Background paper on Covid-19 disease and vaccines

Prepared by the Strategic Advisory Group of Experts (SAGE) on Immunization Working Group on COVID-19 vaccines

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https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/

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I Epidemiology

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2, a newly emergent coronavirus, that was first recognized in Wuhan, China, in December 2019. Globally, as of 19 December 2020, there have been 74.299.042 confirmed cases of COVID-19, including 1.669.982 deaths, reported to WHO.\(^1\) The epidemiological situation is changing rapidly; for updates refer to: https://covid19.who.int/table

WHO defines four transmission scenarios to describe the dynamics of the epidemic: no reported cases (including both zero transmission and the absence of detected and reported cases), sporadic cases, clusters of cases and community transmission. The community transmission (CT) classification is further divided into four levels, from low incidence (CT1) to very high incidence (CT4).

Transmission scenarios:
- No (active) cases
- Sporadic cases
- Clusters of cases
- Community transmission (CT):
  - CT1: Low incidence of locally acquired, widely dispersed cases detected in the past 14 days
  - CT2: Moderate incidence of locally acquired widely dispersed cases detected in the past 14 days
  - CT3: High incidence of locally acquired widely dispersed cases in the past 14 days
  - CT4: Very high incidence of locally acquired widely dispersed cases in the past 14 days

The transmission level classification for a geographic area can change (improve or worsen) over time, and different geographic areas within a country will likely experience different levels of transmission concurrently.

Basic and effective reproduction number (R0 and Re)

The basic reproductive number (R0), defined as average number of secondary infections produced by a case of an infection in a fully susceptible population, determines the epidemic potential. R0 above 1 will lead to further spread. R0 for COVID-19 varied initially between countries, from just above 1 to 5 or higher.\(^2\) Early epidemic growth in many places has therefore been especially rapid until physical distancing or other non-pharmaceutical interventions (NPIs) were put in place. Following their implementation, transmission potential at a given time can be estimated by the effective reproductive number (Re or time-dependant reproductive number). Data from 11 European countries suggested an initial reproduction number R0 estimate of 3.87 [95% CI 3.01-4.66] and a noticeable decrease in Re below 1 following the combined non-pharmaceutical interventions in several European countries.\(^3\) In China, strict community quarantine and mobility restrictions combined with isolation of cases, and contact tracing enhanced by big data and AI\(^4\), led to the complete reported control of the COVID-19 outbreak.\(^5,6\)

Case fatality ratio and infection fatality ratio

The case fatality ratio (CFR) estimates the proportion of deaths among identified confirmed cases. At the early stage of the pandemic, most estimates of fatality ratios were based on cases detected through surveillance and calculated using crude methods, giving rise to widely variable estimates of CFR by country, from less than 0.1% to over 25%. Bias is introduced due to availability of and access to testing.\(^7\) The infection fatality ratio (IFR) estimates this proportion of deaths among all infected individuals. IFR is the proportion of people infected with the virus (including those who did not show symptoms or get
tested) who will die as a result. Serological testing of a representative random sample of the population to detect evidence of exposure to a pathogen is an important method to estimate the true number of infected individuals. Many such serological surveys are currently being undertaken worldwide and some have thus far suggested substantial under-ascertainment of cases. Using variation in demographics, comorbidities and health system capacity, the predicted COVID-19 IFRs for 187 countries range from 0.43% in Western Sub-Saharan Africa to 1.45% in Eastern Europe. Although age is not the only determinant and circumstances vary by country, overall, estimates from several different countries reinforce that age is by far the strongest predictor of the infection fatality ratio (IFR) of SARS-CoV-2 infection. There is an exponential relationship between age and IFR for COVID-19. The estimated age-specific IFR is very low for children and younger adults (e.g., 0.002% at age 10 and 0.01% at age 25) but increases progressively to 0.4% at age 55, 1.4% at age 65, 4.6% at age 75, and 15% at age 85, and exceeds 25% for ages 90 and above. About 90% of the variation in population IFR across geographical locations reflects differences in the age composition of the population and the extent to which relatively vulnerable age groups were exposed to the virus.

Transmission characteristics
The primary transmission mode is person-to-person contact through large respiratory droplets containing the SARS-CoV-2 virus generated by exhalting (especially vigorously), sneezing, coughing, singing and speaking. Transmission through aerosols has also been implicated but the relative contributing role of aerosols is still unclear but much less important than droplet contribution in general community settings. Indirect transmission through fomites that have been contaminated by respiratory secretions is also possible.

Geographic spread and settings associated with high transmission
The spread from the initial epicentre in Wuhan, China, initially followed predicted global air travel patterns. Travel bans and travel restrictions delayed but did not stop global spread. Social contact matrixes (number of contacts, contact frequency, duration of contact, proximity of contacts) drive transmission. Population density is one of the strongest risk factors. Hence, urban centres around the world were often the initial epicentres. Clustering and super-spread events have been associated with mass gatherings, detention camps, prisons, slum dwellings, choirs, religious gatherings, tourist hot spots and abattoirs. Nursing homes and long-care homes for the elderly are at particular risk for high death rates.

Health workers
Health workers are all people engaged in work actions whose primary intent is to improve health. This includes health service providers, such as doctors, nurses, midwives, public health professionals, lab-, health- and medical and non-medical technicians, personal care workers, community health workers, healers and some practitioners of traditional medicine. It also includes health management and support workers, such as cleaners, drivers, hospital administrators, district health managers and social workers, and other occupational groups in health-related activities. Health workers include not only those who work in acute care facilities but also those employed in long-term care, public health, community based care, social care and home care and other occupations in the health and social work sectors as defined by the International Standard Industrial Classification of All Economic Activities (ISIC), revision 4, section Q: Human health and social work activities.

Health workers are at the front line of the COVID-19 response and the provision of essential health services and as such are exposed to occupational hazards that put them at risk of disease, injury and
even death. Several occupational risks for health workers emerged or were amplified by the COVID-19 response, including (1) occupational infections with COVID-19, (2) skin disorders and heat stress from prolonged use of personal protective equipment, (3) toxic exposures from increased use of disinfectants, (4) psychological distress, (5) chronic fatigue, (6) stigma, discrimination, physical and psychological violence.

Mitigating these hazards and protecting health, safety and well-being of health workers requires well-coordinated and comprehensive measures for infection prevention and control, occupational health and safety, health workforce management, mental health and psychosocial support. Insufficient occupational health and safety measures can result in increased rates of work-related illness among health workers, high rates of absenteeism, reduced productivity and diminished quality of care, thus depleting the health workforce – a most critical resource for stopping the COVID-19 pandemic while maintaining the provision of essential health services.

Nosocomial infections, in particular where health care systems are overwhelmed or where there is a lack of personal protective equipment, are frequent. Compared with the general populations, front-line health-care workers were at increased risk especially early on in the pandemic when PPE was not as widely available, with an adjusted Hazard Ratio of 11·61 (95% CI 10·93–12·33).18 With improved PPE, attack rates in HW are decreasing but remain above the risk of the general population.

