always?) as a hypothetical mechanism that is backed by simulations and I do not know what weight to put on that hypothesis. I also have no sense of how to generalise from isolated examples to other cases, although there is no reason why it should be seen as COVID-specific. For multi-dose vaccination regimens, it is even less clear what happens to this mechanism, since we do not know whether boosting leads to formation of new germinal centers or modulation of existing ones.[15]

Before we move on, let me reiterate two points:

- First, these issues are very complex and not only beyond my own understanding, but also not well understood by the experts.
- Second, while I often focus on COVID examples (because they are salient), the mechanisms likely apply in many different diseases.

4.6 Immune memory, previous exposure

The main conclusion from the previous section, however, is that we should consider lowering dosage of priming and boosting doses as two separate problems. For priming, the initial response has to be robust enough. For boosting, however, it is generally accepted among practitioners that lower doses may be better. Various vaccine development guidelines acknowledge this; e.g. WHO, pg 35: "If an immune memory response is elicited in the primary series it may be possible to achieve a robust anamnestic response using a much lower dose of an antigenic component compared to the primary series. A lower boosting dose may also provide a better safety profile (for example, as occurs with diphtheria toxoid)".

[14] To complicate this further, we should also think about T cell response and its role in immune memory. Expansion and differentiation of B cells into memory B cells, which will then persist and determine quality of future immune response, is promoted by follicular helper T cells (TFH), a type of CD4+ cell. Generally, while stronger T cell responses are observed when activated by a high affinity antigen, the relationship between antigen dose and T cell response is less directly related to strength of response and more related to the types of cells that differentiate, including TFH (Keck et al. 2014). But I do not really understand this mechanism.

[15] ChatGPT contradicts me here, saying: "Human studies now show that booster vaccination can stimulate new germinal-centre reactions and recruit existing memory B cells into further rounds of maturation. (Alsoussi et al. 2023) What remains uncertain is how antigen dose and timing determine the magnitude, composition and eventual protective value of these responses."

The relevant mechanism here is not limited to immunity induced by vaccination. Priming can also come from natural infection. This also means that the effectiveness of vaccines may be highly dependent on history of previous infections, as was the case with COVID-19.[16]

However, for natural immunity, the factors that determine this are complex and disease-specific. One mechanism is over-stimulation in previously primed individuals. For example, in post-exposure TB vaccination that I mentioned earlier (Billeskov et al. 2018) T cells primed by prior TB exposure were highly susceptible to over-stimulation. The findings there underscore the importance of carefully optimising antigen doses, especially for therapeutic vaccination of previously exposed/primed individuals, in order to induce T cells of optimal functional quality rather than just maximum magnitude. But we can't generalise this across pathogens, it's just an example.[17]

4.7 Other ideas: anti-vector immunity, interactions with adjuvants, heterologous boost

There are three more concepts that bear at least mentioning, but which I did not have time to cover under this initial exploration:

- **Anti-vector immunity:** For the COVID-19 AstraZeneca vaccine specifically anti-vector immunity has been hypothesised as the responsible mechanism: that is, immune response to the adenoviral vector which delivers the SARS-CoV 2 antigen may confound the response to COVID antigen. Boosting with viral vector may simply lead to neutralisation of the vector and poor response.[18] Currently viral vectors are used for COVID and ebola vaccines only (in development for HIV, malaria).
- **Heterologous prime-boost** ("mix-and-match") strategies involve the activation of a broader range of immune responses.[19] Different vaccine platforms can stimulate distinct aspects of the immune system and mixing can lead to more comprehensive immune response. It also seems to be a good way to avoid anti-vector immunity. However, this is not really in scope of this investigation.
- In **adjuvanted vaccines**, these mechanisms are further complicated by interaction of the vaccine with its adjuvant. Intuitively, given a potent adjuvant, the immune response may be less responsive to changes in dose compared to the

[16] For example, Mateus et al. (2021) found that pre-existing cross reactive T cells enhanced immunogenicity of lower dose of Moderna's mRNA vaccine. There are many papers on prior infections, e.g. Reynolds et al (2021) and, as I discuss in the chapter on modeling health benefits of optimal dosing (section 7), this was translated into models of benefits.

[17] Another factor, albeit one that I have not had time to understand yet and just want to name-check topically, has to do with epitope masking. Zarnitsyna et al give both an overview and mathematical models of this mechanism in influenza and difficulty in creating a universal influenza vaccine that could work against the conserved part of the virus.

[18] AstraZeneca vaccine used two doses with the same adenovirus, but the Russian Sputnik V vaccine, also two-dose, used Ad5 and Ad26, presumably to avoid that issue.

[19] A lot of COVID vaccine research in 2021 focused on heterologous boosting, with generally positive results for mix-and-match approaches. The best example was the trial in the UK. Nowadays, I think general consensus seems to be that heterologous boosting with a good quality vaccine is a good idea.

same vaccine given without adjuvant. Dosing studies often have to vary both the antigen and the adjuvant. See, for example, dose ranging trials for M72 TB vaccine and its AS01 adjuvant.

4.8 Extra example: malaria and RTS,S

Let's look at another example that shows increasing gaps and smaller doses at the same time can lead to better responses. That is the case in RTS,S and malaria. As nicely summarised in a short editorial by McCall, Yap, and Bousema (2020), the series of the initial three RTS,S doses may work better if the third dose was smaller and delayed by several months. They provide a summary of some possible mechanisms. I am not able to parse it, but it seems that cellular immunity plays a role too in fractionation.[20] I should note, however, that it was not clear whether the improved response was due to fractionation, delay, or both (perhaps the consensus has changed since). The affinity maturation explanation may also apply here, but overall it really is a very detailed, complicated, and not well-established mechanism: see the beginning of discussion in (Das et al. 2021).[21]

4.9 Which vaccines make for good fractionation candidates?

Given the above, can we classify vaccines/diseases according to how lower doses are expected to perform? Clearly the mechanisms that favour lower doses or alternative vaccination regimens are highly variable, depending on platform, pathogen/antigen/epitope complexity, the type of immune machinery that they produce, and history of natural exposures. For COVID, it has been sufficient for vaccines to present a spike protein antigen and neutralising antibodies correlated very well to protection from disease. This meant that some generalisable inferences about impact of lowering doses could be made even early on in the pandemic, as we've seen in the initial example in this chapter.

Still, since we've been focusing on immune memory, for general interest it may be instructive to delineate three groups of diseases based on that distinction, which I borrow from an excellent summary article by Pollard and Bijker (2021).

[20] One of the cited articles, a 2020 paper on RTS,S delayed dose by Pallikkuth et al, references the mechanisms we discussed above right there in the title: A delayed fractionated dose RTS,S AS01 vaccine regimen mediates protection via improved T follicular helper and B cell responses

[21] Another interesting topic for further research is the impact of adjuvants on dosing of malaria vaccines (RTS,S, R21) and combination with viral vectors, as in this Nature paper by researchers from Jenner Institute, but this is in mice.

Mechanism	Examples	Hypothetical goal of optimisation approach
Long-lasting protection. Antibody levels stay high enough to be protective long-term, sometimes lifetime	yellow fever ("only 12 known cases of yellow fever post-vaccination have been identified, after 600 million doses have been dispensed" per WHO), measles-mumps, maybe HPV?	Finding the right dose to induce protection; can involve lowering doses, for vaccines that already tend to work well
Memory-dependent protection. Antibody levels drop over time but when exposed, the incubation period is long enough for immune memory to kick in and offer protection	hepatitis B, polio	Optimising for high quality memory, e.g. via timing of doses
Short-term antibody-dependent protection. Antibody levels drop rapidly, and the pathogen's incubation period is too short for memory responses to be fully protective.	influenza, pertussis (acellular), SARS-CoV-2, cholera	Achieving high initial levels of antibodies; public health trade-offs to maximise protection

Three rather obvious caveats:

- It's important to note that these categories are not rigid, many vaccines may exhibit characteristics of multiple groups or fall outside these classifications entirely. For example, hepatitis B vaccine requires high levels of antibodies, but is durable; malaria and BCG vaccines have more complicated mechanisms of protection.
- Whether something is "long-lasting" of course depends on context/risk.
- My hypothetical goals are also a bit of splitting hairs. In each case it depends not just on the quality of the vaccine, but also its supply and each disease needs to be considered separately.

However, the point of this simple table is that it's worth keeping in mind that biological basis for the kind of fractionation that can be done for e.g. yellow fever doesn't really translate into e.g. pandemic influenza, even though in particular situations we want to optimise doses of both of these. I work through a longlist of diseases closer to the end of this investigation, in summary of optimisation targets.

4.9.1 Role of age (host factors)

In this note, when talking about dose optimisation I generally focused on things that are good ideas on average, i.e. assuming every person gets the same dose or schedule.

However, before we conclude, let's point out the obvious heterogeneity in responses.

We already mentioned previous infection status as an important host factor in vaccine response. Another one is age. It is uncontroversial to give smaller doses of some vaccines to children compared to adults, as their immune systems are generally more responsive. So in children higher doses may lead to increased reactogenicity without any benefits. Conversely (and perhaps more interestingly), for influenza we recommend giving larger doses to the elderly population to overcome immunosenescence and improve vaccine efficacy. Similar schemes could also be considered in diseases with steep increase in risks with age, such as COVID. I return to this idea in the section on modeling health benefits of optimal dosing.

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5 Vaccine development perspective

How do we determine the optimal dose during trials?

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

In the chapter on biology (section 4) of optimal dosing I spoke about some of the mechanisms relevant to optimisation, but I didn't really talk about how the dose is decided on in practice or what drives it. What happens when a new candidate vaccine is developed, tested in animals, first tested in humans, and then goes through multi-stage clinical development? At each stage, how are the decisions made on what doses and schedules to use?

The short version of the story is that generally in clinical development it is advantageous to developers to set doses at the "maximum tolerated level" (although that is a term typically used for drugs). Developers do not want to risk going into large-scale, expensive trials with anything less than maximum possible efficacy, even if they do have some information that a smaller dose could have produced a same or very similar response. For that reason, when the dose-response curve is S-shaped, the developers may end up setting the default dose at the top part of the S, the "saturated" part of the response curve. This creates an opportunity for reducing doses in the future. Read on for slightly more in-depth commentary.

5.1 Dose setting for (cancer) drugs: some interesting parallels

I start not with infectious diseases, but with cancer, because it will help fix a few ideas and has some interesting parallels with the project of vaccine optimisation.

A lot of attention is paid to dose-finding in oncology. For older cancer drugs, the clinical development would focus on identifying maximum tolerated dose (MTD). This makes sense for something like chemotherapy (and indeed many, probably most, drugs), where it's safe to assume that higher doses will be better at treating disease, but also increasingly (very) toxic.

In practice, once reaching first-in-humans trials (more on which below), this choice would be done with a very rudimentary dose escalation approach, e.g. a "3+3" algorithm, which was valued for its simplicity: you'd give a drug to three patients at the time and (roughly) keep escalating the dose until observing toxic reaction in two patients. Nowadays developers thankfully opt for adaptive measurement, such as "continual reassessment" method, assigning patients to dose where value of information is highest. Whatever methods are used, there is vast literature and detailed guidance from the regulators on how to do it.

But the MTD approach only makes sense so long as the response and toxicity actually go up with increasing dose (and ideally, for a statistician, they go up *steeply*, because you can only test in a few humans). This is usually *not* the case for more complicated modern cancer drugs, such as immunotherapies. They target cancers more specifically, working through more complicated mechanisms and traditional methods are bound to suggest doses that are too high. Increasingly, then, the drug developers

make use of complex PK/PD modeling to decide which doses move to large-stage trials.[22]

It took a long time to make this change. One suspects that a lot of this development was motivated by very high costs of developing these drugs.[23] Choosing what dose/regimen to go into Phase III trial with is a multi-billion dollar decision.

However, some of the impulse to do this also seems to come from the FDA.[24] There is a short new (Jan 2023) draft guidance document on optimal dosing in development of cancer drugs.[25] It's a short document which is not binding, so none of it may translate into clinical research. However, the FDA does not issue a lot of such documents, so it's still worth noting language that is pretty strong:

- dosage optimisation should happen *prior* to approval; developers should justify their dosage choices, lest the FDA deem that the chosen dose exposes patients to "significant and unreasonable risk"
- "expedited program (e.g., breakthrough therapy designation) is not a sufficient justification to avoid identifying an optimal dosage(s)"
- dosages should be evaluated in parallel-dosage trial, which does not have to be powered for non-inferiority of different doses, but should allow assessment of activity and tolerability: I will return to this important point at the end of my report
- "Perceived difficulty in manufacturing multiple dose strengths is an insufficient rationale for not comparing multiple dosages in clinical trials"

Lastly, it's also worth mentioning that fractionation of these new oncology drugs (often immunotherapies) is also a very important and up-to-date topic and there is mounting evidence that you can have high efficacy even with small doses.[26]

> **Dosing vaccines vs dosing drugs** As a reminder, dose setting for vaccines is not really dependent on body weight, whereas for drugs the main consideration is often size and weight of specific organs. This is logical, since vaccines work in lymph nodes and rely on presentation of a small amount

[22] This is not too relevant, but for context: I mean kind of physiological modeling of pharmacokinetics (to understand how dosing regimen/schedule impacts concentrations of the drug in organs of the body) and pharmacodynamics (how the drug then acts on e.g. tumours). We can do this, because we know much about relevant molecules, physiology, and tumours in order to model all three of these things. We can also measure many of the relevant parameters directly. It's harder to do this for vaccines, although I will talk about parallel world of immunosimulation a bit later in this section.

[23] There is a cultural aspect here, too: trial decisions like this have to work across different disciplines, with clinical pharmacologists working together with modellers and statisticians. Medical people of course favour simple procedures they can implement in the lab. Statisticians often favour overcomplicated ones.

[24] In the report often use the FDA in my examples. Of course a lot of vaccine development also happens in Europe, but to a large extent things here are similar, unless I explicitly emphasise some differences. Beyond that, a lot of clinical research happens in China, but on that topic I can only confess my ignorance and move on.

[25] See also the accompanying paper, but it is more general interest than of relevance to vaccines.

[26] Many of these drugs have high receptor occupancy and long half-life, so it's logical that for some patients you can consider decreasing both frequency and dose. Similarly to vaccines and adjuvants, we increasingly use new cancer drugs as combination treatments, which obviously impacts their dosing.

of antigen, with the immune system doing the rest of work of producing antibodies. Hence focus on pharmacokinetics for drugs, but not for vaccines, unless they are delivered orally. We still use lower doses in children, but this is due to their immune systems being more sensitive, not weight considerations.

5.2 General practice in vaccines: first-in-humans and dose escalation

Back to vaccines. Here, both state-of-the-art and regulatory guidance seem quite different. Let's start with the latter. EMA has more developed "Clinical evaluation of new vaccines" guidelines than the FDA, it seems, but they have little to say about doses: pg 9 simply states that "a range" of doses should be tested in trials and advises to do extra work for viral vectors (for reasons I discuss in biology section).

This is not to knock the regulators, but, to a large extent, a reflection of how much more complicated dose finding in biologics, especially vaccines, is. A typical approach is to use a heuristic on starting dose of a vaccine which is platform-specific and based on experience with similar vaccines.[27]

Of course both drugs and vaccines use animal testing before first-in-humans testing. However, while for drugs we determine doses by using allometric scaling (based on well-developed calculators of interspecies differences in organ sizes, metabolism, additional safety factors etc), dosing vaccines in e.g. mice provides little information on (or is harder to translate to) the appropriate dose in humans is; adjuvants complicate this further (Davis 2008). In the vaccination literature allometric scaling is mainly mentioned in the context of simulation models, more on which in a moment; in practice it seems that researchers just choose doses in humans based on experience; sometimes the same dose is used in humans as in mice, sometimes the factor is 100.[28]

Once the starting dose for human trial is chosen, vaccine developers will escalate dose in small cohorts. The range to escalate over and the rungs of the escalation ladder, also seem to be chosen based on heuristics.[^desc] For example, in Moderna SARS-CoV-2 phase 1, which tested 25, 100, and 250 mcg, section "Justification for dose" simply states that other mRNA trials (for other diseases) tested 10-300 mcg.[29]

The choice of the schedule and dose that continues in large-scale trials then also seems to be largely expert-driven and domain-specific, with the ultimate goal being

[27] For example, for new mRNA vaccines we are likely to see dosages in tens of mcg regardless of whether it's a new influenza or SARS-CoV-2 vaccine. Different technologies have different units: for viral vectors we count number of virus particles, for live vaccines it's cell culture infectious doses. It also depends on what we can measure; e.g. see here. BTW, once again, while there is an FDA guidance on maximum safe dose in first-in-humans trials, it opens by saying that it is not applicable to vaccines.

