Vaccines - What happens next?

By Dylan Liew and Adrian Baskir

COVID-19 Actuaries Response Group – Learn. Share. Educate. Influence.

SUMMARY

As the journey to find a SARS-CoV-2 vaccine continues, we explore what might happen when we reach the finishing line in a UK context. We consider how many people need to be vaccinated to provide herd immunity. The practicalities of administering vaccines to the majority of the population are also examined. Using the experience of flu vaccination, this is uncharted territory for the UK as only 13% of those under 65 were previously vaccinated. The question of prioritising who gets vaccinated first is also considered – do you start with the young and healthy or the most vulnerable? Or key workers? It's possible that people will need multiple vaccines, and this too presents challenges. Finally, how will the so-called "Anti-Vax" philosophy hamper rollout efforts.

Background

News of a Covid-19 vaccine is becoming ever more sanguine.

It has been reported in the media that the UK Government has placed orders for six experimental SARS-CoV-2 vaccines totalling 340 million doses with the latest being an order for 90 million doses from Janssen and Novavax. This equates to approximately 5 doses per person in the UK. Clearly not all of these will work so it's a case of hedging their bets. The road to approved status is arduous. Numerous studies have estimated only around 10% will make it all the way from Phase I trials to "Approved"[iii]. In this article we assume that (at least) one of the six will work and explore the logistics and practicalities of deployment including who to vaccinate, when and what take up rate is required to constitute a successful vaccination programme. A vaccine in and of itself may not solve the crisis overnight.

How many people to vaccinate?

Logistically, the duration it takes to vaccinate the population is partly a function of how many we vaccinate, which **crudely** depends upon:

1) The basic rate of infection - R_0
2) The efficacy rate of the vaccine

The vaccine efficacy rate is not yet clear. Estimates for R_0 for SARS-CoV-2 have varied and are debatable but do exist. The World Health Organisation ("WHO") had initially estimated it from 1.4 – 2.5[iii], with more recent meta-analysis suggesting a higher range of 1.90 – 6.49[iv]. We consider the case $R_0 = 2.5$.

A SIR framework suggests the required % of vaccinated people (or rather immune people) is $1 - \frac{1}{R_0}$ $(60\% \; with \; R_0 = 2.5)$ in order for the disease to "burn-out."

Say 20% of the inoculated do not elicit the required immune response for whatever reason or cannot take the vaccine due to side-effects, leading to an 80% efficacy rate. With:

$$Vaccine\ take\ up\ rate * Vaccine\ efficacy\ rate = \%\ of\ Population\ Vacciniated\ i.e. immune$$

We need:

$$\frac{60\%\ [Required\ immune\ population\ \%]}{80\%\ [Vaccine\ efficacy\ rate]} = 75\%\ [Vaccine\ take\ up]$$

We can rerun this crude calculation with different R_0 estimates, and differing efficacy rates to get differing required % of vaccine take ups.

A recent survey by King's College and Ipsos Mori[v] showed that 53% of respondents were certain/very likely to get a vaccine and a further 20% were fairly likely to. 16% said they would be unlikely to or definitely won't. This interpretation is not aligned to media reporting of the same survey with headlines such as "Only half of Britons say they would get a vaccine" seemingly at odds with the actual survey results. We might also experience different behaviour when an actual viable, tangible, vaccine is placed in front of the respondents rather than considering a vague hypothetical potential vaccine without any specific details that is yet to be seen, and posited for the purposes of a survey response.

U.K. seasonal flu vaccine take up[vi]

Table 1. Observed and extrapolated estimate of number of patients registered and who received influenza vaccine during the 2018 to 2019 season

Total GP registered population	2018/19			2017/18		
	Number of patients registered	Number of patients vaccinated	% Vaccine uptake	Number of patients registered	Number of patients vaccinated	% vaccine uptake
Aged 65 and over	**10,087,978**	**7,260,596**	72.0	**10,032,613**	**7,309,125**	72.9
Aged 65 and over extrapolated	10,435,319	7,510,587		10,286,949	7,494,418	
All patients aged 6 months to under 65 years	**47,627,024**	**6,612,966**	13.9	**47,487,190**	**6,496,582**	13.7
All patients aged 6 months to under 65 years extrapolated	49,266,877	6,840,658		48,691,033	6,661,276	
Total observed (65+ and all patients under 65)	57,715,002	13,873,562	24.0	57,519,803	13,805,707	24.0
Total extrapolated (65+ and all patients under 65)	59,702,195	14,351,245		58,977,982	14,155,694	

By way of comparison, it is instructive to consider recent take up rates for seasonal flu vaccines. From September 2018 to February 2019 (6 months) c. 14 million British patients received the flu vaccine.

