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# Coronavirus Disease-19: An Interim Evidence Synthesis of the World Association for Infectious Diseases and Immunological Disorders (Waidid)

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Coronavirus disease 2019 (COVID-19) is a rapidly evolving, highly transmissible, and potentially lethal pandemic caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of June 11 2020, more than 7,000,000 COVID-19 cases have been reported worldwide, and more than 400,000 patients have died, affecting at least 188 countries. While literature on the disease is rapidly accumulating, an integrated, multinational perspective on clinical manifestations,

immunological effects, diagnosis, prevention, and treatment of COVID-19 can be of global benefit. We aimed to synthesize the most relevant literature and experiences in different parts of the world through our global consortium of experts to provide a consensus-based document at this early stage of the pandemic.

## INTRODUCTION

In December 2019, a cluster of pneumonia cases of an unknown cause was reported in Wuhan city, the capital of Hubei province in China (1). The novel coronavirus, subsequently named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified via deep sequencing of patients' respiratory tract samples (2); the disease was designated in February 2020 by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19) (3). The original cluster of cases was linked to a seafood market with presumed zoonotic transmission, followed by efficient person-to-person transmission (4). Since the initial reports, COVID-19 has rapidly spread from Wuhan to the rest of the world with cases and fatalities increasing rapidly. The WHO declared COVID-19 as a pandemic on March 11 2020.

CoVs are large enveloped non-segmented positive-sense single-stranded RNA viruses, and COVID-19 is the third known zoonotic coronavirus disease after severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (5). While all three of these known zoonotic CoV belong to the β-coronavirus genera (6), SARS-CoV-2 is a distinct new β-coronavirus belonging to the subgenus botulinum of Coronaviridae (2). As COVID-19 is a new and rapidly evolving pandemic, knowledge on the disease pathogenesis, clinical manifestations and diagnosis, optimal treatment, and preventative strategies are evolving. Our goal was to rapidly synthesize the accumulating data through our global consortium of experts and to provide an overall overview on COVID-19 disease.

## SARS-CoV-2 CHARACTERISTICS, VIRAL SHEDDING, AND DIAGNOSTIC TESTING

SARS-CoV-2 has more than 80% homology to SARS-CoV and 50% to MERS-CoV (7). Although the pathogenesis is not yet precisely defined, the virus enters human cells through the ACE2 receptor (8, 9). Replicating strains have evolved, as many mutations and deletions in coding and non-coding regions of SARS-CoV-2 have been detected (10). There is variation in SARS-CoV-2 detection in body compartments (**Figure 1**) (11–15). Consistent with other human CoV (hCoV) (16), SARS-CoV-2 has been shown to be shed by asymptomatic subjects to a yet unknown extent (17–19), and it has been suggested that infectiousness might peak on or before symptom onset (20).