[28] In case you're surprised by this: I did not expect the researchers to use a factor of 1 neither, but that's what I was told by one of the interviewees!

[29] Elsewhere: "Moderna's decision for dosing was based on their previous experience with a bird-flu vaccine candidate rather than quantitative dose optimization." (Desikan et al. 2024) It's standard for all clinical trials to include such a justification, since all clinical study protocols largely follow the same template. Unfortunately, usually these are not made public, so we know what doses are tested, but we cannot check justification for any trial. Pfizer phase 1 trial, which also made protocol available, followed similar logic. Although starting to test at 3 mcg, but anticipating that 10-fold higher doses would be required for potent response.

proving safety and efficacy (set in target product profiles and consultations with regulators). These goals typically focus on individual-level benefits, not public health benefits, for two reasons. First, proving efficacy against transmission (rather than disease) is harder to do. Second, it's harder to extrapolate from breaking transmission to public health benefits, especially for a new pathogen.

At this last stage of clinical development, economic/strategic considerations also enter the picture. Continuing with our example, Moderna chose 100 mcg going into Phase 3, compared to 30 mcg in Pfizer vaccine; it's likely that big part of that decision was in order to "position" mRNA-1273 as the gold standard of efficacy, ahead of vaccines that were being developed by Pfizer, AZ, and Novavax.[30] This approach of going forward with maximum tolerated dose makes sense especially if mechanism of protection is not well characterised.

Overall, it's hard to establish how close or far from optimal these choices are, because developers don't test doses comprehensively. I will return to some ideas on how to explore this at the end of this report.

As I discussed in biology of optimal dosing, the approach to dosing of boosters is different than to prime series. The conclusion to Moderna's mRNA vaccine story (so far) illustrates this nicely. With mRNA-1283, Moderna is now pivoting to using 10 mcg booster (10x lower then original dosing of mRNA-1273), with Phase 3 trial (N=11,400) showing non-inferior efficacy against disease in June 2024. Phase 1 study showed comparable immunogenicity at 10, 30 and 100 mcg.

The new COVID boosters no longer use the spike protein of the "original" virus, since including it was shown to give *weaker* protection against the variants. Moderna's new vaccine uses mRNA coding for just two parts of the protein (NTD-RBD) and is also more stable at higher temperatures.

5.3 Role of modelling

Part of the reason why I brought up models in oncology earlier in this section is that there is now some literature on using model-based approaches in vaccine development. There are more precise definitions and related terms, such as quantitative systems pharmacology or immunostimulation/immunodynamics, but overall this means creating analogous mathematical and statistical modeling tools as in drug development.

I should start by noting that (1) the literature on this seems to be limited and (2) I previously worked in this type of environment (in fact, with some colleagues that I will cite here), so as a statistician and modeller I am primed to emphasise these approaches. I already mentioned the main critique in the chapter on biology of optimal dosing: the models are hard to validate, because we can't directly measure the modelled parameters. When we see these models applied to retrospective data, we should be suspicious: after all, the researchers themselves are incentivised to big up their claims, because advising pharma on multi-billion R&D projects is itself a lucrative budget.

[30] You can also go too low: famously, CureVac, a German biotech decided to go into trials with 12 mcg of mRNA that did not modify uracil (highest dose that had acceptable reactogenicity) and failed.

However, these approaches hold a lot of promise, not least because the alternative is to use purely heuristic-based decision making. We know from drug development, that modelling dose-response can be worthwhile. Desikan et al. (2024) provide the best and most up-to-date overview of the idea of model-informed vaccine development that is suitable for non-modellers.[31] can be used for choosing dose for first-in-humans, then choice of doses (and trial design, as well as go-no-go decisions), or for extrapolation across populations.

In simple terms, what is proposed here is to supplement the subjective, experience-driven parts of development with models. From my perspective (and a bit of experience in drug development) another big potential advantage of these approaches is that they allow us to synthesise (sometimes sequentially generated) information from various sources in a single coherent source. For example: preclinical studies in different animals, phase 1, data from other similar vaccines or different vaccines using the same platform etc. etc.

But for a model to improve on human heuristics, it needs better data: data that needs to be compiled from papers (e.g. dose-response curve for similar vaccines), assuming it ever gets published. It's hard to give an opinion on how much these models can improve on the current state of the field without seeing particular applications and underlying data.

5.3.1 Peaking and saturating curves

An important facet of these modeling papers is that, especially in papers by the group at LSHTM (Benest, Rhodes, White et al), dose-response is either "peaking" (bell-shaped) rather than "saturating" (S-shaped) as dose increases.

In other words, for some vaccines when we increase doses the immune response may diminish, which was the starting point of discussion for the chapter on biology of optimal dosing. However, while I don't think this is strictly speaking a controversial statement, a typical expectation for most vaccinologists when dealing with primary vaccination series is that the curve is saturating, as far as I am aware, so I don't want to overemphasise this without going into some very specific examples.

However, the authors *do* seem to make some specific claims. As per title of one of these papers, "Response Type and Host Species May Be Sufficient to Predict Dose-Response Curve Shape for Adenoviral Vector Vaccines" But based on my cursory reading of these papers, these are based on very limited data and I think more expert input would be needed to evaluate the role this could actually play in vaccine development.

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[31] This is all pretty generic. The "toolbox" includes "statistical models for vaccine dose/efficacy predictions, semi-empirical immunostimulatory/immunodynamics (IS-ID or IS/ID) models, model-based meta-analysis (MBMA), agent-based immune models, bioinformatics and artificial intelligence/machine learning based methods, mechanistic ordinary differential equation based vaccine models, including quantitative systems pharmacology (QSP) models, and virtual clinical trial simulations".

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6 Practical aspects of changing dose

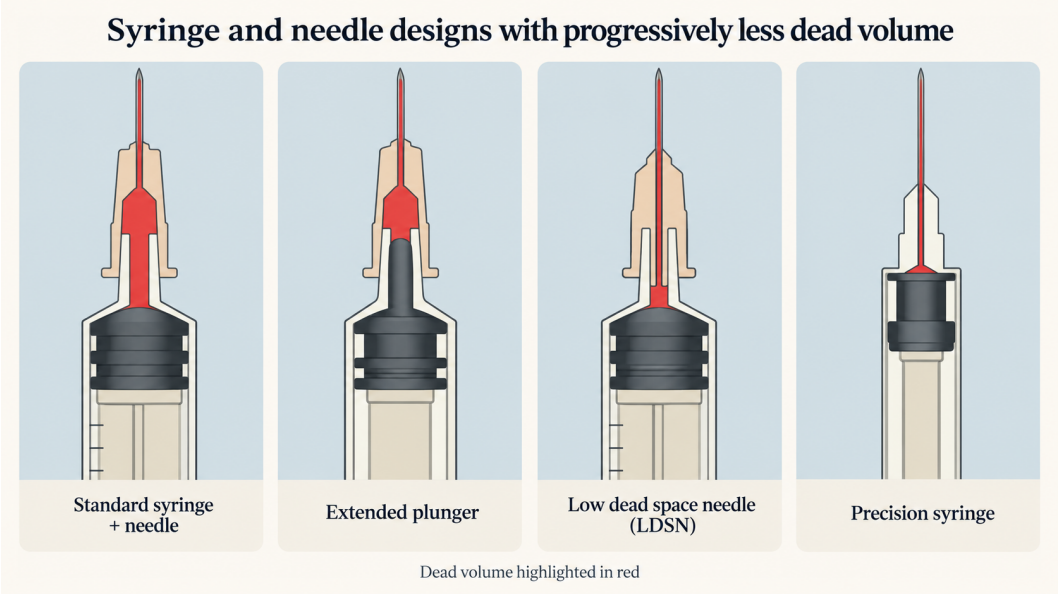
Syringes, vials and intradermal delivery

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

In the case studies of polio and yellow fever fractionation we saw that a standard dose of 0.5mL was swapped for 0.1mL. In some other applications even lower doses were considered. How is that done in practice? Does splitting the "full" dose into N doses automatically mean you can vaccinate N times more people? To answer these types of questions, there are several topics it's good to get familiar with: what syringes are used to vaccinate, how splitting of vials is achieved, and intradermal vaccination.

6.1 Syringes and wastage

Most vaccines are injected. Disposable plastic syringes have been in use since the 1960s. The traditional design has a high dead volume, meaning that there is a lot of space at the end of the syringe where the injected substance can remain, and so the injected volume is also less precise. Low dead space syringe (LDSS) was invented at first for precise insulin injections. You can also use a low dead space *needle* (LDSN) instead to reduce wastage. The different methods are show below.[32]



Left to right: syringe and needle designs with progressively less dead volume (red area); adapted from here. Second from left: extended plunger; third from left: low

[32] What are the volumes we're discussing? For COVID, of the initially approved vaccines: Moderna and AstraZeneca vaccines were injected at 0.5mL, Pfizer vaccine 0.3mL, paediatric vaccinations 0.1mL. Dead space can be as low as 0.03mL up to 0.1mL depending on syringe/needle. By the way, insulin injection uses a similar range of 0.3-1mL, but needs a short needle, 5-13mm, because it's not delivered into the muscle. Vaccination into a deltoid muscle is done with a 1-inch needle.

dead space needle in high dead space syringe. Rightmost: precision syringe used for e.g. insulin injections.

How much of a difference can use of better syringes make in practice? A flu study with 10-dose vials estimated wastage of 2-19% (Strauss et al. 2006), but it's clearly a highly case-specific estimate. The topic saw much interest in early 2021 with the discovery that additional doses of COVID vaccines could be obtained from vials with LDSS/N. In a very nice and comprehensive quantitative study, Le Daré et al. (2021) showed that you could obtain 1-2 extra doses per vial (vials were 5-11 doses) for each of the four vaccines available in early 2021; I recommend looking at the main figure in that study. It's also instructive to see a video of vaccine preparation and drawing an extra dose from Pfizer COVID vaccine vial to understand the extra skill involved. Overall, the healthcare workers would try (and usually succeed) in drawing these extra doses.

Jarrahian, Rein-Weston, et al. (2017) examines how many fractional doses of polio vaccines can be obtained from standard single-dose vials, using different intradermal delivery methods (more on which below). In theory, five fractional (0.1mL) doses could be taken from each vial. However, the actual number of doses obtained ranged from 3 to 5.2, depending on the device. The difference between the nominal and actual number was due to wastage, such as device dead space and wastage in the filling process.[33]

The costs of LDSS themselves does not appear to be substantially higher than high dead space ones. Hence, various authors have recommended switching to LDSS as an industry standard for self-administered medications. However, in the case of vaccinations, where huge volumes of syringes are needed, it's an open question how much the manufacturing can be scaled up in a pandemic setting. For example, a news article on stretching mpox vaccine noted that even though fractional dosing was supposed to produce five doses instead of one, in practice the number was between three and five (see also fractional dosing of mpox vaccine). Lack of LDSS was cited as a factor, suggesting that they are not so readily available even in non-pandemic mass vaccination emergencies in wealthy countries.

6.2 Multidose vial policy: vial size, storage, and multiple punctures

Injectable vaccines come in vials of various sizes. As we saw, for AstraZeneca's COVID vaccine the typically used vial nominally contained 10 doses of 0.5mL. This led to variation in the number of extractable doses, all the way up to 13.

Many vaccines administered in low- and middle-income countries are purchased in multidose vials (MDVs), up to 20 doses per vial. Compared with single-use vials, MDVs sell at a lower price per dose; require lower cold chain, storage, and transport capacity; and generate less waste. Naturally, using fractionation increases the number of available doses per vial.

From the producers' standpoint, MDV is also a faster solution in a pandemic setting:

[33] Some volume is also left behind as wastage in a vial after all possible doses have been extracted; the amount of wastage depends on the device used. Jarrahian, Rein-Weston, et al. (2017) found that the volume retained in vials ranged between 17µL and 312µL (equivalent to over three 0.1mL fractional doses wasted) - although they do not indicate which devices produced the most vial-retained wastage.

it requires fewer glass vials and each vial can be filled faster (as per Pfizer manufacturing team)

MDV with large vials may seem like an obvious choice, then, but we don't always use it. Single dose vials or pre-filled syringes[34] avoid contamination and may reduce wastage when there are few patients, because there is no risk that unused vaccine will have to be discarded once the open vial expires.[35] Healthcare workers may be hesitant to open large vials to reduce waste, which could lead to missed vaccination opportunities when there aren't enough people to vaccinate.

Lee et al. (2010) provide a good overview of these issues, together with economic modelling of when MDV is preferable. They even derive vaccine-specific patient thresholds required to justify use of MDVs. Cost per dose can vary hugely between different vial options depending on demand, but it's hard to generalise from this since this is only a theoretical computation.

Heaton et al. (2017) review ten studies on how the number of doses per vial affects various aspects of immunisation systems such as costs, coverage, wastage, contamination. Predictably, the optimal MDV policy is highly case-specific. Studies differ in estimates of how costs are impacted. Using low-capacity MDVs reduces wastage, [36] but can also lower availability, e.g. because of the higher cold chain burden. One study found that contamination risk was not statistically higher with higher-capacity MDVs.[37] The review also cites measles outbreaks in Ethiopia and Zanzibar, where vaccination rates were lower due to HCWs not opening vials to minimise wastage.

In addition to wastage, there is also the issue of vial stoppers. Each vial has a rubber stopper at the top. Their quality is specified and tested as part of e.g. WHO's prequalification. In assessing suitability of YF and polio vaccines for fractionation, there was no problem with additional punctures (Jarrahian, Myers, et al. 2017), so we should a priori assume that this is possible for all vaccines. However, the manufacturing guidelines are typically for fewer punctures that FD would require, so this needs to

[34] A pre-filled syringe is used e.g. for routine influenza vaccination. More and more, in wealthy countries these are considered as they can save healthcare worker time, which supposedly offsets the additional costs. A new Pfizer COVID vaccine (for 2023-2024) can also come in a pre-filled syringe instead of a single dose vial. If pre-filled syringes became a default mode of distribution for some future vaccines, this would make fractionation impossible. But this seems unlikely in a pandemic, since it is faster to manufacture large quantities of MDV.

[35] As nicely summarised by Kanagat et al. (2020) (discussing the health care workers' perspective): *"Some vaccines contain preservatives, whereas others do not. Under the WHO's multidose vial policy, remaining doses in open vials of vaccines with preservatives can be used for up to 28 days after opening, as long as storage and proper handling conditions are met. However, vaccines without preservatives must be used in a much shorter time frame. Vaccines such as BCG, measles-containing vaccine (MCV), and yellow fever vaccines do not contain preservatives, and they must be discarded within 6 hours of reconstitution or at the end of a session, whichever comes first. Health care workers (HCWs) in low- and middle-income countries who administer these vaccines to their target populations are therefore responsible for deciding when to open a vial, knowing that if not all doses are used within a short frame of time, they will have to be discarded, resulting in open-vial wastage."* See also WHO policy.

[36] In a four-country study, by switching from 10-dose to 5-dose vials, the estimated open vial wastage rate fell by between 56% and 44% across the countries. However, the costs per dose increased due to higher procurement and cold chain costs.

[37] Generally, MDVs are presumed to have a higher risk of contamination as they are used and handled multiple times - the higher their capacity, the higher the risk. For the cited study contamination risk was not part of the original study design, so this particular finding may be biased.