Although almost 73% take up was achieved with the over 65's, we note that as a % of the **registered patients** overall within the U.K. population only 24% received the flu vaccine. With the UK population being almost 68 million, the missing almost 9 million **unregistered** patients would need to be traced and potentially vaccinated too.

It's clear that the over 65s have good uptake habits but for the under 65s, there will need to be a paradigm shift in behaviour in order to get the required vaccine uptake. It is worth noting that seasonal flu vaccinations campaigns in the U.K. have tended to target and focus more on the older population historically, which might have contributed to the lower take up rate amongst the young. And whilst the over 65s as a whole appear on the higher side, the at-risk and most vulnerable over 65's appear to be on a worrying downward trend in vaccine take up[vii].

Whilst it took 6 months to vaccinate 14m people, it does not necessarily follow that it would require a linear extrapolation to get to take 22 months to vaccinate 51m people (75% of 68m) due to additional deployment measures as well as a lower target.

Pandemic Response

The supply and distribution chain of a vaccine, as well as population behaviour under a pandemic is likely to change. The U.K. has a "National Flu Pandemic Service" ("NFPS") for such scenarios, allowing individuals to be triaged via telephone and online rather than in person, to bolster the country's capacity and speed. During H1N1 the NFPS managed to help the NHS increase the number of patients assessed with flu symptoms by 6 times[viii].

Antiviral Collection Points ("ACPs") are likely to be set up to increase the number of options for collecting treatments from just the usual pharmacies and individuals can nominate a "flu friend" to collect on their behalf (perhaps a "corona-companion" would be the better nomenclature) as well as taxis services (so companies such as Uber could venture into healthcare). We have seen similar scaling up in capacity with recent "Drive thru" testing centres. The Centres for Disease Control and Prevention ("CDC") is planning for similar "Points of Dispensing" ("PODs") to open up which could allow private companies to open their own clinics for their own employees. In the case of flu vaccines, corporates already often take responsibility for providing access to vaccines at places of work.

A U.K. government report on lessons learnt from H1N1[ix] included these recommendations for future pandemics:

- Training additional staff to administer vaccines.
- Using private providers.
- Using roving clinics.
- Extending clinic times outside normal working hours.

The rate of vaccine delivery should thus be significantly faster than the 14m patients vaccinated in 6 months for flu cited above. Indeed, the U.K. is now aiming to double their capacity for seasonal flu vaccines to 30m in anticipation of the confounding effects of Covid-19[x].

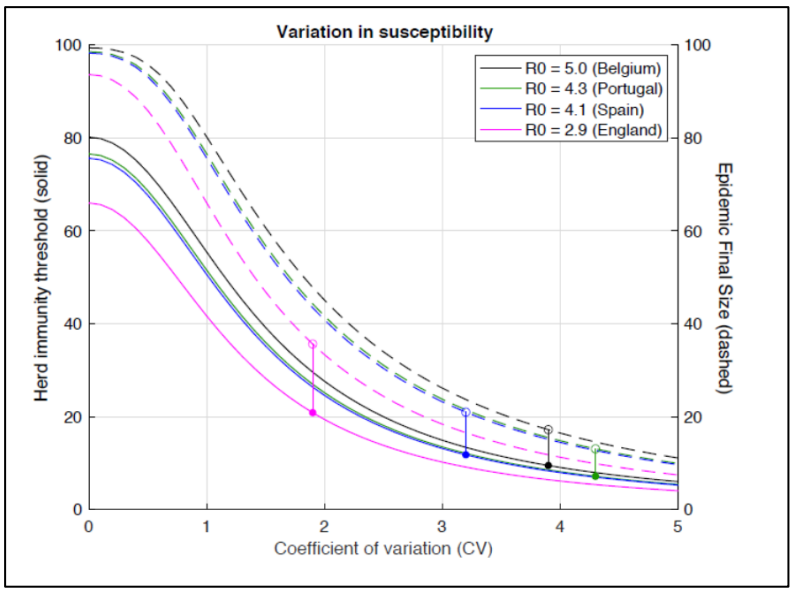
This does not come without challenges. GP surgeries are still likely to represent the vast majority of vaccination centres whilst already facing backlogs and will likely struggle to cope with 5 or 6-fold increases.

