

ASPHER statement on the need for a coordinated, professional approach to policy and planning for COVID-19 vaccination roll-out

The ASPHER COVID-19 Taskforce Vaccination Group

Manfred S Green, Brian Li Han Wong, John Reid, Jose M Martin-Moreno, Nadav Davidovitch, Laurent Chambaud, Lore Leighton, Mohamud Sheek-Hussein, Ranjeet Dhonkal, Robert Otok, John D Middleton

1. Introduction

The Association of Schools for Public Health in the European Region (ASPHER) considers that the core aim of the COVID-19 vaccination programmes should be to achieve vaccine-derived herd immunity worldwide as soon as possible, thereby minimising the spread of the virus between countries and within countries. The overall morbidity and mortality from the disease has been the worst since the 1918 Spanish flu pandemic and more than that experienced during the 1968 influenza pandemic, despite massive restrictions on travel and movement within countries. COVID-19 has disproportionately affected sub-populations, such as the elderly who tend to suffer from more severe disease, minority groups, and workers in selected occupations who are at an increased risk of exposure to the virus. In addition, owners of small businesses, children of school-going age, and their parents have suffered significantly from the consequences of lockdown measures. Vaccine policy, when carefully and sensitively implemented, provides an overarching opportunity to help redress and alleviate the inequalities due to the COVID-19 pandemic.¹

The Race for SARS-CoV-2 Vaccines January 2020 to February 2021

The so-called race for vaccines commenced early, with the original wild-type Wuhan SARS-CoV-2 virus being isolated, first typified and then initial genome sequencing published early in 2020.^{11,12}

For this reason, ASPHER believes that we urgently need to address a number of critical issues related to the implementation plans for global immunization. These include international strategies, government commitment, priority setting and rollout phasing plans, concerns about departure from standard practices during vaccine shortages and

delays, assessment and intervention to minimise vaccine hesitancy, and identification of priorities in research.

2. National government considerations

It is essential that all countries develop detailed immunisation plans for the acquisition of vaccines and vaccination rollout with meaningful timescales to achieve maximal population coverage. Furthermore, they should strive for complete transparency by publishing the results of monitoring programmes and modifications of standard practices, such as the consideration of variation in dosage schedules. There should be rational prioritisation including clarity about population sub-groups such as those with increased vulnerability to severe disease, pregnant and breastfeeding women and children, those performing essential duties, health-care workers and caregivers, and other key workers.² The public should have clear and detailed information on the time distribution of vaccinations (including weekends and holidays). There should be strong communication to counteract fake news and vaccine hesitancy, including the need to explain those events associated with the timing of vaccination but not caused by vaccines.³ As far as the practical aspects of implementation, there should be detailed protocols of the vaccination programmes.

The implementation process should include a number of essential components which are related to quality and field effectiveness. At the country level, there should be formal training programs for vaccinators on the correct technique of intramuscular administration of the vaccine (injection technique skills) so that vaccinators acquire the basic qualifications required to give the injections. They should ensure that the requirement that vaccinated persons to wait at least 15 minutes (30 minutes if they have a previous history of anaphylactic reactions) is carefully enforced and monitored, to minimise the consequences of the rare allergic reactions that may occur after the injection. All vaccinators should be provided with written instructions on vaccination technique and details of possible contraindications to vaccination. This should be accompanied by monitoring of the vaccinators for correct techniques and short refresher courses. It is critical that there are sufficient personnel within the health system to administer the vaccines and there should be contingency plans to recruit further personnel. Impact assessment of the COVID-19 vaccines should be included as an ongoing, scientific process.

3. Priority setting and rollout phasing plans.

We advocate that at the outset, each country should have a transparent and auditable (socio-ecological) policy for addressing vaccine inequalities challenges.⁴ We recognize that the current highest priority setting adopted by most countries covers accepted vulnerable groups as well as health and social care workers. However, there is a judgment to be made about who is at highest risk of exposure, and who is at highest risk of severe consequences of the disease. For this reason, it is important that health and care workers should be one of the first priority groups in view of the high level of occupational exposure to the virus, the need for resilience in this workforce to continue to care for others and uncertainties about the severity, particularly from the new variants of SARS-COV-2.¹ The other high priority group is the elderly, particularly those residing in care homes), who are at a substantially higher risk of severe disease. Caregivers for the elderly should also be prioritised.

We recognise there are sound grounds for vaccinating school teachers and pre-school facility child carers if we wish schools and nurseries to be open and their staff resilient to infection, when other sectors of society are closed. Other key services workers or those occupationally highly exposed could be given high priority. Countries should consider vaccinating key workers who are essential for maintaining overall economic and social resilience, for example, police, power and water workers, nuclear and chemical plant operators.

We encourage collaborative work with disadvantaged communities to engage, gain trust and maximise inclusion. Communal or crowded settings that are prone to outbreaks – such as prisons, migrant camps, detention centres and those supporting homeless people – should be considered for high priority. Due to a less than 100% efficacy of the vaccine, some of the elderly and other high-risk groups will still be at risk of disease. Therefore, it will be necessary to outline a policy for immunising children to reduce the community spread of the virus.¹

Varying schedules or doses should be carried out with caution since they have not been formally tested in clinical trials. However, extrapolations are possible if they are evaluated

carefully with accompanying scientific data. We recognise these variations are based on interpretations of available data which may be based on small numbers and sub-set analyses. Frequently scientific judgements may need to be made on the basis of past experience with vaccines. Some of these variations to vaccine dosage or schedule are shown in the table. All alternative option that goes beyond the technical data sheet of each vaccine (which specifies its characteristics and practical aspects) can be derived from the clinical trials whose results have generated its approval. These must be carefully researched to assess whether or not they affect the impact of the administered vaccine itself.