SARS-CoV-2 can remain viable in aerosols and on surfaces. In studies of experimentally induced aerosols SARS-CoV2 was dete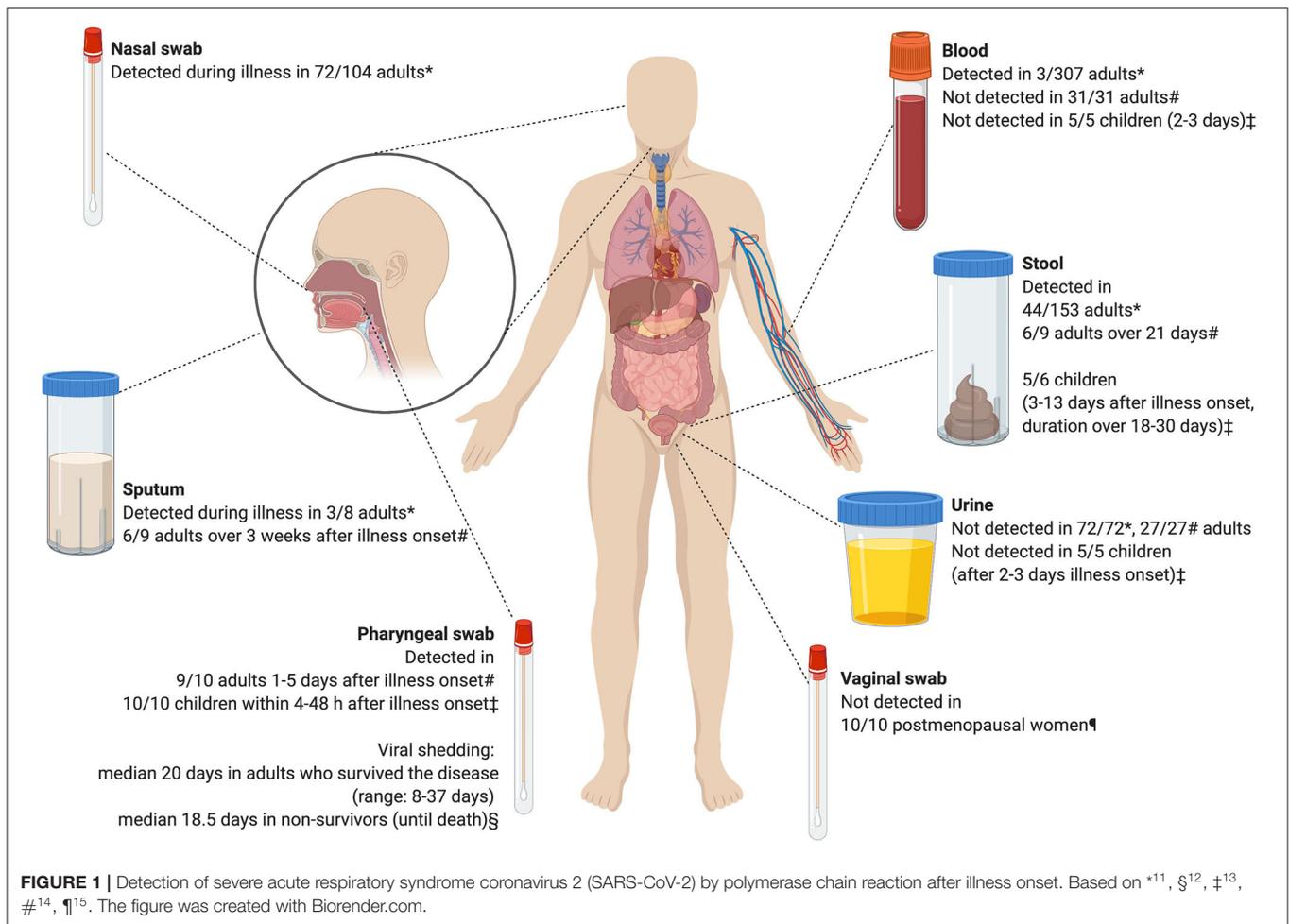cted for at least 3 h in aerosols in one study (21) and for 16 h in another study (22), which also detected viable virus. SARS-CoV-2 was still detected after 72 and 48 h on plastic and stainless steel, respectively. On copper and cardboard, no viable virus was apparent after 4 and 8 h, respectively (21). In addition to droplet transmission, outbreaks of SARS-CoV-2 that are related to indoor crowded spaces have also suggested aerosol transmission (23–25). The recent WHO statement on the transmission of SARS-CoV-2 still concludes that transmission occurs mainly through direct, indirect, or close contact with infected persons through infected secretions (saliva, respiratory secretions, or respiratory droplets) (26).

Nucleic acid amplification tests (NAAT) of SARS-CoV-2 are currently the gold standard for COVID-19 laboratory diagnosis (27). Limitations in testing include the availability of tests, the need for appropriate swabbing, reduced sensitivity later in the course of the disease (14, 28, 29), and a lag time between obtaining testing and receiving the results, leading to a delay in patient-related actions. The use of oropharyngeal saliva with good sampling have matched the sensitivity of a nasopharyngeal swab in the diagnosis of COVID-19, and yet are able to reduce the workload and protective equipment consumption of health care workers (28). Rapid tests reduce this lag time allowing for more immediate detection (30) and are based on isothermal RNA amplification (31), detection of SARS-CoV-2 antigen in the nasopharynx, and detection of antibodies in blood (32). Two rapid NAATs, developed by Luminex and Abbott, providing results in < 1 h have been licensed (32). Rapid antigen detection tests would be a suitable alternative when PCR is not readily available, and it has the advantage of low-cost and short time to results (29, 33) [e.g., Sona Nanotech (Halifax, Canada)].