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Examples of job tasks</th>
<th>Sample prevention and mitigation measures</th>
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</thead>
<tbody>
<tr>
<td><strong>Lower risk</strong></td>
<td>Administrative tasks that do not involve contact with patients, visitors and close contact with other co-workers, telehealth services, remote interviewing of suspected or confirmed COVID-19 patients or their contacts in individual or low-density offices.</td>
<td>• Remote work and teleservices, when possible&lt;br&gt;• Stay home if unwell and after contact with COVID-19 case&lt;br&gt;• Aeration or ventilation without recirculation&lt;br&gt;• Hand and respiratory hygiene&lt;br&gt;• Physical distancing, reducing workplace occupancy and avoiding social mixing&lt;br&gt;• Avoid sharing workstations and work equipment&lt;br&gt;• Cloth masks in common areas and avoiding face-to-face meetings</td>
</tr>
<tr>
<td><strong>Medium risk</strong></td>
<td>Providing care in health facilities and in the community to the general public patients who are not known or suspected of having COVID-19, preliminary patient screening not involving direct contact, work at reception desks, physical examination of or face-to-face contact with patients without symptoms suggestive of</td>
<td>• Telehealth services&lt;br&gt;• Engineering controls – sneeze screens, barriers, workplace modifications&lt;br&gt;• Patient triage&lt;br&gt;• Source control (cloth or medical masks) for patients and visitors&lt;br&gt;• Environmental cleaning and disinfection&lt;br&gt;• Stay home if unwell and after contact with COVID-19 case</td>
</tr>
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</table>
| **COVID-19, working at busy staff work areas within a healthcare facility.** | • Physical distancing, reducing workplace occupancy, avoiding social mixing, restriction of visitors  
• Aeration or enhanced ventilation without recirculation  
• IPC training  
• Hand and respiratory hygiene  
• Medical masks and other PPE according to standard precautions and risk assessment | |
| **High risk** | Clinical triage with in-person interviewing of patients with sign and symptoms of COVID-19, cleaning areas for screening and isolation, entering a known or suspected COVID-19 patient’s room or isolation areas, physical examination and providing direct care for a known or suspected COVID-19 patients not involving aerosol-generating procedures, manipulation of respiratory samples, handling stool, urine or waste from COVID-19 patients, transportation of people known or suspected to have COVID-19 without adequate spatial separation between the driver and the passenger, cleaning after and between transport of patients with suspected COVID-19. | • Engineering, environmental and administrative controls  
• Enhanced ventilation without recirculation, with “clean to less clean” directional design for airflows.  
• Stay home if unwell and after contact with COVID-19 case  
• Physical distancing, avoiding social mixing, restriction of non-essential workers and visitors  
• Source control (cloth or medical masks) for patients and visitors  
• IPC training  
• Hand and respiratory hygiene  
• PPE based on risk assessment (medical mask, gown, gloves, eye protection) and standard precautions | |
| **Very high risk** | Work with COVID19 patients where aerosol generating procedures (e.g. tracheal intubation, non-invasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, sputum induction, bronchoscopy, spirometry, and autopsy procedures) are frequently performed; work with COVID-19 patients in crowded, enclosed places without adequate ventilation. | • Engineering, environmental and administrative controls  
• Ventilation with High Efficiency Particulate Air (HEPA) filters  
• Physical distancing, avoiding social mixing, restriction of non-essential workers and visitors  
• Source control (cloth or medical masks) for patients and visitors  
• Stay home if unwell and after contact with COVID-19 case  
• Hand and respiratory hygiene  
• IPC training, including donning and doffing of PPE |
Non-pharmaceutical interventions
The overarching goal is to control COVID-19 by slowing down transmission of the virus and preventing associated illness and death. Several core public health measures that break the chains of transmission are central to this strategy, including (1) identification, isolation, testing, and clinical care for all cases, (2) tracing and quarantining of contacts, and (3) encouraging physical distancing of at least 1 metre combined with frequent hand hygiene and respiratory etiquette, and the use of face masks, particularly in indoor and crowded environments. These three components should be central to every national COVID-19 response. A differentiated risk-based containment strategy is needed based on the different stages of the outbreak with different measures during the different phases of the response. Pandemic response with strict lockdowns and travel restrictions had a major socioeconomic and mental health impact, including closures of schools resulting in delayed child development, although some countries and island states in Asia, Australasia and the Pacific managed to limit some of the deleterious health and economic impacts experienced elsewhere. According to the recent report of the pulse survey, disruptions of essential health services were reported by nearly all of the 105 responding countries, and more so in lower-income than higher-income countries. The great majority of service disruptions were partial, which was defined as a change of 5–50% in service provision or use. All services were affected, including essential services for communicable diseases, non-communicable diseases, mental health, reproductive, maternal, new born, child and adolescent health, and nutrition services.

Policy-makers continue to debate strategies to reduce deaths and the demand on health care utilization, in addition to considering major collateral damage to the economy, society, mental health and other outcomes: (a) containment or suppression of COVID-19, which aims to reverse the rate of epidemic growth, thereby reducing new case numbers to low levels, and (b) mitigation, which focuses on slowing but not necessarily stopping epidemic spread – to reduce peak healthcare demand while protecting those most at risk of severe disease from infection, and c) elimination.

II The virus
SARS-CoV-2 is a new coronavirus closely related to SARS-CoV and genetically clusters within Betacoronavirus subgenus Sarbecovirus. SARS-CoV-2 is a positive-stranded RNA virus of approximately 29,000 base pairs from lineage B of the genus betacoronavirus covered with distinctive spikes about 9-12 nm in size. Those spikes facilitate viral entry. The first whole genome sequence was published on January 5 2020, and thousands of genomes have been sequenced since this date. Over 57,000 genome sequences have been deposited in the GISAID EpiCoV database. A meta-analysis of different estimates of the time to the last common ancestor of the virus indicates that the pandemic could have started sometime between 6 October and 11 December 2019. A mutation in the spike protein, D614G, has emerged and is spreading globally. There is currently no evidence that any of the mutations accumulated since the introduction of the SARS-CoV-2 virus in the human population have any effect on disease severity, but possibly on infectivity. SARS-CoV-2 can cross species. At the time
of writing, a new variant named VUI-202012/01 (the first “Variant Under Investigation” in December 2020) was reported, and is defined by a set of 17 changes or mutations. One of the most significant is an N501Y mutation in the spike protein that the virus uses to bind to the human ACE2 receptor. Changes in this part of spike protein may, in theory, result in the virus becoming more infectious and spreading more easily between people. The implications of this new variant on vaccine development/efficacy of currently developed vaccines are unknown at this point in time.

**Natural immunity to SARS-CoV-2**

SARS-CoV-2 infection induces both B-cell (antibody) and T-cell specific immune responses. Serological studies have most focused on the Spike (S) and Nucleoprotein (NP) although responses to other viral antigens are also reported. There is also interest in antibodies to the receptor (ACE2) binding domain (RBD) of the trimeric S protein as these are predicted to interfere with viral entry into the host cell and thus to be neutralizing and protective. Although the relative importance of B- and T-cell responses in clearance of the virus and in the maintenance of protection remains unclear at this time, there is some evidence that the magnitude of responses is positively associated with the severity of disease, perhaps relating to the size of viral load experienced by the patient.

**Immunity prior to exposure to SARS-CoV-2:** Numerous studies demonstrate that a proportion of the population have some level of cross-reactive immunity to SARS-CoV-2 without ever having been infected by the virus. The cross reacting immunity includes T-cells recognizing SARS-CoV-2 NP and non-spike protein seen in 40-60% of the population but no antibodies, however other studies have found cross-reactive antibodies in the younger population of unexposed individuals and in a significant proportion of the population in some sub-Saharan countries, which may explain to some extent explain the lower mortality seen in the African continent. It is hypothesised this cross-reactivity derives from previous exposure to other low-pathogenic coronaviruses and it is not known whether there is any biological significance to this cross-reactivity in terms of protection or enhancement from COVID-19.

**Duration of immunity to other human coronaviruses:** In non-SARS, non-MERS human respiratory CoV infections, protection is transient. Waning antibody contributes to susceptibility to reinfection within 1 year. SARS-CoV-1 shares about 86% homology with SARS-CoV-2. Early studies suggested SARS antibody declined within 3 years after infection; however, more recent studies have demonstrated that SARS neutralizing antibodies can still be detected 12–17 years after infection and T-cell responses are still measurable 15 years later. No evidence is currently available on the role of this immunity on protection from subsequent infection.