We believe other models of targeted implementation of vaccination should be carefully evaluated. This would be particularly the case if more formal disease eradication strategies were to be adopted (e.g. pursuit of localised foci of infection to help achieve full elimination in any remote areas or outlying community, following the 'ring vaccination' approach applied in smallpox eradication)

4. Assessment of vaccine hesitancy and interventions to minimise the impact

Vaccine hesitancy is likely to remain a major problem, particularly since we are dealing with new vaccines, some of which are based on novel technologies. Despite the high compliance in the initial vaccination campaigns, this may be due to vaccinating the "easy to reach" population first. Later in the campaigns we may encounter more resistance. There is evidence that such resistance is more common in minority populations, perhaps due to less trust in the authorities. It is essential that we identify misinformation and disinformation that will gradually emerge around vaccines, to know where the problems are and to counteract them.⁵ Also, interventions should be designed so as to take into account behavioural aspects for acceptance and uptake of COVID-19 vaccines. It is important to identify the possible resistant groups and the reasons for their resistance to the vaccine. In this way, tailored information programs can be developed and shared internationally.⁶

It is also necessary for appropriate public information campaigns to communicate realistic expectations of what mass vaccination will achieve and when. Social distancing and non-pharmaceutical interventions will remain necessary for a considerable time before substantial suppression of viral transmission will be achieved.⁷ Side effects and

complications of vaccination need to be understood and acknowledged. We cannot be reliant on pharmaceutical industry public information nor can there be collusion with pharmaceutical companies on post marketing surveillance issues. Unless public information and surveillance are clearly authoritative and independent, vaccination programmes may attract distrust and disillusionment from the general public and vaccine hesitancy may grow.

5. Research questions

The current state of what is known about COVID-19 vaccines raises numerous questions and has implications for further research. Examples of some of these issues are as follows:

The duration of vaccine -induced immunity is still unknown. While immunisation may produce immunity, it remains unclear whether it reduces shedding of viable virus at infectious dose levels. It may therefore prevent illness but not prevent spread. As a result, non-pharmaceutical protections, including masks and social distancing, will continue to remain in place for some time. There is still uncertainty regarding the percent of the population that needs to be immunised in order to achieve herd immunity, locally, regionally and globally. With the new mutant strains showing a much greater capability to spread effectively, the percentage may be much more than the figure of around 70 percent, that was initially proposed. In order to achieve any form of herd immunity, we will have to vaccinate children. At this stage, we are still awaiting trial results on the safety of the vaccines in children under the age of 16.

The role of antibody surveys is also being assessed and the length of time immunity is maintained remains a very important question. Moreover, we cannot forget the need for the vaccine production system to be ready for antigenic adaptations of variants or strains that could escape the immunity generated by the original antigens. The adaptive capacity and the time for such adjustment must be anticipated and precisely known.

Concerns about departure from standard practices during vaccine shortages and delays as highlighted above in section 4 also require continuing research. Varying schedules or doses should be carried out with caution since they have not been formally tested in clinical trials. However, extrapolations are possible if they are evaluated carefully with accompanying scientific data.

6. The need for an updated evaluative framework for assessing vaccine efficacy and effectiveness in times of COVID-19.

ASPHER's emerging approach is guided by our broader aspirations during the pandemic. The pandemic is a time for a rethink on the conventional public health evaluative approaches, and to embrace wider perspectives on how to protect populations. Some of these aspirations can be summarised in the following objectives:

- To better and more widely explain as well as promote health literacy and population awareness and resilience.
- To educate and inform about key public health evidence and concerns via our Schools of Public Health and our other partnerships.
- To advocate for transparency, fairness and equity in vaccine decision making processes in Europe, and work with our global alliances on this.
- To provide expert perspectives via our COVID-19 Task Force.
- To inform future work such as on competencies frameworks for public health professionals on infectious disease epidemiology, on developing vaccine programmes, and on wider work on public health science and policy-making.

This paper sets out a way of looking across the spectrum of SARS-CoV-2 and COVID-19 vaccines science, planning and implementation, and policy and decision-making dimensions so that we can identify the various questions that are being asked and that need to be answered.

A newer conceptual framework for vaccine research was proposed in 2018.⁸ This had a number of layers and concepts, including acknowledging modern sciences pace of change. It also recognises that vaccine knowledge and science is far wider than conventionally described and requires many types of scientific perspectives. *“The diverse scientific fields that investigate how vaccines work and why they fail continue to evolve, yet definitions related to such advances have not kept pace”.*

It may now be argued that the rapid vaccine responses and pandemic pace, from early in 2020 to February 2021, has accelerated many scientific and policy challenges and necessitated amended public health and wider professional responses. Indeed, the first

approved vaccine for COVID-19 from Pfizer was developed in less than a year, which is a much faster timeframe than that of traditional vaccine development. Phase 3 is usually achieved in 1-4 years.⁹ Indeed the Johnson & Johnson company regard up to 10 year timeframe as possible for a vaccine's development.¹⁰ They have addressed the issues of balancing urgency, acceleration, and building from recent other vaccine advances along with issues of precaution, safety, quality, scrutiny, and not cutting corners.

