COVID-19 vaccination and prioritisation strategies in the EU/EEA

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Key facts

- Prioritisation of COVID-19 vaccination should take into account several dimensions and needs to be contextualised.
- The choice of optimal vaccination strategy depends on the objective, e.g. reducing mortality, saving life years or reducing pressure on the healthcare system.
- The optimal prioritisation also depends on the characteristics of the vaccine, in particular its efficacy against infection and therefore onward transmission.
- If a vaccine does not protect against transmission, the most effective and efficient approach is to prioritise the vaccination of those groups at highest risk of severe disease and death.
- Substantial reductions in mortality and pressure on the healthcare system could be achieved by the direct protection of high-risk groups, even if viral transmission is ongoing within the population.
- Vaccination of healthcare workers is beneficial since it improves the resilience of the healthcare system. The benefit would be heightened if the vaccine were effective against infection, and therefore transmission, since it would offer indirect protection to patients, residents of long-term care facilities and other high-risk individuals.
- Although vaccinating adults aged 18-59 years is not the most effective or efficient strategy when vaccine supply is limited, consideration should be given to specific groups or settings that may have a disproportionate risk of exposure.
- Given the many unknowns in relation to COVID-19 vaccines’ characteristics, deployment, supply, and uptake, and to future appearance of vaccine escape variants, non-pharmaceutical interventions should continue to be applied, as recommended by public health authorities, in the initial months following the introduction of COVID-19 vaccination.
- Vaccination strategies will need to be adaptable over time to unfolding events taking into account the emerging evidence.

Background

Since December 2019 and as of December 2020 there have been over 15 000 000 cases of COVID-19 reported in the European Union (EU), European Economic Area (EEA) and the United Kingdom (UK), including over 375 000 deaths [1]. All EU/EEA and UK countries have reported COVID-19 cases, but the spread of the outbreak and the number of infected people vary within and between countries. Most EU/EEA countries and the UK are experiencing a second increase of cases during these final months of 2020 and although the number of performed tests is higher than those carried out in spring, the high and rising positivity rate show that the actual cases have increased.
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is mainly transmitted through saliva droplets, and prolonged physical proximity is considered the main risk factor for infection. The virus affects infected individuals differently according to age and preconditions. There is an increased risk of hospitalisation, admission to intensive care units (ICU) and death with increased age and for those with certain underlying conditions [2,3]. It is estimated that up to 30% of the population of the EU/EEA is either over 60 years old or has one of the underlying conditions, such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, malignancies, Down syndrome, liver disease, certain neurological diseases and weakened immune systems, associated with risk of severe illness from COVID-19 [4]. Other factors, such as obesity and smoking, have also been observed to be associated with risk of severe illness from COVID-19 [5-8].

In the absence of a curative treatment or a vaccine, non-pharmaceutical interventions (NPI), such as physical distancing, have been used to curb the pandemic. However, there are concerns about the long-term sustainability of following such preventive measures in terms of population acceptance and compliance, as well as the potential social and economic consequences. In addition to NPIs, the development and use of safe and effective vaccines against COVID-19 is considered the most promising option for containing the pandemic in the long term.

An unprecedented number of vaccine candidates against a single disease and with various characteristics are currently under development. These vaccines are being developed using different technological platforms, both those already established and new ones, such as mRNA vaccines [9]. On 21 December 2020, the European Medicines Agency (EMA) recommended granting a conditional marketing authorisation for the Pfizer/BioNTech COVID-19 vaccine in the EU in people from 16 years of age. At the time of writing, the EMA Committee for Medicinal Products for Human Use is performing a rolling review procedure for three vaccines (AstraZeneca/Oxford, Janssen-Cilag International NV, and Moderna). One of these vaccine developers (Moderna) has now also applied for Conditional Marketing Authorisation to the EMA [10]. On 2 December 2020, the UK government accepted the recommendation from the UK Medicines and Healthcare Products Regulatory Agency to approve the Pfizer/BioNTech COVID-19 vaccine for use in the UK [11].

At the time of writing, evidence of some of the key characteristics of COVID-19 vaccines, such as immunogenicity, efficacy and safety, is becoming available [12-14]. It is not yet fully clear from Phase 3 clinical trials how effectively the upcoming COVID-19 vaccines will reduce disease severity and deaths in the population and if they also will prevent infection and decrease transmission of the disease. Also, the duration of protection from vaccination against COVID-19 is unknown. Phase 3 trials are also limited in terms of statistical power and length of follow-up for providing definite answers on clinical endpoints for specific target groups. Furthermore, since COVID-19 is a novel disease, there are several unknowns despite intense ongoing research. The full extent of interaction between host and virus is not known, and neither is the protective immunological response mechanism nor its duration.

It is expected that the initial supply of COVID-19 vaccines will be limited. It will therefore be very important for countries to identify priority groups to be vaccinated in the initial phase, before moving to subsequent phases in which vaccines presumably will be offered to an increasingly larger part of the population, possibly on a routine basis. The process of prioritising which groups to vaccinate in the initial phase needs to be fair, transparent and continuously updated, based on new available knowledge. Countries will also need to develop comprehensive vaccination strategies in line with their public health objectives, as well as taking into account incidence, burden and geographical distribution of COVID-19. Over time, these strategies will need to be adapted to epidemiological changes, new evidence on disease pathogenesis and risk groups, vaccine supply, and new knowledge about safety, immunity and protection from the available vaccines.

Mathematical modelling is important for supporting the identification of priority groups for vaccination against COVID-19 and the development of efficient and effective vaccination strategies. By using data on demography, COVID-19 epidemiology, and prevalence of risk groups in the population, mathematical modelling can be utilised to compare the potential impact of different vaccination strategies targeting different groups based on assumptions on vaccine characteristics, vaccine supply and uptake [15]. Mathematical modelling alone is unable to provide a single answer on what is the best strategy to adopt for the roll-out of COVID-19 vaccination. However, it can provide insights into some of the most influential factors for decision-making according to different scenarios and public health objectives.

