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How should we conduct pandemic vaccination?

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ABSTRACT

Vaccination plays an important role in pandemic planning and response. The possibility of developing an effective vaccine for a novel pandemic virus is not assured. However, as we have seen with SARS-CoV-2 vaccine development, with sufficient resources and global focus, successful outcomes can be achieved in a relatively short period. However even when vaccine is available it will initially be scarce. When one becomes available, how should it be distributed?

In this paper we explicate how ethical thinking that is carefully attuned to context is essential to decisions about how we should conduct vaccination in a pandemic where demand exceeds supply. We focus on two key issues. First, setting the aims for a pandemic vaccination programme. Second, thinking about the means of delivering a chosen aim. We outline how pandemic vaccine distribution strategies can be implemented with distinct aims, e.g. protecting groups at greater risk of harm, saving the most lives, or ensuring societal benefit. Each aim will result in a focus on a different priority population and each strategy will have a different benefit-harm profile. Once we have decided our aim, we still have choices to make about delivery. We may achieve at least some ends via direct or indirect strategies. Such policy decisions are not merely technical, but necessarily involve ethics. One important general issue is that such planning decisions about distribution will always be made under conditions of uncertainty about vaccine safety and effectiveness. However, planning how to distribute vaccine for SARS-CoV-2 is even harder because we understand relatively little about the virus, transmission, and its immunological impact in the short and long term.

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1. Introduction

The World Health Organization urges its member states to plan and prepare for infectious disease emergencies including pandemics. Vaccination is an important component of pandemic planning [1]. Pandemic plans have focused on pandemic influenza, until recently considered the most likely threat. Human pandemics are caused by novel viruses that usually originate in birds or other animals and adapt to become transmissible among people. This novelty means that at the time of virus emergence there is little or no pre-existing immunity in the population. In consequence, the virus can circulate more easily and potentially be associated

with more serious illness. Pandemic vaccines can mitigate much of the harm caused by infection by protecting individuals, stopping transmission, or both. Pandemic influenza vaccine takes time to design, test and manufacture but its role in pandemic management is clear. The possibility of developing an effective vaccine for a novel pandemic virus will be less assured. However, as we have seen with SARS-CoV-2 vaccine development, with sufficient resources and global focus, successful outcomes can be achieved in a relatively short period. In the case of any available pandemic vaccine, at least initially, demand will be greater than supply. This means that we must prioritise access to initially limited vaccine resources, which requires a decision about what the principal goals of the pandemic vaccination programme should be.

In 2018 and 2019 the authorship team were involved in a multidisciplinary program of research, funded by the Australian Federal Government, focused on planning for how we should

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prioritise access to initially scarce vaccine in the case of an influenza pandemic. The current coronavirus pandemic has highlighted that pandemic planning focused on influenza does not necessarily provide an operational plan for other, less anticipated, viral pandemics. It has similarly widened our thinking about how pandemic vaccine access might be prioritised. In this paper we: (i) examine the ethical issues involved in setting aims for vaccination programmes in pandemics; and then, (ii) identify and describe the key relevant ethical and practical differences between strategies that may deliver such aims. We then examine how the epidemiological and microbiological characteristics of any pandemic impacts upon and shapes the ethical concerns using pandemic influenza and SARS-CoV-2 as examples.

2. Prioritising pandemic vaccines: What are we aiming to achieve?

Pandemic vaccines, like other health care interventions, are a finite resource. When they are scarce, we must decide how we should allocate them as demand will outstrip supply. Vaccination strategies are always informed by values and we can see this by considering different possible aims for a pandemic vaccine programme. Specifying any aim or goal (we use these terms interchangeably) may be contentious. Aims can be implicit rather than explicit. Goals might include things like mitigating morbidity or mortality by protecting those at greater risk of infection, explicitly focusing on saving the most lives, or ensuring societal benefit. It is tempting to think that a vaccine programme can achieve all of these things. Some programmes may aim to achieve a single or multiple goals, and in the latter case aims may be in tension and cannot be achieved simultaneously without trade-offs. The key aims of a pandemic vaccine programme (and some of the implications of their adoption) include the following three options.