ASPHER stance as of February 2021:

- That pandemic and associated vaccine responses are going well beyond preconceived or traditional vaccine related scientific frameworks and research models.
- That the scientific, ethical, and political decisions that have been taken were not fully or widely anticipated or prepared for globally or in individual countries.
- That the global public health and scientific community have not always been able to communicate clearly the uncertainties or convince policy-makers and others of the most effective actions.
- That ethical and moral dilemmas have surfaced about social inclusiveness and equitable distribution of vaccine inside countries and across world populations.
- That given the concerns that were raised early about potential vaccine hesitancy or indeed even vaccine resistance might be key challenges, countries have not collaborated together enough and may thus aggravate public mistrust in some ways.
- That transparency, safety, and effectiveness of vaccine-related decision-making could be challenged, in the short and longer term, if the conventional safer, slower, and robust evaluative systems are not able to deal with the pressure of time, uncertainties, commercial interests, and not only considering the wider social and economic dimensions of the pandemic given its extreme emergency footing.
- That the role of all country-level vaccine public health advisory bodies (NITAGs*) should be reinforced and placed central to informing policy making decisions, and not ignored by politicians or by isolated government employed professionals.
- That the wider pandemic-related public health and scientific advisory systems should be demonstrably informed and supported by the full academic and service based public health community to enable transparent and evidence-based decisions.

*(*National Immunisation Technical Advisory Groups)*

There are a variety of reasons for ASPHER to consider an updated evaluative framework.

The global severity and rapid spread of this virus in the first year of the pandemic has fuelled biomedical sciences urgency and innovation. However, this has the potential for missing or ignoring important public health issues or evidence or not promoting wider engagement of

social and management sciences and applied research on how best to respond to rapid change. We believe that there should be a stronger international research focus on how the SARS-CoV-2 virus affects not only those in different age groups and with underlying medical conditions, but also those with others risks such as ethnicity, and disadvantaged groups with poor living and working conditions.

The emergence of new lineages and variation from virus mutation within human transmission chains.

The virus quickly showed mutation changes, with new lineages and then within a year of genome sequencing has showed several new strains/variants (UK, South Africa, Brazil, Nigeria). By 28th of January 2021, the Variant of Concern (VOC) 202012/01 (lineage B.1.1.1.7), that originated in the county of Kent (in September 2020), UK, had become the most common new variant in the USA.¹³

International collaboration and genomic databases like GISAID,¹⁴ will aid close monitoring as long as there are widespread and representative sampling capabilities across the world. Each variant strain needs to be identified quickly and genomically, and characterised to show its virulence and treatability, transmissibility, identifiability within current national virus testing schemes, and its ability to evade immune responses derived from either natural infection or from vaccines.

Much of the rapid vaccine development focussed on ways to deliver spike proteins as antigens, usually by presenting mRNA to our immune systems for auto-production of the spike, and protection via subsequent humoral and cellular immune responses. Spike antigen vaccine technology is expected to evolve as part of rapid adaptive research, to respond better to mutations and new variants. Other vaccine technologies are also expected to see if additional non-spike antigens or virus particles can give more fundamental immune responses that may cope better with future mutations. Uncertain future scenarios and the 'imperfect future immunity'¹⁵ may lead us to agreeing to more flexible and contingent approaches for shaping public health responses against the future global complexity and unpredictability. The goals that are set for vaccines may need to be tempered as evidence

unfolds on actual effectiveness in real situations against threats of mutations, global vaccine inequity, delivery failures, and vaccine hesitancy.

ASPHER will continue to look for balance across the decision making and to ensure that all new ways of researching and evaluating vaccine approaches are pursued in addition to standard clinical trial and rollout metrics. The **Table in Appendix 1** illustrates the range of parameters that should be kept under scrutiny.

7. Calls for Action

As Europe's representative organisation for schools of public health, ASPHER calls upon national governments to:

- Carefully and sensitively implement clear vaccination policy;
- Develop detailed immunisation plans and establish meaningful timescales for vaccination roll-out, detailing what resources are required and what to do in less-than-ideal conditions;
- Give special consideration to logistics, storage, and distribution aspects of vaccination roll-out, including but not limited to:
 - Mask wearing and social distancing in vaccination hubs;
 - Involvement of other health professional groups (e.g. pharmacists, vets, dentists, etc...) and the military (in less-than-ideal situations);
- Develop a technological platform which would enable tracking of different national level Vaccination Information Systems; this would facilitate the monitoring and registration of vaccinated individuals, while strictly respecting the confidentiality of the information as well as the traceability of the different vaccines);
- Establish a common vaccination card with interoperable management tools, which would further facilitate the management and traceability of vaccination processes within and between countries/regions as well as between different possible providers of vaccination services (public or private);
 - This should be done in a coordinated way with WHO guidance and adapted to the context of each country; the model used for yellow fever vaccination can be adapted for the COVID vaccine;

- The concept of a potential “passport” is still under discussion both nationally and internationally and, if explored, will need careful handling;
- Adequately assess the monitoring and verification of vaccine effectiveness;
- Ensure the monitoring and documentation of adverse events occurring close in time after vaccination;

Furthermore, we call upon schools of public health to:

- Immediately include a module on pandemic preparedness in their degree programmes;
- Collaborate and pool resources to develop training programs that would help to address the critical shortage of highly qualified professionals in this field.