How many people do you really need to vaccinate?

$1 - \frac{1}{R_0} = 60\%\ (with\ R_0 = 2.5)$ may be a naïve assumption, closer to an upper bound than a best estimate.

Through interventions such as social distancing, the current rate of infection R_t has fallen significantly below the $R_0 = 2.5$ estimate. Importantly for this purpose, using R_0, the assessment of disease's innate potential rate of infection, needs to be considered in the context of "heterogeneity of susceptibility." Not everyone is as likely to be infected in August as in January.

We can hypothesize that the most likely to get infected are, by definition, more likely to have already been infected. Those uninfected by now may be the ones with stronger immune systems. However, early on, the U.K. shielded those thought to be the most vulnerable. The uninfected may simply have been less exposed rather than possessing any stronger immune system. Of the uninfected, how much can we attribute to the interventions placed by the state, and how much can we attribute to them being less likely to catch the disease in the first place? Is there any heterogeneity in susceptibility? Or is everyone just as likely to catch Covid-19?

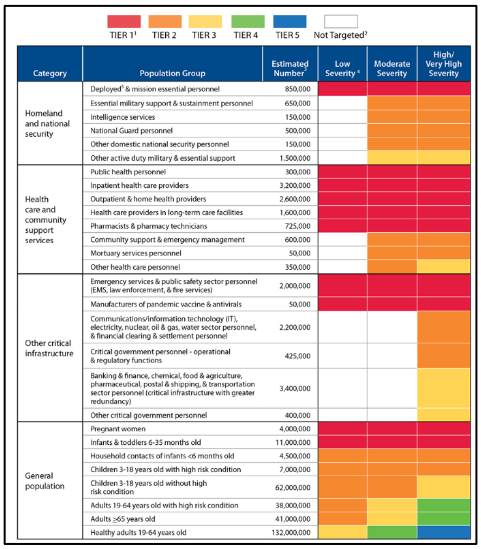


Aguas et al.[xi] show on the left how as heterogeneity (measured by the "coefficient of variation") increases (x-axis), the required % immune (left y-axis) decreases. Their current best-estimate for each country's heterogeneity is shown by the coloured dots e.g. for England their coefficient of variation is estimated just under 2 (and $R_0 = 2.9$) then the required immunity for the virus to begin to burn out should be 20% (pink solid line and dot). After then allowing for smaller pockets to spread, lag etc. the final % of England infected is predicted to be around 38% (pink dotted line and dot). Interesting, although Portugal is modelled assuming the second highest basic rate of infection (4.3), their level of heterogeneity has been estimated to be much higher than the rest (with their CV over 4) leading to the lowest % of required immunity at 10%.

Who gets it first?

Inevitably not everyone will be lucky enough to have a viable vaccine ready for them the day after it is approved for use. Some prioritisation will be needed.

In the U.K. this is decided by the Joint Committee on Vaccination and Immunisation ("JCVI"). They work on a "pandemic-by-pandemic" basis, deciding who is at most risk, who will gain the most benefit from treatment etc. They don't hardcode any prescribed rules as to how this is determined – it will depend on the disease and the vaccine.


TIER 1[1] TIER 2 TIER 3 TIER 4 TIER 5 Not Targeted[3]

Category	Population Group	Estimated Number[2]	Low Severity[4]	Moderate Severity	High/ Very High Severity
Homeland and national security	Deployed[5] & mission essential personnel	850,000			
	Essential military support & sustainment personnel	650,000			
	Intelligence services	150,000			
	National Guard personnel	500,000			
	Other domestic national security personnel	150,000			
	Other active duty military & essential support	1,500,000			
Health care and community support services	Public health personnel	300,000			
	Inpatient health care providers	3,200,000			
	Outpatient & home health providers	2,600,000			
	Health care providers in long-term care facilities	1,600,000			
	Pharmacists & pharmacy technicians	725,000			
	Community support & emergency management	600,000			
	Mortuary services personnel	50,000			
	Other health care personnel	350,000			
Other critical infrastructure	Emergency services & public safety sector personnel (EMS, law enforcement, & fire services)	2,000,000			
	Manufacturers of pandemic vaccine & antivirals	50,000			
	Communications/information technology (IT), electricity, nuclear, oil & gas, water sector personnel, & financial clearing & settlement personnel	2,200,000			
	Critical government personnel - operational & regulatory functions	425,000			
	Banking & finance, chemical, food & agriculture, pharmaceutical, postal & shipping, & transportation sector personnel (critical infrastructure with greater redundancy)	3,400,000			
	Other critical government personnel	400,000			
General population	Pregnant women	4,000,000			
	Infants & toddlers 6-35 months old	11,000,000			
	Household contacts of infants <6 months old	4,500,000			
	Children 3-18 years old with high risk condition	7,000,000			
	Children 3-18 years old without high risk condition	62,000,000			
	Adults 19-64 years old with high risk condition	38,000,000			
	Adults ≥65 years old	41,000,000			
	Healthy adults 19-64 years old	132,000,000			

