International vaccination: Potential impact on viral evolution and UK public health

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This paper summarises the current scientific consensus and hypothesis on the role of global vaccination in emergence and importation of new variants, and identifies key areas of uncertainty for making future projections and policies. We highlight key considerations for future policymaking, and where that could be guided by new evidence. Some aspects relate to medium-term decisions (~3 months) and others to long-term issues (~12 months) as travel and behaviour returns to baseline.

Executive summary

Context

- The biggest threat to the UK's health security and response to the SARS-CoV-2 pandemic is the emergence (and establishment within the UK) of variants that either have increased transmissibility, increased disease severity, escape prior immunity, or a combination of these characteristics [high confidence]
- Substantial global circulation of SARS-CoV-2 will lead to the evolution of new variants and continued risk of importation to the UK [medium confidence].
- Increased international vaccination by donation/sharing of purchased doses, or supporting increased manufacture, has the potential to reduce the appearance and establishment of variants internationally, as well as the risk of their importation to the UK [medium confidence].

Evolutionary considerations

- It is unknown how levels of vaccination change the relative risk of the appearance and establishment of an immune escape variant. Most current variants of concern emerged before mass vaccination or high population immunity from infection [medium confidence]. Any level of population immunity may increase selection pressure for immune escape variants but there is no evidence to suggest this pressure would be greater for vaccine-induced immunity than immunity driven by infection [medium confidence].
- At the individual level, partial immunity may create conditions that favour onward transmission of variants with immune escape-associated mutations [low confidence]. However, it is not yet clear how different vaccines, dosing regimes, or immunity from previous infection may intersect with different variants and individual host characteristics to influence the emergence of immune escape variants [medium-high confidence].
- If immunocompromised or populations otherwise vulnerable to chronic infections are shown to be a significant source of new variants with concerning characteristics, then focussing global vaccination efforts to these populations (and their contacts) may reduce the risk of new variants of concern emerging [medium-high confidence].

Risk of importation of novel variants

- As the number of travellers to the UK increases so will the risk of importation of variants and the burden on genomic surveillance systems [high confidence]. The number of importations that would result in the establishment of local transmission of a new variant is difficult to predict due to overdispersion and the unpredictability of variant characteristics such as transmissibility [high confidence]. Border measures are likely to delay but not prevent introduction [high confidence].
- If vaccination continues to protect against infection, and reduce onward transmission, then requiring travellers to be vaccinated is likely to reduce the risk of importation but may exacerbate inequalities if international vaccination coverage remains low and heterogenous [high confidence].
- Imported cases are less likely to lead to outbreaks and established community transmission in the UK if transmission in the UK is controlled, by population immunity or non-pharmaceutical interventions [high confidence].
- It is unclear which domestic communities may be at higher risk from imported variants. Increasing domestic vaccination in all groups or those with higher exposure to international travellers is likely to reduce the probability of establishment of transmission after importation [high confidence].

Benefits of international vaccination

- A successful domestic strategy hinges on achieving low numbers of infections globally to reduce the emergence of novel variants of concern [medium-high confidence].
- Establishing the optimal priority or targeting of international vaccination efforts is complicated by biological uncertainties and logistical complexities (e.g. distribution, vaccine hesitancy, regional stability, etc). In the short term, prioritisation of countries with higher volumes of travellers coming to or from the UK (or for whom more open borders are economically desirable) could be considered [low confidence].
- Multilateral cooperation and a commitment to increasing global vaccination rates, in part by sharing resources such as doses, is highly likely to have the biggest impact on the incidence of infections globally and thus the biggest impact on the risk of the emergence of new variants [medium-high confidence].

1. Introduction

The biggest threat to the UK's health security and response to the SARS-CoV-2 pandemic in the medium to long term is the emergence (and establishment within the UK) of variants which have any of the properties of:

a. **increased transmissibility (or faster growth through any means)**
b. **higher severity (causing worse health outcomes)**
c. **escape prior immunity (from previous infection or vaccine)**
d. **any combinations of the above.**

The steps on the pathway from international emergence to establishment of domestic transmission in the UK on which interventions can act:

a. A variant first **appears** through mutation in the unknown source location
b. The variant **establishes** transmission in that location
   note: (**emergence**: both a and b together)
c. The variant is **imported** to the UK
d. Establishment of transmission of the variant in the UK.

Increased international vaccination by donation or sharing of doses or supporting manufacture, has the potential to reduce the risks of the first three steps, hence reducing the threat to the UK.