**Scope and objective**

This document builds on a previously published ECDC report, ‘Key aspects regarding the introduction and prioritisation of COVID-19 vaccination in the EU/EEA and the UK’ [15]. By using mathematical modelling, this document provides EU/EEA countries with information on factors that may affect the choice of COVID-19 vaccination strategies, according to different target groups and based on scenarios of hypothetical vaccine characteristics.

The objectives of this document are to show:

- How the objective of a vaccination strategy should be informed by the characteristics of the vaccines available;
- How the prioritisation of certain population groups may help achieve the objective of the vaccination strategy.
Target audience

The target audiences for this document include public health institutes and professionals involved in COVID-19 vaccination planning, national immunisation technical advisory groups (NITAGs), Ministries of Health and other decision-making bodies involved in the planning of COVID-19 vaccination campaigns at national and subnational level in the EU/EEA.

Description of the mathematical model

The mathematical model used to conduct this analysis is an extension of the existing ECDC COVID-19 dynamic compartmental model, which has previously been described in detail [16]. In brief, the model simulates the transmission of SARS-CoV-2 in the EU/EEA and the progression to COVID-19 disease, including mild cases which remain in the community and severe cases which are admitted to standard hospital wards or to intensive care units. It is age-structured, accounting for the differential risk of severe disease and death by age.

The model incorporates data on non-pharmaceutical interventions and testing rates over time since February 2020 and is calibrated to available data on number of confirmed cases, hospital admissions, ICU admissions and COVID-19 deaths for each member state of the EU/EEA. In this analysis, the model is fitted to epidemiological data up to 1 December 2020 to simulate the background naturally acquired immunity. We model the whole EU/EEA population.

The objective of this analysis is to compare the relative effectiveness and efficiency of different vaccine prioritisation strategies by target group. This analysis is not intended to make a forecast of how COVID-19 epidemiology will evolve in the EU/EEA in the vaccination era. The latter will depend on vaccine characteristics, future policy on non-pharmaceutical interventions and other behavioural change. We model an artificial scenario of steady ongoing transmission as a 'test ground' for exploring the factors that will influence vaccination policy. In the baseline analysis, we make the limiting assumption that naturally acquired immunity lasts longer than 24 months.

We simulate the introduction of a number of different vaccination strategies comparing each with a universal vaccination strategy where all adults are vaccinated. To illustrate the factors that may drive prioritisation, we assume in the baseline scenario that the whole target group is vaccinated on the same day i.e. that there is adequate supply and 100% uptake. We assume two vaccine doses are required per person. The impact of vaccination is assessed as the total number of deaths prevented, life years saved and hospital and ICU admissions prevented in one year following the date of vaccination.

We model alternative vaccine characteristics. If the vaccine prevents infection, the vaccinee becomes immune. If the vaccine prevents mild disease then, if infected, the vaccinee has an asymptomatic infection. Individuals with asymptomatic infection are assumed to transmit the virus 35% as effectively as symptomatic individuals [17]. We assume that in the pre-vaccination era, 17% of cases are asymptomatic [18]. If the vaccine prevents severe disease then, if infected, the vaccinee has a mild clinical presentation. We assume that cases with a mild clinical presentation reduce their contacts by 75% after diagnosis, cases with severe presentation (equivalent to hospitalisation) are assumed to be isolated after diagnosis.

Baseline characteristics used in the modelling of a hypothetical vaccine against COVID-19

**Baseline vaccine**

**Healthy adults under the age of 60 years**

- Efficacy against severe disease: 95%
- Efficacy against any clinical disease: 50%
- Efficacy against infection: 0%
- Duration of protection: 24 months

**Adults aged 60 years and over**

- Efficacy against severe disease: 70%
- Efficacy against any clinical disease: 30%
- Efficacy against infection: 0%
- Duration of protection: 12 months

**Adults under the age of 60 years with preconditions**

- Efficacy against severe disease: 70%
- Efficacy against any clinical disease: 30%
- Efficacy against infection: 0%
- Duration of protection: 18 months
Our baseline analysis assumes that the vaccine is 95% effective at preventing severe disease in healthy adults, with protection lasting at least 12 months. The efficacy against severe disease is lower (70%) in adults aged 60 years and over and in those with relevant medical preconditions. The efficacy against clinical disease of any severity is 50% in healthy adults and 30% in older adults and those with preconditions. In the baseline analysis we assume no efficacy against infection and therefore onward transmission. However, we do consider alternative scenarios where the vaccine has an efficacy of 20% or 50% against infection and a subsequently higher efficacy against clinical disease.

For each strategy, we present its effectiveness in terms of deaths averted, life years saved and hospital and ICU admission averted, compared with a strategy of vaccinating all adults. We also present the efficiency of each strategy for each of these measures i.e. the relative impact of one dose of vaccine, compared with a universal strategy. The full table of results is presented in the Annex.

**Glossary**

Efficacy: The reduction in incidence of infection or disease in a vaccinated group compared to an unvaccinated group having accounted for other differences between the groups e.g. in a clinical trial.

Effectiveness: The observed reduction in outcomes of interest e.g. death, disease incidence or life years saved as a result of vaccination. This measure accounts for the ‘real world’ effects e.g. transmission dynamics, demography and behaviour.

Efficiency: The ratio of effectiveness and number of doses administered i.e. the impact per dose on an outcome of interest.

**Strategy 1: Vaccination of people at risk of severe outcomes**

Since the burden of COVID-19 morbidity and mortality is known to be disproportionately high in certain groups, one potential strategy is to vaccinate those who are at greatest risk of developing severe disease, requiring hospital or intensive care unit (ICU) treatment or dying. This may include older people or those with underlying health conditions. Such a strategy would only be effective if the COVID-19 vaccines prevent severe disease within these groups who, by their nature, may have reduced capacity to mount a sufficient immune response [19]. The efficacy of the vaccine in older adults and those with underlying health conditions should be evaluated and monitored through information from Phase 3 trials and post-marketing studies. Adjusting vaccine formulas, increasing dosage or adding adjuvants may elicit adequate protection in some groups. Other groups may not be eligible for vaccination due to certain health-related issues.