8. Conclusion

The vaccination campaigns are likely to be complex with serious challenges at every step. The most important issue will clearly be supplies of vaccines. However, priorities, planning and execution of the vaccination campaigns will entail multiple tasks, each requiring expertise and resources. A carefully planned vaccination campaign with adequate allocation of resources is essential to achieve optimal results in the shortest possible time. The rapidly changing epidemiological factors will require flexibility in the face of an increasingly complex pandemic. There are still many unanswered questions which will require accelerated research. Strong international collaboration, with the active involvement of the World Health Organisation is essential to meeting the varying challenges. Finally, we need to use the lessons learned from the COVID-19 pandemic to prepare for the next pandemic.

References

1. Annex A: COVID-19 vaccine and health inequalities: considerations for prioritisation and implementation [Internet]. GOV.UK. [cited 2021 Jan 15]. Available from: <https://www.gov.uk/government/publications/priority-groups-for-coronavirus-covid-19-vaccination-advice-from-the-jcvi-30-december-2020/annex-a-covid-19-vaccine-and-health-inequalities-considerations-for-prioritisation-and-implementation>
2. WHO Technical Advisory Group on Behavioural Insights and Sciences for Health Behavioural considerations for acceptance and uptake of COVID-19 vaccines. Geneva: World Health Organization; 2020.
3. MODULE 6 – Overview and outcomes - WHO Vaccine Safety Basics [Internet]. [cited 2021 Jan 15]. Available from: <https://vaccine-safety-training.org/overview-and-outcomes-6.html>
4. COVID-19: vaccinator competency assessment tool [Internet]. GOV.UK. [cited 2021 Jan 15]. Available from: <https://www.gov.uk/government/publications/covid-19-vaccinator-competency-assessment-tool>
5. Dror AA, Eisenbach N, Taiber S, Morozov NG, Mizrahi M, Zigran A, et al. Vaccine hesitancy: the next challenge in the fight against COVID-19. *Eur J Epidemiol*. 2020 Aug 1;35(8):775–9.
6. Glossary - WHO Vaccine Safety Basics [Internet]. [cited 2021 Jan 15]. Available from: <https://vaccine-safety-training.org/glossary.html>
7. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. [cited 2020 Sep 1]. Available from: <https://covid19.who.int>
8. Crowcroft NS, Klein NP. *A framework for research on vaccine effectiveness*, *Vaccine*, 2018; 36 (48): 7286-93. <https://doi.org/10.1016/j.vaccine.2018.04.016>. (accessed 02/02/2021)
9. Pfizer 2021 – *Our Science – The Four Phases of Clinical trials*. <https://www.pfizer.com/science/clinical-trials/guide-to-clinical-trials/phases> (last accessed 06/02/2021)
10. Johnson & Johnson, 2021. *The 5 Stages of COVID-19 Vaccine Development: What You Need to Know About How a Clinical Trial Works*, <https://www.jnj.com/innovation/the-5-stages-of-covid-19-vaccine-development-what-you-need-to-know-about-how-a-clinical-trial-works> (accessed 06/02/2021)
11. Zhou, P., Yang, XL., Wang, XG. *et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin*. *Nature* **579**, 270–273 (2020). <https://doi.org/10.1038/s41586-020-2012-7> (accessed 07/02/2021)
12. Wu, F., Zhao, S., Yu, B. *et al. A new coronavirus associated with human respiratory disease in China*. *Nature* **579**, 265–269 (2020). <https://doi.org/10.1038/s41586-020-2008-3> (accessed 07/02/2021)

13. Centers for Disease Control. *Emerging SARS-CoV-2 Variants*. Atlanta, CDC, 28th January 2021. <https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging-variants.html> (accessed 02/02/2021).
14. GISAID - COVID-Miner. *Geographical distribution on RBD*. <https://covid-miner.ifo.gov.it/app/countries> (accessed 07/02/2021)
15. Saad-Roy CM, Wagner CE, Baker RE. *Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next 5 years*. *Science* 370, 811–818 (2020) DOI: <https://doi.org/10.1126/science.abd7343>

***Appendix 1. ASPHER - Assessing vaccine efficacy and effectiveness in times of COVID-19
Is the Pandemic a time for a rethink on the public health evaluative approaches?***

Initial ASPHER SARS-CoV-2 vaccine science and strategies- an outline research and evaluation framework.

This table sets out a range of research and evaluation concerns that are being or should be addressed. A balanced and comprehensive programme of research and evaluation would have resources and capability to examine all these public health concerns, set out below. A systematic approach, with a strong eco-social and inequities focus, if mobilised in such a broad way, would need additional targeted public health funding and capacity, that would be complimentary to the more heavily funded vaccine technologies industries or in related standard research institutions.

ASPHER’s vaccine statements and resources can be found via the [COVID-19 Task Force page](#)

Table 1. Pandemic Pace: the acceleration of the emergency situation demands updated international agreements on vaccine research, efficacy studies, rapid adaptive analysis, and broader evaluation of programmes and policies.