In this paper, we explore the evolutionary arguments for the effects of vaccination, consider in more detail international importation routes, and combine these to draw out consequences for a successful strategy for the UK for international vaccination. Finally we highlight the key unknowns, and areas where further work is urgently needed.

2. Evolutionary considerations of vaccination effects on novel variants

Increasing international vaccination will reduce the number of cases in which new variants can appear (lower prevalence at source), the probability of local establishment (lower reproduction ratio at source) and the probability of importation to the UK (lower prevalence at source). A possible counterargument is that vaccination may directly affect appearance and selection for immune escape variants (infection- or vaccine-induced). **Overall, we argue that increasing international vaccine coverage is very likely to help prevent the emergence of variants.**

Mutations that affect one of transmissibility, severity, or immune escape can affect other properties, and it is not clear how these are interlinked in terms of their underlying biology or in terms of selection (1). For example, transmissibility and immune escape may be linked for SARS-CoV-2: the spike (S) glycoprotein is both the main target of neutralizing antibodies (2) and houses the receptor binding domain (RBD) that binds to the human ACE2 cellular receptor and modulates transmissibility (3). Further, it is not currently possible to predict the limits of transmissibility or severity for potential future variants.

At the scale of individuals, partially-immune hosts may create conditions that favour onward transmission of variants associated with immune escape. If there is no immunity, mutations associated with immune escape will not have a selective advantage (4), whereas if immunity (infection- or vaccine-induced) is complete, such that these mutations cannot achieve onward transmission, they will not spread either. However, the exact characteristics of such partially-immune hosts, and how

particular vaccines, dosing regimes, or variants may intersect to create conditions that favour appearance of immune escape variants remains unclear.

Partially immunized individuals (i.e. in receipt of a single dose for a two-dose vaccine) have also been suggested as creating a context allowing selection for such variants (5; 6; 7). Expansions of sequencing and surveillance worldwide, including sequencing of any breakthrough cases in vaccinated individuals (and their contacts) are required to establish the nature of this risk, and will also inform our understanding of the degree to which immune escape co-varies with transmissibility and health outcomes.

Characteristics of infected individuals may also matter for variant emergence. Immunocompromised hosts and chronic infections have been suggested as a source of variants (8; 9; 10; 11). If immunocompromised or populations otherwise vulnerable to chronic infections are shown to be a significant source of new variants with concerning characteristics, focussing global vaccination efforts to these populations (and their contacts) may reduce the risk of new variants of concern emerging.

To date, emergence has occurred in the context of little or no vaccination (12); thus variants, including variants with a degree of immune escape, can clearly arise as a result of the infection of unvaccinated populations. **Any level of population immunity may increase selection pressure for immune escape variants but there is no evidence to suggest this pressure would be greater for vaccine-induced immunity than immunity driven by infections.**

Moving to the scale of populations, the relative risk of selection for immune escape in vaccinated versus unvaccinated populations is unknown. However, increasing numbers of cases provide more opportunities for escape mutations to appear (13). If immune escape is more likely to appear in vaccinated individuals than unvaccinated, then at the population level this will cause risk of immune escape to be greatest for a partially vaccinated population: when there is an appreciable proportion vaccinated yet prevalence can still run high (14). Currently however, many countries already have some level of partial vaccination coverage and remain at risk of high future SARS-CoV-2 prevalence - here any assistance to reduce prevalence will help mitigate the appearance and establishment of variants.

3. Risk of importation and establishment of transmission of novel variants

The simplest estimation of the risk of importing a novel variant to the UK is the prevalence of a variant in a given location multiplied by the volume of travel from that location to the UK. Reducing either or both of these factors may lower this risk, as would isolating and detecting infected and infectious arrivals through quarantine and/or testing of travellers. Increased international vaccination is likely to affect the former (both through appearance and establishment as described above), and decrease the risk of importation and need for border controls. Maintaining long term border controls or reduced travel is likely to be expensive, and only delay rather than prevent importation.

Prevalence estimates in source locations may be under-ascertained and lagged due to limited surveillance and delays in reporting (15). The surveillance of variants is limited further by genomic sequencing capacity which is mostly concentrated in high-income countries. Variants may only be detected after importation into a country with established testing and sequencing, at which point the

variant may be well established in the origin location and seeded widely elsewhere through international travel.

The number of international travellers arriving/returning to the UK remains significantly lower than before the pandemic[1], but is likely to increase over time. This will increase both the risk of importation and the burden on border surveillance. Travel volumes to some locations may change rapidly if new border restrictions (domestic or international) are introduced. Travellers may also pass through intermediate countries before reaching the UK subject to different regulations, or to avoid border restrictions.