**Strategy 1a: Vaccination of people at risk of severe outcomes due to older age (≥60 ≥70 or ≥80 years)**

**Introduction**

Older adults are more likely to develop severe symptoms of COVID-19 and the risk of hospitalisation, ICU admission and death increases sharply with age. Data collected by ECDC up until 6 December 2020 show that in the EU/EEA and the UK, the chance of a person aged over 80 years being admitted to hospital with COVID-19 is over four times higher than a person in their 50s. The chance that they will die from the disease is 7.4 times as high [20]. Almost two thirds of all COVID-19 deaths in the EU/EEA and the UK up to 6 December 2020 were in people aged 80 years and over, while 95% were people aged 60 years and over [20].

The primary objective of vaccinating older people is direct protection against developing severe disease. A secondary objective, particularly in an initial period of limited vaccine supply, may be to alleviate the pressure on the healthcare sector since fewer people would be admitted to hospital and intensive care units.

It is known that, due to immunosenescence, older adults often respond less effectively to vaccination [19]. As such, the age-specific efficacy of COVID-19 vaccines must be balanced against the burden of disease in each age group. Mathematical modelling is a helpful tool to illustrate this trade-off.

We model three age-dependent strategies:

1. Vaccination of all adults aged 60 years and over (~241 million doses)
2. Vaccination of all adults aged 70 years and over (~131 million doses)
3. Vaccination of all adults aged 80 years and over (~52 million doses)
Results

If a vaccine only prevents severe disease, and that with an efficacy 25% lower in older adults, but does not prevent transmission (direct protection), vaccinating only adults aged 60 years and over would prevent 90% of the deaths that would be prevented by a universal adult vaccination programme. Adding all other adults aged 18-59 years would have little marginal benefit, accounting for the further 10%. Vaccinating only adults aged 80 years and over would be 43% as effective, in terms of preventing death, as vaccinating all adults (Figure 1A).

Since the number of doses needed to vaccinate only those aged 80 years and over is significantly lower than the other age-dependent strategies, this is the most efficient approach in terms of deaths averted per dose. One dose of this vaccine administered to a person aged 80 years and over is almost six times more effective at preventing death than a dose given in a universal vaccination programme (Figure 1C).

However, on average, preventing a COVID-19 death in a younger person would result in more life years saved. In fact, vaccinating only adults aged 80 years and over with such a vaccine saves only 2% of the life years saved by vaccinating all adults. Vaccinating adults aged 60 years and over with this vaccine would save 59% of the life years saved by vaccinating all adults (Figure 1B). One dose of this vaccine administered to a person aged 80 years and over is only 32% effective at saving life years as a dose given in a universal vaccination programme. However, one dose of this vaccine administered in a programme that focuses on adults aged 60 years and over is 176% as effective at saving life years as a dose given in a universal vaccination programme. This is the most efficient age group to prioritise in terms of life years saved (Figure 1D).

If the vaccine has even limited efficacy against infection, and therefore transmission, (20% in healthy adults, 10% in older adults and the baseline efficacy against clinical disease), it offers some indirect protection to those not vaccinated by reducing transmission of the virus. In this case, the relative effectiveness and the efficiency of prioritising older adults is reduced and vaccinating only adults aged 60 years and over prevents only 70% of deaths compared with vaccinating all adults (Figure 1A). The stronger the efficacy against infection (and therefore transmission), the larger the indirect effect and the lower the marginal benefit of prioritisation.

Figure 1. Relative effectiveness and efficiency of targeted vaccination by age, compared with a programme in which all adults are vaccinated

Discussion

The risk of COVID-19 hospitalisation, ICU admission and death increases steeply after the age of 60 years [20]. Even if a vaccine were less efficacious at preventing disease in older people, the disproportionate burden of morbidity and mortality in this group means that vaccination is beneficial. In terms of preventing death, vaccination of the oldest individuals (those over the age of 80 years) is the most efficient use of a vaccine. However, given
that they have shorter life expectancy, the most efficient choice in terms of life years saved is to vaccinate people aged 60 years and over.

Vaccinating according to age group is a practical approach, and easy to communicate. It is historically associated with good vaccine uptake and can be considered an efficient and pragmatic option to reduce COVID-19 morbidity and mortality if vaccine supply is insufficient to vaccinate the whole population.

Epidemiological and demographic data and vaccine supply will contribute to driving decisions regarding which age groups to target in each country. As age structures differ across EU/EEA countries, there will likely be a variation on the age limits for vaccination of older adults in different countries. Based on individual country data and depending on vaccine availability, countries may consider initially targeting older age groups with increased risk of hospitalisation, ICU admission and death from COVID-19.

**Strategy 1b: Vaccination of people at risk of severe outcomes due to preconditions**

Individuals with certain underlying health conditions (preconditions) have higher morbidity and mortality from COVID-19 compared to healthy people [21]. The preconditions significantly associated with COVID-19-related hospitalisation, ICU admissions and death include diabetes mellitus, chronic cardiovascular disease, chronic respiratory disease, chronic kidney disease, immunocompromised states (e.g. organ transplant), cancer, chronic liver disease, certain neurological disorders, trisomy 21 and sickle cell disease [5,7,8]. The individual risk of hospitalisation and death increases with the number of preconditions. As knowledge about risk factors for severe COVID-19 is still growing, the causality and magnitude of risk from each of these underlying medical conditions should be monitored and periodically reviewed [22].

Targeting individuals with preconditions known to be associated with increased risk of severe COVID-19 disease may be an efficient approach to reducing hospital admissions, ICU admissions and mortality. However, singling out all individuals with relevant underlying health conditions may be challenging or controversial. Clinical trials may not have tested the vaccines in a sufficient number of people with each underlying health condition. It is therefore possible that vaccine efficacy and safety may be suboptimal in some of those groups. Moreover, some individuals with underlying medical conditions may not be eligible for vaccination due to their health status.

Estimating the proportion of people in an age group who have one or more relevant preconditions is not straightforward. In many EU/EEA countries, data are not available, and in some preconditions are counted separately, meaning that some individuals may be double-counted. We base our estimates on data provided in a modelling study using prevalence data and UN population estimates [23], and estimate the odds ratio of COVID-19-related death given one or more preconditions from data reported to ECDC [24].