Research and evaluation Steps or levels	Types of research approaches	Issues and challenges.
1. Vaccine Research origination	Background technical reviews of useful vaccine knowledge such as SARS and MERS, (Ebola etc), new genomics, and wider science and technology.	There was rapid origination and learning from all relevant historical or recent vaccine research. Some lessons were learned from research into SARS, MERS and Ebola vaccines, plus preparation for Disease X, such as the standby Adenovirus vector cell lines. “By January 23, CEPI initiated its first three programmes to accelerate development of vaccines against this novel pathogen, when just 141 cases of the virus had been confirmed worldwide”. ¹ While much of the early impetus was towards vaccines from genetic and vector virus vaccines, we await further evidence on inactivated virus vaccines, attenuated virus vaccines and protein antigen vaccines. ²
	Preclinical testing	Testing responses in laboratories on primates or other non-human subjects; for instance for immune responses against initial infection or in reinfection challenges. ^{3,4} While primates usually offer the most comparable animal models there may be some objections to largescale testing and regarding their welfare.

2. Vaccine Clinical Trials and Safety studies	Phase 1	Peer reviewed reports may available some months after initial preprints. ⁵ The smaller number of Phase 1 subjects may be rolled into phase two larger group as vaccine experimental safety results becomes more assured and they further focus on immune responses.
	Phase 2	Peer reviewed publication may be relatively delayed. ⁶ Also concern that governments may act early on Phase 2 results but before phase 3 results more widely available. ⁷ While hope is to be expected from earlier phase results, ⁸ there has to be caution also given small numbers and lack of efficacy data.
	Phase 3	<p>There has been some concern over speed of research conduct and faster regulatory approval processes for vaccines. Some elements of phase 1-2 studies may not be required such as on carcinogenicity, genotoxicity and toxicokinetics.</p> <p>In the UK the Pfizer-BioNTech Covid-19 vaccine was given authorisation (Regulation 174) on 1st December 2020 for temporary supply by the UK Department of Health and Social Care and the Medicines & Healthcare products Regulatory Agency. Full details were made open and followed a rolling review process that was aiming to be rigorous while maintaining speed of evaluation of the vaccine.⁹ It was judged that a formal Ecotoxicity/Environmental Risk Assessment was not required for this application, due to no significant such risks perceived.</p> <p>Regulatory agencies need to see data based on adequate numbers in the phase 3 trials, reported to enable overall calculation of efficacy after one and two doses with stated confidence intervals.^{10,11} These numbers can then be scrutinised widely. The European Medicines Agency granted ‘conditional marketing authorisation’ three weeks later on 21st December 2020, after ‘thorough evaluation’ and EMA concluded an overall 95% efficacy reducing symptomatic cases in people over 16 years old in the clinical trial, and high efficacy across vulnerable clinical and age groups.¹² Overall efficacy was calculated from 7 days after the second dose of vaccine.</p> <p>Greater speed and openness might be needed to build confidence in vaccines from outside the traditional European/USA pharmaceutical sectors. Efficacy results from the vaccine developed in Russia have since been made available for debate and consideration.¹³</p> <p>Efficacy re-analysis of Pfizer-BioNTech vaccine efficacy data: As part of subsequent PHE re-analysis there is a newer approach posited for definitions of efficacy, <i>“A reasonable interval to use for post first dose VE would therefore be from >14 days to the time of the second dose (scheduled 21 days</i></p>

		<p>after the first dose) or to 7 days after the second dose base on the assumption the second dose would not have induced a response in this interval.”¹⁴ Such a technical refinement is biologically and epidemiologically plausible and may become more accepted and useful, if further data is supportive, from more convincing numbers across different vaccine trials. If accepted, it could improve vaccine efficacy rates and rule out infected cases who were too early after vaccination to have gained any protection. This might also help in risk communication if there is further evidence on suspicions that some vaccinees reduce their protective behaviours shortly after vaccination in the belief that they are protected immediately after vaccination.</p>
	Phase 4	<p>It is standard practice with new products to require phase 4 studies. EMA – “Companies are required to provide monthly safety reports in addition to the regular updates required by the legislation and conduct studies to monitor the safety and effectiveness of the vaccines as they are used by the public. Authorities will also conduct additional studies to monitor the vaccines”.¹² This involves follow up of trial vaccinated cohorts, Post-marketing surveillance systems and studies, plus Adverse Event reporting to regulators.</p> <p>For public health purposes the latter should be independently structured, funded and conducted separately from vaccine manufacturers studies, and should command public and professional trust. WHO guidance is long-standing,¹⁵ and needed to be updated following experiences like Ebola Virus vaccine development for the outbreak in DRC, including the need for wider public engagement.¹⁶ The WHO Emergency Use Listing Procedure (EUL) in December 2020 could be viewed as a reasonable start to meet pandemic requirements, albeit subsequent COVID-19 pace of change may not enable wider engagement. ¹⁷ Any initial time limited arrangements and pre-conditions need to be followed up within the WHO evaluative mechanisms.¹⁸ Summary communication of such approval processes’ complexities might be aided by infographics and other visual tools for professionals and public, as in EMA and FDA examples.^{19,20}</p>
3. Rapid Adaptive Research – to help answer emerging questions by reanalysis of current trial datasets, or by using expanding	Targeting virus mutations and variant development with adapted or new vaccines	There will be a need to adapt existing SARS-CoV-2 vaccines and their delivery, to cover significant new variants or when the disease surges for other reasons. ^{21,22} This remains a central concern in the COVID-19 vaccine strategy evolution.
	Age or other risk groups - subgroup analysis with sufficient numbers for confidence	There are age specific questions about effectiveness in elderly and children. Subgroup analysis of specific age groups are challengeable particularly on the basis of their small numbers. A recent study looking at an expanded phase 1 trial group of only 40 people over age 56, did not find major differences between those age 56 and over, versus those under 56 who were known from the original trial. ²³ Some countries may adopt more precautionary, and controversial, approaches for