2.1. Protecting those at greater risk

A risk is a probability of a harm of a certain magnitude occurring. Protecting people who are at greater risk from infection involves determining which risks are relevant and then choosing which of those risks to prioritise. Risks, depending upon the infectious agent, might relate to the increased burdens of morbidity and mortality associated with medical conditions that arise from infection, such as co-morbidities (e.g. people with diabetes, heart problems, chronic lung disease, etc.), or be demographically based (e.g. adults aged over 60, children, pregnant women, etc.), or social (e.g. First Nations communities, disadvantaged groups, homeless, those in prisons or refugee camps, etc.). Groups may be at higher risk of both exposure and poor outcomes (e.g. Australian First Nations living in large multi-generational groups in poor housing), exposure alone (e.g. workers in crowded conditions, such as meat packing plants), or outcome alone (e.g. very elderly). Depending, then, on the disease in question and how the idea of risk is construed different cohorts may be prioritised. Certain risks are likely to be privileged in vaccination program planning and implementation because they are easier to articulate, measure, and respond to than others. For example, it is easier to target children through a school-based campaign than it is to target people living in very crowded or poor-quality housing. There is, therefore, a danger that, if we are not careful, the very choice of risks to focus on may inadvertently increase disadvantage. The justification for prioritising those at greatest risk must also pay attention to, and potentially call upon, a number of different ethical considerations including, for example, ideas of justice that prioritise on the worst off, a focus on increasing health equity, or responding to need.

2.2. Saving the most lives possible

Saving the most lives is a common goal of vaccination programmes. This aim might appeal to ideas of efficiency and attempting to achieve the best overall outcomes with our actions. A consequentialist approach to prioritisation is popular in public health (and welfare policies more generally). It is strongly egalitarian, in that each individual is considered to be of equal value to all others. This egalitarian goal can be operationalised in different ways. It might mean giving everyone an equal chance of access to an available vaccine (perhaps where vaccines are distributed randomly, such as though a lottery) or if we are interested in saving the most lives we may demonstrate our egalitarian commitment by prioritising those most in need as a means to the most efficient outcome, thereby saving the most lives possible. A consequentialist goal does not necessarily entail sacrificing those at greatest risk. However, there is a danger that a pandemic vaccine programme might be structured in such a way that while it saves the most lives, it unintentionally treats people who may benefit from vaccination unequally. For example, a distribution that focused on urban areas may well save the most people, but it does not treat urban and rural dwellers equally in the sense of providing an equal chance of protection and may perpetuate existing inequalities associated with access to effective healthcare and resources allocation.

2.3. Ensuring societal benefit

Another possible goal of vaccination, particularly pertinent to pandemics, is acting to ensure the best possible societal outcome through minimising social disruption or sustaining vital systems and social cohesion. This goal may be justified through the prospect of preventing serious social and economic disruption, not just focusing on a response to the immediate infection. It is likely to prioritise the protection of particular occupational groups as a way to safeguard services and infrastructure which are important to everyone in that society. Workers can continue to work safely and some degree of normal social and economic activity can be maintained. Such groups will include health care workers, aged care workers, police, supermarket workers, teachers, utilities workers, etc.

2.4. Why should we prioritise our goals?

It is important to explicitly clarify the goals of any pandemic vaccination programme. There are several reasons for this. First, it is not clear that every pandemic vaccination programme will have the same aim. Aims must be decided in response to the epidemiological characteristics and impacts of the pathogen and the broader pandemic context. Second, aims should be made explicit to ensure they are clear, transparent, and appropriate. People should be able to understand the rationale for interventions they are expected to participate in, both so that they are making informed decisions, but also to maintain or bolster a sense of trust in public health institutions and in vaccination. Third, aims can be in tension or conflict. If there is more than one relevant aim, it must be clear how they are to be combined, including any prioritisation within the aims themselves. Lastly, being explicit about the aims for pandemic vaccination programmes allows us to explore how we should best achieve those aims. In the next section we outline and discuss the difference between direct and indirect vaccination as distinctive strategies for achieving the desired aims of a pandemic vaccination programme.