The proportion of adults aged 70 years and over who have at least one precondition known to be associated with severe COVID-19 disease is high (76.8%). For this reason, we combine our analysis of prioritisation of vaccination by preconditions with age-targeted strategies.

We model three strategies additionally targeting people with preconditions:

1. Vaccination of all adults aged 60 years and over and younger people with preconditions (~347 million doses)
2. Vaccination of all adults aged 70 years and over and younger people with preconditions (~158 million doses)
3. Vaccination of all adults aged 80 years and over and younger people with preconditions (~80 million doses)

**Results**

The marginal benefit of extending an age-targeted vaccination programme to include younger adults with relevant preconditions is high. As defined above, 43% of the deaths prevented by a universal vaccination programme can be prevented by only vaccinating adults aged 80 years and over. If younger adults with preconditions are included, this increases to 97% of the deaths being prevented. Indeed, a strategy of vaccinating adults aged 60 years and over and younger adults with preconditions is 98% as effective in preventing mortality as vaccinating all adults (Figure 2A).

In terms of life years saved, extending a programme of vaccinating people aged 80 years and over to include younger adults with preconditions increases the effectiveness from 2% to 83% of that of a universal vaccination strategy (Figure 2B). This approach is the most efficient, in terms of life years saved, of all the age and age/precondition strategies that we consider (Figure 2D). In terms of deaths averted, the inclusion of younger people with preconditions is less efficient. The additional doses prevent fewer deaths than the doses that are administered to adults aged 80 years and over (Figure 2C).
Discussion

Implementing a strategy that prioritises the vaccination of those with preconditions may be challenging. Not all individuals with an increased risk of severe COVID-19 will have a precondition clearly diagnosed and there will be some with borderline classifications (e.g. mild hypertension, moderate obesity, glucose intolerance). In addition, some preconditions may not be causally associated with severe COVID-19 and others may be only weakly associated with an increased risk of severe COVID-19.

In an initial phase of COVID-19 vaccine deployment with limited supply, it could also be highly problematic to perform a prioritisation among different types of preconditions, as data on the magnitude of the risk associated with each precondition may not be fully reliable or applicable to all groups and contexts. Finally, communicating such a strategy and reaching out to all individuals with one or more preconditions may be logistically complicated or simply not feasible.

A large proportion of older adults has a precondition that places them at higher risk of severe disease or death when infected with SARS-CoV-2. As a result, it may be more practical to target a whole age group, even though the marginal benefit of including younger adults with preconditions is high. As vaccine supply increases, countries will need to decide whether the challenge of targeting younger people at heightened risk is worthwhile or whether it would be more pragmatic to extend to the whole age group.

Strategy 2: Vaccination of healthcare workers

Introduction

Healthcare workers are exposed to SARS-CoV-2 due to their professional activity. In addition, they are in close contact with patients and vulnerable individuals at high risk of severe COVID-19. A study carried out between March-April 2020 in the UK and the US estimated that frontline healthcare workers had a 3.4-fold higher risk than people living in the general community for reporting a positive test, adjusting for the likelihood of receiving a test [25]. However, it should be noted that due to improved infection prevention and control measures, including the increased availability of personal protective equipment for healthcare workers in recent months, these earlier estimates of higher risk of infection in healthcare workers during the early phase of the pandemic may have decreased in some settings. Healthcare workers are, in addition, exposed to higher virus concentrations, especially from severely ill patients, which may influence disease severity [8]. Healthcare workers are also considered essential workers during a pandemic and are needed to ensure that a well-functioning healthcare system is maintained while hospitals are under pressure. Additionally, the age range of healthcare workers and their average health status means that they are also likely to respond well to vaccinations in general, and therefore also to COVID-19 vaccination. For these and other possible reasons (e.g. reciprocity, in terms of honouring obligations to those individuals who bear significant additional risks and burdens of COVID-19 response for the benefit of society), healthcare workers can be considered as a priority group for COVID-19 vaccination.
If vaccination against COVID-19 protects against infection and therefore transmission, vaccinating healthcare workers will provide indirect protection to individuals who are hospitalised or residing in long-term care home facilities, as well as those individuals who cannot be vaccinated due to certain health-related issues. Thus, the early vaccination of healthcare workers would have a dual benefit.

If vaccination against COVID-19 only protects against symptomatic disease, and not against infection, the impact of vaccinating healthcare workers will be reduced, as it will be limited to the direct protection of healthcare professionals (including those at risk of severe COVID-19). Vaccinating healthcare workers will then mainly aim at protecting them from severe COVID-19 and at maintaining staff availability during phases of high community transmission, but will not indirectly protect patients or residents of long-term healthcare facilities.

The term ‘healthcare worker’ describes a large and diverse group of people. Such a strategy could focus on the prioritisation of healthcare workers who are most exposed to SARS-CoV-2 (e.g. healthcare staff working in COVID-19 wards or emergency rooms), those most at risk of transmitting the disease to vulnerable individuals (e.g. nurses, healthcare staff in long-term care facilities, healthcare workers in haematology, transplant units or centres, oncology, etc.) or all patient-facing staff in healthcare facilities, whether or not they are clinically trained.

We model a strategy of vaccinating all healthcare workers, assuming that they comprise 3% of the adult population, assuming that the hazard ratio for infection is 3 [25]. We define the proportion of healthcare workers in each age group using data from the OECD [26]:

1. Vaccination of healthcare workers (~27 million doses)

**Results**

If a vaccine does not protect against infection and onward transmission, vaccinating healthcare workers has a limited effect in terms of preventing death. Such a programme would prevent only 3% of the deaths of a universal vaccination programme (Figure 3A), which means that although far fewer people are vaccinated, the relative impact per dose is only 0.77 (Figure 3C). Vaccinating healthcare workers alone would save only 1% of the life years saved by vaccinating all adults (Figure 3B), which means the relative efficiency in this regard is 0.27 (Figure 3D). Unless a vaccine protects against infection, and therefore transmission, the vaccination of healthcare workers is the least effective and least efficient strategy in terms of both deaths averted and life years saved.