**Immunity resulting from SARS-CoV-2 infection:** Studies on duration of immunity following COVID-19 illness are hampered by low specificity of some commercial assays with high false positivity rates. A recent study using independent assays against the receptor binding domain (RBD) and NP demonstrated that neutralizing antibodies to SARS-CoV-2 are stably produced 6–7 months after infection, even in patients who had mild symptoms. Anti-nucleoprotein antibody titers diminished more rapidly than neutralizing anti-spike S2 and RBD antibodies. It is not yet known for how long these neutralizing antibodies will continue to be produced, nor what level of protection they will afford. Although re-infection and persistent infections have been described in isolated case reports or case series, an increasing body of evidence shows that antibodies can last at least 6 months. Longer observation time will allow to address the question on the durability of antibodies which will be important for vaccine development against COVID-19.
Correlates of protection
Correlates of protection are valuable tools for the regulatory evaluation of vaccine protection as they allow determination of vaccine efficacy without the need to rely on clinical outcomes such as disease symptoms, infection parameters and hospitalization. The ability to assess the protective efficacy of a vaccine by measuring the proportion of vaccinees who mount a particular immune response instead of measuring actual clinical outcomes has significant advantages: clinical evaluation can be more straightforward when simply based on validated and quantifiable laboratory methodology. However, the establishment of a specific correlate of protection is a very complex and challenging task that requires a comprehensive evaluation and sound understanding of the interrelationships between vaccination, specific immune response responses and their relative contribution to protection, and clinical outcomes such as COVID-19 disease or disease severity.

Most persons infected with SARS-CoV-2 mount a detectable antibody response between day 10 and day 21 after infection. T-cell responses directed against the SARS-CoV-2 spike protein have also been measured in COVID-19 patients and appear to correlate quite well with IgG antibody titres. However, it is currently unclear if/how antibodies or T-cell responses in infected persons contribute to protective immunity, and what quantity (e.g., antibody titers) of specific immune response effectors are required to achieve protection.

To date, no correlates of protection for COVID-19 have yet been established and the search for a valid immune correlate of protection from COVID-19 is still ongoing.

Viral shedding
Over the course of the infection, the RNA of the virus has been identified in respiratory tract specimens 1-2 days before the onset of symptoms. The virus can persist for up to eight days in mild cases, and for longer periods in more severe cases. Prolonged viral RNA shedding has been reported. The high viral load close to symptom onset suggests that SARS-CoV-2 can be easily transmissible at an early stage of infection and pre-symptomatically.37 Asymptomatic individuals can also transmit the infection rendering disease prevention and control in the community more challenging.

III Clinical aspects

Pathophysiology vs immunopathogenesis
The large majority of human infections with SARS-CoV-2 are asymptomatic or minimally symptomatic with a very clear increase in the likelihood of serious pathology developing with increasing age. It is also inferred from severe cases occurring in front line healthcare workers that exposure to large numbers of infectious particles either all at once or by repeated exposure may be associated with a worse outcome. The lower respiratory tract is a dominant site of severe pathology with pneumonia and acute respiratory distress syndrome developing usually one to three weeks after onset of symptoms. However, many other organ systems can be affected including cardiovascular dysfunction, coagulopathy, gastrointestinal disturbance, central nervous system pathologies and multi-organ failure. The relatively slow progression to severe disease in many cases, coupled with evidence that viral loads from the respiratory tract are often relatively low by this stage, has led to the proposal that immune and inflammatory responses may be responsible for the pathophysiological events leading to respiratory failure, the need for intensive care support and the many deaths reported. This hypothesis is supported both by histopathological evidence obtained post-mortem and the strong evidence that treatment with steroids ameliorates outcome in the context of respiratory failure. Broadly, the understanding of COVID-19 that exists at present would suggest that, as with other viral infections, validated anti-viral therapy is likely to be effective only if administered early in the course of the infection, whereas general
or targeted anti-inflammatory therapies may be of benefit as significant illness emerges. There are theoretical concerns that antibody-enhanced disease could occur in individuals who have naturally-acquired antibodies to SARS-CoV-2, cross-reactive antibodies induced previously by other coronavirus infections, or antibodies induced by immunisation. To date there is no direct evidence that this occurs, but it remains an important issue for vaccine development and safety monitoring.

**Incubation, clinical features, and severity**

The median incubation period for symptom development is 5.1 days (95%CI 4.5 to 5.8 days).\(^{38}\) It has been estimated that 97.5% of those who develop symptoms will do so within 11.5 days (95% CI 8.2 to 15.6 days) of infection.

COVID-19 disease can have three stages: early infection marked by viral response, a pulmonary phase and lastly, a hyper-inflammation phase marked by host inflammatory response. The early infection stage is typically associated with fever, dry cough, and mild constitutional symptoms. The pulmonary phase is associated with shortness of breath with or without hypoxia. The hyperinflammation phase is associated with acute respiratory distress syndrome, shock, and cardiac failure. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.\(^{39}\)

Approximately 10-20% of symptomatic infected individuals develop more severe disease, requiring hospitalization, however, this risk is unevenly distributed in the population, being significantly higher in individuals of older age, and those with underlying conditions.\(^{40}\) A recent review estimated the pooled proportion of patients out of all hospitalized patients to be admitted to intensive care unit (ICU) at 10.96% (95% CI: 6.6-17.6).\(^{41}\) A peer-reviewed database study examined outcomes in 3,222 young adults (age 18-34 years) who required hospitalization for COVID-19 in 1,030 U.S. hospitals and health care systems: 21% required ICU admission, 10% required mechanical ventilation, and 2.7% died. Young adults with more than one comorbidity (morbid obesity, hypertension, and diabetes) faced risks comparable with middle-aged adults without them. More than half of those requiring hospitalization were Black or Hispanic.\(^{42}\) Growing evidence indicates that in addition to specific co-morbidities, sociodemographic factors are also important risk factors for disease severity and mortality.\(^{43,44}\) Acute respiratory distress syndrome (ARDS) is the major complication in patients with severe disease and can manifest shortly after the onset of dyspnoea. Other complications include arrhythmias, acute cardiac injury, and shock. Thromboembolic complications, including pulmonary embolism and acute stroke have been reported. Some patients have laboratory evidence of an exuberant inflammatory response, which have been associated with critical and fatal outcomes. Other inflammatory complications and auto-antibody-mediated manifestations have been described. Disease classification by severity categories has been proposed including mild (patients with mild clinical symptoms without pulmonary lesions), moderate (fever and other respiratory symptoms with radiologic evidence of pulmonary lesions), severe cases requiring hospitalization (patients with respiratory distress and hypoxia), and critical (cases requiring ICU admission due to respiratory failure which requires mechanical ventilation, shock, or any other organ failure that needs ICU monitoring and treatment).

Although asymptomatic infections have not been systematically studied, some studies estimate that around 20-50% of infections are asymptomatic, with clearly higher proportions in children.\(^{45}\)
Long-term sequelae, also coined “long COVID”
The full range of COVID-19 disease including long-term sequelae is still to be fully understood. Aside from anecdotal evidence, there is as yet little research on this issue. Italy reported that nearly nine in 10 patients (87%) discharged from a Rome hospital after recovering from COVID-19 were still experiencing at least one symptom 60 days after onset. They found that 13% of the 143 people were completely free of any symptoms, while 32% had one or two symptoms, and 55% had three or more. Although none of the patients had fever or any signs or symptoms of acute illness, many still reported fatigue (53%), dyspnoea (43%), joint pain (27%), and chest pain (22%). Two fifths of patients reported a worsened quality of life. The post-hospitalisation COVID-19 Study (PHOSP-COVID) aims to recruit 10,000 patients across the UK, who will be followed for more than a year [https://www.phosp.org].