datasets as trials recruitment continued.		not agreeing to use in children and elderly in relation to particular vaccines. Maintaining impartiality is a likely issue, especially for countries that have deep vaccine production histories, to avoid political influences. Children under age 16 are not licensed for vaccine use and could only receive it now under exceptional clinically-argued circumstances. However, examples are emerging, e.g. to include research for children, age 6-17 years. ²⁴ .
	Optimal delivery for dosages	There is interest in the impact of delayed second dose schedules on efficacy, as this allows more people access to scarce vaccine stocks. Reanalysis of original data may assist in refining arguments. ²⁵
	Mixed vaccine types and new regimes	There is interest in researching combinations of two or more vaccines, or alternating vaccines, instead of single vaccine as 2 or more/booster doses. For example, a new trial covering over 800 over 50 age volunteers will include alternating the Oxford -AstraZeneca and the Pfizer vaccines. ²⁶
	Horizon scanning for emerging/new technologies in vaccines	This can include regular reviews of the range of current candidate vaccines ²⁷ and also involve more novel experimental approaches. A recent review up to 3 rd February shows how four key dimensions might be monitored. These are for each vaccine; can it be produced at scale, priced affordably, allocated globally so that they are available where needed, and widely deployed in local communities? ²⁸
4. Programme and Field effectiveness research and evaluation	Effectiveness studies of health outcomes and impacts during rollout	There is a need to agree how to best do this in a rapid emergency context to maintain international comparability and public confidence. Will each country's results be comparable at least in Europe, if not globally?
	Vaccine failure studies	There is a need to consider vaccine failure in rapid reviews during rollout and also ensure ability to check quality of local reporting data.
	Vaccine uptake studies	This will involve a review of factors such as vaccine delivery issues, and also vaccine hesitancy or of active vaccine resistance. Conspiracy theories and disinformation, amplified in social media, are also concerns.
	Vaccine science disputes and media reporting	Given current high volumes of smaller numbers, rapid reporting and later peer review there is ample scope for misunderstandings and complements of evidence. The mixture of competition between commercial, political and scientific interests is likely to fuel controversy. There is much scope for more independent systematic reviews across vaccines clinical trials and later field studies.
5. Evaluating Strategic goals –	Health systems protection goals – impacts on resilience	Assessing how successful was targeting high risk groups in health and social care who needed protection and resilient continuity of workforce.

<p>Covering mitigation, control, and elimination goals in wider context – with wider models of effectiveness research and evaluation.</p>	models to protect key workforce	
	Clinical and age-related vulnerability goals – impacts on reducing severe morbidity and mortality in key groups	Underpinning much of the mainstream vaccine modelling being done. This is normally covered well in preliminary Phases 1-3 literature. However timely delivery and uptake in key target groups needs to be assessed early on.
	Key assets protection goals	Consider if there are highly valued human assets that need better protection in particular workforces that will lead to major social benefits.
	Outbreak aversion goals	There is a need to consider how outbreaks might be averted in known vulnerable groups or communal settings that could be protected in vaccination programmes. Examples include prisons and detention centres, homeless shelters, and higher risk non-healthcare occupational/industrial settings.
	Equity and inequalities goals analysis (global and/or national)?	How far does the country model set out high risk groups other than on clinical vulnerability? There is a need for more debate and openness about the underlying social and political values in each country. The WHO Roadmap ²⁹ - ' <i>three rationales</i> ' is a useful way to assess options as stages of vaccine delivery are planned and staged. Their 3 examples were - <ul style="list-style-type: none"> • <i>Health workers at high to very high risk of becoming infected and transmitting SARS-CoV-2 in the Community Transmission epidemiologic setting</i> • <i>Sociodemographic groups at significantly higher risk of severe disease or death</i> • <i>Social/employment groups at elevated risk of acquiring and transmitting infection because they are unable to effectively physically distance</i>
	Assessing costs and value of life and other ethical parameters;	Vaccine production and marketing costs vary. There are differential vaccine delivery costs such as cold/freezer chain requirements and in human resources. Health economics analyses will be needed such as Cost-effectiveness studies and Cost-benefit analysis to see how we can look at returns on investment across different vaccine strategies. QALY estimates have been produced and raise important questions. ³⁰ Ultimately key ethical questions should not be explained as purely scientific and need to be developed ethically as transparent rational valuation approaches; broadly either intrinsic valuation of life and disability or socially instrumental values such as protecting workforces. ³¹ There will remain a need to continue to evaluate the 'ounce of prevention' that we look for, ³² to see which country ultimately gets the best mixes of investment and health or other outcomes.