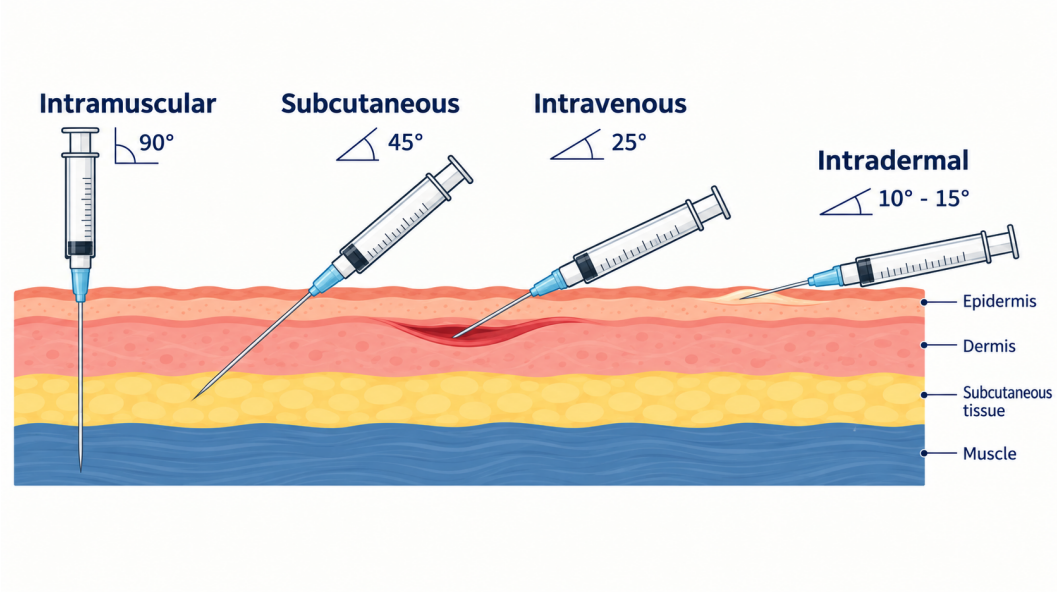
be verified every time. Moreover, in the mpox case there also appeared to be a problem with vial stoppers being loose, which made it hard to deliver many doses. But this may be anecdata.

Quick reminder on what routes different vaccines use

- **Mucosal**: flu (nasal), cholera and rotavirus (oral), polio (oral)
- **Intramuscular** (most vaccines): COVID, flu, polio, hepB, DTP, HPV, PCV, …
- **Subcutaneous** (typically live vaccines): MMR, YF, varicella, zoster
- **Intradermal**: BCG TB, also possible for rabies

6.3 Intradermal delivery and new technologies for ID

Typically, injectable vaccines are delivered into the muscle (often inactivated vaccines) or subcutaneously (often live vaccines). Intradermal injections are routinely used for the BCG vaccine (using a specialised needle and syringe). The basic technique of ID injection (originally developed for TB) is to use an oblique angle when piercing the skin, like so:



Using ID injections targets dermis layer of the skin, which is rich in antigen-presenting cells and facilitates vaccines reaching lymph nodes. This means ID can elicit broad and lasting responses using both innate and adaptive immunity. For this reason, it is seen as a natural choice for fractionation, since it can lead to a more potent immune response at lower doses compared to SC or IM delivery. Schnyder et al. (2020) provide a fantastic overview of ID vs IM/SC studies up to 2020.[38]

With this in mind, why wouldn't more vaccines be administered intradermally? First, there are more local reactions with ID injections, which may make them less acceptable; as I will discuss below, some ID methods may however be relatively painless

[38]There is some literature specifically on experiments comparing ID vs IM delivery of the *same* doses, but it's not something we test comprehensively.

compared to IM injections.[39] However, the main issue raised by decision makers is that it is a more difficult technique which requires special training and can lead to less consistent results. (Experts seem to differ on this point.) The reasons for this difficulty lie in the precise depth and angle a traditional syringe has to be positioned in order to give an ID injection.

With this in mind, several ID technologies have been developed as alternatives to traditional BCG needle and syringe:

- **Adapters** which can be placed on regular syringes and limit the depth and angle of the needle during injection. See Tsals et al for an early trial. A more recent study, Bashorun et al. (2022), notes that the unit cost for injections via intradermal adapters is much higher than injections via a traditional BCG needle and syringe, but that this cost might be largely offset when the effect of dose sparing (eg fractionation) and reduced operational costs (including training HCWs) is accounted for. (Also see note on fIPV below.) The ID adapter technology was supported by PATH, but there are no recent reports on its use, nor on the commercial adapter produced by West Pharmaceutical Services that was used in both of the studies mentioned above.
- **Jet injector devices** are an old technology which has been largely retired due to safety concerns. However, a new generation of jet injectors, such as the ID Pen Injector, MIT Canada's MED-JET H4, and Tropis have been developed and do not have the same contamination risks as old injectors. It consists of a small injection device and disposable syringe.[40] Tropis has been used for polio and pre-qualified by the WHO in 2018.[41] The production was scaled up after it was authorised for COVID-19 vaccines.[42]
- **Microneedles** are needles less than about 1 mm long which can be mounted on regular syringes or delivered using arrays/patches. (*Since writing this I learned that Open Phil commissioned a separate investigation into this topic, hence I did not look into this more; I leave this note here for posterity.*) They are easy to deliver and almost painless, but it's largely a futuristic technology. They include NanoPass' MicronJet which has received FDA clearance as an ID delivery de-

[39] [On the other hand], "The intradermal administration of fractional doses of inactivated poliovirus vaccine appears to be safe and preferred by parents and health care providers. A questionnaire administered to parents of infants in the fractional-dose group reported a strong preference for this route of administration. When the parents were asked why they preferred intradermal administration, the vast majority of parents responded with a comment that 'the baby does not cry.' "

[40] Resik et al analyses the immune responses from fractional IPV (polio vaccines) administered by Tropis and the ID Pen. Compared to the BCG syringe, there is no difference in immune response for Tropis, but the ID Pen is significantly lower.

[41] Tropis was piloted for fractional dose of IPV vaccine in Pakistan and Somalia and now in Nigeria, under a USD 1.5M grant from USAID DIV, see here.

[42] It's hard to say how cost competitive the technology would be at scale. The cost of the device is in the hundreds of dollars, but per WHO specification it can deliver 30,000 injections. Syringe costs are likely in cents, compared to traditional single-use syringes which cost between US$0.03-0.04 according to the WHO.

vice,[43] DebioJect,[44] and VAX-ID.[45] Jarrahian, Rein-Weston, et al. (2017) uses all of these devices in their study, but note that higher costs and cold chain requirements of pre-filled microneedle devices mean they may be inappropriate for use in LMICs. See Menon et al. (2021) for an overview.

The largest use case of ID fractionation to date is fractional dosing of polio vaccine. Okayasu et al. (2017) provide a very nice overview of different devices that were evaluated in clinical studies of fIPVs: adapter, syringe with short needles, microneedle, and jet injectors. It seems that adapters and Tropis were assessed most favourably, although their cost is 10-20x higher than conventional syringes. In large scale rollouts BCG needles were used. Bashorun et al. (2022) compare the three methods.

Technologies that avoid large needles are important as they may reduce vaccine hesitancy. A number I often saw cited was 1 in 10 people fear needles, but I have not found a good source for this. McLenon and Rogers (2019) note that approximately 1 in 13 healthcare workers in hospitals avoided influenza vaccination because of a fear of needles.

I close this section by noting an obvious question I was not able to answer: why are LDS syringes not used for all medications? They reduce waste, are not considerably more expensive, and are readily available (insulin syringes are commonly LDS). It's unclear to me why standard, high dead space syringes would be used at all, unless the small cost difference adds up dramatically at scale. Is there some kind of market failure there?

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[44] Vescovo et al compare the efficacy of rabies vaccinations in healthy 18-50 year-olds using 3 different injection routes: ID using the DebioJect microneedle device, ID with a standard needle using the Mantoux method, and intramuscularly with a standard needle. Metrics of pain were significantly lower using DebioJect, and no significant differences in immune responses/levels of protection were observed between the 3 routes. However, the 3 sample groups only had 22 volunteers in them each.

[45] Two very early stage trials of VAX-ID: this and this

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7 Health benefits from optimisation

What models say about the potential to save lives

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

In this section I try to develop a sense of how large benefits of optimal regimens can be. I cover three things. First, I briefly talk about what types of optimisation are of interest to decision makers and how it is modelled. Second, I talk through some notable estimates in the literature, to give us a sense of how large benefits can be. Third, I point out some reasons for skepticism. I then try to summarise what we know.

To keep the length of references manageable, I provide references for what I consider the most worthwhile reading material. Relatively less important papers are referenced as URLs.

7.1 What is vaccine optimisation

As mentioned at start, within this investigation I focus on changing dosage and gaps, which I sometimes refer to as "optimisation". However, the public health decision makers and advisory boards (e.g. WHO SAGE, NITAGs) think about that term more broadly. I think it is instructive to understand their perspective.

Note that in this section I am mainly interested in situations where there is already something like a default policy, rather than the scale of benefits from optimising during vaccine development, which I discuss separately.

In general, decision makers can consider for optimisation:

- allocation/population (who gets vaccinated and in what order: e.g. designating high risk groups or high-risk areas, ring vaccination etc.),
- dose,
- gaps between doses,
- timing of vaccinations: relative to age (e.g. rotavirus vaccine to maximise protection during high risk period), epidemics (especially seasonal, e.g. flu, malaria) or timing of other vaccines (e.g. to use multivalent vaccines or bundle several different vaccines at the same time),
- combining with other interventions (for controlling spread of epidemics, achieved through combination with NPIs, antivirals), use of multi-dose vials or other delivery technologies.

Each of these can be considered with or without constraints, meaning either a fixed budget or a finite supply of vaccine. I ignore modeling on how to minimise costs alone, but of course a lot of cost modeling is done to find optimal ways of meeting vaccine coverage targets.

We can optimise for different objectives: an obvious one is minimising deaths, but people may also want to pursue a strategy which avoids reaching hospital capacity, reduces infections, avoids wastage, or minimises some form of economic burden.[46]

Optimisation is achieved through epidemiological models, typically classical compartmental models of mathematical epidemiology.[47] The main feature of these models is their ability to account for dynamic risk of infections and the impact of vaccination on "flattening the curve". The models are either fitted to retrospective data (to consider vaccination counterfactuals) or are simply theoretical simulations, with parameters drawn from previous epidemics. Then either several counterfactuals are generated and compared according to the objective.

7.2 What magnitude of impact can optimisation have?

Here are some practical examples, just to give some sense of what kind of impact these strategies can have, according to their authors. This is a very rough characterisations of the following papers and the numbers are of course not comparable, because I am summarising very different types of estimates. I am also leaving out some common limitations of these models, I will talk about them in the next section.

7.2.1 Targeting and timing vaccinations

First, there is group and age prioritisation. Typically we choose between vaccinating transmitting individuals vs the ones at higher risk of severe outcomes.

- For example, for influenza it has long been a practice to vaccinate the elderly and debate over whether to vaccinate schoolchildren. A model suggested that there is 10% extra benefit from targeting children (ages 5-17); this type of modelling helped inform the decision to offer flu vaccine to schoolchildren in England and Wales.
- For COVID, most authors sensibly suggested targeting individuals at high risk of mortality. But it's interesting to see what the magnitude of impact was. In Bilgin et al. (2023) deaths reduced by about a third if prioritising the highest risk groups. Prioritisation model by Bubar et al. (2021) was another very lucid example of COVID case. They show that averted deaths can go from 33% to 50% in severe epidemics (so, benefits increase by about a half), although for smaller epidemics there is much less, sometimes zero, difference.
- For malaria, this vaccine rollout paper shows how optimal geographical allocation of malaria vaccine under supply constraint can have considerable impacts (although not easy to summarise in this instance). A lot of similar modeling is done routinely.

[46] In some cases, decision makers try to solve the inverse problem: what level of coverage has to be achieved to eliminate certain pathogens or maintain herd immunity.

[47] Sometimes agent-based models are used for fine-tuning certain decisions. They may not be necessary for estimating the magnitude of benefits, but they can be much better at predicting complex behaviours. A classic example is this flu paper by Ferguson et al, model from which was also the basis of early COVID modelling in the UK.

Another type of optimisation considers timing. Thompson et al. (2022) model that aligning RTS,S vaccination (the primary series of 3 doses) to season, rather than age, could avert 25%-75% additional cases. That is because efficacy of malaria vaccine decreases from 80% after 3 doses to ~30% over 12 months (which also shows why 4th dose is needed). This is an impressive figure, but, as we will discuss later, this type of optimisation has to be carefully considered against other practical factors of implementing a mass vaccination programme.

These are interesting and important examples of the type that decision makers pay close attention to. I started with it because I also wanted to cite some numbers for the magnitude of improvement that are relevant in these problems, although, once again, this is only a very rough summary. I now move to the models of gaps and dosing, which are the focus of this doc.

7.2.2 Increasing gaps

This topic got a lot of coverage during COVID, given an early finding that immune responses could be more potent when gaps were extended. I discuss this mechanism in the note on biology of optimal dosing and here only cover the models of benefits. There are also some results for cholera vaccine, which are very timely in 2024 due to ongoing shortage of that vaccine.

7.2.3 COVID vaccines: 12-week gaps

For cases such as COVID, a simple rule of thumb model here may suffice (as was perhaps evidenced by national advisory boards quickly moving to extended gaps): extending the gaps allows for a short-term doubling of coverage (all "second" doses are used to immunise new individuals). If the high-risk population is several times larger than the short-term vaccination capacity, then benefits may double even without taking into account impact on stopping transmission. And unlike fractional dosing, the logistical constraints do not apply.

Many analyses of public health impacts of extending time between two doses were produced and they largely confirmed large benefits of this approach. In one more recent example (unlike many other papers, based on retrospective analysis), Imai et al. (2023) estimated that extending the second dose from 3 to 12 weeks averted 60k hospitalisations and 10k deaths in the first 9 months of 2021 in England. This would mean a roughly 20% increase in hospitalisations and deaths averted. These large gains were generally matched by other models I am aware of. [48]

7.2.4 Cholera: prioritising single dose during shortages

Oral cholera vaccine is typically given in two doses, 1-6 weeks apart. There are persistent shortages which are ongoing even now and during outbreaks in South Sudan

[48] These other examples include an early simulation model 20-30% reduction in cases; modeling to optimise gaps that generally supported increasing gaps from 3-4 weeks to 8-12 and similar work in England; another widely cited agent-based model found very large increases with severely constrained supply. A country-specific model for European middle-income countries found about 10% decrease in burden from moving to longer gaps.

(2015), Zambia (2016) a decision was made to switch to a single dose until more supply became available.

There has been some modeling of benefits of single dose vaccination, first by Azman et al. (2015) and more recently by Leung, Eaton, and Matrajt (2022) who suggest that 20-80% more deaths can be averted during outbreaks by using the optimal one dose strategy instead of two doses (but maintaining two doses reserved for children under five, for whom the vaccine is less effective). This is based on three different actual outbreak settings. These results appear promising, but I have not seen them receive much attention and the crucial parameter for these models, effectiveness of single dose relative to two doses, needs more data.

7.2.5 Optimising dosing

I discuss using lower vaccine doses for COVID, yellow fever and mpox in individual case studies. Each of these has some accompanying modeling on benefits of fractionation; here I recap their magnitudes of benefits. Another important example is influenza, where the option considered is usually to increase dosage in the elderly (as much as 5-fold increase in the amount of antigen). Something similar could be done in COVID, too. I have not found much fractionation modeling for other diseases.

7.2.6 Fractionation to spare doses: COVID, yellow fever, mpox

For fractionation, the basic result in some modeling studies is that benefits are inversely proportional to fractionation, multiplied by vaccine effectiveness. For example, if you can vaccinate 5x more people but there is a 20% chance that the lower dose does not work (and the full dose always does), the benefits are 4 times higher, assuming it's OK to ignore "leakiness" and sterilising immunity: more on that below.

Therefore a simple principle that some papers mention is that an n-fold increase in the speed of vaccination is worthwhile as long as efficacy does not decrease more than n-fold. But as with other cases, this has to be verified within models that consider infectious disease epidemiology.