COVID-19 in children
SARS-CoV-2 infections in children rarely cause severe illness or deaths. When children do exhibit symptoms, they are usually mild and may be non-specific, gastrointestinal disturbance being reported alongside respiratory features and fever. About 2 months into the pandemic, cases of a hyper-inflammatory and/or toxic shock-like syndrome began to be reported and this Multisystem Inflammatory Syndrome in Children (MIS-C) is now thought to be a rare late manifestation of SARS-CoV-2 infection perhaps in individuals who are susceptible either genetically or because of co-morbidities or both. For this reason, careful monitoring for any such rare disease manifestations remains important in the evaluation of safety of candidate vaccines against COVID-19.

COVID-19 in pregnancy
Recent evidence has shown that pregnancy is associated with an increased rate of hospitalizations, ICU care, and mechanical ventilation, but not death, in pregnant women vs age-matched non-pregnant women. In a prospective study of infected pregnant women vs age-matched non-infected pregnant women, pregnancy and neonatal outcomes were similar but the risk of ICU care was far higher in infected pregnant women. Obesity, hypertension, diabetes, and increased age are associated with severe COVID-19 in pregnancy, and pre-existing maternal co-morbidity may increase risk of ICU admission. During January 22-October 3, CDC in the United States received reports through national COVID-19 case surveillance or through the National Notifiable Diseases Surveillance System (NNDSS) of 1,300,938 women aged 15-44 years with laboratory results indicative of acute infection with SARS-CoV-2. Data on pregnancy status were available for 461,825 (35.5%) women with laboratory-confirmed infection, 409,462 (88.7%) of whom were symptomatic. Among symptomatic women, 23,434 (5.7%) were reported to be pregnant. After adjusting for age, race/ethnicity, and underlying medical conditions, pregnant women were significantly more likely than were non-pregnant women to be admitted to an intensive care unit (ICU) (10.5 versus 3.9 per 1,000 cases; adjusted risk ratio [aRR] = 3.0; 95% confidence interval [CI] = 2.6-3.4), receive invasive ventilation (2.9 versus 1.1 per 1,000 cases; aRR = 2.9; 95% CI = 2.2-3.8), receive extracorporeal membrane oxygenation (ECMO) (0.7 versus 0.3 per 1,000 cases; aRR = 2.4; 95% CI = 1.5-4.0), and die (1.5 versus 1.2 per 1,000 cases; aRR = 1.7; 95% CI = 1.2-2.4). Stratifying these analyses by age and race/ethnicity highlighted disparities in risk by subgroup.

Although the absolute risks for severe outcomes among women were low compared to other risk factors such as age, pregnant women were at increased risk for severe COVID-19-associated illness. Additionally, pregnant women are more likely to experience preterm birth and their neonates are more likely to be admitted to a neonatal ICU. Among 3,912 live births in the United States with known gestational age, 12.9% were preterm (<37 weeks), higher than the reported 10.2% among the general U.S. population in 2019. Among 610 infants (21.3%) with reported SARS-CoV-2 test results,
perinatal infection was infrequent (2.6%) and occurred primarily among infants whose mother had SARS-CoV-2 infection identified within 1 week of delivery.\textsuperscript{51} Vertical transmission is possible. 2,059 published cases with pregnancy outcomes resulted in 42 abortions, 21 stillbirths, and 2,015 live births. Preterm birth occurred in 23% of cases. Around 6% of pregnant women required admission to an intensive care unit and 28 died. There were 10 neonatal deaths. From the 163 cases with amniotic fluid, placenta, and/or cord blood analyzed for the SARS-CoV-2 virus, 10 were positive. Sixty-one newborns were positive for SARS-CoV-2. Four breast milk samples from 92 cases showed evidence of SARS-CoV-2.\textsuperscript{52}

**Breastfeeding**
There is limited risk that SARS-CoV-2 can be transmitted via human milk. Consequently, WHO and other organizations such as CDC, UNICEF and the Royal College of Obstetricians and Gynaecologists recommend that mothers continue to breastfeed their infants.\textsuperscript{53} Indeed, the main concern in this instance is the mother's ability to follow the strict contact precautions to avoid spreading the virus via the recognized horizontal routes.

**Risk factors for severe disease and death**
Older age is consistently associated with more severe disease and mortality.\textsuperscript{40} Other identified risk factors include male sex, and comorbidities including hypertension, chronic cardiac disease, non-asthmatic chronic pulmonary disease, chronic kidney disease, liver disease and obesity, particularly BMI >40, were associated with higher in-hospital mortality.\textsuperscript{40} Moreover, people with multiple comorbidities are at a higher risk for COVID-19 related adverse outcomes.

**COVID-19 in persons living with HIV (PLHIV)**
In a population-based cohort analysis of UK primary care data and linked national death registrations, 17 282 905 adults were included, of whom 27 480 (0.16%) had HIV recorded.\textsuperscript{54} People living with HIV had higher risk of COVID-19 death than those without HIV after adjusting for age and sex: hazard ratio (HR) 2.90 (95% CI 1.96-4.30; p<0.0001). The association was attenuated, but risk remained high, after adjustment for deprivation, ethnicity, smoking and obesity: adjusted HR 2.59 (95% CI 1.74-3.84; p<0.0001). In another study, established poor prognostic factors for COVID-19 patients, such as age and comorbidities, remained the main determinants for PLHIV.\textsuperscript{55} A systematic review found that PLHIV with well-controlled disease are not at risk of poorer COVID-19 disease outcomes than the general population.\textsuperscript{56} A study from the Western Cape Province, South Africa, however, did find that HIV increased risk of COVID-19 mortality (adjusted hazard ratio [aHR]:2.14; 95% confidence interval [CI]:1.70; 2.70), with similar risks across strata of viral load and immunosuppression.\textsuperscript{57} Current and previous tuberculosis also increased COVID-19 mortality risk (aHR [95% CI]:2.70 [1.81; 4.04] and 1.51 [1.18; 1.93] respectively). The risk for COVID-19 death associated with HIV was 2.39 (95% CI:1.96; 2.86) with population-attributable fraction of 8.5% (95% CI:6.1; 11.1). However, the authors acknowledge that their analyses may over-estimate the HIV-associated risk COVID-19 death due to residual confounding.

**COVID-19 and Immune suppression and Cancer**
A review of published reports on the clinical characteristics and outcomes of COVID-19 patients with pre-existing, compromised immune systems including patients who possess pre-existing primary antibody deficiency and those who are organ transplant recipients on maintenance immunosuppressants. indicates different clinical outcomes for the patients with pre-existing PAD, depending on the underlying causes.\textsuperscript{58} For organ transplant recipients, drug-induced immune suppression alone does not
appear to enhance COVID-19 mortality risk - rather, advanced age, comorbidities, and the development of secondary complications appears required.\textsuperscript{58} COVID-19 in kidney transplant patients is associated with high rate of disease severity and fatality.\textsuperscript{59} The clinical challenges of cancer management, including aging, immunosuppression, and comorbidities, make cancer patients more vulnerable to COVID-19 with different clinical manifestations, disease severity, and outcomes.\textsuperscript{60}

**COVID-19 and Down Syndrome**

Down syndrome, which is caused by trisomy 21, is characterized by immune dysregulation, anatomical differences in the upper respiratory tract, and higher rate of comorbidities.\textsuperscript{61} To evaluate Down syndrome as a risk factor for death from COVID-19, a comprehensive analysis of individual-level data in a cohort study of 8.26 million adults in the United Kingdom was conducted.\textsuperscript{62} Adjusted for age and sex, the Hazard Ratio (HR) for COVID-19–related death in adults with versus without Down syndrome was 24.94 (95% CI, 17.08 to 36.44). After adjustment for age, sex, ethnicity, BMI, dementia diagnosis, care home residency, congenital heart disease, and a range of other comorbid conditions and treatments, the HR for COVID-19–related death was 10.39 (CI, 7.08 to 15.23); for hospitalization, it was 4.94 (CI, 3.63 to 6.73).\textsuperscript{62}