3. The means to our chosen ends: Direct and indirect vaccination strategies in a pandemic

Once we have chosen our desired aims or goals for our pandemic vaccination programme we can begin to focus on different approaches to achieving them. *Direct protection* strategies are intended to, above all else, protect the individual that is vaccinated. Such a strategy can be used to further any of the aims as outlined above. Where target groups are prioritised, they are offered the vaccine on the assumption that some individuals in that group will directly benefit from it and that, thereby, population morbidity and mortality will be lower as a result. Such a strategy might be particularly important when we focus on the aim of protecting those held to be at greatest risk of severe disease outcomes. An example of this was prioritising pregnant women, who were at higher risk of hospitalisation and death during the 2009 H1N1 outbreak [2].

Vaccination can also offer *indirect protection*. Indirect protection strategies are intended to capitalise on protection extending beyond the individual receiving the vaccination (though the vaccinated individual may benefit from it), because of reduced transmission of disease. For example, it has sometimes been proposed that annual seasonal influenza vaccination should be implemented by vaccinating school children as a method of reducing spread to those held to be at greater risk (e.g. elderly people) [3–5]. A focus on indirect protection is not the same as one seeking to bring about herd immunity. Herd immunity occurs when a sufficiently high proportion of the population is immune to a disease, through vaccination, so that infection can no longer circulate. Indirect protection strategies, by contrast, seek to reduce transmission to certain at-risk groups, through the targeting of other groups who are held to have a key role in transmission within society. Prioritising the aim of saving the most lives might encourage a strategy of focusing on indirect vaccination in some cases, where we have good evidence that by vaccinating one group, we have the best possible population impact, thereby indirectly protecting those at greatest risk. In some cases, we might be able to have a strategy that achieves both direct and indirect benefit. For example, where we choose to prioritise an aim of ensuring societal benefit, we might choose to prioritise certain key occupational groups, such as health care or aged care workers, because they gain direct protection themselves, but also can play a role in indirect protection for those most at risk in society.

3.1. Benefit-harm considerations

One of the key ethical considerations to discuss in relation to the choice between such strategies is how benefits, risks, and burdens are defined, evaluated and distributed. The main potential benefit of vaccination is the ability to continue normal daily life through protection from infection. This benefit applies to both any vaccinated individual and, through aggregation, to society as a whole. Serious iatrogenic harms from pandemic vaccination are possible but likely to be extremely rare and are most likely to be mild (e.g. rash, fatigue, fever). Possible burdens will include factors such as having to take time off work to be vaccinated (with the potential for lost income) or travel to access vaccination facilities, paying for the vaccine, or anxiety about being vaccinated. How should we evaluate such factors in relation to pandemic vaccination and how are they likely to be distributed?

A strategy of direct protection will tend to concentrate our focus on the intended benefit and any risk upon the vaccinated individual: where the person who is expected to benefit from the intervention is the one bearing the (extremely small) risk associated with the choice to be vaccinated. Benefit is by no means guaranteed as the vaccinated individual may not come into contact with

the infectious agent, or they may be unlucky enough to have been vaccinated but not have full immunity conferred. Weighing up distribution of potential benefits and risks for any individual in a direct protection strategy is fairly simple. We weigh the chance of the individual benefiting against any risks and any relevant burdens to them. However, any assessment of benefits and risks in a direct strategy is more complex than it looks at first, as we are not only interested in harms and benefits relating to individuals, but also populations. Public health is sometimes thought to be concerned with whether aggregated benefit (however construed) outweighs population harms. In a direct protection strategy, we should be interested in evaluating expected net benefit for the targeted cohort from the intervention. Any anticipated harms to and burden experienced by the cohort are expected to be outweighed by benefit to the group.