For COVID, I give more context in case study of fractional dosing of COVID vaccines. Focusing on models only, Więcek et al. (2022) (hey, that's me!) find that a large share of deaths can be averted. This is just a hypothetical simulation study, but with reasonably realistic parameters. We can think of this model generically as one where we can choose between a slower, high efficacy vaccine (e.g. full dose) and faster, lower efficacy vaccine (e.g. through fractionation). If there is no drop in efficacy from fractionation, then doubling speed of vaccination averts between quarter and half of deaths (depending on the intensity of the epidemic). But there are limits to the usefulness of fractional dose: for example, the model suggests that switching from a 70% to a 2x faster 35% effective dose would increase mortality. This is because benefits from spreading coverage more broadly are outweighed by less protection among those most at risk.[49]

[49] I am aware of one more effort to model fractionation of COVID vaccines, where modeling was also done specifically for India, in two more specific modeling papers: one and two; this was combined with cost-effectiveness analysis and considered booster campaigns, which our paper did not.

For mpox, Dimitrov, Adamson, and Matrajt (2023) projected up to 70% fewer infections if there was a large supply constraint and good vaccine efficacy from fractional dose (both assumptions turned out to be correct, I believe).

A simple modeling paper by Wu et al. (2016) projected large numbers of infections averted from fracitonal dosing of yellow fever vaccine, using data from vaccination campaign in Kinshasa, with up to about 60% reductions in infection attack rate if (as was subsequently shown to be the case) VE did not decrease by much.

There is also an older example of modeling on how to optimally use a stockpile of flu vaccine during pandemics by Riley, Wu, and Leung (2007). The authors found that it is optimal to spread coverage and the optimal solution would reduce infections by roughly 5-10 p.p. (which in relative terms would mean up to 20% fewer cases).[50]

7.2.7 Age- and risk-specific dosing: COVID and influenza

COVID. The models above assume optimal dosing is a binary problem: you either vaccinate with the standard dose or give a lower one to everyone. But this is not quite right: we routinely give lower doses to children. It would be not just wasteful, but potentially very harmful to give the same dose of COVID vaccine to infants. On the other end of the scale, we know that immune response weakens with age.

In a work-in-progress paper I am working on with some colleagues (not yet public), we find that for an epidemic like COVID (steep risk profile, fast transmission), when vaccine supply is small, the extra benefits of age-optimal dosing are rather small: it's OK to simply find the optimal fractional dose that covers most of the high-risk population.

This optimal dosing was not part of a wider discussion in 2021, but the mindset of heterogneous risks was reflected in the discussions about extending gaps between doses. There was talk by modellers about initially giving two doses to high risk individuals and a single dose to the rest of the population (example of a single dose paper). There was also a conversation on giving one dose to people who had a confirmed infection, since that was sufficient to mount good immune response.

Influenza. But part of the reason for these small extra benefits from switching to age-specific dosing is that COVID vaccines work pretty well in the first place (or at least we assumed so in our models). This is not the case for flu and so it's worthwhile to mention it here as an example of increasing doses having positive effects.

There is an issue of vaccine mismatch due to viral drift, where the vaccine is poorly protective in everyone in a given season. These cases probably need to be resolved on the vaccine development side. But in cases where there is a match, the vaccines can still have low effectiveness and short durability, especially in the elderly. Small increases in vaccine effectiveness would help avoid many severe outcomes (here is a simple calculation). A high dose influenza vaccine is recommended for >65 year olds, at least in the US. A Phase 3 RCT estimated that it reduces risk by about a quarter compared to standard dose (then trivalent, now quadrivalent). I have not

[50] There is also [another model for dosing during influenza pandemics], which also recommends low doses, but I have not had time to review it.

seen good modeling papers that confirm health benefits, but it should be obvious that if efficacy increases, there are large health gains. I've seen some discussion of two-dose vaccination could also help.

7.3 Some limitations of typical models of benefits

There are several limitations that are common to many models of benefits, including many (probably most) that I cited. And all of these limitations apply to the two main optimisation problems we are interested in here, i.e. dosing and schedules, although their impact will vary case-by-case.

7.3.1 Efficacy against disease or infection? Sterilising immunity

This one is probably obvious to any reader of this document, but it's worth spelling out. As Derek Lowe nicely put it, "there are vaccines and there are vaccines". By efficacy we typically mean efficacy against *symptomatic* disease, which obviously can be measured more easily than infection. Additionally, some vaccines can eliminate pathogens before they could infect and replicate within the host.

This is not the case for influenza or SARS-CoV-2, which drift and mutate into new variants. To predict benefits of vaccines we have to make some assumptions on how efficacy against disease can translate to breaking transmission, i.e. efficacy against infection. But data that we have on this is not as comprehensive as on efficacy against disease.[51] In broad terms, this is likely the most valuable of the missing pieces of information that would allow the modellers better assess benefits.

7.3.2 Wastage, logistics, feasible speed-up from optimisation

When considering fractionation or extending gaps, there is obviously potential for wastage. First, I discussed various dosing-related problems (splitting vials, dead volume in syringes, difficulties in intradermal dosing) in the note on how change in dosing is implemented in practice. Then there are logistical constraints: if considering a counterfactual of faster vaccination (through expanding supply, more equitable distribution, lower doses, better schedules), is there sufficient capacity to deliver these additional shots? This is something that modelling tends to purposefully ignore, typically due to lack of data or because it's highly context-specific.

7.3.3 Behaviour change

Typically counterfactual scenarios in epidemiological models assume the same behaviour of agents over time, i.e. people making virus-transmitting contacts over time at the same rate. The effect of vaccination is simply through modifying the risk of these contacts. Some models also include dynamic non-pharmaceutical interventions, e.g. lockdowns or school closures. But it's rare for models to include behavioural

[51] This was famously a big controversy around COVID-19 vaccines, with a mix of conspiracy theorists and right-leaning commentators complaining about how the promise of vaccines breaking transmission was used to "force" vaccines on everyone, e.g. via COVID passports. This author will refrain from commenting on that issue, but there is a nice, comprehensive fact check from Reuters on that issue.

change in response to changing risk. A classic example in that category is people engaging in more risky behaviour after vaccination. Ignoring this can obviously overstate benefits of (faster) vaccination.[52]

7.3.4 Exacerbating epidemics

Earlier, I cited a paper on targeting school children for flu vaccination. Another paper by De Boer et al estimates costs per QALY of childhood influenza vaccinations in the Netherlands, finding an overall *increase* in seasons with higher incidence of flu. It's based on a model that is quite simple relative to others we discussed here, but the general principle can be found in other papers.[53]

Where vaccine-induced protection wanes over time (and where there is no constant revaccination), mass vaccination may simply be a way of pushing more cases forward in time. This is of course very valuable, but inasmuch as the decision maker cares about long-term impacts, they may have to (1) simulate longer periods, (2) consider long-term revaccination dynamics, (3) be explicit about temporal discounts.

7.3.5 Leaky vaccines

This one is somewhat related to sterilising immunity. Yellow fever modelling paper by Wu et al. (2016) makes an important distinction between all-or-nothing and "leaky" vaccines. In the former case a 50% effective vaccine means that 50% of people develop total immunity and the rest get no benefit. In the latter, all people have 50% chance of avoiding infection on contact. Typically, for a new vaccine/pathogen we do not know which one is closer to the truth: this type of knowledge requires e.g. human challenge studies.

The latter hypothetical is worse, because everyone can still get infected, just more slowly, whereas in the all-or-nothing case the epidemic eventually runs out of steam as the susceptible population shrinks/herd immunity develops. This means that the benefits of fractional dosing can be overstated when there are steep decreases in efficacy. This critique extends to our paper on COVID vaccines!

7.3.6 Selection pressure

Compared to "standard" vaccination, delaying doses or giving smaller doses of a vaccine increases the number of individuals with partial immunity, which could increase the rate of viral escape from immunity. This happens because at moderate levels of immunity (1) the virus is under pressure to evolve, but (2) it can still replicate enough to generate new (escape) variants. Saad-Roy et al. (2021) discuss this issue specifi-

[52] This problem affects models of retrospective data most often: the modellers will typically derive transmission dynamics over time and then generate counterfactuals by modifying only one factor of interest (e.g. rate of vaccination), *ceteris paribus*.

[53] For example, in our paper on impact of accelerating COVID vaccinations , which mainly focused on late 2020 in the US and the UK, we always found considerable increases in health burdens in the subsequent waves in 2021. Predictably, this effect was highly dependent on how quickly protection wanes and we did not assume any changes to booster campaigns.

cally with COVID vaccines' delayed 2nd dose in mind.[54] But Cobey et al. (2021) posit that dose-sparing regimes may in fact lower the risk, by slowing transmission. I agree with that assessment, but it's important to note that any such debate is very pathogen-specific and this is a very important risk to consider.

7.3.7 How much of a problem are these?

My highly subjective assessment is that it makes sense to discount the benefits by 10-20% for wastage and behaviour change each, unless models include it. For sterilising immunity and the last three, an assessment is needed on a disease-by-disease basis. For many vaccines that are highly effective and/or where supply constraints may ease over time, these concerns will have little or no impact on final magnitude of benefits. It is worth remembering that we are more likely to consider fractionation in cases where there is little loss in efficacy (that was the case in all of our case studies) and the models typically look at much starker trade-offs.

However, this quick tour of optimisation models leaves us with one big question: how do decision makers actually interact with models? I will try to address this in a separate section.

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8 How optimisation decisions are made

Why changing doses is difficult, even during outbreaks

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

Here, I want to provide a few thoughts about how decisions on optimisation were reached. These are not comprehensive case studies and there is some repetition of information about COVID here from other chapters. Unlike other chapters, this one is largely a personal view and I'm sure many experts may see this differently.

I will talk about COVID and influenza. For polio and yellow fever endorsements, see the relevant case studies to understand how decisions were reached. I would have liked to also investigate the case of mpox further (to understand how the FDA's approval of lower dose was triggered), but when writing this chapter I have not been able to schedule meetings with relevant experts.

8.1 COVID: fractional dosing

Clinical research on lower doses. In 2021, there was a lot of interest in this topic from clinical researchers. There were maybe a dozen groups we identified that were working on this. While there was a lot of trials in wealthy countries, LMICs were also well-represented and the researchers typically had some ties to and support from local decision makers to explore this. From first hand experience, there was interest in, among others, Brazil, Colombia, Thailand, Indonesia, Nigeria.

At a workshop in Chicago we had several clinical research groups discussing and presenting their results and in an unsystematic review in 2021, we identified about 40 trials with data on fractional dosing. Typically these would be immunogenicity trials with small arms of 10-100 subjects. In Viana in Brazil, half doses of AstraZeneca vaccine were tested in an observational study (>20,000 half doses), with positive results. Open Phil supported a trial in Nigeria.

I explained in the biology section why lowering booster doses is usually seen as a better/safer bet. With that in mind, CEPI explored lower doses of boosters and designed a platform trial around this. It's hard to untangle if any of these studies impacted subsequent decisions, but Moderna did eventually lower doses.

Understanding benefits and policy outreach. Back in 2021 I believe there were only three groups of researchers who published on benefits of fractionation.[55] I described rationale and results in other chapters. I worked on this together with a couple of colleagues (economists) at Michael Kremer's lab at University of Chicago and Michael himself. I believe our group was the only one that mainly focused on reaching out to decision makers.

[55] First, one that I was part of, which was started off as an informal group of economists, named Accelerating Health Technologies and eventually largely headed by Michael Kremer. Second, Ben Cowling (University of Hong Kong) and several others advocated for fractionation in Nature Medicine and modelled using it in India. A few researchers from LUMC also supported dose sparing in Lancet Global Health.

Regulators and pharma. As far as I am aware, regulators approving vaccines did not request for vaccine makers to conduct any additional immunogenicity studies. In 2021 vaccine makers did not have financial incentives to recommend using lower doses of their vaccines. Contracts were signed in advance, guaranteeing large volume purchases (specified as number of doses), so recommending going to lower doses would simply slash their profits.[56]

Decision makers. We presented our paper to WHO SAGE twice and even had a chance to pitch this idea to WHO DG in person. We talked to several decision makers at national level, including heads of medical research councils and health ministers. Generally, I got an impression from conversations in LMICs that officials were interested in pursuing this on an individual basis, but needed more research (immunogenicity) and outside support to adopt lower doses. But it's obviously hard to generalise from several conversations.

8.2 COVID: extended gaps between two doses

A decision that *did* happen was the UK increasing spacing between doses of COVID vaccines. Other countries then followed. A few thoughts on how the decision was reached in the UK:

- The main relevant endorsement that the UK's government likely relied on was by Joint Committee on Vaccination and Immunisation. JCVI publishes minutes of its meetings; for extending doses they published a short note that showed evidence on immunogenicity and efficacy of one dose, not public health benefit. A few weeks later they also published rudimentary modelling supporting this decision.[57]
- JCVI is a relatively close-knit group of excellent vaccine researchers. Based on their experience, it was likely seen as "natural" that extending gaps *could* stimulate immune response. Even without any additional modelling, this was enough to reach a decision to extend from 3-4 to 12 weeks.
- In first half of 2021 many countries followed, e.g. Canada opted for 16 weeks, as did Spain for under 60s. Germany went with 6 weeks, India with 12-16, same with Thailand. But given some of the initial opposition (see below), UK's decision was crucial. In many countries, including the UK, the gaps were then shortened (e.g. to 8 weeks) when supply constraints eased and risk surged again.

A few words on arguments against, a few of which I think are worth citing verbatim:

[56] I believe (but this is only based on various conversations and may be completely off) that they did not want to cooperate with researchers who wanted to conduct additional efficacy trials or to investigate alternative doses.

[57] (This is all minor, but to all who are interested:) not to give an impression that the idea originated in JCVI or that they were the only relevant advisors on the matter. Switch to 12 weeks was authorised by MHRA and communicated to vaccinators by UK's chief medical officers on 31 Dec 2020. SAGE, which was an advisory group specifically for COVID, also spoke in favour. SAGE meetings featured a lot of modeling and are available online. Other decision makers, whose involvement is not clear; Chief Medical Officer and Chief Scientific Adviser to the gov't, as well as the vaccine task force likely played the role here. We know that they both were highly receptive to public health arguments and worked directly with epidemiological modellers.

- WHO advised against this. British Medical Association protested the decision. I think it sums up why doctors should not be solely responsible for public health. Choice quotes: "if that was the right thing to do then we would see other nations following suit", "UK should adopt this best practice based on international professional opinion"; it was called unreasonable, unfair on patients, and too logistically difficult to do (because of rescheduling appointments). But most voices in the UK were supportive.
- Less so in the US. FDA advised against it as "premature and not rooted solidly in the available evidence". "These are all reasonable questions to consider and evaluate in clinical trials."
- This STAT article, with opinions from a lot of sceptical experts, also summarises the opposition, e.g. "they are also effectively turning that country into a living laboratory. The moves are based on small slices of evidence mined from"subsets of subsets" of participants in clinical trials, as one expert described it for STAT"

8.3 COVID: why gaps and not lower doses?

If gaps were optimised, was it not also *practically* possible to switch to lower doses based on the evidence already available in early 2021? Probably not. As we've seen throughout this report, dosing decisions for initial doses are more complicated from biological viewpoint and fractionation requires more programmatic considerations. For a new disease without established correlates of protection this was a very tall order. However, what factors could have enabled a different decision? A few ideas:

- Generating more clinical evidence: capacity for running more comprehensive immunogenicity trials for lower doses existed in 2020, but it was not used; trials of lower doses happened mainly in 2021. I presume this could also be achieved through more pressure from regulators on vaccine makers.
- Establishing correlates of protection and rate of waning of protection
- A highly-motivated country willing to be the first mover
- A pre-existing example of fractionation in a pandemic setting. Perhaps also a pre-defined transparent decision making framework around this
- Someone within the global health establishment to champion this idea effectively
- More coordination among small-scale trials of lower doses (platform design) and/or living synthesis of evidence
- Global pool of doses and lab resources to run trials in places that were willing to implement this idea

8.4 Another decision making example: fractionation for influenza in Canada

A few years back Canada's NITAG, National Advisory Committee on Immunization (NACI), undertook an evaluation of fractional doses of influenza vaccine with both IM and ID delivery and recommended against it. Justification is available online and

worth reading if interested in influenza (it is a short document). I will provide a short commentary on a few aspects of it that I found interesting.