Modelling has shown that interventions such as testing prior to the flight or upon arrival (repeatedly or in combination with quarantine) may reduce both the number of imported infections, and also the potential for onward transmission, but has also highlighted important limitations (16; 17; 18; 19; 20; 21). The effectiveness of such interventions will largely be dependent on the degree of participation and adherence, voluntary or otherwise, to the specified strategy and the volume of cases.

Both modelling and real-world assessment of stringent border measures, e.g. as in Australia and New Zealand, indicate that border interventions may delay and reduce the frequency of, but not prevent, case importation due to the accumulation of small risks over time (22). The number of importations that result in a high chance of established local transmission is difficult to predict due to large variation in the secondary case distribution of SARS-CoV-2 (overdispersion, or "superspreading") (23; 24), but variants with higher R are likely to establish local transmission after fewer introductions. Delaying establishment of community transmission gives an opportunity to implement domestic interventions which limit the extent of community transmission. Maintaining stringent restrictions on travel over the long-term carries significant economic and social costs which must be weighed against the benefits of reducing the frequency of importation.

Requiring travellers to be vaccinated may also reduce the risk of importation if vaccination continues to protect against infection. As such, increased international vaccination may reduce the risk of importation and thus allow for increased travel from a greater number of countries. However, this may exacerbate inequalities if international vaccination coverage remains low or heterogeneous. In the long term, genomic surveillance and testing of incoming vaccinated travellers is likely to be needed but would decrease the risk of importing vaccine-escape strains only if coupled with interventions limiting onward transmission.

If infected travellers are arriving into a country where the effective reproduction number, R, of the variant is low or below 1, either due to the impact of contact rate reducing NPIs or population immunity (either from vaccination or previous infection), then imported cases will be less likely to spark outbreaks and establish community transmission (25)**.** If vaccination coverage is low, heterogeneous, or ineffective against variants, there is potential for extensive community transmission within susceptible subpopulations. It is unclear what factors drive emergence of variants, therefore which locations they may occur, and thus which domestic communities may be at-risk for importation. Domestic vaccination campaigns should prioritise increasing vaccination coverage, including in hard-to-reach groups and those with higher exposure to all international travellers, to reduce the probability that importations lead to establishment of transmission.

[1] https://www.eurocontrol.int/covid19

4. Potential domestic benefits from international vaccination

Taking into account the importation and evolutionary considerations above, **a successful domestic strategy hinges on achieving low numbers of infections globally to prevent the emergence of novel variants**. In the short term, a domestic focus for vaccination combined with import controls may have utility, but in the medium to long term and COVID-19 endemicity (26), cooperating to drive global mass vaccination is likely to be better for the UK, for two reasons:

1. Substantial global infection prevalence will lead to evolutionary pressure and likely emergence of variants. The presence of variants internationally may require prolonged maintenance of border measures and additional local interventions to delay/prevent establishment of new variants, entailing significant economic costs.
2. Medium-term strategies to achieve local control of transmission depend on the reproduction number and immune escape of circulating variants. Given the history of the pandemic, we cannot exclude the evolution of more transmissible, more severe, and less vaccine-susceptible variants (27). Importation and establishment (as border measures are unlikely to be infallible) of such variants of concern in the UK would decrease the feasibility of local control.

International coordination to raise global vaccination coverage, for example by dose-sharing, will enable most effective leveraging of available doses. **Establishing the optimal priority or targeting of international vaccination efforts is complicated by biological uncertainties and logistical complexities (e.g. distribution, vaccine hesitancy, regional stability, etc)**. In the short term, prioritisation of countries with higher volumes of travellers coming to or from the UK (or for whom more open borders are economically desirable) could be considered.

Regional and global control of infection requires an ambitious programme of mass (ideally regional) manufacture and global dissemination of vaccines. This demands multilateral cooperation and commitment but is likely to result in domestic and global benefits by controlling transmission, reducing the spectre of evolution, and improving the capacity to develop and manufacture booster doses as the evolutionary goalposts shift. These outcomes are likely to generate considerable returns on the substantial required investment.