However, if a vaccine protects against infection, the relative effectiveness and efficiency of vaccinating healthcare workers increases. Vaccinating healthcare workers with a vaccine that offers 20% efficacy against infection (and an increased efficacy of 70% against clinical disease) would prevent 23% of the deaths prevented by a universal vaccination programme (Figure 3A), which increases the relative impact of each dose to 6.13 (Figure 3C). That is, each dose of this vaccine administered in a healthcare worker only programme prevents roughly six times as many deaths as a dose given to an adult chosen at random. Vaccinating healthcare workers with a vaccine that offers 50% efficacy against infection would prevent 41% of the deaths prevented by a universal vaccination programme (Figure 3A), which increases the relative impact of each dose to 10.95 (Figure 3C). That is, each dose of this vaccine prevents roughly 11 times as many deaths as a dose given to an adult chosen at random.

The effectiveness and efficiency in terms of life years gained follows a similar pattern. If a vaccine has 20% efficacy against infection, a healthcare worker programme would save 23% of the lives saved by vaccinating all adults (Figure 3B), a relative impact of 10.87 (Figure 3D). A vaccine with 50% efficacy against infection (and an increased efficacy of 95% against clinical disease) administered to healthcare workers only would save 41% of the lives of a universal vaccination programme (Figure 3B), a relative impact of 11 (Figure 3D). That is, 11 times as many life years are saved by each dose of the vaccine given to a healthcare worker than to an adult chosen at random.

The higher the degree of protection against infection, the larger the indirect effect, making a healthcare worker vaccination programme increasingly more effective and more efficient.
Figure 3. Relative effectiveness and efficiency of targeted vaccination of healthcare workers, compared with a programme where all adults are vaccinated

Discussion

Prioritising healthcare workers for vaccination is of particular importance during outbreaks in healthcare settings or when there is widespread community transmission, especially when the pressure on healthcare is high and increasing. During a low community transmission phase of the pandemic, attention should be naturally shifted more towards individuals at the highest risk of developing severe COVID-19.

It also needs to be noted that healthcare workers, after an initial phase of the pandemic where they were at high risk of infection due to limited availability of personal protective equipment and of in-hospital COVID-19 control procedures in many places, are now more effectively protecting themselves during work and may be at an increased, but lower than before, risk of infection. Their exposure also depends on the pressure on the healthcare system caused by large numbers of hospital admissions of COVID-19 patients.

Considerations should be given to prioritisation of healthcare workers based on individual exposure, risk of transmission to patients (if the vaccine confers indirect protection), and individual risk of severe COVID-19 due to age, preconditions or other conditions.

As outlined above, if a vaccine against COVID-19 does not prevent infection and onward transmission, the objective of vaccinating healthcare workers is mainly to directly protect them against occupational exposure and to maintain functional healthcare services. Considerations could be given to sub-prioritise healthcare workers particularly exposed to risk of infection with SARS-CoV-2, aged 60 years and over with some underlying condition. If the vaccine provides even a limited efficacy against infection and onward transmission, priority should be given to healthcare workers in close contact with patients or residents at high medical risk of severe COVID-19 (e.g. healthcare staff in long-term healthcare facilities or organ transplantation units).

Effectiveness and efficiency of vaccinating healthcare workers against COVID-19 would increase if the vaccine prevents infection and onward transmission reasonably effectively.
Strategy 3: Vaccination of adults 18-59 years old

Introduction

A vaccine that prevents infection with SARS-CoV-2 and not only COVID-19 disease will reduce transmission of the virus in the population, offering indirect protection to those who are not themselves vaccinated. If this is the case, theoretically the most efficient vaccination approach is to target the groups with the highest number of effective contacts, as they are at risk both of exposure to the virus and of onward transmission [27]. For diseases like influenza and pneumococcal disease, the main drivers of disease transmission are children or adolescents, thus vaccinating them causes a strong indirect protection in the older age groups [28,29]. It is not currently clear whether a certain group of the population is a main driver of COVID-19 transmission.

Individuals in risk groups for severe disease and death from COVID-19 are expected to be more risk-averse compared to the rest of the population that is not at high risk of severe COVID-19. Furthermore, many countries are adopting cocooning strategies to protect the groups most at risk of severe COVID-19, who are thus less exposed to infection compared to the rest of the population. Therefore, people at lower risk of severe COVID-19 due to younger age or absence of underlying conditions are expected to have more effective contacts for disease transmission. Moreover, the role of asymptomatic transmission from young and middle-aged adults in COVID-19 pandemic has been recognised [30]. Additionally, some societal groups are at increased risk of infection due to their living conditions or to occupational exposure. For these reasons, vaccination of the adult population under the age of 60 years (which includes most individuals with a high number of social contacts and those living in societal or occupational settings where risk of transmission is high) could be considered an effective way to achieve control of viral circulation in the community if a vaccine provides sterilising immunity. However, vaccinating younger people with a vaccine that only reduces disease severity may lead to them taking less stringent measures to self-isolate and therefore actually increasing transmission with no protective benefit to vulnerable people.

There are some practical challenges to consider concerning this approach. Firstly, this group is largely composed by healthy and active adults, who are not a usual target of vaccination campaigns and can be hard to reach or may be hesitant to take the vaccine since they do not see benefit to themselves. Secondly, the number needed to vaccinate to prevent a COVID-19 hospitalisation or death by targeting all individuals 18-60 years old may be high in a non-intensive viral circulation scenario, thus making the whole approach quite inefficient. Thirdly, if the upcoming COVID-19 vaccination does not protect against infection and onward transmission, this approach is not a viable option as its objective is to efficiently reduce viral transmission within the community. Lastly, and more importantly, this approach may have a stronger impact on the number of COVID-19 infections compared to other approaches, but a smaller one on hospitalisations and deaths, as the latter tend to occur much more often in the older age groups not targeted by this approach.

We model a strategy of vaccinating all adults ages 18-59 years:

1. Vaccination of all adults aged 18-59 (~249 million doses)

Results

If a vaccine prevents COVID-19 disease but does not prevent infection, and thereby transmission, it may lead to a reduction in the number of infected people who are self-isolating. As a consequence, the level of community transmission may increase, leading to a higher number of confirmed cases, hospital and ICU admissions and deaths. A programme to vaccinate 18-59 year olds with a vaccine that only offers direct protection against disease may lead to a decrease in deaths in younger adults, but an increase in older adults due to the increased background transmission. We estimate that overall the number of deaths may be the same as if there had not been a vaccination programme (Figure 4A) but, since the deaths that do occur are instead in older people, some life years would be saved (Figure 4B).