Vaccination strategies that aim for indirect protection entail a potentially more controversial consideration of the relationship between benefits and risks. When in possession of a sufficiently large amount of a vaccine that stops onward transmission as well as disease expression, the aim of indirect protection is to vaccinate a particular cohort with the aim of reducing spread in the population generally, as a means to protecting a different group at increased risk. The group targeted for vaccination is not at particular risk of complications from infection and may be at much lower risk of complications than the wider population. That means that neither the vaccinated individual nor the targeted cohort are where the intended benefits of the strategy lie. This makes a risk–benefit equation potentially more contentious as the people bearing the risk from vaccination are not the people who are the target beneficiaries of the intervention. Some argue that such a strategy is unjust [6]. However, we need to take care not to assume too strict a segmentation of different groups in society. If we target school children for the benefit of the elderly, for example, those children are likely to have family members in the group we are aiming to protect [7]. Not all interests relevant to the individual are direct interests of the vaccinated individual.

3.2. Benefits and public goods

The ethical justification of direct strategies, as noted above, is easier to appreciate because of the focus on the individual and benefits (and any risk) to them. An indirect strategy or one that is a mix of direct and indirect can also seek to appeal to society or population-level arguments in addition to those at the individual level. For example, an individual derives some benefit from living in a society where we choose to tackle a pandemic as a whole population. Some have argued that a resultant reduction in infectious disease constitutes a public good [8]. For example, the creation and maintenance of sufficient levels of so-called ‘herd immunity’ in a population provides a joint protection for all, including those who are not vaccinated (for whatever reason) [9]. The strength and resonance of public good arguments in a pandemic are likely to be calibrated to the severity of any pandemic, the population’s experience of morbidity and mortality, the social and economic disruption it is causing, and the level of trust in public institutions.

4. Aims and strategies, vaccine attributes and epistemic uncertainty

It is very difficult to assess the relative benefits and harms of pandemic vaccination in advance of its widespread use. This is because there are a great many unknowns that are central to how benefits and harms of the vaccination would be assessed. No-one knows what the next pandemic will be like. We do not know what the pathogen will be, how serious it will be, how easily

and extensively it will spread, how it will be transmitted, nor who will be most affected. We do not know whether or not a suitable vaccine will be developed and important characteristics including impacts on transmission, safety profile and dose requirements may require whole population use before they are confirmed. We do not know how long vaccine protection will last [10]. Planning for vaccination in the absence of certainty is, clearly, a difficult task. Decisions can be held until there is some clear evidence about which aims and strategies are likely to be appropriate and achievable, but this approach risks looking unprepared. A more desirable alternative is to make a broad set of decisions in advance of a pandemic as part of a wider pandemic plan. Such decisions rely on taking a best guess, but if flexibility and the capacity for quick change is built into planning then aims and strategies can be adapted to reflect evidence as it is generated.

Practical uncertainties contribute to ethical uncertainties. There is a risk that vaccine development will be rushed to meet critical need. Uncertainty about how a vaccine will work in the population coupled with the time sensitivity of rollout mean that there is the potential for reduced benefit and increased risk. This may have implications for indirect protection strategies where vaccinees (often children) are asked to bear risk for the benefit of others. Conversely, if the vaccine is developed and available quickly and pandemic infection is still in its first wave then the chance of being infected may be great, meaning increased chance of benefit. If vaccine development and rollout take longer than anticipated and pandemic infection has been very efficiently and quickly transmitted, then the benefit of the intervention may be minimal. If vaccine rollout is slow and protection from any vaccine wanes quickly, herd immunity may be difficult or even impossible to attain. These issues have implications for the benefit-harm balancing act that is used to justify many public health interventions – if the intervention is unlikely to provide net benefit it is unlikely to be ethically justifiable. If dose requirements differ by age, ethical decisions may have to consider efficiency. For example, it may be difficult to justify prioritising a demographic that needs two doses of scarce vaccine to confer an acceptable degree of immunity when others may only need one dose to achieve the same.

After this review of the possible aims for pandemic vaccination programmes, and the use of possible direct, indirect and mixed strategies, we turn to the particular context of vaccination during the SARS-CoV-2 pandemic.

5. SARS-CoV-2 vaccination

The greatest uncertainty in the first year of the SARS-CoV-2 pandemic has been whether or not a vaccine will be developed, and *when* this may occur. At December 2020 there are over 200 vaccine candidates in clinical or preclinical evaluation, with a small number in Phase III trials [11]. Effective vaccines for SARS-CoV-2 are now being licensed, and remain a necessary condition to ease stringent social controls presently required to reduce infection spread. In this section we assess possible SARS-CoV-2 vaccination pathways in light of the aims and strategies outlined above.