	Elimination goals – possible strategies	Issues of whole population approaches and whether reducing transmission in children is a key aim. We will probably need to consider dual or multi track vaccine approaches as in influenza programmes. There is a need to evaluate vaccine policy in the context of its evolution alongside NPIs and with wider relevant population/societal changes – such as economic decline, regional conflicts, social inclusion programmes or strategic links to sustainable development approaches
	Risk communication analysis, with whole COVID-19 strategy public and policy support studies	Analysis of public support and understanding is needed. There is a need for evaluating the levels of wider public support to see the developing place of vaccines amongst broader clinical/scientific advances, and in respect of strategic efforts for future use of NPIs and for enabling social and economic recovery.
	Strategic review – as a cycle – with regular reprogramming of above goals and programmes	Good first steps are evident in ECDC reviews across EU/EEA countries that show useful early comparisons. ^{33,34} As recently as 2019 a systematic review identified how political, economic, administrative, regulatory, logistical, ethical, and social (PEARLES) challenges could be overcome to advance clinical research preparedness and responses to emerging epidemics by searching the literature. ³⁵ A need for urgency and rapidity for evaluation was foreseen for between epidemics, but equally we contend such rapid cycles are now required during COVID-19, intra-pandemic. Rapid and comprehensive reviews will be needed inside each country as well as at across countries, that should include equity issues for regions and all vulnerable groups. This is needed at least within 6-9 months of vaccine launch. Realism and timescales for a rapid strategic review. This is easier in adopting constant dynamic expert consideration with government led adjustments. However, it remains to be seen how inclusive such periodic reviews will be in terms of consultation and wider population engagement, and in reaching out to excluded groups.

References:

1. Coalition for Epidemic Preparedness Innovations. *A leap forward in vaccine technology* (CEPI 01/02/2021) https://cepi.net/news_cepi/a-leap-forward-in-vaccine-technology-2/
2. British Society for Immunology. *Types of vaccines for COVID-19*. <https://www.immunology.org/coronavirus/connect-coronavirus-public-engagement-resources/types-vaccines-for-covid-19> accessed 08/02/2021
3. Yu J, Tostanoski LH, Peter L, et al. *DNA vaccine protection against SARS-CoV-2 in rhesus macaques*. *Science* 2020;369 (6505)806-811 DOI: <https://doi.org/10.1126/science.abc6284>

4. Chandrashekar A, Liu J, Martinot AJ, et al. *SARS-CoV-2 infection protects against rechallenge in rhesus macaques*. *Science*; 14 Aug 2020: Vol. 369, Issue 6505, pp. 812-817 DOI: <https://doi.org/10.1126/science.abc4776>
5. Jackson LA, Anderson AJ, Roupael NG, et al. *An mRNA Vaccine against SARS-CoV-2 — Preliminary Report*. *N Engl J Med* 2020; 383:1920-1931
DOI: 10.1056/NEJMoa202248
6. Logunov DY, Dolzhikova IV, Zubkova OV, et al. *Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia*. *Lancet* 2020; 396: 887–97. DOI: [https://doi.org/10.1016/S0140-6736\(20\)31866-3](https://doi.org/10.1016/S0140-6736(20)31866-3) = heterologous recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac (Sputnik V)
7. Thiagarajan K. *Feature. Covid-19: India is at centre of global vaccine manufacturing, but opacity threatens public trust*. *BMJ* 2021; 372 Doi: <https://doi.org/10.1136/bmj.n196>
8. Stower, H. *Seeds of hope in COVID-19 vaccine preliminary data*. *Nat Med* 26, 1170 (2020). <https://doi.org/10.1038/s41591-020-1031-0>
9. Medicines and Healthcare Products Regulatory Agency. *Summary of the Public Assessment Report for Pfizer/BioNTech COVID-19 vaccine*. MRHA 2020. <https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-public-assessment-report-for-pfizerbiontech-covid-19-vaccine> (accessed 09/02/2021)
10. Fernando P, Polack FP, Thomas SJ, Kitchin N, et al. *Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine*. *N Engl J Med* 2020; 383:2603-2615. DOI: <https://doi.org/10.1056/NEJMoa2034577>
11. Voysey MV, Clemens SAC, Mahdi SA, et al. *Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK*. *Lancet* 2020, 397 (10269) 99-111. DOI: [https://doi.org/10.1016/S0140-6736\(20\)32661-1](https://doi.org/10.1016/S0140-6736(20)32661-1)
12. European Medicines Agency. *EMA recommends first COVID-19 vaccine for authorisation in the EU*. EMA 2020. <https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu> (accessed 09/02/2021)
13. Logunov DY, Dolzhikova IV, Shcheblyakov DY, et al. *Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia*. *Lancet* 2021; S0140-6736(21)00234-8.
DOI: [https://doi.org/10.1016/S0140-6736\(21\)00234-8](https://doi.org/10.1016/S0140-6736(21)00234-8)
14. Public Health England. *Annex A: Report to JCVI on estimated efficacy of a single dose of Pfizer BioNTech (BNT162b2 mRNA) vaccine and of a single dose of ChAdOx1 vaccine (AZD1222)*. PHE 2021.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/949505/annex-a-phe-report-to-jcvi-on-estimated-efficacy-of-single-vaccine-dose.pdf (accessed 09/02/2021)