I should say up front that I will be using this document as a strawman. I have not interviewed the authors and I may be trivialising aspects of what ultimately was a complex decision. So please think of this as a purposefully simplified example. I think it is an important one, because it highlights the gap between the kind of evidence I discuss throughout this report and information that decision makers are interested in.

NACI concluded that for IM fractionation, there is weak evidence and therefore it should not be used. No real quibbles here, it's common sense that further lowering vaccine effectiveness for flu is not a good idea. See also the note on influenza in modeling health benefits of optimal dosing.

For ID delivery, there are many studies and the meta-analysis found no significant differences. In the subset of the older adults, also no differences. As I discussed in the chapter on how change in dosing is implemented in practice, there is also a large meta-analysis on ID vs IM vaccination, with 30 flu studies (Schnyder et al. 2020), which generally favoured ID. However, the recommendation was to not use ID for two main reasons.

8.4.1 Limited evidence?

First, "although there is some limited evidence on the use of fractional ID doses in adults ≥65 years of age, including those with chronic health conditions, there is no evidence of fractional dosing in other adult high risk-groups." I am not sure whether that's a reasonable worry or just more status quo bias.

Broadly, the problems I have with this are:

- **Unclear evidentiary standards and totalising approach.** For which groups do they think evidence is not sufficient? If these groups are reasonably well-defined, why not give full doses to the high-risk individuals? We already have a practice in many countries where for 65+ we give "high" dose and "standard" dose to the rest of population. But here it seems the choices are either fractionation for everyone or not at all.
- **Highly conservative approach to evidence overall.** We can only consider interventions that are shown to be non-inferior in head-to-head randomised trials, with uninformative and informative priors. We cannot extrapolate evidence: e.g. if we have studies on seroprotection against H1N1 and H2N3, we cannot synthesise them to increase statistical power. Seemingly we need to treat each subpopulation and each strain as if they were completely separate problems. Ditto for dose-response: even if 3 micrograms are shown to work very well, we must remain agnostic about whether 6 mcg will. (This is an overall critique of systematic reviews, not this report.)
- **No public health benefits perspective.** There is no modeling health benefits of optimal dosing. Here, it seems the whole decision is based on reviews of

individual-level benefits. What if the average effect is blunted by 10%, but you can vaccinate three times as many people?

I hasten to add that not all decision makers follow these standards. But, unfortunately, I think it's quite common in the broader world of evaluating health technologies.

8.4.2 Low feasibility?

Second, there are "several feasibility issues" with ID administration. They actually read like a good summary of issues that I covered in the note on how change in dosing is implemented in practice; I can cite some of them directly:

- "only possible when influenza immunizations have been packaged as multi-dose vials and not as pre-filled syringes" and "multi-dose vials are not always available midway in the season"
- "requires a different gauge needle" and "multi-dose vials (which are not always available midway in the season if supplies run low)"
- "significant training" required to get vaccinators ready to deliver ID injections
- most studies "used micro-needle injectors for administration, which are not yet authorized or widely available in Canadian settings"
- fractionation would "require a novel communication and consent plan for any off-label dosing if it were adopted"
- implementation would require monitoring of supplies as multi-dose vials will run (and the program has to be modified)

These are valid concerns, but also an example of status quo bias: there is no cost-benefit analysis, just a description of how things are. A somewhat unkind summary would be: "since things are different to how they would need to be, this is not feasible".

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9 Finding targets for optimisation; disease-specific summaries

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

9.1 Is it *worth it* to optimise any vaccine?

To begin to answer this question, synthesising information from all previous sections, I first create a longlist of questions that we should ask before exploring optimisation for any vaccine/disease combination. **These are not sufficient conditions, nor are they necessary.** We should think of them as so-called "enablers": the more of these conditions are obtained, the more we should consider prioritising a given vaccine for optimisation.

9.2 Factors that make a vaccine worth optimising

9.2.1 Individual benefits

Can the vaccine be optimised in a way that increases efficacy/safety for some individuals?

- **Positive results already exist** on alternative doses/schedules OR **limited testing was done before** (i.e. there are no negative results).
- There are **existing correlates of protection**.
- It's **fast to generate more data** on different schedules, e.g. we can use human challenge studies (e.g. influenza).
- **Favourable immune memory profile**; for example, the vaccine requires boosters (e.g. COVID-19 in 2020–2021) OR has high response at the current regimen (e.g. yellow fever); see *Immune memory and optimisation goals*.

9.2.2 Population benefits

Assuming individual benefits, are there large societal benefits from optimisation?

- **Supply is limited in the short term** (e.g. cholera in 2024).
- The supply limitation **can't be resolved through economic means**.
- There is **need to quickly expand coverage** (e.g. mpox in 2024).
- **Promising modelling results** show reductions in burden from optimisation or generally from (quickly) increasing coverage.

9.2.3 Feasible implementation

Would this work in the real world, especially in the contexts that benefit most (e.g. LICs)?

- **Decision makers are willing to support adoption** (e.g. polio).
- There is a **fast regulatory path** (e.g. emergency use authorisation, like mpox in 2022).

- There is **programmatic and logistical feasibility** to optimising.
- It's **possible to (quickly) measure effects** where this change is rolled out (e.g. there is a good surveillance or a healthcare records system that allows for a case-control effectiveness study).

9.3 Short assessments for most common diseases

Next, I try to synthetise what I learned while writing this report grouped by disease, limiting myself to three bullet point summary per each. I provide tentative recommendations.

I look at about 15 common diseases that we vaccinate against. This is not a complete list and does not include some important vaccines in development, I think of it as a good starting point for further investigations, so some of the recommendations here are about gaps in my own knowledge.

I do not provide any references in this chapter, but stick to hyperlinks to papers, because there is a lot of material here and a lot of it is not articles, but webpages anyway. Just one last reminder that I am not an expert on these diseases.

These are in no particular order.

9.3.1 polio

- I discuss fractionation of polio vaccine in fractional dosing of polio vaccine, where I talk about switch from trivalent to bivalent OPV and supplementation with (fractional) IPV. It appears that the shortage of IPV has been managed successfully through expansion of supply.
- Fractionation was carried out in many countries and immunogenicity of fIPV was deemed sufficient, making this a useful supply.

Recommendation: nothing to be done for polio, but it would be great to learn more about rollout in LMICs, as a case study for future programs that require fractionation/ID delivery. I have not had time to do it for this report.

9.3.2 cholera

- Oral cholera vaccine is typically given in two doses, 1-6 weeks apart. There are persistent shortages (the linked article is a good source for why that is unlikely to be resolved soon despite new developments) and during outbreaks in South Sudan (2015), Zambia (2016) a decision was made to switch to a single dose until more supply became available.
- I talk about cholera in modeling health benefits of optimal dosing; one model suggests that 20-80% more deaths can be averted during outbreaks by using the optimal one dose strategy instead of two doses, although not late during outbreaks.

- More primary research is needed.[58] Vaccine effectiveness can be good (76%, although not in children), but it wanes over time. A new article on effectiveness estimates from DRC vaccinations in 2020 suggest that there is good protection up to three years following one dose.[59] Also promising research on boosting 2-3 years later, with lower dose here and here and some on single lower dose, but this is likely just proof of concept and I have not looked into this deeper.

Recommendation: Given persistent and hard to resolve shortage, this should be one of the main targets for further investigation. There is definitely interest in optimal dosing and schedules, but is the relevant research happening fast enough?

9.3.3 mpox

- There is a case study on fractional dosing of mpox vaccine
- This case is fascinating by comparison to polio, yellow fever or COVID, because it featured a rapid FDA approval for lower dose and a successful rollout in a high-income country. This seems to have worked well.

Recommendation: It feels like mpox has enough interest and research support. However, it may be a crucial case study for other diseases. It would be good to understand the decision making process in the US, interviewing FDA and CDC staff about criteria that were used to recommend lower doses and how this impacts future plans.

9.3.4 rotavirus

- There are four WHO prequalified rotavirus vaccines.[60] Given in 2-3 oral vaccine doses, rotavirus vaccine has been successfully rolled out in the last decade in many countries.
- Global coverage is only around 50% and the market is currently assessed to be at risk due to dependence of supply largely on one manufacturer, but there are new RV in the pipeline and alternative suppliers.[61]
- Estimates of effect differ between LICs and HICs. See here: "not only is the immediate vaccine efficacy lower – 98% in low child mortality countries versus 66% in high child mortality countries – but also the vaccine efficacy decreases faster in high child mortality countries over time". So it has to be considered in

[58] Wellcome and UK's FCDO has sponsored a lot of cholera research, including optimisation and vaccine research, in a project called Joint Initiative on Epidemic Preparedness for Cholera.

[59] It's not the only source of data, but probably the best one; per the study paper: "To date, there has been one randomised trial conducted in Bangladesh between 2014 and 2016, and seven observational studies conducted between 2009 and 2016 in Guinea, Haiti, India, Malawi, Sudan, Zambia, and Tanzania (Zanzibar), reporting effectiveness estimates of a single dose of the current generation of kOCVs. Aside from the trial in Bangladesh, all estimates were based on secondary analyses that the studies were not powered to estimate."

[60] There are 12 different presentations of four vaccines, all given orally in 2-3 doses. 3/4 of all vaccinations use GSK's RV1 in 1-dose tube, which has the advantage of coming in two doses only and no cold storage requirements, but there are now competitors with good shelf life, multidose vials, and no cold chain requirements.

[61] UNICEF's 2022 report on supply and demand is a great summary. A lot of research is already supported by BMGF.

the right setting. In case of shortages, there is some protection from single dose and enough evidence to switch to single dose during shortages: see this paper

Recommendation: it feels like dose sparing it would only be justifiable in acute shortages and the main solution right now is to improve market efficiency and to research more effective RVs. For existing vaccines, are decision makers considering rotavirus dose sparing? What evidence should be generated in advance? It would require connecting with some experts on rotavirus specifically.

9.3.5 yellow fever

- There is a case study on fractional dosing of yellow fever vaccine. Fractional doses were used to control outbreaks starting in 2016.
- Overall fractionation has been proven as a tool for managing outbreaks and it seems the consensus has shifted to the point where it's seen as a viable strategy by decision makers.

Recommendation: Fractionation could be investigated as a cost-saving option. This would probably require interviews with experts. Other than that it seems this is a fixed problem.

9.3.6 tuberculosis

- For childhood vaccination there is long-lasting protection from intradermal vaccination with BCG and probably there isn't much room for improvement, especially considering that new TB vaccines are in development.
- For new TB vaccines (e.g. M72, which launched a large Phase 3 trial earlier this year), optimisation based on immune response data will be difficult, because mechanism of protection is complicated and there are no established CoP's. According to new Gavi strategy, TB vaccines have a very high effect in DALY terms, compared to other vaccines. Therefore it's worth considering them.[62]

Recommendation: (1) investigate how doses were chosen in TB vaccines that are currently in development; (2) interact with groups working on TB immune response to understand the current state of research into correlates of protection.

9.3.7 hepatitis B, DTP, Hib, MMR

- These paediatric vaccines are often combined into multivalent vaccines. They all work well: DTP and MMR avert all deaths, hepatitis B (HBV) >80%; the focus must be on keeping coverage high. Some optimisation possible on timing of doses since several doses are needed, but I have not looked into it further.[63]

[62] It's also worth noting that for the subunit H56 TB vaccine candidate, development of which stopped at Phase 2, there were a couple of modeling papers on non-peaking dose-response; see Billeskov et al and Rhodes et al. In other words, more antigen led to *worse* immune responses. (See also: biology of optimal dosing)

[63] MMR is delivered subcut, others are intramuscular. I believe a lot of microneedle papers from the last decade are on the two toxoid vaccines (i.e. DT in DTP)

- Old DTP (DTwP) vaccine had a discussion on fractionation in 1980s; at a glance fractional doses were shown to work well in avoiding adverse events while still offering good protection, but there were worries about pertussis effectiveness. I imagine for newer DTaP vaccines, where the adverse events are less of a concern, the only reason to move to lower doses would be to reduce costs. The new vaccines are also known to be less effective.
- As far as I am aware, no fractionation was done for HBV or Hib vaccine[64] I have not had time to look into hep C developments while writing this report.

Recommendation: It feels like for these the focus has to be on keeping coverage high (or improving HBV e.g. via adjuvants, to cover the last 10% of the population that do not mount immune response), but I did not have time to investigate this more or interview experts.

9.3.8 pneumococcus

- Pneumococcus conjugate vaccines (PCVs) in children are the success story for advance market commitments.[65] The financing scheme ensured a low price and allowed Gavi to deliver PCV to over 200-300 mln children in the last decade. However, countries are transitioning out of Gavi supported PCV program (source) and the global coverage is at about 50%; more countries also need to introduce PCV. Cost of PCV for countries not included in the Gavi scheme (which I saw reported as about five-fold higher) is one of the main barriers.[66]
- This has motivated some research in recent years. Note that I have not had time to look the research the following research myself. There is a trial in Niger led by Epicentre (MSF). It's likely completed, but I have not investigated it further. Then there is a review in Vaccine which identifies fractionation as a promising method for dose sparing. The same group very recently conducted a trial in Kenya (via KEMRI) and identified 40% dose of Pfizer's PCV as a promising target, this is currently a preprint The paper explicitly states this is tested as a cost-saving measure for countries that are transitioning out of Gavi-supported PCV program, but I do not know how widely considered these schemes are.
- Based on WHO position paper and SAGE WG, I think there is an ongoing interest in both fractional dosing and optimisation of vaccine schedules.

Recommendation: (1) investigate whether the primary research on dosing and schedules is progressing fast enough, (2) connect with researchers to understand if there is any modelling for health and cost impacts of optimisation

[64] There are a lot of papers on timing of hep B vaccine. See introduction here which lists 15 papers. The study itself suggests that in adults there is flexibility in timing of 2nd and 3rd dose of vaccine, but this is not too important for this investigation, since seroprotection rates are high.

[65] There are three PCVs in LMICs: two with 10 serotypes (GSK, SII; similar but not the same) and 13 (Pfizer/Wyeth). The latter accounts for over 90% of vaccinations. All vaccines are 3 doses, given intramuscularly. There are now also some newer versions approved with more serotypes (15, 20-valent). I focus on children here, there is also pneumococcal polysaccharide vaccine (PPSV). PCV is primarily used in children, while PPSV is used in adults and has different serotypes.

[66] See Gavi website article on the transitioning out and [UNICEF report on supply and demand from 2020] (I could not find a newer one) for a lot of useful statistics. See especially the graph on page 6 on the growing demand.

9.3.9 rabies, shingles

- Rabies vaccine is expensive. There is evidence on effectiveness of intradermal delivery with lower doses (Schnyder et al compile over 30 studies) which can reduce costs 2-5 times. WHO endorses ID vaccination with lower doses as post-exposure prophylaxis, but it is not seen as default.
- Shingles is even more expensive. It does not have mortality burden, but it is very painful. Fractionation looks promising based on the only trial ever.[67] Whether the large cost savings from fractionation of zoster vaccine are worth it depends on vaccine economics. Decision makers should investigate this further and it feels cheap to fund this research, but it has small implications in terms of DALYs.

Recommendation: given associated burden, these two items may be "nice to haves" compared to others on the list in terms of health burden: (1) varicella zoster ID trial and (2) understanding why rabies vaccine intradermal delivery is not treated as default. Not essential, but cost savings may be very large, so in the context of fixed budgets the impact may be large.

9.3.10 COVID vaccines

I provide a case study on fractional dosing of COVID vaccines and use COVID as a running example in chapters on modelling benefits and biology. The potential for optimisation is very large, but the SARS-CoV-2 R&D is by far the most resource-intensive R&D domain in vaccine development. New boosters from Moderna have already dropped doses by a factor of 10.

Recommendation: I don't think there is a research agenda for COVID specifically, but there is value in detailed retrospective analysis of conditions needed for endorsement of lower doses in pandemic. See some ideas in decision making on optimal dosing (section 8).