Key organisations have recently released recommendations for how SARS-CoV-2 vaccine should be prioritised [12–16]. Encouragingly, these have explicitly discussed ethics and values in ways that was unusual in pre-SARS-CoV-2 pandemic plans [17]. They do not include discussion of direct and indirect strategies, however, and we take up that discussion here.

It is clear that the nature of the vaccine production process means that in any pandemic scenario there will initially be insufficient vaccine for everyone that may want it. In any scenario it is likely that pandemic first responders and frontline healthcare staff will have first access to pandemic vaccine [17]. Prioritising this

group satisfies all of the aims we have suggested and combines direct and indirect protection, should vaccine reduce transmission. However, scarcity requires making decisions about which aim or aims are key for the programme and a set of decisions about which additional groups should be given priority for the vaccine. The timing of vaccine availability will impact upon the choice of strategies that might be employed to meet agreed aims, because current and previous infection rates in the population will impact upon the vaccine's effectiveness (and thus benefit-harm ratio considerations).

5.1. Protecting those at greatest risk

Vaccination aims ought to be determined by the particular context of any pandemic and altered according to severity and spread of infection, the effectiveness of other public health measures that have been used to mitigate pandemic spread, and the availability of treatments. A complicating factor may be that it will not be known at the time of rollout whether the vaccine provides sufficient immunity in all age groups, the number of doses needed, or whether different ages will require different doses for immunity to be conferred. It seems clear that elderly people are at greatest risk of harms from COVID-19 [18], but the effectiveness of a SARS-CoV-2 vaccine in that group will not be established until it is in wide use. There are other groups that we can confidently predict will be at greater risk. It is already known that certain population groups shoulder a greater burden in any pandemic (e.g. First Nations peoples, homeless people, prison populations) and there is evidence in the SARS-CoV-2 pandemic of serious harms being associated with socioeconomic status and/or race [19,20].

Protecting those at greatest risk of infection can be achieved using either direct or indirect strategies. The greater the risk of severe illness from SARS-CoV-2, the more likely the at-risk individual is to benefit from direct protection via vaccination, and the more justifiable direct protection strategies are. There are, however, at least three possible scenarios where an indirect protection strategy looks preferable: where the benefit to both vaccinees and risk groups is expected to be significant; where particular risk groups are unlikely to gain benefit from direct vaccination; and where vaccine may carry higher risk of harm to a particular risk group. Previous pandemic planning and literature have focused indirect strategies on school children. This is because there is evidence that it works (at least for seasonal influenza) and because, in some countries, in-school vaccination already exists. It is unlikely that school children would initially be prioritised for a SARS-CoV-2 vaccine, however. The trials to date have rarely included children, and the need for urgent rollout means that there will be a degree of uncertainty about a vaccine's safety profile when it is first available. Coupled with uncertainty about the degree to which children spread SARS-CoV-2 infection, the benefit-harm equation is not yet likely to tip on the side of benefit.

While children are the group most commonly targeted in indirect protection strategies, at-risk groups can also be protected by prioritising vaccine to those *other* people with whom they have contact. Occupational groups such as aged care workers and people providing in-home and welfare care can be prioritised for direct protection so that they can be safe at work and provide continuity of care, even in outbreak situations. Depending on vaccine characteristics they may also be less likely to transmit infection to people at greater risk of severe illness. Some industries that involve close contact with high risk populations – aged care, quarantine security – are likely to be casualised and encourage work across multiple facilities. In casual work the opportunity for paid sick leave is much less likely and jobs may be lost as a result of legitimate absenteeism, leading to work attendance in people who are unwell. Industries requiring close proximity and physical work in recog-

nised high transmission risk settings such as meatworks may also be prioritised to reduce spread to others. Other public health measures have been effective in preventing spread of infection in the COVID-19 pandemic, however, and many people in higher risk populations have been able to avoid illness through isolation. Assuming that it is acceptable and feasible for at risk groups to continue to isolate until there is sufficient vaccine available for the wider population, the effectiveness of isolation may free up a vaccination program to focus on other aims, such as saving the most lives or ensuring societal benefit.