15. Folb PI, Bernatowsks E, Chen RT, et al. *A Global Perspective on Vaccine Safety and Public Health: The Global Advisory Committee on Vaccine Safety*. Am J Public Health 2004, 94, No. (11) 1926-31. DOI: [10.2105/AJPH.94.11.1926](https://doi.org/10.2105/AJPH.94.11.1926) (also see https://www.who.int/vaccine_safety/about/en/vaccine.pdf)
16. Smith MJ, Ujewe S, Katz R, Upshur EG. *Comment; Emergency use authorisation for COVID-19 vaccines: lessons from Ebola*. Lancet 2020, 396, (10264), 1707-1709. 2020 DOI: [https://doi.org/10.1016/S0140-6736\(20\)32337-0](https://doi.org/10.1016/S0140-6736(20)32337-0)
17. World Health Organisation. *Emergency Use Listing Procedure Version 13 December 2020*. WHO, Geneva, 2020. https://www.who.int/docs/default-source/medicines/eulprocedure.pdf?sfvrsn=55fe3ab8_7
18. World Health Organisation. *Consideration for evaluation of COVID-19 vaccines. Points to consider for manufacturers of COVID19 vaccines (Version 25 November 2020)*. WHO, Geneva, 2020.
19. US Food and Drug Administration. *The Path for a COVID-19 Vaccine from Research to Emergency Use Authorization (infographic)*. FDA 2020. <https://www.fda.gov/media/143890/download>
20. European Medicines Agency. *Fast-track procedures for treatments and vaccines for COVID-19 (infographic)*. EMA 2020. https://www.ema.europa.eu/en/documents/leaflet/infographic-fast-track-procedures-treatments-vaccines-covid-19_en.pdf
21. Wu K, Werner AP, Moliva JI, et al. *mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants*. bioRxiv 2021.01.25.427948; doi: <https://doi.org/10.1101/2021.01.25.427948>
22. Sabino EC, Buss LF, Carvalho MPS, et al. *Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence*. Lancet 2021; 397:452-54 DOI: [https://doi.org/10.1016/S0140-6736\(21\)00183-5](https://doi.org/10.1016/S0140-6736(21)00183-5)
23. Anderson EJ, Roupheal NG, Widge AT, et al. *Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults*. N Engl J Med 2020;383:2427-38. DOI: <https://doi.org/10.1056/NEJMoa2028436>
24. Oxford Vaccine Group. *Oxford University extends COVID-19 vaccine study to children*. University of Oxford 2021. <https://www.ovg.ox.ac.uk/news/oxford-university-extends-covid-19-vaccine-study-to-children>
25. Oxford Vaccine Group. *Oxford leads first trial investigating dosing with alternating vaccines*. University of Oxford 2021. <https://www.ovg.ox.ac.uk/news/oxford-leads-first-trial-investigating-dosing-with-alternating-vaccines>
26. Hunter PR, Brainard J. *Estimating the effectiveness of the Pfizer COVID-19 BNT162b2 vaccine after a single dose. A reanalysis of a study of 'real-world' vaccination outcomes from Israel*. MedRxiv Preprint posted 08/02/2021. Doi: <https://doi.org/10.1101/2021.02.01.21250957>
27. Belete TM. *Review on Up-to-Date Status of Candidate Vaccines for COVID-19 Disease*. Infect Drug Resist. 2021;14:151-161 DOI: <https://doi.org/10.2147/IDR.S288877>

28. Wouters OJ, Shadlen KC, Salcher-Konrad M, et al. *Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment*. Lancet 2021, DOI: [https://doi.org/10.1016/S0140-6736\(21\)00306-8](https://doi.org/10.1016/S0140-6736(21)00306-8)
29. [World Health Organisation](#). *WHO - SAGE ROADMAP FOR PRIORITIZING USES OF COVID-19 VACCINES IN THE CONTEXT OF LIMITED SUPPLY; Version 1.1*. Geneva; WHO 2020 <https://www.who.int/publications/m/item/who-sage-roadmap-for-prioritizing-uses-of-covid-19-vaccines-in-the-context-of-limited-supply> (accessed 08/02/2021).
30. Kohli M, Maschio M, Becker D, Milton C, Weinstein MC. *The potential public health and economic value of a hypothetical COVID-19 vaccine in the United States: Use of cost-effectiveness modelling to inform vaccination prioritization*. Vaccine 2021;39(7):1157-1164 DOI: <https://doi.org/10.1016/j.vaccine.2020.12.078>
31. Giubilini A, Savulescu J, Wilkinson D. *Queue questions: Ethics of COVID-19 vaccine prioritization*. Bioethics 2021;00:1-8 Doi: <https://doi.org/10.1111/bioe.12858>
32. Longo DL. *SARS-CoV-2 Vaccination — An Ounce (Actually, Much Less) of Prevention*. N Engl J Med 2020; 383:2677-2678 DOI: <https://doi.org/10.1056/NEJMe2034717>
33. European Centre for Disease Prevention and Control. *Overview of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA and the UK*. ECDC, Stockholm, 2020. <https://www.ecdc.europa.eu/en/publications-data/overview-current-eu-eea-uk-plans-covid-19-vaccines>
34. European Centre for Disease Prevention and Control *Overview of the implementation of COVID-19 vaccination strategies and vaccine deployment plans in the EU/EEA 1st February 2021*. ECDC, Stockholm, 2021. <https://www.ecdc.europa.eu/en/publications-data/overview-implementation-covid-19-vaccination-strategies-and-vaccine-deployment>
35. Sigfrid L, Bannister PG, Katherine Maskell K, et al. *Political, economic, administrative, regulatory, logistical, ethical, and social (PEARLES) challenges to clinical research responses to emerging epidemics and pandemics: a systematic review*. Lancet 2019; 394(2):S86 [https://doi.org/10.1016/S0140-6736\(19\)32883-1](https://doi.org/10.1016/S0140-6736(19)32883-1)