# 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

*22 December 2020*



WHO reference number: WHO/2019-nCoV/vaccines/SAGE_background/2020.1

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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.[8] 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. [9] 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 exhaling (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.[10] Travel bans and travel restrictions delayed but did not stop global spread.[11] 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.[12] Hence, urban centres around the world were often the initial epicentres. Clustering and super-spreading events have been associated with mass gatherings, detention camps, prisons, slum dwellings, choirs, religious gatherings, tourist hot spots and abattoirs.[13-15] Nursing homes and long-care homes for the elderly are at particular risk for high death rates.[16]

**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.[17]

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 1: Risk categories, job tasks and mitigation measures for primary prevention of occupational exposure to SARS-CoV-2 among health workers.***[19]

| *Risk category* | *Examples of job tasks* | *Sample prevention and mitigation measures* |
|---|---|---|
| *Lower risk* (caution) | 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. | • Remote work and teleservices, when possible<br>• Stay home if unwell and after contact with COVID-19 case<br>• Aeration or ventilation without recirculation<br>• Hand and respiratory hygiene<br>• Physical distancing, reducing workplace occupancy and avoiding social mixing<br>• Avoid sharing workstations and work equipment<br>• Cloth masks in common areas and avoiding face-to-face meetings |
| *Medium risk* | Providing care in health facilities and in the community to the general public patients who are <u>not</u> 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 | • Telehealth services<br>• Engineering controls – sneeze screens, barriers, workplace modifications<br>• Patient triage<br>• Source control (cloth or medical masks) for patients and visitors<br>• Environmental cleaning and disinfection<br>• Stay home if unwell and after contact with COVID-19 case |

| *Risk category* | *Examples of job tasks* | *Sample prevention and mitigation measures* |
|---|---|---|
| | COVID-19, working at busy staff work areas within a healthcare facility. | • Physical distancing, reducing workplace occupancy, avoiding social mixing, restriction of visitors<br>• Aeration or enhanced ventilation without recirculation<br>• IPC training<br>• Hand and respiratory hygiene<br>• 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 COVID19. | • Engineering, environmental and administrative controls<br>• Enhanced ventilation without recirculation, with "clean to less clean" directional design for airflows.<br>• Stay home if unwell and after contact with COVID-19 case<br>• Physical distancing, avoiding social mixing, restriction of non-essential workers and visitors<br>• Source control (cloth or medical masks) for patients and visitors<br>• IPC training<br>• Hand and respiratory hygiene<br>• 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<br>• Ventilation with High Efficiency Particulate Air (HEPA) filters<br>• Physical distancing, avoiding social mixing, restriction of non-essential workers and visitors<br>• Source control (cloth or medical masks) for patients and visitors<br>• Stay home if unwell and after contact with COVID-19 case<br>• Hand and respiratory hygiene<br>• IPC training, including donning and doffing of PPE |

| *Risk category* | *Examples of job tasks* | *Sample prevention and mitigation measures* |
|---|---|---|
| | | • PPE (respirator N95 or FFP2 or FFP3, gown, gloves, eye protection, apron) |

**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.[20] 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[21], 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.[22] The great majority of service disruptions were partial, which was defined as a change of 5–50% in service provision or use.[22] 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[23], 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.[24] 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.[25] 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.[26] 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[27], 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.[28] It is hypothesised this cross-reactivity derives from previous exposure to other low-pathogenic coronaviruses[29] 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.[30] SARS-CoV-1 shares about 86% homology with SARS-CoV-2. Early studies suggested SARS antibody declined within 3 years after infection;[31] 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.[27] 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.