Anti-SARS-CoV-2 antibodies (IgM/IgG) appear 4–5 days after infection (34, 35), and the seropositivity rate is 50 and 100% after 7, and 14 days of infection, respectively (14). Serology can thus confirm infection in cases that are negative by PCR/antigen detection in patients presenting after 2 weeks from symptoms onset, and in symptomatic contacts of a confirmed case, where contact happened more than 7 days before testing (28).

## IMMUNE RESPONSE TO SARS-CoV-2

The innate immune system provides the first line of defense against viral attacks. However, evidence emerging from *in vitro*, *ex vivo,* and *in vivo* animal models and human studies suggest that SARS-CoV-2 drives an inappropriate innate inflammatory response characterized by low levels of IFN I and III interferon alongside high-inflammatory cytokines, particularly IL-1RA, and IL-6 (36, 37). COVID-19 patients with mild-moderate disease

**FIGURE 1 |** Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction after illness onset. Based on [*11], [§12], [‡13], [#14], [¶15]. The figure was created with Biorender.com.

experience a low-grade innate response (38), while those with severe disease have high plasma levels of pro-inflammatory cytokines and chemokines such as IL-2, IL6, IL-7, TNF-α, G-CSF, MCP-1, MIP-1α, and IP-10 (39–41). Furthermore, upregulated chemoattractant chemokines cause the local trafficking of multiple inflammatory cells, including macrophages, natural killer (NK) cells, neutrophils, and T cells, all of which contribute to immunopathology (36). This also accounts for the well-described association between high neutrophil count and disease severity (42).

Neutralizing antibodies (nAbs) against SARS-CoV-2 are thought to be a key component of adaptive protective immunity, yet many patients who recover from COVID-19 only develop low levels of nAbs, while those with severe disease experience an early rise, suggesting a more nuanced role for nAbs, and a possible contribution to immunopathology (43). In addition to neutralization, antibody-induced complement mediated cytotoxicity is also thought to contribute to COVID-19 disease severity (43). Antibodies to both SARS-CoV and MERS-CoV wane with time, it will be important to know whether SARS-CoV-2 antibodies confer long-lasting immunity and protection. Infection with hCoVs other than SARS-CoV and MERS-CoV are

common and also induce coronavirus-specific antibodies, some of which are cross-reactive with SARS-CoV-2 but of different functional quality (44). Poor or non-nAbs antibodies may drive the antibody dependent enhancement (ADE) of disease, leading to greater disease severity on subsequent contact with the virus (45). This could hinder the development of safe and effective SARS-CoV-2-specific vaccines (46), however, ADE has not yet been described in patients suffering from COVID-19 (43).

CD4+ and CD8+ T cells are important in controlling viral infections, including SARS-CoV and MERS-CoV (47–50). Our understanding of the role of T-cell mediated immunity (CMI) in COVID-19 is only just being teased out, but a number of studies report virus-specific CD4+ and CD8+ T cells in COVID-19 individuals, particularly CD8+ T cells. These cells are mostly of an activated, and in some reports more exhausted, phenotype (51). It has been suggested that dysregulated T cell function may contribute to the immunopathology observed in COVID-19. While those with mild-moderate disease maintain their lymphocyte counts and have more polyfunctional T cells, studies variously report lower or higher cytotoxicity of CD8+ T cells in those with severe disease (51). The lymphopenia that accompanies severe SARS-CoV-2 infection (52, 53) might suggest

viral-induced suppression of CMI, although this could also be due to lymphocyte trafficking to the site of infection (51).