The CDC on the other hand have issued a detailed prioritisation plan and framework[xii] (higher tiers getting higher prioritisation). The prioritisation is a function of the severity of the pandemic. For more severe pandemics, adults with a high risk condition are deprioritised – the U.S. favouring ensuring their infrastructure is secured first under this scenario. They also raise that, whilst the elderly may be the most susceptible, transmission within this cohort could be lower, perhaps due to isolation and shielding. The young may be the ones spreading the disease, contributing to the chain of transmission, so inoculating them may have a greater and faster impact on lowering R_t. Rather than prioritise on risk of symptoms, risk of spreading may be the more salient factor. It is also often the case that vaccines tend to be less effective with age, the younger tending to mount a stronger immune response[xiii]. Hence the U.K. prescribe different vaccines to different ages for the seasonal flu[xiv] as illustrated in the table below.

Age Group	Recommended Vaccine	Reason
6 months - 2 years	Egg-grown quadrivalent vaccine	LAIV is not suitable for children under two
2 - 17 years	Live attenuated influenza vaccine (LAIV)	
18 - 64 years	Quadrivalent influenza vaccine, egg grown or cell based	
65+	Adjuvanted trivalent influenza vaccine	"Adjuvant" is added to make the vaccine more effective in older people

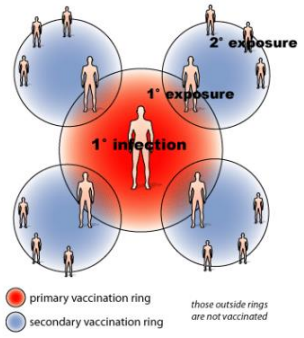
We might be faced with options such as successfully vaccinating 90% of a young population who are spreading and exposed to the disease (whilst supporting a country's infrastructure and economy) with low vulnerability, vs successfully vaccinating 60% of a highly vulnerable older population.

The older, vaccine-resistant population, may gain more benefit from lowering the probability that a younger person infects them, and returns to the labour force faster, whilst shielding for longer. This raises a number of ethical issues that policy-makers will need to navigate. A QALY type assessment on who would get the most life expectancy added from a vaccine may be considered too.

The JCVI issued limited interim advice on priority groups[xv], including frontline healthcare workers, and those that were "shielded" for now.

A risk-weighted lottery where everyone stands a chance of being first in line, but those bearing more risk getting better odds could help avoid any explicit or implicit discrimination in vaccine distribution and settle any ties.

Whilst it is scarce and logistically arduous to deploy vaccines e.g. taking a long time to rollout, some countries may adopt a tactical, targeted, and more efficient strategy like "ring vaccination[xvi]" used to combat Ebola and Smallpox[xvii] illustrated to the right.



But this relies on:

1. Infected people quickly realising they are infected – difficult for asymptotic cases (rare for diseases like Ebola but not for Covid-19).
2. Being able to quickly get a test.
3. The ring of contacts being rapidly contacted and vaccinated.

A reliable, quick, test, trace, and vaccinate programme is a pre-requisite for this – something which has eluded the UK to date.

There can be only one

Some vaccines may be better suited to some cohorts and countries than others (perhaps greater efficacy or lower side effects), thus one vaccine may be rolled out in some places faster than others. Given that the UK has pre-purchased 6 to date, at some stage, a choice may need to be made regarding viability.

Some groups may be better equipped to shield than others, with less exposure to the disease. The gross inequities of this virus will need to be addressed with vaccine allocation just as much as the effects of the disease and lockdowns.