9.3.11 influenza

- Seasonal influenza vaccines are reformulated annually based on predicted circulating strains. Vaccine effectiveness varies year to year due to strain match and individual factors. For routine vaccination, the main topics childhood vaccination, higher dosage in the elderly, development of new vaccines.
- There has been a lot of research on intradermal vaccination in flu. See Section 3.3 of Schnyder et al for a good overview of data from over 30 studies published post-2000 which compare IM to ID and clearly indicate that there is a dose sparing potential from switching to ID doses.
- A lot of dose sparing solutions were investigated following the 2009 H1N1 pandemic.[68] There are some strategic plans for pandemics which stockpile antigens

[67] One of the interviewees estimated a very rough cost of such a trial for this at 250,000 EUR for 100 participants. The difficulty with conducting such a trial is that read-out of immune response results can't easily be done in a lab by the researchers.

[68] Notably, Canada's NITAG, National Advisory Committee on Immunization, undertook an evaluation of fractional doses of influenza vaccine with both IM and ID delivery and recommended against it. I

for particular strains and adjuvants, but I have not been able to find good references for this; it was only mentioned to me by one of experts.

Recommendation: Understand national strategies against pandemic influenza, as these are potentially important. Then some relevant research could also be supported.

9.3.12 malaria

- RTS,S is being rolled out, typically with 3 initial doses and 4th dose later. Difficulties with malaria vaccine rollout have been reported on widely. There are supply and demand problems and logistical issues (cold chain storage is required, children need to be followed up for all four doses). That means that optimising schedules or manipulating doses is very valuable, but also has to happen against the backdrop of all these issues. Worth looking at new WHO position paper (May 2024).
- RTS,S has moderate efficacy. In modeling health benefits of optimal dosing (section 7) I gave examples of how timing of 4th dose appropriately could increase benefits by 25-75%. There is a lot of research on delayed fractional dose. I also talk about mechanisms in biology of optimal dosing (section 4).
- Given low effectiveness of what's currently available, new vaccines may be crucial.[69] There are over 50 vaccine candidates, six in clinical trials, but malaria is a tough target, especially given limited correlates of protection. It's also worth also remembering that RTS,S was developed in 1980s; the focus in malaria should be on market design, as per this excellent summary.

Recommendation: there has been a lot of focus on improving malaria vaccines and their rollout. I'm unsure about this one and I'd recommend talking to experts.

include a long commentary on it in the note on decision making on optimal dosing.

[69] Mechanism of protection currently relies on high titres of antibodies, but it only takes one sporozoite entering liver for the disease to then develop. One of the researchers interviewed for the report was excited by a prospect of a vaccine with modified parasite, which would give T-cell immunity against liver stage. See the chapter on biology of optimal dosing for more context.

10 Research agenda

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

10.1 Conclusions and next steps

Two main points emerge from the notes I compiled:

1. Optimal use of vaccines could have large impacts in particular situations, often working as a complement to market design. Because the biological mechanisms involved are pretty general, there are many candidate vaccines. Both vaccine development and decision making on immunisations are likely not optimal.
2. Optimisation is technologically feasible, but under the status quo can be prohibitively expensive and politically undesirable.

What are the solutions? An obvious, but also pie-in-the-sky, solution would be systemic, aimed at redesigning the paradigm of evidence generation and decision making. In broad strokes, that means (1) conducting faster and cheaper trials on relevant questions and (2) public health decision making that is responsive to new evidence and comfortable with risk-benefit analysis under uncertainty. Effecting even small change to either of these is of course an incredibly complex problem. At the same time, this may be the most worthwhile task.

Instead, I focus on an at-the-margins approach of making many isolated contributions to this problem by a funder spending money wisely to sponsor individual initiatives or pieces of research. What kind of difference could such a funder make?

I suggest a few projects that apply across many vaccines/diseases (see previous section for disease-specific recommendations). I divide this list into

- six projects that could be implemented soon,
- six extra areas to investigate (which could translate to some projects),
- six pathways to future change (things that seem feasible to do, but they need more info).

10.2 Four potential projects that could be done right now

10.2.1 1: Connecting different groups/stakeholders

I got an impression that there are several groups where there is potentially need for more exchange of information. I'd recommend first interviewing

Stage 1, fact finding (deeper investigation/narrower scope than this document), partitioned into particular groups, with a defined set of questions for each:

- Vaccine researchers: current/best practices for first-in-human dose choices, dose de-escalation, and tools that they use for escalating doses and picking dosing schedules in Phase 1-2

- Regulators (FDA, EMA, MHRA): their attitude to vaccine dosing and schedules in clinical development, e.g. requirements and guidelines for dose finding, dose and schedule justification. In particular, understand if there are plans to develop guidelines for dosing/schedules during clinical development.
- Modellers (experts on model-based vaccine/drug development methods): the current state of these tools, prospects for wider adoption.[70]
- Decision makers (WHO, Gavi, at least several national level case studies): what exactly is needed to change vaccine dosing or schedules in specific contexts (i.e. specific diseases, in specific countries, across several case studies)

Stage 2, workshops/working groups; depending on the outcomes of stage 1. Each of this can be a separate project in its own right, this list is grouped for convenience (and because I expect only a couple of them to be genuinely worth doing):

- Conduct a workshop for researchers if it feels like there needs to be some exchange of information on dose/regiment selection (e.g. dose escalation or first-in-human dosing, de-escalation best practices)
- Conduct a workshop putting together researchers and regulators, e.g. to scope potential guidelines for dose selection and dose justification. Possible also work on a brief addressed at regulators for proposed changes to regulatory approach.
- Conduct a workshop connecting clinical researchers and modellers, to discuss value and adoption of models in clinical development.
- Create a working group connecting decision makers and regulators to create concrete proposals aimed at making better and faster vaccine optimisation decisions. (At the time of writing I am already in conversation about this with colleagues at Center for Global Development.)

Broadly speaking, intended outcomes of these would be better vaccine dosing/schedule decisions during development, more dose de-escalation data being generated, more incentive to consider lower doses in seeking approval, and faster decisions around recommending alternative vaccine regimens.

10.2.2 2: Write a "big name" paper to raise awareness of benefits of dose sparing or fractionation

An obvious recommendation in such situations, but in this case there is an extra justification that these topics may genuinely be somewhat unfamiliar to relevant decision makers.[71] Note that the message would be specifically about lower doses or increasing gaps between doses, i.e. stretching supply.

The idea would be to write a research article or commentary that summarises basic information covered in this report and potentially makes several general recommen-

[70] Why investigate this more? Even if researchers switch their mindset to more comprehensively testing more doses and schedules early in vaccine development, there is no guarantee that this will yield optimal results. On the other hand, it's unclear whether some of the modelling approaches are practically valuable or just mainly proofs-of-concept that are not ready to be used in most practical cases.

[71] A good example for work in that category is a recent article showing safety and growing adoption of human challenge studies.

dations. This could be then used to start or progress some conversations with decision makers.

What we know:

- Optimisation has many benefits. It plays especially crucial role in pandemics
- Fractionation and delayed doses has been shown to be beneficial and successfully implemented for several diseases; it's been shown to be feasible even in difficult settings
- It has not been systematically tested and there are reasons to believe it could benefit more existing vaccines

Example recommendations of such an article could be

1. Sponsor more optimisation research for existing vaccines (e.g. de-escalation)
2. More emphasis on socially optimal choices during clinical development (as opposed to leaving it until/after the approval)
3. Develop frameworks for dose sparing decisions during shortages

This project can also include some awareness building, e.g. by op-ed writing etc, but I think this is less valuable than one or two articles by widely respected researchers.

10.2.3 3: Further investigating dose de-escalation: literature review and sponsoring studies

This project is potentially most directly valuable of the four listed here, but the description is short, because I have least information to plan this ahead of time. This project would probably have two sub-component.

Conduct literature review

As one expert put it, "if you had a paper with some exemplars on how you can drop dose 10x would, this would motivate people." A starting point would be to conduct a literature review on choice of doses at each stage of development, to get a sense if they initially under- or overdose. I have not been able to investigate this deeply, but it seems that there isn't much literature on this.

Sponsor some small studies

Following the literature review, there may be some obvious promising vaccine candidates for which we would like to systematically conduct de-escalation studies. Some isolated examples already exist and are cited in this report, but this is usually done ad hoc and it would take more expertise.

10.2.4 4: Support proof-of-concepts for trials

I propose trying out two proofs of concept for clinical trials that can help inform the choice of optimal vaccine schedules.

Phase 3 RCTs with multiple doses

If late into clinical development several doses or schedules look like good candidates in large-scale trials, it may be worth randomising people into several arms/schedules.[72] COVID-19 is a good example; if 50, and 100 mcg doses of Moderna's mRNA-1273 had similar immunological profile following Phase 2 and both seemed likely to work, why for Phase 3 not randomise patients 1:1:2 to 100 mcg, 50 mcg, and placebo respectively? Data in vaccinated patients could then either be merged to calculate a single efficacy metric (as it was de facto done in the AstraZeneca vaccine trial) or synthesised through dose-response modeling (using immunological data). Such a trial may still be underpowered for proving non-inferiority of the lower dosage, but it provides many times more data than the original trial.

Clinical trials of efficacy against infection, not just against disease

Let us imagine a hypothetical epidemic, where cases are growing exponentially and the spread is not controlled, but a new vaccine potentially offers some protection against infection. The optimal dosing in the case of transmission-breaking vaccine is going to be different.[73] Thus generating data on sterilising immunity may be very important for vaccine optimisation. This may look like "traditional" field trials with regular testing of a large population and studying secondary infections.

What to do

In both of these cases the objective would be two-fold

(1) consider trial design under realistic conditions (e.g. based on retrospective analysis of COVID)

(2) describe both risk-benefits of statistical trial designs that are not commonly used, in the sense of utility of generated information for both general licensure and making more optimal vaccine schedule choices (e.g. a trial with multiple doses may get closer to socially optimal dose but reduce overall approval probability), but also accounting for patient risks and costs

(3) (optionally) in both cases consider how these data could be generated by using human challenge trials

10.3 What I still don't understand

There are several areas that feel like they could yield some tangible projects, but which I was not able to investigate for this report because I ran out of time or were not able to schedule relevant meetings.

- How market design and AMCs could impact not just supply, but also optimisation. Related to this, get more of a perspective of health economists: ones working in

[72] Why is this not done? Developers don't see this as an option, because trials are so expensive and they would like to avoid anything that would increase trial sizes, even modestly. Most researchers and regulators may be averse to considering this because they are generally resistant to synthesising information in clinical trials: we demonstrated this unwillingness to generalise in several examples throughout the document.

[73] If we knew the vaccine offered protection from infection, then it may be optimal to quickly give it to as many people as possible (at the dose at which there is enough efficacy against infection), to break transmission/reach herd immunity. If that is not the case, then we may focus on vaccinating the at-risk individuals (at the dose at which there is efficacy against disease).

LMICs on acceptability and value of lower doses and ones specialising in pricing, to understand how unilateral decisions to fractionate would impact prices.

- Interview experts on optimisation in particular vaccines, especially on connections with policy. (More context in summary of optimisation targets.) I have three particular recommendations: Andrew Clark on optimisation of rotavirus vaccines, Ian Spicknall (and someone extra at FDA) to better understand the case of mpox modeling and approval (which may have implications for future epidemics in wealthy countries), Andrew Azman or Justin Lesler on cholera vaccine.
- Model-based vaccine development experts, together with some vaccine developers, to understand current decision making process and how better tools could benefit the process. Examples of interviewees here would be LSTHM modellers and Tom Evans, ex-CEO of Vaccitech.
- Find policy experts knowledgeable about national strategies against pandemic influenza and other pandemic threats, assess existing plans.
- Investigate more practical questions on ID dosing. For example, what are the barriers to widespread ID vaccination in terms of availability of LDS? Can we make LDSS more widely available? Is it feasible to accelerate availability of jet injectors?

10.4 What to do next

These are further projects that appear feasible and worthwhile, but they work less well as immediate follow-up projects: for example because (1) scope is large, (2) scope needs to be defined better, (3) there are some "path critical" steps on the way, or (4) we are less certain how directly they would relate to more optimal choices.

- **Primary research, correlates of protection.** This one is most wide-ranging and perhaps obvious: if we want to avoid making dosing decisions based on clinical trials of 10,000's of subjects that compare different doses, we need strong understanding of how immune response is achieved. To name one specific target here (from my interviews), while we have correlates of protection for influenza, we also know that with adjuvants the mechanism of protection changes. So a simple model of dose-response will predict low efficacy for low dose of flu vaccine coupled with adjuvants, but some experimental data suggests this is not the case. Supporting research into this type of problems would be crucial for optimisation in pandemic influenza.
- **Emphasise dosing/schedules and public health perspective in regulatory guidelines; encourage/demand optimisation for publicly funded vaccines.** As I discussed, the guidelines have little to say about justification of optimal dosing and even less about public health benefits. It is not the job of regulators to worry about supply, but if multiple doses perform similarly, they could encourage manufacturers to seek approval for a range of doses. There are obvious reasons why we should not simply push too hard to approve lower doses, e.g. immune escape; usually it's better to overshoot with doses, if there is enough sparing. But this is not an argument against generating relevant data for dose sparing,

which regulators could request from vaccine makers. This should especially be done in the cases where vaccines are publicly funded.

- **Push for clinical trial data to be made available, quickly.** A lot of data that are useful for developing new vaccines are siloed. For example, if I am developing a new CVOID mRNA vaccine and want to understand how waning of protection depends on dosing, I can probably develop good priors (= make better decisions for my trial) based on individual-level immunogenicity time-course data from Pfizer and Moderna trials. Currently the best case scenario is that I can find some of the relevant data and then digitise some plots by hand. Same point about doing this more aggressively for tax-sponsored vaccines applies here.
- **Comprehensively and continuously identify gaps in evidence on optimal use.** This report attempts to point out some gaps, but it is nowhere close to a comprehensive review for all vaccines that are in routine use or clinical development. A group focused specifically on this type of evaluation (and continually bringing them into hands of relevant groups: WHO, Gavi, NITAGs, ...) may be valuable. This may be simply fostering collaboration between health technology assessment groups rather than setting up any new capacity, but in any case it needs to be explored.
- **Establishing clear evidence requirements and framework for dose sparing decisions, especially in pandemics.** There has been a lot of discussion about how to "beef up" vaccine prioritisation decisions both globally and in particular countries. I have not been able to investigate this in detail, but it seems that what would be needed here is to bring more of optimisation perspective into systems that exist or are being set up. In plain text, this is about having a blueprint for relevant decision makers that they could use to make better choices on dosing/schedules in the next pandemic.
- **Establish feasibility of intradermal delivery**. ID has been proven as a viable alternative for many vaccines and may be necessary for future pandemics. However, decision makers seem wary of it: I discussed in detail the assessment of ID delivery of influenza vaccines. Finding opportunities to roll it out at scale, while simultaneously working with decision makers may help overcome this. There have been various large proof-of-concept studies for ID delivery of IPV, but I wonder if this needs to be done for other vaccines or in more specific settings.
- **Fostering commercialisation of new administration methods.** This one is a bit outside of my area of expertise, but the benefits to optimal dosing are clear: if the ID delivery devices were cost-effective and more convenient than IM delivery, then it would be easier to decrease/adjust dosing.

10.5 Five reasons to be negative about these proposals

There are many criticisms at many levels that can be mentioned here, but I wanted to reiterate five points that I may have not made sufficiently in my notes:

- New technologies may blunt the value of fractionation in the longer term. New vaccine platforms will deliver better vaccines, cheaply and with supply difficulties. Increasingly, the move toward combination vaccines and pre-filled syringes

may close the window for the type of fractionation I focussed on here.

- Optimisation is always just a complement to maximising supply and coverage. And its uncertain (to me) what effect changes to dosing would have on costs and supply.
- There is no immediate exciting research that I was able to identify. E.g. none of my interviewees or sources that I read had a specific suggestion for an optimisation study that needed to be funded urgently. All the projects discussed are a form of gradualism.
- It will always be hard to meet the threshold of certainty that decision makers require. For example, even with a much more comprehensive research agenda on optimisation of COVID vaccines in 2020-2021, I still suspect that data on lower doses would not be deemed sufficient.
- Any optimisation is difficult and doesn't work in isolation. If trying to speed up vaccinations, the law of the minimum kicks in: sometimes there are other logistical, administrative, programmatic constraints. You have to plan for all of these things in order to make a difference.