**Populations at risk of severe disease outcomes**

About 20% in the world’s population is above 65 years of age.\textsuperscript{63} About 1.7 billion (UI 1.0-2.4) people, comprising 22% (UI 15-28) of the global population, have at least one underlying condition that puts them at increased risk of severe COVID-19 if infected (ranging from <5% of those younger than 20 years to >66% of those aged 70 years or older). It is estimated that 349 million (186-787) people (4% [3-9] of the global population) are at high risk of severe COVID-19 and would require hospital admission if infected (ranging from <1% of those younger than 20 years to approximately 20% of those aged 70 years or older). The share of the population at increased risk is estimated to be highest in countries with older populations, African countries with high HIV/AIDS prevalence, and small island nations and countries in the South-East Asia Region with high diabetes prevalence.

**Diagnosis**

Laboratory confirmation of acute SARS-CoV-2 infection requires direct detection of viral RNA in respiratory tract specimens through nucleic acids amplification, usually PCR. Test performance varies by presence of symptoms, timing of collection, type of sample collected, and type of test.\textsuperscript{64} As viral RNA does not correspond to the presence of live viable viruses, detection of viral RNA does not necessarily mean that the virus can be transmitted, particularly in patients that have persistent positive PCR after symptom resolution.

Antigen detection tests have been made available more recently, and also provide evidence of acute infection and transmissibility of disease. However, test accuracy is lower and more false negatives results are expected when compared to PCR.

Antibody detection tests are available and may be relevant mainly for public health surveillance. They are based on detection of IgM, IgA, IgG, or total antibodies in blood. Most patients develop antibodies 7 days after viral exposure. Recent evidence suggests that asymptomatic and oligosymptomatic patients are less likely to produce IgG antibodies. As a result, antibody testing is not useful in the setting of an acute illness, and should not be used as a passport to immunity.

**Treatment**

No specific antiviral treatment to date has shown significant reduction in mortality. According to the new WHO guidance, WHO recommends the use of corticosteroids in severe and critically ill
COVID-19 patients. WHO suggests not to use these drugs in other patients (e.g. those with mild/moderate illness). Treatment and management guidelines are also available from the Infectious Diseases Society at [https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).

There is increasing research on the use of monoclonal antibodies and convalescent sera.

**IV COVID-19 Vaccine Development (general)**

WHO is working in collaboration with scientists, business, and global health organizations through the ACT-Accelerator to speed up the pandemic response. WHO regularly updates a landscape analysis of COVID-19 vaccines in clinical development. To guide the efforts of vaccine developers, WHO has drawn up Global Target Product Profiles (TPPs) for COVID-19 vaccine. The TPPs outline the minimum and desired attributes of a safe and effective vaccine, and cover two types of vaccines: vaccines for the long-term protection of people at higher risk of COVID-19, such as healthcare workers; and vaccines that stimulate a rapid onset of immunity for use in response to outbreaks.

The speed, breadth, and magnitude of the effort to develop vaccines against COVID-19 has been unprecedented. The on-going global effort draws upon decades of research on both endemic (i.e., hCoV-229E, -NL63, -OC43, and -HKU1) and epidemic (i.e., SARS-CoV and MERS-CoV) human coronaviruses, particularly the structure of the Spike (S) protein and its role in coronavirus pathogenesis, the importance of neutralizing antibody directed against various S protein epitopes in providing protective immunity, and the interrogation of the theoretical risk of vaccine-enhanced disease in animal models. The effort also draws upon decades of vaccine and adjuvant development, both conventional and novel platform approaches. For example, advancements in vaccine platforms based on nucleic acid technology, viral vectors, and structure-based trimeric subunit proteins now allow vaccine candidates to progress to manufacture of thousands of doses shortly after the target genetic sequence is described. The global effort on over 300 candidate vaccines has significantly increased the likelihood that both the composition and supply of vaccines will meet the needs of the many use cases and of the demand for billions of doses of vaccines against COVID-19. By December 2020, more than 11 vaccines are in Phase 3 trials.

**Vaccine safety**

The Brighton Collaboration has developed standard templates for benefit-risk assessment of vaccine technologies for the main COVID-19 platforms (nucleic acid, protein, viral vector, inactivated viral, and live attenuated viral vaccines). The Global Advisory Committee on Vaccine Safety (GACVS) has recommended that any review of the safety of new vaccines be based on these templates as they offer a structured approach to evaluating safety. The templates are currently being completed by some of the COVID-19 vaccine developers, especially for the vaccines in an advanced phase of clinical trials.

Adverse Events of Special Interest (AESIs) (serious or non-serious) are events of significant medical and scientific concern specific to the sponsor’s program or product. These require ongoing monitoring and communication by the investigator to the sponsor and might require further investigations and rapid communication by the trial sponsor to regulators. They could be related to vaccines in general, specific vaccine platforms or the disease. The Safety Platform for Emergency vACCines (SPEAC) has made an initial list of 18 AESI, some of which, including generalized convulsions, Guillain Barré syndrome and anaphylaxis, already have a Brighton Collaboration case definition, while many COVID-19-related events do not have such a definition. The priority AESI for which case definitions are being developed include enhanced disease after immunization and multisystem inflammatory syndrome. Other case
definitions have been prioritized. SPEAC is also reviewing published evidence to identify the background incidence rates in target populations and the causes, risk factors and differential diagnoses and map the AESI to the corresponding codes of the International Classification of Diseases (ICD) and the Medical Dictionary for Regulatory Activities.

**Immunoaassays for licensure of COVID-19 vaccine products**

Current clinical trials apply clinical endpoints such as protection from COVID-19 disease to evaluate vaccine efficacy. Full licensure can only be granted after the clinical data package has been completed, which may occur at a later point in time. Clinical data packages should also include analysis of relevant immune response effectors such as neutralizing antibody titers, selected T-cell responses and cytokine profiling that can be instrumental for future establishment of correlates of protection for COVID-19 vaccines. It is important to note that methodologies applied for the quantitative determination of immune responses should be appropriately validated in order to generate meaningful results. In addition, usage of international reference material will provide the possibility to compare results obtained in different laboratories. The WHO Expert Committee on Biological Standardization (ECBS) is working on standardization of assays.

**V Vaccine Impact Modelling**

To elicit and review COVID-19 vaccine impact modelling work the SAGE Working Group i) issued a request for information (RFI) highlighting prioritised questions and initial vaccination scenarios; ii) reviewed responses to this RFI and invited modelling groups to present their findings at weekly modelling subgroup meetings; and iii) systematically reviewed the published COVID-19 modelling literature including preprints and grey literature. Over 25 modelling groups from academia, industry, government and international organisations have responded to the RFI, which covered both health and economic impacts. Initial key findings are summarised here, focusing on evidence for prioritisation of specific groups for vaccination during the initial period of constrained vaccine supply.