It is feasible that there will be different successive versions of a vaccine, improving on the last rather than getting everything right the first time. Multiple vaccines help diversify risk against any single vaccine having side-effects or disruptions in the supply chain. This also mean these issues and decisions must be considered multiple times. Multiple vaccines also foster confusion and distrust in a time when there is some "anti-vax" sentiment. Consider the operational risk implications of having 2 different vaccines requiring 2 doses, at different times, in circulation simultaneously. Perhaps this is why the JCVI has taken a more flexible approach than the CDC – waiting to see the minutiae and specifics of the vaccine and disease.

The Table below demonstrates the length of immunity provided by several other disease vaccines[xviii]. It's unclear if any SARS-CoV-2 vaccine will provide lifelong immunity or only short duration immunity and whether boosters will be required. Furthermore, the time gap between initial vaccine and booster provision may be greater than the period of protection provided. This would potentially lead to another virus "wave" until the booster can be administered.

Disease	Estimated duration of protection after recommended doses of vaccine	Comments
Whooping cough	4-6 years	Booster at age 11
Tetanus	96% protected 13-14 years, 72% >25 years	Boosters at 45 & 65 years of age
Polio	>99% protected for at least 18 years	Boosters when travelling to certain countries
Mumps	>10 years in 90%, waning slowly over time	Duration of immunity varies in different populations
Varicella	One dose - unknown Two doses >14 years to date	Mild breakthrough disease can occur within 2 years when only one dose is given. Immunity is boosted when virus is still in circulation

Other practical considerations

Importantly the basic factors must not be overlooked. How much will a vaccine cost? What resources and equipment will it require? Will we have enough of them? What are the methods of production? How long will it take to produce? Will it require freezing and cold storage chains, or will the innovative mRNA methods avoid this? Whatever the method, the road to inoculation will be far from simple.

Whilst a proper examination of the King's College survey results gives more cause for optimism than the media headlines it generated, there remains a concern that people will not come forward to be vaccinated as required – either adopting an "anti-vax" approach or simply waiting to see whether a more effective vaccine emerges. This will provide public health officials with further challenges in convincing the public of the necessity, efficacy and safety of having the vaccine. In the same way that immunity passports were contemplated to get the economy going through antibody tests, it may require "vaccine passports" to incentivise vaccination. This could be a pre-requisite to enable passport holders freedom of movement. Many countries already mandate vaccinations for children, such as Australia's "No jab, no play" program[xix]. States may also consider financial incentives such as simply directly paying people to be vaccinated, or entry into yet another "inoculation lottery", or perhaps more indirect forms like rewarding people with discounts or extra benefits. Rewards and disincentives, carrots and sticks in whatever form may still be somewhat bounded in their impact. Ultimately, the decision will come down to the perceived risk of the virus vs. the perceived risk of the vaccine, and who in society is willing to accept this risk?

References and notes

[i] https://pubmed.ncbi.nlm.nih.gov/29394327/

[ii] https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

[iii] https://www.who.int/news-room/detail/23-01-2020-statement-on-the-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

[iv] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7280807/

[v] https://www.kcl.ac.uk/policy-institute/assets/coronavirus-uncertainties.pdf

[vi] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/804889/Seasonal_influenza_vaccine_uptake_in_GP_patients_1819.pdf

[vii] https://www.bbc.co.uk/news/uk-53889184

[viii] https://bmjopen.bmj.com/content/4/2/e004174

[ix] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/216168/dh_117133.pdf

[x] https://www.wired-gov.net/wg/news.nsf/articles/Most+comprehensive+flu+programme+in+UK+history+will+be+rolled+out+this+winter+24072020122500?open

[xi] https://www.medrxiv.org/content/10.1101/2020.07.23.20160762v1.full.pdf

[xii] https://www.cdc.gov/flu/pandemic-resources/pdf/2018-Influenza-Guidance.pdf

[xiii] The CDC observed during H1N1 people born before 1940 already exposed to H1N1 fared better than the young and hand hence say "Given these considerations, pandemic planners should consider developing and exercising alternate plans to be prepared to target healthy younger adults over older adults or vice versa, depending on how the pandemic affects these age groups."

[xiv] https://vk.ovg.ox.ac.uk/vk/inactivated-flu-vaccine

[xv] https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi/interim-advice-on-priority-groups-for-covid-19-vaccination

[xvi] https://en.wikipedia.org/wiki/Ring_vaccination

[xvii] https://www.scq.ubc.ca/smallpox-then-and-now/

[xviii] https://www.immune.org.nz/vaccines/efficiency-effectiveness

[xix] https://www2.health.vic.gov.au/public-health/immunisation/vaccination-children/no-jab-no-play