However, if a vaccine has 20% efficacy against infection (and an increased efficacy of 70% against clinical disease) and therefore offers indirect protection through the reduction of transmission, vaccinating younger adults (18-59) would prevent 69% of the deaths prevented by a universal vaccination programme (Figure 4A). This leads to a two-fold increase in efficiency compared with vaccinating all adults, since the number of doses required is lower (Figure 4C). Since most of the deaths prevented are due to reduced circulation of the virus and not direct protection of the vaccine, the relative effectiveness in terms of life years saved is 72%, compared with vaccinating all adults (Figure 4B).

If a vaccine has 50% efficacy against infection (and an increased efficacy of 95% against clinical disease), and therefore offers indirect protection through the reduction of transmission, vaccinating younger adults (18-59 years) would prevent 88% of the deaths prevented by a universal vaccination programme (Figure 4A) since circulation of the virus is reduced to a lower level. In terms of deaths averted, a strategy to vaccinate only younger adults has 2.5 times as much impact per dose as a strategy to vaccinate all adults (Figure 4C). The relative effectiveness in terms of life years saved is 89%, compared with vaccinating all adults (Figure 4B), meaning that a dose of the vaccine administered in a programme to vaccinate younger adults saves 2.6 times the number of life years of a dose.
administered in a universal vaccination programme. This is because in a programme that aims to reduce the transmission of the virus, there is a diminishing marginal benefit of each additional dose and fewer people are vaccinated in a targeted programme.

**Figure 4. Relative effectiveness and efficiency of targeted vaccination of adults aged 18 to 59 years, compared with a programme in which all adults are vaccinated, by efficacy of vaccine against infection**

**Discussion**

Given the practical challenges of targeting younger adults (aged 18-59), it is unlikely that this approach will be part of a COVID-19 strategy in the initial phase, when supply will be more limited. If a vaccine is unsafe or inefficacious in older adults and those with underlying conditions, a programme of indirect protection could be considered. This approach would reduce COVID-19 morbidity and mortality, only if the vaccine prevents infection and therefore onwards transmission. Otherwise, vaccination of adults 18-59 years of age should not be considered as an optional strategy in the initial phases of COVID-19 vaccine deployment. It is possible that some specific groups or occupations more at risk of exposure to the virus can be identified and considered in certain settings and contexts. However, in general, other approaches should be prioritised in the context of initial limited supply or in case the COVID-19 vaccines showed very limited efficacy against SARS-CoV-2 infection and onward transmission.

Vaccinating all adults aged 18-59 years with a vaccine effectively preventing transmission is a potential approach for reducing viral circulation and reaching disease control. However, it is not the most rapid, effective or ethical way of reducing hospitalisations and deaths in groups at increased medical risk of severe COVID-19.

**Strategy 4: Universal vaccination (everyone aged 18 years and over)**

**Introduction**

Universal vaccination against COVID-19 implies that the vaccine is given to the whole population and aims to vaccinate every single individual who is eligible for vaccination.

If the available COVID-19 vaccines are effective against SARS-CoV-2 infection and onward transmission, universal vaccination would lead to a strong reduction of viral circulation in the whole population, and may eventually lead to herd protection, depending on the vaccine efficacy and the duration of protection. A vaccine efficacious against SARS-CoV-2 infection and onward transmission will also indirectly protect individuals who cannot be vaccinated. If a high vaccination coverage is sustained over time with high vaccine efficacy and long duration of protection,
universal vaccination will also make possible to set COVID-19 elimination goals. COVID-19 eradication is not considered a feasible goal due to the existence of non-human reservoirs of SARS-CoV-2.

Universal vaccination could be considered the most equal approach, albeit assuming enough vaccine doses available for everyone who can get vaccinated. Unfortunately, this is unlikely to be the case for several months following the introduction of COVID-19 vaccines into the market, as vaccine supply is foreseen to be limited in the presence of a large global demand.

If the COVID-19 vaccine is only able to prevent symptomatic disease (and not infection and onward transmission), universal vaccination will not be able to effectively lead to indirect protection and herd immunity. Additionally, different groups of the population may respond differently to the vaccines.

As the duration of protection from vaccination against COVID-19 is currently unknown, a short duration of protection will imply the need for re-vaccination of a very large numbers of individuals with massive implications for vaccine production, procurement, supply and logistics.

Finally, universal vaccination, involving tens of millions of individuals over a relatively short period of time, could increase the risk of reporting adverse events non-causally associated with vaccination. This has the potential to undermine COVID-19 vaccination acceptance and uptake, as well as vaccination confidence in general.

We model the strategy of vaccinating all adults as the baseline for our analysis of prioritisation strategies:

1. Vaccination of all adults aged 18-59 (~720 million doses)

**Results**

All results shown for the other strategies are reported as comparison with vaccination of all adults (see above).

**Discussion**

Vaccinating everyone is the most effective approach if the aim is to minimise the overall burden of COVID-19, but it comes at a very high price in terms of time, cost, resources and logistics. Supply will not be sufficient to vaccinate everyone for many months after the introduction of the vaccines against COVID-19, so the implementation of a universal vaccination is not considered feasible during at least the first half of 2021. Additionally, with a universal vaccination there would be more concerns about vaccine uptake, in particular among people not at heightened risk of severe disease. This may lead to several pockets of unvaccinated individuals in the population that cannot be traced or reached without well-functioning immunisation information systems in place.