5.2. Saving the most lives

We consider that the aim of saving the most lives is likely to be operationalised in the same way as protecting those at greater risk of illness. This is because vaccine will be available after the population has experienced pandemic morbidity and mortality, and there will ideally be indications at that point (if not clarity) about which groups have been carrying the greatest burden of infection. Targeting those groups is likely to be an effective way of reducing pandemic deaths and thus an efficient use of scarce vaccine. In the unlikely event that there is no evidence about which groups should be vaccinated with an aim of saving lives, indirect protection (saving lives by reducing spread) should be considered. In the case of SARS-CoV-2, a combination of direct and indirect protection via essential service worker vaccination seems likely to be an effective and efficient use of scarce vaccine.

5.3. Ensuring societal benefit

The aim of ensuring social benefit has thus far been considered as a response to a catastrophic pandemic situation in planning, and is less likely to be supported than aims of saving lives and/or protecting those at highest risk. This is because timely vaccine availability has been an assumption underpinning pandemic plans due to a focus on influenza, where social and economic disruptions would likely be short-term in nature. The COVID-19 pandemic has had catastrophic consequences in some locations and in some populations and much less so in others. Yet, it is nonetheless likely that ensuring social benefit will be a key aim of many vaccination programs when a SARS-CoV-2 vaccine is available. This is because the pandemic has resulted in widespread and significant negative economic and social consequences. A vaccine is being held up as the likely endpoint for relaxing social and mobility restrictions and opening borders. This is particularly important for countries that have adopted effective suppression or elimination strategies because they have a largely virus-naïve population. Complete reintegration back into the international economy can only occur and border controls can only be relaxed after a vaccine is available. It is also likely that the aim(s) of SARS-CoV-2 vaccination will be the subject of significant debate as their potential to begin to ameliorate pandemic-related social and economic disruption will be a high priority for governments. This is because it has broader and longer-term consequences for society and a wider range of health outcomes than an immediate focus on saving lives potentially lost to COVID-19.

The COVID-19 pandemic has highlighted different ways of considering the balance of benefit and risk associated with vaccination. Social isolation has been proven to be protective against infection but obviously has many costs and burdens to individuals and society. As individuals decide whether or not to participate in a SARS-CoV-2 vaccine programme, they may be more willing to bear any possible vaccine associated risks because of their experience of the public health restrictions and the advantage of the ability to move freely in the community and across borders. However, SARS-CoV-2 vaccine risks are likely to be less clear than for many

vaccines. This is both because vaccine development is being fast-tracked [21] and because trial participants report uncomfortable side effects [22]. Counterbalancing this, the benefits of immunity may also be increased by permitting greater social and economic participation. Assuming an effective and safe vaccine becomes a reality, the benefit of vaccination will extend beyond protection from infection.

6. Conclusions

The relative importance of different vaccination strategies depends on determining clarity in the aim or aims of the vaccination programme. The COVID-19 epidemic has prompted different ways of thinking about how to prioritise scarce pandemic vaccine. The uncertainty surrounding vaccine availability means that there has been a strong focus on other public health measures and these have proved effective at reducing and stopping spread of infection in some places. They have also fundamentally changed how many people live. The current situation has further highlighted the need for vaccination to be considered as part of a suite of measures that may be used in a pandemic rather than being proposed in isolation. This is especially true if vaccine uptake is not high. So far, we have seen a whole of society response to the current pandemic. Carrying this response through to vaccination suggests that ensuring societal benefit is likely to be a key aim of any eventual SARS-CoV-2 vaccine programme. A focus on a total societal response to a pandemic makes the distinction between direct and indirect strategies less significant than they are for other vaccines. The balance of benefit and harm will differ between scenarios and populations but it is vitally important to account for all relevant benefits and harms to individuals and different groups in society. Assuming that the risk of vaccination is not unacceptably high, and this is not an unreasonable requirement of a publicly accessible vaccine, none of the strategies we have discussed present a scenario where benefit is a priori outweighed by harm.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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