Multilateral cooperation and a commitment to increasing global vaccination rates, in part by sharing resources such as doses, is highly likely to have the biggest impact on the incidence of infections globally and thus the biggest impact on the risk of the emergence of new variants (26). There are circumstances where considerable impact can be achieved by a single country sharing resources with others. For example, during the smallpox eradication effort the US financed smallpox elimination in India with $100 million USD, the rest covered by India. This altruistic move was also strongly in US self-interest as it could not stop its domestic smallpox vaccination campaign until the virus was eradicated elsewhere in the world. There was also a strong economic case for resource sharing, since the US saves its entire contribution on smallpox eradication every 26 days (massive return on investment). We cannot predict where novel variants will emerge, so a unilateral targeted approach is likely to only have a limited effect. While there is high prevalence of COVID-19 in many different areas of the world with different levels of surveillance capacity, domestic intervention and border measures are needed to lower the risk to the UK from new variants. As such, reducing the probability of emergence of new variants globally is in the UK's local interest. This can be best achieved in a coordinated multilateral effort of resource sharing and supporting development, manufacture and global deployment of vaccine and booster doses (28).

5. Key uncertainties and future needs

While the principle that decreasing global prevalence by increasing international vaccination is critical to decreasing the risk posed by new variants to the UK, there are a number of key areas of uncertainty which make prediction and precise strategy design extremely challenging. Here we note the major areas of uncertainty underlying the conclusions above, which require further research:

5.1 Duration of infection- and vaccine-induced immunity:

Although the current consensus is that adaptive immune responses following natural SARS-CoV-2 infection are fairly robust and long lasting (29; 30), the picture is less clear in the face of emerging variants (31; 32; 33), particularly the delta strain (34; 35; 36; 37). The expected duration of both infection- and vaccine-induced immunity is unclear. If and why immunity wanes and the time-scale over which this occurs will impact the level of community immunity (38; 39; 40; 41) and the probability of establishment of new variants (5). Waning immunity allows more breakthrough infections, especially if prevalence remains high, but the effect on probability of generating new variants is unknown. New evidence on the duration of immunity could require altered vaccination strategies, including for booster vaccinations. However, as always through this: if total global prevalence is lower then the total risk is lower.

5.2 Immunocompromised people and chronic infections as higher risk for variant emergence:

Infection of immunocompromised individuals has been linked with viral evolution and the emergence of variants (8; 42). More evidence is urgently needed if infection of these individuals increases risk of creation of variants. Global vaccination, genomic surveillance, diagnostic testing for SARS-CoV-2, and mitigation measures could be targeted to these groups and their contacts, although the global distribution and their prevalence is unknown. For example, data on HIV/SARS-CoV-2 co-infection are still scarce, particularly in terms of within-host viral evolution in coinfected hosts. In the absence of targeted measures, global reduction of prevalence remains a leading tool in minimising opportunities for variant emergence.

5.3 Probability of variant emergence in vaccinated vs unvaccinated groups:

It is not known whether variant emergence is more likely in fully- or partially-immunised groups, or those with infection-induced immunity. Vaccine-induced immunity appears strong, and major variants so far have emerged in the context of little vaccination.

5.4 Feasibility of targeted border restrictions as an approach:

Targeting of border restrictions to countries with evidence of new variants will be very challenging because:

- We currently cannot predict the likely context of emergence and therefore likely locations.
- Weaker surveillance systems (especially in genomic surveillance) in emergence locations and potential de-prioritisation of COVID-19 surveillance means we may not get an early signal even of increased transmission in a particular location. Therefore domestic UK or border surveillance (or that of other nations) may be the earliest signal of a new variant (as observed for gamma variant). Building or maintaining international surveillance could also benefit the UK.

- By the time a variant is identified there is likely to already be international seeding, including to the UK. The UK has high travel volumes so has consistently received exogenous variants early. Therefore, targeted restrictions are challenging, especially if there is effort to circumvent them via alternate travel routes.
- Once a variant appears and establishes, the speed of reaching dominance and increasing cases has been extremely rapid (for example, alpha and delta variants). Therefore the timescale on which targeted interventions must be enacted is very short, especially for variants with increased transmissibility.

5.5 Vaccine dose and efficacy

Optimal strategy will depend on the details of vaccine action, in particular:

- Dose fractionalisation could increase the number of doses available, as long as immunity achieved by fractional doses is equivalent to full dose (6; 43).
- There is increasing evidence of variable efficacy between vaccine types, and higher efficacy is much better in terms of minimising risk of emergence as it decreases the number of partially immune hosts. Similarly single-dose vaccines avoid a period of partial immunity seen for 2-dose vaccines, however total achieved efficacy needs to be equivalent. A vaccine which prevented severe disease but had little effect on transmission would be concerning for escape.
- New evidence on efficacy or immune responses to mixed-dose strategies could ease vaccine deployment logistics by removing the need for homologous doses and verification of first-dose vaccines.

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