**Age:** The infection fatality rate (IFR) for SARS-CoV-2 rises steeply (exponentially) with age, such that the risk of death following infection is estimated to be several hundred times higher in those aged 65+ years compared with children and young adults (20-30 years old). Vaccinating older adults first, rather than younger adults or children, therefore tends to be optimal when seeking to minimise COVID-19 deaths or years of life lost (YLL), irrespective of underlying demography or patterns of contact by age. This strategy has been shown to be optimal for minimizing COVID-19 deaths even for vaccines with substantially lower efficacy in older adults and for vaccines that are effective against infection and disease or only against disease, when age is the only prioritization dimension considered. If vaccination does prevent infection, the optimal strategy to minimise the number of SARS-CoV-2 infections is to target younger age groups (e.g., 20-40 years old), based on their typically higher contact rates and exposure to infection. In certain specific scenarios, particularly when \( R_e \) is not much greater than 1 and vaccine supply is substantial and immediate, this strategy can also minimise COVID-19 mortality; however, for realistic, gradual vaccine supply scenarios and given the uncertain impact of vaccination on SARS-CoV-2 infection and shedding, modelling work is generally not supportive of this strategy in the early phases of vaccine rollout. In some countries, older adults residing in care homes or other congregate settings have experienced a disproportionate burden of COVID-19 severe outcomes relative to their population size; however, only two unpublished models have been identified looking at this subpopulation of older adults.
Underlying health conditions: Few models to date have included prioritization strategies considering groups at higher risk of severe disease outcomes following infection because of comorbidities (e.g., diabetes, obesity, transplant patients). Most comorbidities increase in prevalence with age and are in part addressed by strategies that prioritize the eldest first. The exact ordering of priority groups with respect to age and comorbidities varied among model outputs, depending on the data used for the relative risk (RR) of severe outcomes in each group and assumptions about the vaccine mechanism of action.\(^{72,80}\) In general, although the RR may be high for some conditions, the absolute risk for younger adults with comorbidities is typically lower than healthy older adults (75+ years) and so the oldest age-groups remain higher priority. However, for a vaccine that prevents infection, differences in mortality reductions may be minimal between strategies that prioritize older adults versus adults of all ages with comorbidities that are highly positively correlated with age.\(^{72,80}\) No modelling results have been identified yet that assess comorbidities in detail in LMICs, where differing demography and prevalence of comorbidities may alter this conclusion.

Essential workers: Models that included health and social workers generally prioritised these groups when minimising mortality or infections, given their relatively high exposure and potential to transmit infection to vulnerable individuals.\(^{72,81}\) In addition to health and social care workers, other occupations may be prioritised for vaccination to protect those services judged essential to society or the economy (e.g. teachers, transportation workers, police, etc.). There may also be other reasons to prioritise these groups, based on occupational exposure to infection and prevalence of comorbidities or risk factors for COVID-19. Modelling studies in the U.S. that included generic “essential worker” subpopulations characterized by higher exposure risk and (in one model) comorbidities, found that prioritizing vaccination of essential workers with initial limited vaccine supply was optimal or close to optimal in minimizing infections or deaths with a vaccine that prevents infection; however, with a vaccine that does not prevent infection, vaccinating older adults continued to be the optimal strategy for mortality reduction.\(^{74,80}\) When considering estimated SARS-CoV-2 infection risks by specific essential worker occupation, the one model identified (for the U.S.) found that age-based infection fatality risk was a more important determinant of the optimal vaccine allocation scheme than occupation-based infection risk.\(^{82}\)

Groups at high risk of infection: Prioritising groups more highly exposed to infection, for example as a result of their occupation, socio-economic status or location of residence, results in a greater reduction in infection and mortality compared with strategies that do not prioritise these groups when a vaccine reduces infection or transmission. Models that favoured early vaccination of health workers and other highly-exposed occupations (essential workers) based on this principle were reviewed;\(^{72,74}\) however, very limited modelling work has tackled the question of prioritising specific geographic locations or communities for vaccination (e.g., based on seroprevalence or urban versus rural location), including congregate settings (e.g., prisons, dormitories).

Equity: No models identified to date have considered the distribution of health impacts within countries across socioeconomic dimensions such as race, ethnicity, gender, household income or wealth. Models that examined vaccine allocation among countries found strategies that distribute vaccine equally in the first stages were optimal or close to optimal.\(^{75}\)

Cost-effectiveness, economic impacts, and value of vaccination: No models have been identified specifically addressing the RfI questions with respect to the economic impacts of prioritizing different groups for vaccination under initial limited supply. Two estimates found that COVID-19 vaccination
would be cost-effective from the healthcare sector perspective by conventional thresholds in the settings modelled (UK£20,000 per Quality-Adjusted Life Year in the U.K., assuming vaccine prices ranging from UK£10-£942 per dose and not including other vaccination delivery costs). One model of COVID-19 vaccination in the U.S. found that vaccination could avert direct medical costs of US$151-$738 billion and productivity losses of US$527-$2,355 billion across different vaccine efficacy and coverage levels when R=2.5, although the costs of the vaccine and vaccination program were not estimated in a formal cost-effectiveness analysis. Analyses of the economic impact of a COVID-19 vaccine (with unspecified VE and mechanism of action) that reduces the need for physical distancing or lockdowns and restores economic activity have suggested a high societal value in terms of averted GDP losses. The IMF’s most recent Global Economic Outlook assumed that social distancing would be wound back in 2021 as vaccination was scaled up, resulting in global growth of 5.2% in 2021; growth could otherwise be three percentage points lower if vaccination (and other disease control measures, e.g., therapeutics) are less widely or quickly available. In contact-intensive sectors alone, equitable global access to a vaccine across country-income groups would avert an estimated US$3.4 trillion (3.7%) in global GDP losses annually that would otherwise be incurred in the absence of any vaccine; if vaccine access for low- and middle-income countries (besides China and India) is delayed, global GDP losses could still be US$0.3 trillion per year. Delivering vaccine to low-income countries has been estimated to yield an almost five-fold return on investment in terms of averted GDP losses alone (range: US$1.9-$12.6 per dollar invested). Investing in vaccine access for low- and lower-middle-income countries has also been estimated to be economically favourable for major donor countries. Several willingness-to-pay studies have also been conducted for hypothetical COVID-19 vaccines across country settings, generally finding high individual willingness-to-pay, though correlated with income and other sociodemographic characteristics, which may suggest a need for subsidized or free access for some subpopulations.

Herd-immunity and the critical vaccination threshold: The potential for vaccination to eliminate SARS-CoV-2 from a population depends on vaccine effectiveness against infection and virus shedding, which are currently unknown. Multiple modelling groups have shown the relationship between the critical threshold for vaccination coverage above which R_e<1, vaccine effectiveness, duration of immunity, and the reproduction number. Even with a vaccine that is efficacious against infection, the critical vaccination threshold in the absence of continued implementation of non-pharmaceutical interventions (NPIs) is likely to be very high given estimates of the SARS-CoV-2 basic reproduction number. Continued implementation of NPIs could allow local elimination of infection at lower vaccination coverage levels. However, given current limited levels of vaccine supply and uncertainty about vaccine effectiveness against infection, the magnitude and timing of vaccination’s contribution to herd immunity in specific country settings is currently unknown.

VI Public health objectives and prioritization for COVID-19 vaccination

Values Framework

The SAGE Working Group on COVID-19 Vaccines created the WHO SAGE Values Framework for the allocation and prioritization of COVID-19 vaccination. These documents serve to underpin the public health objectives and principles of vaccine prioritization necessary to provide guidance nationally on prioritization of target populations during vaccine supply constraints. The Values Framework was endorsed by SAGE and by the WHO Director-General and posted online on 14 September.
The Framework articulates the overall goal of COVID-19 vaccine deployment, providing six core principles that should guide prioritization decisions and twelve objectives that further specify the six principles.