After an initial phase of limited supply, universal vaccination is the preferable strategy only if the vaccine is very safe and effective, protects against infection and onward transmission, and induces a sufficiently long duration of protection. In such a case, and given sufficiently high and sustained vaccine uptake, an elimination strategy is a realistic goal and herd protection is attainable.
Final considerations

One significant source of uncertainty in predicting the future epidemiology of COVID-19 is the duration of naturally acquired immunity. If people who have previously been infected with the virus become susceptible again, this will have an impact on vaccine prioritisation strategies. Strategies that aim to reduce the circulation of the virus with a vaccine that has some effect on reducing transmission will be more robust to increasing re-susceptibility of the population than strategies that focus on direct protection. This is because each dose of vaccine effectively reduces susceptibility of the population beyond the person who is vaccinated, in contrast to the loss of naturally acquired immunity, which increases it. The model has been fitted to epidemiological data up until 1 December 2020 to give a baseline of naturally acquired immunity. We assume that vaccination takes place on 1 January 2021, but in reality it will be later for most people and staged. Depending on the non-pharmaceutical measures in place in the meantime, the immunity profile of the population may change over time either due to additional infection or waning immunity.

In our baseline analysis, we assume that duration of vaccine protection is longer than the timeframe we consider. As vaccine protection wanes, more doses will be needed to maintain immunity. A strategy that relies on indirect protection is more resilient to waning immunity than a direct protection strategy. If the virus were to mutate substantially, a higher proportion of the population would be susceptible and vaccine efficacy may be reduced. In this case, the effectiveness of any vaccination programme would be diminished.

In this baseline analysis, we also assume that the vaccine is administered at one point in time. This is unrealistic and vaccines will become available in batches, in line with production. In this case, prioritisation strategies which focus on direct protection would see a step-wise impact over time. A strategy based on the ability of a vaccine to reduce infection, and therefore transmission, would have a ‘smoother’ impact in such a supply scenario, since each additional dose has a smaller marginal effect in reducing the circulation of the virus in the community.

We assume that vaccine uptake, and therefore acceptance, is 100%. This is also a limiting assumption and consideration should be given to the relative uptake between groups. If it is comparable across the population, it would not affect the optimal prioritisation strategy.

If a COVID-19 vaccine is efficacious in preventing symptomatic disease in older adults but does not prevent transmission, the highest impact in terms of both deaths averted and life years saved is gained by vaccinating adults aged 60 years and over and younger adults with preconditions. There is little marginal benefit in vaccinating healthcare workers, and in this case vaccinating healthcare workers (either alone or in conjunction with older people) is the least effective and least efficient strategy in terms of both deaths averted and life years saved. When it comes to maximising the health benefits in an initial limited supply scenario, the highest efficiency in terms of deaths averted is gained from vaccinating adults aged 80 years and over, but in terms of life years saved the most efficient strategy is to extend the programme to include younger adults with preconditions.

If a COVID-19 vaccine also moderately prevents transmission, the highest impact in terms of both deaths averted and life years saved is also gained by vaccinating adults aged 60 years and over and younger adults with preconditions. However, the added benefit of prioritising older adults over the rest of the adult population is reduced. During the initial limited supply, the highest efficiency in terms of deaths averted is also to vaccinate adults aged 80 years and over, although including healthcare workers is almost as efficient and prevents more deaths in total. In terms of life years saved, vaccinating healthy adults aged 18-60 years becomes the most efficient strategy, although a plentiful supply of vaccine would be needed.

With a vaccine that also prevents transmission, the option of reducing viral circulation in the population by vaccinating younger individuals who are possibly more exposed to the virus, and therefore at risk of onward transmission, becomes a more competitive option to consider. However, in the short term and with limited supply, this option would not be the one that would guarantee the maximum gains in terms of reduced hospitalisations and deaths. This approach is therefore not optimal in the roll-out of COVID-19 vaccines, but could become an interesting supplementary option as supply increases, depending on the capacity of the vaccine or vaccines to prevent infection and onward transmission.

Other target groups not included in the mathematical modelling

Another primary group that can be considered for prioritisation for vaccination is essential workers, who are considered critical for maintaining societal functioning. This could include social care workers, frontline workers, teachers, childcare providers, transportation workers and food and essential goods retail workers. Reducing infection and sickness within these groups allows these workers to continue providing services to the general population and to indirectly protect those vulnerable to severe disease that need to access these services, such as taking public transportation and going to grocery stores.

Occupational settings where there is a lack of physical distancing are also increasing the risk for viral transmission due to the risk of close contacts with COVID-19 cases [31]. Insufficient or incorrect use of personal protective equipment is also considered a risk factor. Additional settings with little ability to physical distance may include prisons, migrant centres, crowded housing and homeless shelters and those living in other closed environments...
such as people living with disabilities in care homes and supported living settings. Consideration should be given to these specific settings when deciding upon priorities for COVID-19 vaccination.

**Practical considerations**

In the initial phases of the vaccine deployment, it is expected that demand will exceed supply. It will be important to manage expectations through appropriate communication about limited supply, vaccine safety and efficacy, priority groups and the rationales behind these choices. Vaccine acceptance is expected to become increasingly relevant over time as supply grows. Transparent communication about vaccine safety and efficacy characteristics, and objectives of the vaccination, will need to be initiated as early as possible by all institutional sources in order to counter any misinformation or disinformation.

People with previous COVID-19 infection were not excluded from Phase 3 trials, and there is no current evidence of harm or absence of efficacy. As the exact duration of natural immunity from COVID-19 infection is currently unknown, at this stage it is advisable not to exclude people with previous COVID-19 infection from vaccination. Nevertheless, these aspects need to be followed up and updated according to the emerging evidence.

Important unknowns remain and should not to be overlooked. For example, potential viral antigenic drifts could generate immune escape variants that the vaccine could not protect against. The estimates of vaccine efficacy to date are also based on short follow-up after vaccination, so it is currently unclear what the duration of protection of each vaccine will be. Additionally, it is not known from the Phase 3 trials whether COVID-19 vaccines can prevent infection and onward transmission, and if so, to what extent. Therefore, it remains uncertain whether the vaccination strategies can be developed with the aim of reducing viral circulation in the community through herd protection. There is also currently no information about vaccine safety and efficacy in pregnant and lactating women who are possibly at increased risk of severe COVID-19, in children below the age of 12 years and in people with certain preconditions (e.g. immunocompromised individuals). There are limited data available about vaccine safety and efficacy in adolescents 12-18 years old, in people with certain preconditions and in frail individuals. Finally, there is no information about safety and effectiveness of off-label schedules (e.g. use of half-dose, combined use of different vaccines, prolonged intervals between doses) in case of limited vaccine supply or logistical issues. Other significant unknowns pertain to manufacturing and logistics, as this is an unprecedented global effort with very large numbers and many uncertainties about manufacturing and potential delays in distribution and issues with storage.