I think that's all! Thanks for reading, this has been really nice to work on.

The rest of this document is an appendix containing my four case studies.

Appendix: four case studies

11 Case study: fractional dosing of COVID vaccines

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

Important note: *this is the first case study I drafted for this report and it's a bit dated/too basic; I wanted to focus on other new material rather than refresh it. Other sections of the report have much more relevant information on COVID, so I'd simply encourage reading other sections first.* ***Lastly, this is about 2021; I talk about the important case of lowering doses of boosters for Moderna mRNA vaccines elsewhere in the report.***

11.1 Scale of shortage of COVID vaccines

COVID has caused over 774 million confirmed cases and a death toll currently (early 2024) estimated at 29 million excess deaths. Despite safe and effective vaccines being available since December 2020, the estimated number of excess deaths was particularly high in 2021, at 13 million (44% of the total death toll), and remained high in 2022 (7.4 million), especially in countries with low vaccination rates.

The rapid rollout of vaccines[74] saved tens of millions of lives - one paper estimates between 13.7 million and 31.4 million deaths were averted during the first year of vaccination alone (Watson et al. 2022).[75]

Due to the scale of the pandemic and the novelty of the vaccines, supply constraints were inevitable. The vaccine supply chain was complex and plagued with bottlenecks on key inputs, ranging from bioreactor bags to plant extracts. High income countries, which tended to secure vaccine supply by signing contracts early, had given 1.67 vaccine doses per person by the end of 2021, rising to 2.22 by the end of 2022; for low income countries these figures were 0.10 and 0.35, respectively.

In an effort to increase vaccine access in low- and middle-income countries (LMICs), the COVAX initiative was launched in April 2020, coordinated by UNICEF, Gavi, CEPI, and the WHO. The initiative pooled funds from wealthier nations and organisations to buy vaccines in bulk and distribute them across participating countries: by its close in December 2023, 146 countries had received doses. Unfortunately, recipient countries (largely LMICs) often got their vaccines late and in insufficient numbers. Considerable quantities of doses donated via COVAX were wasted because they were donated close to their expiration dates.[76]

[74] The genetic sequence of SARS-CoV-2 was published on 11 January 2020, and the first vaccine human clinical testing began 2 months later, on 16 March. The first vaccine that underwent large-scale clinical trials was approved on 2 December 2020, representing an unprecedented speed of vaccine development. Previously, the fastest development, from viral sampling to approval, was a mumps vaccine in the 1960s which took 4 years. For an overview of COVID vaccine development, see Thanh Le et al. (2020), Ball (2020).

[75] This model by a team at Imperial College is quite subjective (especially as it's hard to design a realistic no-vaccination counterfactual) and it's not possible to estimate these quantities precisely, but it does underline the huge magnitude of benefits of vaccination.

[76] COVAX aimed to deliver 2 billion doses by the end of 2021. By the end of the scheme 2 years later, that number had still not been reached. Over 100 million COVAX doses were rejected in December

11.2 Potential rationale for fractional dosing

In this section I focus on the perspective of dose-response relationship on neutralising antibodies and vaccine efficacy against disease. I talk about COVID more broadly in biology of optimal dosing.

Unlike some other situations in which fractional dosing has been used, for COVID it was likely that there would be decrease in individual efficacy when using lower doses. Yet fractional dosing offered a potential solution to the shortages and wastage. It could have accelerated vaccinations globally and all countries could have benefitted from more supply.

In Więcek et al. (2022) together with co-authors we attempted to summarise individual-level biological evidence for fractional dosing as it stood in 2021 and conducted epidemiological modeling. (The conclusions in the rest of this section are largely drawn from that paper.) In Phase 1/2 clinical trials, different doses of several vaccines were tested.[77] There was no statistical difference between the immune responses (in the sense of neutralising antibody, NAb, titres) provoked by fractional doses of certain vaccines and the larger standard doses.[78]

The strong, predictive relationship between NAb levels and vaccine efficacy was emphasised soon after vaccine approvals, e.g. by Khoury et al. (2021). Taking this strong relationship as a given, we hypothesised that fractional doses of some vaccines were likely more efficacious than some of the standard doses of other vaccines that were approved at that point.

We used an epidemiological model to simulate a range of pandemic scenarios where vaccinations are constrained by supply shortages.[79] We found that even under conservative assumptions the fractional dosing regimes resulted in both fewer infections and fewer deaths in vast majority of scenarios. The differences could be very large, reducing deaths even by 50% under some conditions, but the magnitude of benefits really depended on the scenario.

Another epidemiological model by Du et al. (2023) estimated the cost-effectiveness of using fractional booster doses in India.[80] They found that fractional booster doses could yield health-related net monetary benefits of up to $11bn over 200 days, com-

2021 alone, largely because they were delivered too close to their expiration date. This was especially problematic in LMICs due to poorer logistics and storage systems (including refrigeration). In February 2022, there were over 1.6 million expired doses in the vaccine stocks of 19 African countries (source). In November 2021, around 1 million doses expired in Nigeria alone (source).

[77] These dose-ranging studies included doses that were both larger and smaller than standard doses. They had small sample sizes, ranging from 15 to 190 participants.

[78] Indeed, the fractional doses of some vaccines exceeded the NAb response of other approved vaccines. For example, the 50% dose of Moderna's vaccine (the best-studied vaccine in terms of dose-ranging) produced a higher NAb response than the standard doses of Oxford/AstraZeneca's, COVAXin's, Johnson & Johnson's, and Pfizer's.

[79] We looked at different scenarios where we varied many key assumptions: efficacy of the standard dose against death and infection, ratio of efficacy of fractional dose to standard dose, epidemic growth rate, and fraction of dose. We assumed that speed of vaccination is inversely proportional to dose, i.e. 1/4 dose also means that four times more doses can be administered each day.

[80] Their paper specifically examines the AstraZeneca vaccine. The epidemiological model is age-stratified and incorporates the AstraZeneca vaccine's efficacy drop-off over time.

pared to full (unfractionated) booster doses.[81]

Yang et al. (2022) conducted a systematic review and meta-analysis of dose-finding results (including trials of fractional vs standard doses), estimating the dose-response relationship in terms of antibody response. They also predicted vaccine efficacy based on immune responses. They find that fractional doses of mRNA and protein subunit vaccines are likely to induce immune responses that result in over 50% efficacy against COVID, including its variants.

11.3 How could fractional dosing be implemented in clinical practice?

Similarly to other case studies I present, there are practical difficulties associated with fractional dosing, which vary depending on the implementation method used. Advisory groups would have to assess how many times vials can safely be punctured and whether smaller volumes can consistently be drawn into syringes. Healthcare workers would likely have to be trained to administer fractional shots safely. Adjusting the fill and finish process could involve a significant short-term cost (in terms of both time and money) due to the scale of vaccine manufacturing and the complexity of supply chains and delivery systems. Other bottlenecks in supply chains are also likely to impede the expansion of vaccinations: there was a shortage of glassware such as vials and syringes during the COVID pandemic.

However, these issues were completely parallel to what we describe in the yellow fever and polio case studies, suggesting that they could be overcome.

11.4 Other solutions to shortages

One potential solution to vaccine shortages is simply to increase supply capacity. But during COVID, despite huge worldwide demand, there was an acute shortage for around a year - vaccine manufacturers couldn't increase production fast enough. This cost many lives. In India, the number of vaccine doses per 100 people was 0.0 in January 2021, only rising to 23.2 by the end of June 2021 (compared to 115.4 in the UK). Between April and June 2021 inclusive, estimated excess deaths per 100,000 rose from under 100 to just under 260 in India, compared to a decline from just over 170 to under 165 in the UK. Similar cases of low vaccination rates followed by high mortality occurred across LMICs.

Another option is to improve incentives and vaccine market design. (Josh: do I also mention the fact that vaccine trials are optimised for individual outcomes (maximise benefit:risk ratio) rather than public health outcomes?

And how licencing process is first past the post, so main reward for producers is being the first to develop a vaccine meeting the target profile, which discourages experimentation during the development process and after the licence is granted)

[81] The health-related net monetary benefit of using ⅛ fractional boosters relative to standard boosters is estimated to be $6bn and $2bn under slow and fast transmission scenarios, respectively. If delivery costs can be divided by fractionation, these figures are $11bn and $2bn, respectively. Note, however, that these central estimates have wide confidence intervals that incorporate negative values.

Castillo et al. (2021) estimates that there is a huge gap between the private value and the social value of an additional vaccine course. The former, in terms of the price manufacturers receive, is between $6 and $40. The latter is between $500 and $1000. This huge positive externality means that vaccines are massively underprovided by manufacturers relative to the social optimum - government intervention is required to address this. However, large-scale government support for vaccination development, manufacturing, and rollout were already in place in many countries during the pandemic.[82] They were vital for expanding vaccination supply, yet shortages remained.

Another strategy is dose spacing - increasing the intervals between doses. In the first half of 2021, many countries, at the suggestion of their national immunisation advisory groups, undertook this strategy, in order to conserve limited vaccine supplies and expand protection to more people (using a "first doses first" strategy). However, the emergence of new virus strains, against which single doses were less efficacious, as well as the gradual easing of supply shortages, curtailed the use of dose-spacing strategies.

11.5 Gaps in evidence

Implementation of fractional dosing was perhaps not feasible for several reasons. I discuss policy questions in a separate note. Here I start with clinical aspects only, summarising what information was and wasn't available.

As mentioned above, we only have Phase 1/2 evidence for fractional doses, and even these trials had small sample sizes. The model in Khoury et al. (2021) underpins the assumptions of fractional dosing's efficacy. It identifies a strong predictive relationship between neutralising antibody levels and vaccine efficacy for standard doses, however, neutralising antibodies (NAbs) are only one aspect of immune response. At the time, there was debate on how closely NAbs correlated with disease protection. There is currently no clinical data on how fractional dosing may impact cell-mediated immunity, which is especially associated with durable protection from severe disease.[83]

There is also a lack of evidence on the duration of fractional doses' effectiveness. "Duration of Effectiveness of Vaccines Against SARS-CoV-2 Infection and COVID-19 Disease: Results of a Systematic Review and Meta-Regression - The Lancet" (n.d.) finds that, on average, vaccine efficacy or effectiveness against both infection and symptomatic COVID disease drops by over 20 percentage points from 1 month to 6 months. For effectiveness/efficacy against severe disease, that figure was 10 percentage points.[84] Fractional doses could plausibly have worse drop-offs in protection over

[82]The best known funding programme was the US federal government's Operation Warp Speed, which gave billions of dollars in funding to pharma companies to develop vaccines. It also invested in manufacturing capacity for each vaccine candidate during their development to scale up potential future production. Operation Warp Speed also involved public and private partnerships for vaccine development. The UK government also provided billions of pounds in funding for the vaccine rollout.

[83]Więcek et al. (2022) argue that, due to the connection between cell-mediated immunity and protection from severe disease, there is unlikely to be a large dropoff in protection from severe disease when fractional dosing is used.

[84]The authors find that 81% of vaccine effectiveness/estimates remains above 70% after 6 months. Wu et al. (2023), published almost exactly a year later, found vaccine effectiveness fell, within a year, by 21,

time. This uncertainty has implications for assessing the public health benefits of fractional dosing. Specifically, fractional doses could merely prolong life until the next pandemic wave (possibly of a more infectious variant), where protection drops off and the death toll rises.[85]

Another concern is that, if fractional doses offer less protection (i.e. only partial immunity), selection pressure could rise, resulting in the emergence of more infectious and vaccine-resistant variants. (I also talk about this more in modelling health benefits of optimal dosing.) Cobey et al. (2021), however, claims that preliminary evidence indicates fractional dosing (and other dose-sparing strategies) would actually reduce the risk of vaccine-resistant variants emerging. As long as vaccines provide some protection from resistant variants, the reduction in prevalence (number of cases) and incidence (rate of new cases) is likely to reduce the rate of variant emergence and the speed of adaptation. In other words, the public health-level benefits are likely to outweigh the risk of vaccine-induced evolution. However, modelling this to get an idea of how the risks trade off against the benefits is complicated; we discuss some attempts in another note.

Other concerns include how the effects of fractional doses may vary across demographic groups (particularly vulnerable groups such as immunocompromised or elderly individuals), and the magnitude of the positive effect of a reduction in the incidence of side effects from smaller doses.

However, for at least one vaccine, the consensus was that the original standard dose was set high: the original recommended dose for the Moderna vaccine was 100µg.[86] This later changed to 50 µg.[87]

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13, and 5 percentage points for infections, hospitalisations, and mortality, respectively. These figures were for all COVID strains, including delta and omicron.

[85] This "rebound" mechanism is discussed in Więcek et al. (2023), in the more general context of earlier vaccination. The authors use a model to estimate how many deaths would be averted by earlier vaccinations. However, extending the time horizon of their model can actually result in an increased number of deaths relative to the status quo, due to the model's sensitivity to the duration of vaccine protection and the "rebound effect": reductions in mortality in the initial wave are offset by higher cases and mortality in later waves.

[86]

[87] "U.S. COVID-19 Vaccine Product Information CDC" (2023): see "Moderna At-a-Glance".

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12 Case study: mpox vaccine

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

In a sudden public health emergency caused by mpox in 2022-23 there was not enough supply of the only mpox vaccine (Jynneos/Imvanex, made by Bavarian Nordic) to immunise the at-risk population (men who have sex with men). Unlike other case studies presented, this affected all countries, e.g., in the US over 3mln doses were needed to vaccinate high-risk population and the estimated shortage was 50%. UK had a stockpile of 50,000 and moved to order 150,000 (source). It's safe to assume that in other countries the shortages would be larger.

Jynneos/Imvanex (live smallpox and mpox vaccine) was initially approved for SC injection in two doses. The fractional dosing approach is to give two 1/5 doses (0.1mL instead of 0.5mL) intradermally. This is a "regular" vaccination, just done at 5-15 degree angle and using a smaller needle and syringe.

What was done in 2022

In August 2022 FDA gave emergency use authorization (EUA) for this FD based on the only RCT from 2015 (n=300, comparing 0.1mL ID arm to 0.5mL IM); immunogenicity was deemed "nearly identical," as was safety (source). A few things to note:

- However, there are no defined correlates of protection against mpox, i.e. we don't actually know how well mpox virus-neturalising antibodies protect against disease or transmission, so this was definitely a decision made with considerable uncertainty.
- Note that this was an actual EUA for this specific mode of application. This is in contrast to other recommendations which are made not by drug regulators and constitute off-label vaccine use guidelines.
- CEO of Bavarian Nordic wrote to the FDA comissioner to raise some concerns about using small sample to make decisions
- EMA's Emergency Task Force advised use of FD based on the same data. UKHSA piloted use of FD and UK's JCVI recommended use of intradermal doses.
- UK's pilot was also because they wanted to resolve programmatic issues

In parallel there was a debate on First Doses First. In the US FDA advised states against it, while some experts suggested that it may work.

What we learned since 2022

Following the public health emergency we learned that:

- Based on an immunogenicity study (N=225), the antibody titres were similar between SC full dose and ID 1/5 dose two weeks after second dose; 1/10th ID dose was inferior (source).
- 2 fractional doses are superior to one SC standard dose and no different to 2 SC standard doses per this NEJM study (N=145).

- A large mpox vaccination effectiveness study (case-control design, N = 2,193 cases, 8,319 controls) found lower effectiveness of one dose compared to two doses (VE = 36% with one, 66% with two doses) but no comparison of effectiveness of ID vs SC administration route as the study was not powered to detect them.
- Studies also note that a very important determinant of immune response is previous smallpox immunisation. There has been some discussion about general level of antibodies following two doses being low and therefore need for a third dose of vaccine in the future.
- Data from US roll-out suggests that both options are well-tolerated, although ID has more local reactions. People complete their 2 doses at same rates regardless of ID vs SC.

It seems that generally the conclusion is that this worked well, but there isn't yet enough evidence about ID to make strong conclusions.