**Table 2: Values Framework at a Glance**

<table>
<thead>
<tr>
<th>Goal Statement</th>
<th>Objectives</th>
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<tbody>
<tr>
<td>COVID-19 vaccines must be a global public good. The overarching goal is for COVID-19 vaccines to contribute significantly to the equitable protection and promotion of human well-being among all people of the world.</td>
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<table>
<thead>
<tr>
<th>Principles</th>
<th>Objectives</th>
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<tbody>
<tr>
<td>Human Well-Being</td>
<td>Reduce deaths and disease burden from the COVID-19 pandemic; Reduce societal and economic disruption by containing transmission, reducing severe disease and death, or a combination of these strategies; Protect the continuing functioning of essential services, including health services.</td>
</tr>
<tr>
<td>Equal Respect</td>
<td>Treat the interests of all individuals and groups with equal consideration as allocation and priority-setting decisions are being taken and implemented; Offer a meaningful opportunity to be vaccinated to all individuals and groups who qualify under prioritization criteria.</td>
</tr>
<tr>
<td>Global Equity</td>
<td>Ensure that vaccine allocation takes into account the special epidemic risks and needs of all countries; particularly low-and middle-income countries; Ensure that all countries commit to meeting the needs of people living in countries that cannot secure vaccine for their populations on their own, particularly low- and middle-income countries.</td>
</tr>
<tr>
<td>National Equity</td>
<td>Ensure that vaccine prioritization within countries takes into account the vulnerabilities, risks and needs of groups who, because of underlying societal, geographic or biomedical factors, are at risk of experiencing greater burdens from the COVID-19 pandemic; Develop the immunization delivery systems and infrastructure required to ensure COVID-19 vaccines access to priority populations and take proactive action to ensure equal access to everyone who qualifies under a priority group, particularly socially disadvantaged populations.</td>
</tr>
<tr>
<td>Reciprocity</td>
<td>Protect those who bear significant additional risks and burdens of COVID-19 to safeguard the welfare of others, including health and other essential workers.</td>
</tr>
<tr>
<td>Legitimacy</td>
<td>Engage all countries in a transparent consultation process for determining what scientific, public health, and values criteria should be used to make decisions about vaccine allocation between countries; Employ best available scientific evidence, expertise, and significant engagement with relevant stakeholders for vaccine prioritization between various groups within each...</td>
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country, using transparent, accountable, unbiased processes, to engender deserved trust in prioritization decisions.

To provide recommendations for allocating vaccines between countries and prioritizing groups for vaccination within each country, the Values Framework needs to be complemented with information about specific characteristics of vaccines, the benefit-risk assessment for different population groups, the amount and pace of vaccine supply, and the current state of the epidemiology, clinical management, and economic and social impact of the pandemic. Hence, the final vaccination strategy is defined by an interpretation of the Values Framework in the light of these features, and specific to the characteristics of vaccine products as they become available.

Public health objectives and prioritization for COVID-19 vaccination: Prioritization Roadmap

The SAGE Working Group on COVID-19 Vaccines created the WHO SAGE Roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply. This document builds on the foundation of the Values Framework by suggesting public health strategies and target priority groups for different levels of vaccine availability and epidemiologic settings. The Prioritization Roadmap was endorsed by SAGE and by the WHO Director-General and posted online on 20 October.

Guiding considerations of the Prioritization Roadmap

1. The Roadmap must remain fully aligned with the WHO SAGE Values Framework for the allocation and prioritization of COVID-19 vaccination that preceded it.
2. To be useful in driving discussions at regional and national levels, the Roadmap needs to be kept as straightforward and concise as possible.
3. The Roadmap may be revisited through i) rolling review as new information becomes available; and ii) ongoing dialogue with RITAGs and National Immunization Technical Advisory Groups (NITAGs).

Key Assumptions of the Prioritization Roadmap

- The Roadmap assumes any vaccine deployed is either fully licensed or under emergency use authorization.
- The current degree of uncertainty regarding age-independent vaccine efficacy of any specific vaccine was considered (for example, a scenario in which the vaccine is assumed to have the same efficacy at all ages, and another scenario in which the vaccine is assumed to have much lower efficacy in older adults). However, the Roadmap relies on the underpinning assumption, supported by current modelling results, that, given the many-fold higher mortality rate among older individuals, even a vaccine with relatively low efficacy in older adults would not significantly change the recommendations for priority use cases in older populations. If however it were determined that vaccine efficacy in older adults relative to other age groups were so low that individual protection and public health impact became significantly suboptimal, the individuals in older age groups in each scenario would likely be moved to a lower priority use case. This relative efficacy is likely to vary with different vaccines.
- Similarly, it was assumed that there would not be substantive differences in vaccine efficacy in subgroups (for example, people with comorbidities that increase the risk of severe COVID-19 such as HIV-positive status).
The Roadmap assumes that non-pharmaceutical interventions are in place to varying degrees as vaccines are introduced and coverage expands. The Roadmap further assumes that vaccine efficacy will not deteriorate if use of non-pharmaceutical interventions is relaxed.

Although a vaccine’s effect on reducing transmission is an important consideration in the recommendations for use, direct evidence of impact on transmission will likely not be available when the first vaccines are authorized for use. The Roadmap assumes that at some point demonstrated evidence of vaccine effectiveness in reducing transmission will be available, sufficient to justify prioritizing vaccination of some groups on the basis of their role in transmission.

The Roadmap does not account for variation in population seropositivity rates or existing degree of protection within countries or communities which may have already experienced a high degree of community transmission.

Prioritization exercises undertaken for development of the Roadmap did not directly take account of severe disease, as the risk of this will be closely correlated with the risk of death. Similarly, long-term sequelae from SARS-CoV-2 infection have not been taken into account as evidence on chronic morbidity is still emerging.

Epidemiologic setting scenarios

The differing epidemiologic setting scenarios in the Roadmap take into consideration the relative benefits and potential risks of vaccination, proposing three broad epidemiologic settings: (i) Community Transmission, (ii) Clusters of Cases, and (iii) No Cases or sporadically imported cases.

Vaccine supply scenarios

Three scenarios of constrained vaccine supply are considered in the Roadmap for each epidemiologic setting scenario: a Stage I scenario of very limited vaccine availability (ranging from 1–10% of each country’s total population) for initial distribution; a Stage II scenario as vaccine supply increases but availability remains limited, (ranging from 11–20% of each country’s total population); and a Stage III scenario as vaccine supply reaches moderate availability (ranging from 21–50% of each country’s total population) (Table 3).

The Roadmap recognizes that many countries’ prioritization decisions will be tied, in part or in whole, to vaccine distribution through the COVAX Facility. Stages I and II in the Roadmap correspond to the Phase 1 supply of up to 20% of each country’s population detailed in the latest draft of the WHO Fair allocation mechanism for COVID-19 vaccines through the COVAX Facility. The Roadmap’s Stage III scenario aligns with the Allocation Framework’s Phase 2 supply of more than 20% population coverage.

Overall public health strategies by epidemiologic setting and vaccine supply stage

Within the Roadmap, SAGE recommends overall public health strategies, grounded in the Values Framework, for each of the three epidemiologic scenarios (Table 3). These strategies accommodate the dynamic nature of vaccine supply and epidemiologic conditions in each country.

Staging of priority groups relative to group size
The staging of priority groups is sequential. If there is insufficient vaccine supply to cover the priority groups in Stage I, the intention is that all these groups are offered vaccine before groups enumerated in Stage II. With the exception of Stage Ia and Stage Ib, the priority groups within a vaccine supply stage are not ordered for prioritization. The assignment of priority groups was based on assumptions about the size of different priority groups in high-, middle- and low-income country settings. For some priority groups, even estimates of the sizes of different groups are not available. Considerable national variation is expected. In some countries, the amount of vaccine projected for a vaccine supply stage may be insufficient to cover all the priority groups assigned to that stage and countries will have to prioritize groups within stages.