Decisions on whom to vaccinate first depend on several additional factors, including vaccine products’ characteristics, target groups for which data on COVID-19 vaccine safety and efficacy are currently available, ethical and equity considerations, logistics (e.g. how to effectively deliver the vaccine to the target groups, ultracold storage requirements), procurement and supply, and vaccine acceptance in different target groups, among others.

Issues with vaccines supply, logistics and storage may have an impact on the implementation of vaccination strategies and may affect their overall impact. As vaccine supply will not immediately be enough for all people in the target groups for vaccination, the impact of any vaccination strategy will not initially be sufficient to lift non-pharmaceutical interventions. More clarity in the coming months about different vaccines’ characteristics (number of doses needed, interval between doses, reactogenicity and safety, effectiveness in different groups and against different endpoints, duration of protection) and trends in vaccine supply, deployment and uptake will help Member States decide when and how to lift non-pharmaceutical interventions. Vaccination strategies will thus need to be adaptable and data-driven.

**Conclusions**

Prioritisation of COVID-19 vaccination should take into account several dimensions and needs to be contextualised. By looking at the impact of vaccination on health outcomes, based on modelling, we can conclude the following:

- The choice of optimal strategy depends on the objective, e.g. reducing mortality, saving life years or reducing pressure on the healthcare system.
- The optimal prioritisation also depends on the characteristics of the vaccine, in particular its efficacy against infection and therefore onward transmission.
- If a vaccine does not protect against transmission, the most effective and efficient approach is to prioritise the vaccination of those groups at highest risk of severe disease and death.
- Substantial reductions in mortality and pressure on the healthcare system could be achieved by the direct protection of high-risk groups, even if viral transmission is ongoing within the population.
• Vaccination of healthcare workers is beneficial since it improves the resilience of the healthcare system. The benefit would be heightened if the vaccine were effective against infection, and therefore transmission, since it would offer indirect protection to patients, residents of long-term care facilities and other high-risk individuals.

• Although vaccinating adults aged 18-59 years is not the most effective or efficient strategy when vaccine supply is limited, consideration should be given to specific groups or settings that may have a disproportionate risk of exposure.

**ECDC internal contributors**

Kim Brolin, Edoardo Colzani, Helen Johnson, Kate Olsson, Lucia Pastore Celentano
References


## Annex. Comparison of the relative effectiveness and efficiency of different prioritisation strategies

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### COVID-19 vaccination and prioritisation strategies in the EU/EEA

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#### 20% efficacy against infection in all adults, 70% efficacy against clinical disease

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#### 50% efficacy against infection in all adults, 95% efficacy against clinical disease

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<td>85%</td>
<td>2.53</td>
<td>95%</td>
<td>2.85</td>
</tr>
<tr>
<td>70+</td>
<td>131</td>
<td>84%</td>
<td>4.66</td>
<td>72%</td>
<td>3.97</td>
<td>65%</td>
<td>3.61</td>
<td>84%</td>
<td>4.62</td>
</tr>
<tr>
<td>80+</td>
<td>52</td>
<td>57%</td>
<td>7.78</td>
<td>38%</td>
<td>5.20</td>
<td>38%</td>
<td>5.18</td>
<td>55%</td>
<td>7.53</td>
</tr>
<tr>
<td>60+ and preconditions</td>
<td>347</td>
<td>100%</td>
<td>2.08</td>
<td>100%</td>
<td>2.08</td>
<td>99%</td>
<td>2.05</td>
<td>100%</td>
<td>2.07</td>
</tr>
<tr>
<td>70 + and preconditions</td>
<td>286</td>
<td>100%</td>
<td>2.53</td>
<td>100%</td>
<td>2.51</td>
<td>98%</td>
<td>2.48</td>
<td>100%</td>
<td>2.52</td>
</tr>
<tr>
<td>80+ and preconditions</td>
<td>249</td>
<td>100%</td>
<td>2.89</td>
<td>100%</td>
<td>2.88</td>
<td>98%</td>
<td>2.84</td>
<td>100%</td>
<td>2.88</td>
</tr>
</tbody>
</table>
### COVID-19 vaccination and prioritisation strategies in the EU/EEA

<table>
<thead>
<tr>
<th>Prioritisation group</th>
<th>Number of doses administered</th>
<th>Relative reduction in number of deaths</th>
<th>Relative impact per dose in terms of deaths averted</th>
<th>Relative number of life years saved</th>
<th>Relative impact per dose in terms of life years saved</th>
<th>Relative reduction in number of hospital admissions</th>
<th>Relative impact per dose in terms of hospital admissions averted</th>
<th>Relative reduction in number of ICU admissions</th>
<th>Relative impact per dose in terms of ICU admissions averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare workers only</td>
<td>27</td>
<td>41%</td>
<td>10.95</td>
<td>41%</td>
<td>10.87</td>
<td>43%</td>
<td>11.51</td>
<td>40%</td>
<td>10.65</td>
</tr>
<tr>
<td>60+ and HCW</td>
<td>265</td>
<td>98%</td>
<td>2.65</td>
<td>95%</td>
<td>2.57</td>
<td>90%</td>
<td>2.45</td>
<td>97%</td>
<td>2.64</td>
</tr>
<tr>
<td>80+ and HCW</td>
<td>80</td>
<td>72%</td>
<td>6.54</td>
<td>61%</td>
<td>5.49</td>
<td>62%</td>
<td>5.62</td>
<td>71%</td>
<td>6.44</td>
</tr>
<tr>
<td>18-59</td>
<td>249</td>
<td>88%</td>
<td>2.53</td>
<td>89%</td>
<td>2.58</td>
<td>93%</td>
<td>2.68</td>
<td>88%</td>
<td>2.54</td>
</tr>
</tbody>
</table>

* + denotes years and over

Colour legend: colours represent a gradient where green is the comparatively most beneficial figure and red is the comparatively least beneficial figure.