Modelling

In retrospect fractionation was very likely the right decision, but what about public health benefits assessment at the time?

Only modeling in the public domain that I am aware of has been done by Dimitrov et al. This is adaptation of a compartmental epidemiological model (a very typical approach) applied to a population in Seattle, by experienced modellers; I discuss it in modeling health benefits of optimal dosing. I was told by one of the authors that this did not drive any policy.

However, there has been a lot of modelling of mpox outbreaks in the US done by a group at CDC led by Ian Spicknall, e.g. here. I am uncertain what role the modelling has played in the decisions and it would be good to understand that.

13 Case study: inactivated polio vaccine

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

There is no cure for polio, but mass vaccination since the mid-20th century has eradicated the disease in many countries. Since 1988 the goal has been a complete eradication of polio. This was achieved using the live-attenuated (Sabin) oral polio vaccination (OPV)[88]; for an overview see Tevi-Benissan et al. (2017). However, OPV can undergo genetic changes during intestinal replication, resulting in vaccine derived polioviruses and is capable of causing paralytic polio[89].

A viable alternative to OPV which does not suffer from that problem is an inactivated polio vaccine (IPV). However, producing IPV requires careful biosafety measures, which makes it more expensive. Okayasu et al. (2017) report that supply was less than half of the initial commitment made in 2014. Around that time, IPV cost (procured via UNICEF) was 20 times higher than OPV. The total costs of including IPV in routine immunisation (alone or in combination with OPV) are roughly 3-5 times higher than OPV.[90] For cost projections that I cite see Thompson and Kalkowska (2021).

This means that most countries use a combination of (varying number of doses) OPV and "supplement" it with IPV, as has been recommended by the WHO since 2013, ideally with two doses of IPV.[91] This increased demand has led to higher costs: the last WHO's Global Polio Eradication Initiative budget was about USD 1 bln per year. More importantly, it led to a continuing shortage of IPV in middle and low income countries, which have been ongoing since the middle of 2010's.

13.1 Why was fractionation needed? How is it done?

The long-term solution to this shortage is to establish a local capacity to produce IPV from attenuated Sabin strains, which requires less stringent safety precautions as the conventional production of IPV. We will return to that below. In parallel a new version of OPV (nOPV) was developed and WHO and UNICEF are working to expand supply of OPV (Bandyopadhyay and Zipursky 2023).[92]

During the period of transition to new OPV, using fractional doses of IPV (fIPV) has

[88] Sabin's oral vaccine (live attenuated) was designed to prevent vaccine-induced polio which Salk's vaccine (killed virus) caused more of; it's worth reading its short history here

[89] The risk of this occurring is very low (1 in 1,000,000). OPV and IPV also have distinct advantages, e.g. different properties in breaking transmission, with IPV (which, unlike OPV, mainly provides humoral immunity) being unable to stop the spread of polio. I simplify here by referring to "OPV" whereas in reality we differentiate between several OPVs, which can target various combinations of three serotypes of polio; (wild) type 2 has been eradicated, therefore countries have been moving from trivalent to bivalent OPV. Meanwhile IPV can be made from wild types or from Sabin strains, more on that in the text. But all of that is incidental to our discussion of IPV.

[90] I simplify things to make them legible: there are about two dozen different immunisation strategies, most of which combine a version of OPV with an IPV over several doses.

[91] This was recommended as part of the switch away from old OPV, which happened circa 2016.

[92] The Sabin strain IPV was developed by Sinovac with support from the Gates Foundation and is currently undergoing Phase IV clinical trials. The WHO prequalified the vaccine for use in June of 2022 press release and some countries had already licensed it for use.

been a common solution to supply shortages (Roland W. Sutter and Zaffran 2019). The WHO SAGE supported the development of the fIPV approach for several years and has endorsed its use since 2016, the same time that countries were recommended to introduce one dose of IPV in the polio vaccination.

Fractionation of polio vaccine has been tested in the past and even used in 1950s in Denmark.[93] Therefore there was already good reason to believe it would be a viable alternative to standard doses and the WHO SAGE also had several years to collect additional data.

The fractionation of IPV (fIPV) is two 1/5 doses intradermally compared to a single intramuscular dose. This is done using a BCG needle, but can also use an injection device (adapter or jet injector), which I will discuss in how change in dosing is implemented in practice.[94]

13.2 What were the results? What is the current state of the polio vaccinations?

Shortage of IPV seems to have started at least in 2014, with a lot of reports of global shortages in 2016. Back in 2016 the hope was that it would be resolved in about two years. However, that means that several birth cohorts in many countries missed immunisation with IPV. A 2019 report projected shortages would occur for another few years.[95] However, this seems to have been resolved in the last few years. Per UNICEF 2023 update there is now sufficient supply for countries to give two doses of IPV from five different manufacturers.

Meanwhile, Sri Lanka, India, Bangladesh, Nepal, Cuba, Ecuador, Oman, Somalia, Gambia (and possibly more countries, as I have not searched systematically) have all used fractional dosing of IPV.

New data suggest that the fIPV approach also improved immunogenicity: a literature review from 2017 identified four studies which showed large improvements in seroconversion and antibody titers. More recently, we can find similarly positive findings from Ecuador, evidence that antibodies decline similarly for fractional doses and full doses (here) and for superiority of 2 fIPV doses over 1 full IPV dose in India (here). A 2021 meta-analysis confirmed its efficacy across 14 studies (Mashunye et al. 2021).[96]

Generally immunological studies conducted during rollouts seem to conclude that fIPV

[93](Okayasu et al. 2017): "Trials conducted between 1957 and 1979 … as well as pilot studies … in India in the 1990s, found that, when provided as the primary series or as a booster dose, an intradermal fIPV dose of 0.1 mL (one fifth of the full 0.5-mL dose) induced a similar immune response as a full intramuscular dose. Despite these promising results, fIPV was not widely adopted except in Denmark, where it was the standard method of IPV vaccination in the mid-1950s."

[94]fIPV also requires extra punctures of vials, from 10 to 50 times, since the vials are 2-10 doses; Jarrahian et al. (2017) assessed that this is okay to do.

[95]Some contemporary reports on shortages (mostly for completeness). In several countries a vaccine-derived poliovirus occurred after 2016 following the switch in immunisation practice (Somalia, DRC, Nigeria), see Roland W. Sutter and Cochi (2019). Shortage in India: link 1 and link 2. Intermittent supply of polio vaccine in Ghana (due to insufficient supply): link 1 and link 2 mention shortage of all vaccines, including OPV.

[96]Conversely, data suggest that a single fractional dose is inferior to a single standard dose.

was a viable alternative: Sri Lanka, Bangladesh, Gambia, Somalia, Oman, although I have not read them. On the cost side, based on detailed review by Thompson and Kalkowska (2021) it seems that switching to fractional doses had a potential to reduce the total cost of polio immunizations by about 40% (a rough approximation by me; I use past tense as these costs are dynamic, depending on supply/demand).

While on the way to eradication, polio continues to affect even wealthy countries: in 2022 US and Israel found type 2 vaccine-derived poliovirus and UK and Canada found it in in environmental samples. There are recent stories of cases in e.g. Mozambique and Burundi.

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14 Case study: yellow fever

These notes are based on a shallow investigation into optimal dosing conducted in 2023–2024. This material may not be up to date and is still being revised by the author (autumn 2026).

Yellow fever (YF) is endemic in most of Sub-Saharan Africa and South America (tropics and sub-tropics. YF is transmitted by *Aedes aegypti* and has a high reproductive number. There are 200,000 cases per year, 90% in Africa, with up to 80,000 deaths, although estimates are imprecise.

WHO recommends vaccinating infants (9-12 months, given together with measles vaccine) against YF in endemic countries. It's a simple live attenuated 17D vaccine (in use since 1938, developed by Max Thiler at Rockefeller Foundation), costing about a dollar per dose.

A single dose is good enough due to antibodies produced being sufficient to provide immunity for the rest of your life. Hence YF is a good candidate for fractionation (see the classification in biology of optimal dosing). The vaccine works almost perfectly: seroconversion rate is almost 100% and immunity develops fast (7-10 days).

14.1 Supply shortages during outbreaks

There has been a renewed push to increase vaccinations this century in high risk places due to increases in numbers of cases. WHO is leading a campaign to eliminate YF epidemics by 2026.[97][98] The global population at risk is 900 mln, with 2/3rds of it in Africa.

Countries (e.g. recently Nigeria) have been adding YF vaccination to their routine immunizations. YF vaccines are manufactured using the "traditional" process which involves eggs (yielding 300-400 doses per egg), which is slow and makes it difficult for manufacturers to rapidly increase supply due to the rate limiting reliance on eggs in the manufacturing process (Vannice, Wilder-Smith, and Hombach 2018).

The supply grew from 20mln around 2000 to 90mln in 2016 and then >150mln in 2019, 2020.[99] However, the demand still outstripped it: Montalvo Zurbia-Flores, Rollier, and

[97] Lindsey et al. (2022) report: *"the multi-partner global Eliminate Yellow Fever Epidemics (EYE) Strategy was established in 2017 to improve detection, outbreak preparedness, and response. The EYE Strategy has 3 main objectives: (1) to protect at-risk populations through immunization; (2) to prevent international spread of the disease through vaccinating high-risk workers, enforcing International Health Regulations and supporting the development of resilient urban centers; and to contain outbreaks rapidly by improving surveillance and timely access to validated diagnostic tests and emergency vaccines."*

[98] Urbanisation in Africa is a factor, due to increasing risk of large outbreaks in cities, where it's hard to break transmission and burden would obviously be much higher. To stop epidemics, WHO recommends coverage of 80%, but modeling suggests 90%-95% in some places (esp. in Africa, urban areas) Ndeffo-Mbah and Pandey (2020)]

[99] Supply (per Wikipedia): "As of 2013, there were four WHO-qualified manufacturers: Bio-Manguinhos in Brazil (with the Oswaldo Cruz Foundation), Institute Pasteur in Dakar, Senegal, the Federal State Unitary Enterprise of Chumakov Institute in Russia, and Sanofi Pasteur, the French pharmaceutical company. Two other manufacturers supply domestic markets: Wuhan Institute of Biological Products in China and Sanofi Pasteur in the United States"

Reyes-Sandoval (2022) reports that yearly shortage is something about 60 mln doses on average.

The bulk of existing supply goes to routine immunisation and preventive mass vaccination. That demand is typically met and UNICEF also stockpiles several million doses each year for outbreak. However, stockpiles are typically not sufficient, especially given logistical constraints. Lindsey et al. (2022) summarise the situation well. In 2016, there was a major YF outbreak in Angola that spread to the Democratic Republic of Congo (DRC) and threatened to spread to China as well via expatriate workers who traveled home. The outbreak required 30 million people to be vaccinated as quickly as possible, which promptly exhausted available supplies. Also in that period another outbreak was observed in coastal Brazil, where YF had not been observed for nearly 80 years. Same authors note that more outbreaks occurred in dozen African countries in 2021 and early 2022 alone.

To reiterate, the issue is not just one of insufficient stockpiles, but also timeliness: when outbreaks occur, it's hard for sufficient number of doses to reach the at-risk population even when sufficient supply exists "on paper", due to logistics and wastage.

14.2 Role of fractional dosing

The WHO recommended use of FD vaccines to control YF outbreaks in 2016 (WHO n.d.). The rationale for using fractional dosing (FD) for YF outbreaks largely arose from a pressing sense of pragmatism. Due to the high effectiveness of the yellow fever vaccine, fractional dosing was seen as a common sense solution. Their rationale for recommending FD was largely based on 3 randomised controlled trials performed between 2008 and 2014 that explored the efficacy of fractional doses compared to full doses of YF vaccines.[100] Each of these three trials found that fractional doses were non-inferior to full dose vaccines in immunogenicity, though all trials did share the same limitation of small sample size. Despite the limitations of the references available, the WHO approved use of FD in response to the multiple pressing YF outbreaks around the world in 2016, with the caveat that FD should only be used during outbreaks where vaccine supplies are limited.

FD proven a suitable solution to mass vaccination during the outbreaks of 2016, with more than 7 million people in the DRC vaccinated in 1 week (Roozen, Roukens, and Roestenberg 2022) and 17 million people vaccinated in Brazil (source). These results were hardly surprising, given that average doses of YF vaccine are 12-40 times more potent than the WHO's recommended minimum (Vannice, Wilder-Smith, and Hombach 2018).

Some modeling was also done to understand if future outbreaks could be similarly controlled with FD, e.g. by Wu et al. (2016) . I discuss it in section on modeling population benefits.

[100] one, two and three

14.3 How is fractionation implemented?

Dose: Full dose is 0.5mL, distributed in a 2, 5, 10 and 20-dose vial. Fractional dose is 0.1mL. Route: While intradermal delivery was assessed, the WHO recommendation and clinical practice is for subcutaneous or intramuscular delivery. There are some programmatic considerations[101] for FD but its use in mass vaccination is entirely feasible. Vial stopper performance was also assessed as sufficient (Jarrahian et al. 2017).

Fractional dose was recommended for vaccines from all manufacturers, but we know that they differ in their potency. However, there appears to be a lot of headway in terms of dosage needed to reach the WHO recommended threshold. [102]

14.4 Other solutions to shortages

It's possible that using market design to increase supply of the existing YF vaccine. While I have not researched this, given low cost of the vaccine it's likely that there was a market failure. However, the current technological process means that setting up additional capacity is difficult. I have not established whether with increased procurement in recent years the risk of shortages has declined, but given the logistical constraints in outbreaks, it's unlikely that this can be solved simply by market design.

As Montalvo Zurbia-Flores, Rollier, and Reyes-Sandoval (2022) report, "Many vaccine platforms have been investigated to circumvent some YF-LAV restrictions, albeit none seem to fulfil all the requirements. Inactivated, DNA and poxvirus-based viral vector vaccines examined so far may avoid the risk inherent of live-attenuated vaccines but require the administration of multiple doses to achieve the same level of protective long-lasting immunity. Thus, further alternative strategies are still needed to improve YF vaccination and intervene in future outbreak emergencies."

14.5 Evidence gaps and future role for fractionation

Why would we not switch to fractional doses as the default choice, not just in shortages? Overall data that emerged in recent years are positive, but while the standard dose has been in use for over 80 years, for fractional dose there is still not enough long-term evidence and data in specific subpopulations. These evidence gaps are a subject of ongoing debate: Hansen, Staples, and Barrett (2023) summarise them in good detail. Roukens and Visser (2023) and Montalvo Zurbia-Flores, Rollier, and Reyes-Sandoval (2022) also provide summary of newer findings.

WHO position (2017) was that children under two and people-living-with-HIV should receive a standard dose until further evidence becomes available. Recent studies

[101](Section 10 here): "Due to the limited heat stability of YF vaccine after reconstitution, opened multi-dose vials of YF vaccine must be kept between +2°C and +8°C, and must be discarded at the end of the immunization session, or within six hours of opening".

[102]Vannice, Wilder-Smith, and Hombach (2018): *"This decision was based on simple math. WHO-prequalified yellow fever vaccines are highly potent, with average doses between 12,874 and 43,651 international units (IU) — far above the WHO's recommended minimum of 1000 IU. In principle, the quantity of vaccine virus in fractional doses of standard vaccine would therefore still exceed the WHO's minimum requirement"*. In studies reported by Roukens and Visser (2023) the standard dose of Russian-manufactured vaccine had a dose 67 times higher than the WHO recommended threshold for immunising dose, while the Senegalese vaccine was 7 times the threshold.

have shown promising results in these two populations, but have also identified lower antibodies levels in FD compared to full dose: study 1 and study 2. The clinical relevance of these lower antibody levels is unclear. (Also, in some way this is a reassuring example of tailoring the dose to individual, which we will discuss elsewhere.)

An additional complication of FD is the wide variance in potency of YF manufactured doses. While we mentioned that the WHO pre-qualified vaccines have high potency, the range is very large: from 1,995 log10 IU to 2,511,886 log10 IU (WHO n.d.). This raises the question if all WHO-prequalified YF vaccines are suitable for fractional dosing, or if some are more appropriate than others. Here, too, we do not know how this correlates with durability of immunity, onset of immunity or seroconversion.

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