**Considering comorbidities in vaccine prioritization**

The evidence on specific comorbidities and the increased risk of severe COVID-19 is increasing. What is already clear is that i) several comorbidities increase this risk; ii) the increase in risk varies between specific comorbidities, and thus equity concerns would arise if all comorbidities were to be given similar weight; iii) in many countries, if everyone with a comorbidity were to be prioritized in early vaccine supply scenarios, those eligible for vaccination would well-exceed supply; and iv) the list of relevant comorbidities will be location dependent.

Based on these considerations, countries should use relevant local and regional data to identify the comorbidities associated with different levels of risk from COVID-19 (for example, significant versus moderate risk). One approach is to identify the additional risk associated with each comorbidity. Another approach is to prioritize individuals who have two or more relevant comorbidities. This document discusses comorbidities and risk factors elsewhere.
Table 3: Roadmap for settings with Community Transmission

<table>
<thead>
<tr>
<th>Vaccine availability</th>
<th>Stage I: very limited (for 1-10% national population)</th>
<th>Stage II: limited (for 11-20% national population)</th>
<th>Stage III: moderate (for 21-50 % national population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>la: health workers at high to very high risk of acquiring and transmitting infection</td>
<td>- Older adults (not covered in Stage Ib) - Individuals with co-morbidities or health status determined to be at significantly higher risk of severe disease or death - Socio-demographic groups at significantly higher risk of severe disease or death - Health workers engaged in immunization delivery - High priority teachers and school staff</td>
<td>- Remaining teachers and school staff - Other essential workers outside health and education - Pregnant women - Health workers at low to moderate risk of acquiring and transmitting infection - Personnel needed for vaccine production and other high-risk laboratory staff - Social/employment groups at elevated risk of acquiring and transmitting infection (unable to effectively physically distance)</td>
</tr>
<tr>
<td></td>
<td>lb: older adults defined by country/region specific age-based risk</td>
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VII Considerations on seroprevalence and need for SARS-CoV-2 testing prior to vaccine administration

The SAGE Working Group considered that there was currently insufficient evidence on the degree and duration of protection conferred by SARS-CoV-2 infection relative to that conferred by vaccination, and that no correlates of protection had yet been established that could be reliably assessed through available testing platforms (e.g., serology tests, antigen tests).

In terms of benefits and harms, although prioritizing individuals without prior SARS-CoV-2 infection might increase the health benefits per vaccine dose administered, implementing a pre-vaccination screening program might reduce vaccination coverage overall for a given vaccine supply due to the added logistical and messaging complexity of determining prior infection status. The benefits of such a prioritization strategy would likely be greatest at the start of a COVID-19 vaccination program when vaccine supply is most limited; however, this would also be the most challenging implementation period for each country’s immunization program when the added complexity of a screening program could be most harmful to a smooth and rapid launch and to building public confidence in a new vaccine. Public health messaging around who would be eligible for vaccination would be complex, especially in the many settings with continued limited testing availability and given the evolving and variable landscape of testing products and diagnostic algorithms. Potential public confusion about who is eligible for vaccination and misinformation around immunity may suppress vaccine uptake, which could outweigh any benefit of prioritizing individuals without prior infection for vaccination. Individuals with prior infection may face higher exposure risk conditions (e.g., urban slums, essential workers in occupations that do not permit physical distancing); if immunity acquired from infection is less protective or less
durable than vaccine-induced immunity, then prioritizing vaccination for individuals with less exposure risk may not reduce future infections on a population basis.

In terms of values, preferences, and equity, the Working Group considered that individuals without prior SARS-CoV-2 infection may be more vulnerable if exposed, but individuals with prior infection may be more likely to be exposed. If higher exposure risk is correlated with sociodemographic groups experiencing greater disadvantage, then denying vaccination to individuals with prior infection may reinforce existing societal inequities. The Working Group also recognised that infection may result from individual choices not to adhere to recommended prevention measures that reduce exposure (and not only from structural or contextual conditions that make such adherence more challenging); from this perspective, it may be perceived as more fair to prioritize vaccination access for individuals who adhered to recommended prevention interventions and thereby avoided infection. As a practical public health policy, however, the Working Group concluded that it was not feasible (or necessarily desirable) to distinguish the behavioural, contextual, and serendipitous factors that led to infection at the individual level as a basis for vaccination prioritization.

In terms of resource use, adding a pre-vaccination screening program to prioritize vaccination of individuals without prior infection would increase overall costs of the COVID-19 vaccination program; however, the cost-effectiveness of this strategy is unknown and could be favourable depending on the unit costs for tests and vaccines as well as the background population seroprevalence. Such a screening program might also have benefits beyond the vaccination program in terms of increased testing that can influence individual behaviour change and public policy.

In terms of feasibility, the Working Group considered several aspects of how a screening program might be implemented, including the type of test (e.g., serology, antigen), timing of screening (e.g., before or at time of vaccination), evidence of test result required (if not conducted at time of vaccination), whether individuals with prior infection would be denied vaccination at the point of care, and whether such a screening program might be time-limited until vaccine supply increases. The Working Group concluded that implementing such a pre-vaccination screening program was unlikely to be programmatically feasible in most country settings, given continued limited SARS-CoV-2 testing access and pre-pandemic limitations in medical records systems. The Working Group further concluded that implementing any pre-vaccination screening program would likely delay roll-out of COVID-19 vaccine and could reduce uptake of the vaccine (e.g., through adding uncertainty about whether an individual who presents for vaccination will receive vaccine, through individuals self-diagnosing based on clinical symptoms and assuming that they have had COVID-19 and therefore do not need the vaccine for personal protection).
**Table 4: Considerations for whether pre-vaccination testing should be used to prioritize vaccination to individuals without prior SARS-CoV-2 infection**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Hypothesized evidence direction</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Problem Statement</td>
<td>Unknown</td>
<td>Unknown duration of immunity, correlates of protection</td>
</tr>
<tr>
<td>Benefits (Clinical, Epidemiological)</td>
<td>Mixed</td>
<td>Increased vaccine impact per dose (especially under initial very limited supply), but could reduce coverage overall due to logistical and messaging complexity</td>
</tr>
<tr>
<td>Harms (Clinical, Epidemiological)</td>
<td>Unfavourable</td>
<td>If naturally-acquired immunity is less protective or durable than vaccine-induced immunity, not vaccinating those with prior infection who may have higher exposure risk could offset benefits; messaging complexity may suppress vaccine uptake</td>
</tr>
<tr>
<td>Values and Preferences</td>
<td>Unknown</td>
<td>May not be acceptable if infection risk is correlated with sociodemographic groups</td>
</tr>
<tr>
<td>Resource Use: Cost</td>
<td>Unfavourable</td>
<td>Increased cost for testing/screening</td>
</tr>
<tr>
<td>Resource Use: Cost-Effect.</td>
<td>Mixed</td>
<td>Depends on test and vaccine costs, and underlying community seroprevalence</td>
</tr>
<tr>
<td>Equity</td>
<td>Mixed</td>
<td>Those who are SARS-CoV-2 naïve may be more vulnerable if exposed, but those already infected may be more likely to be exposed; may be feasible only in HICs</td>
</tr>
<tr>
<td>Feasibility (Vaccination)</td>
<td>Unfavourable</td>
<td>Increases logistical and messaging complexity for already ambitious roll-out; most relevant for initial very limited supply when logistics are most fragile; challenging to communicate, which may suppress vaccine uptake; testing/screening challenging to implement given testing limitations and evolving diagnostic products/algorithms</td>
</tr>
</tbody>
</table>
VIII References

26. Covid-19: New coronavirus variant is identified in UK. https://doi.org/10.1136/bmj.m4857
43. de Souza CDF, do Carmo RF, Machado MF. The burden of COVID-19 in Brazil is greater in areas with high social deprivation. J Travel Med 2020.
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