## CLINICAL MANIFESTATIONS AND PROGNOSIS

### Children

Several reports of COVID-19 in children have been published (13, 54–59). Children aged <18 years compromised 1 and 1.7% of US (60) and Italian COVID-19 cases (61). In a review of 171 children with COVID-19 from China, fever was present in 41.5% (54), nearly 16% were asymptomatic, and 7% had radiologic features of pneumonia with no symptoms. Although three patients required invasive mechanical ventilation, all had coexisting medical conditions and all patients recovered. In another study from China of 2,135 children with COVID-19 (34% laboratory-confirmed, 66% had suspected disease), 90% were asymptomatic or had mild-moderate disease (59), and one child died. Other smaller case series reported that most children with COVID-19 presented with fever, cough, sore throat, and a small percentage had vomiting and diarrhea (13, 55–58). The virus may persist in the stool of children but whether this is transmissible has not been shown (62). Data on 2,527 pediatric patients reported to the US CDC showed that 73% of 293 children (with data on symptoms) had fever, cough, or shortness of breath. Of 745 children in the US series with information on hospitalization, 147 (20%) were hospitalized and 15 (2%) were admitted to the ICU. Of 345 patients with information on comorbidities, 80 (23%) had at least one comorbidity with chronic lung, and cardiovascular disease most common. Three patients died (60).

Recent data from one New York City pediatric hospital revealed that 16/50 (32%) of those admitted required mechanical ventilation, comorbidity was found in 33/50 (66%), and that the most common comorbidity was obesity reported in 11/50 (22%) patients (63). Only one fatality was reported from sudden cardiac arrest that followed a period of severe hypoxemia. In this cohort, infants, and immune-compromised children did not suffer from severe disease, but the numbers were small (63). Another study on hospitalized children admitted to a tertiary care center in New York City revealed that 14/46 (30.4%) were obese, but this comorbidity was not associated with admission to the PICU, and one patient died (CFR of 2%) (64). A recent study of 46 Canadian and US pediatric intensive care units reported on 48 patients admitted during a 3-week period. Notably, only 35% of the 46 hospitals reported admissions of children with COVID-19 to the PICU, which further emphasizes that severe disease is relatively less frequent in children. In this small cohort, comorbidity was noted in 40/48 (83%), 18/48 (38%) required invasive ventilation, and the overall CFR was 4.2% (65).

A newly described inflammatory disease related to SARS-CoV-2 has recently been reported in children. It has been termed Pediatric Multisystem Inflammatory Syndrome (PMIS) or Multisystem Inflammatory Syndrome in Children (MIS-C). Reports from Europe and the U.S. describe critically ill children with fever, rash, conjunctivitis, abdominal complaints,

shock, and significant cardiac dysfunction (66–71). Several of the children described appeared to have had a history of prior SARS-CoV-2 infection several weeks earlier or have anti-SARS-CoV-2 antibodies detected. Case definitions have been developed to better characterize these patients (72). Empiric treatment has generally involved high-dose intravenous immunoglobulin (2 g/kg), steroids, and rarely more targeted anti-inflammatory medications such as anakinra (68–71).

### Pregnancy

Small case series described the clinical features in pregnant women with COVID-19 (73–75). Signs and symptoms in pregnant women were similar to non-pregnant individuals (76). Chen et al. (73) reported that all 9 women in their report with COVID-19 had cesarean sections, 2 for fetal distress, 2 for preterm premature rupture of the membranes, and one for preeclampsia. Overall, premature delivery is reported in 47% (15/32) of COVID-19 cases in pregnancy (77). Recently, a 2nd trimester miscarriage in a pregnant woman with COVID-19 was reported, with SARS-CoV-2 detected by PCR in the placenta (78).

Vertical transmission of SARS-CoV-2 to the infant is a potential concern (79–81). Some reports have not documented vertical transmission of SARS-CoV-2 (73–75, 82), others have described potential transmission (83). A report of 10 sick neonates born to women with COVID-19 had fetal distress, premature labor, respiratory symptoms, and one died, but vertical transmission was not documented (82). Small case series reported on the presence of anti-SARS-CoV-2 IgM at birth or early life in asymptomatic newborns of women with COVID-19 (84, 85). The presence of IgM in newborns suggests that it is of fetal origin. Out of 33 newborns of women infected with SARS-CoV-2 during pregnancy, three had early-onset SARS-CoV-2 infection, but their outcome was favorable and it is unclear whether they were infected in-utero or after birth (86, 87). Overall, growing evidence suggests that vertical transmission is not to be expected (88, 89).

The UK Royal College of Obstetricians and Gynecologists most recent statement published April 17 2020 recommends that antenatal care to be continued routinely, and attention for the hypercoagulable state of a pregnant woman in view of COVID-19 hypercoagulability, has to be considered, as well as the mental health of pregnant women (90). Although it was suggested that neonates should be isolated when infected (91), the WHO and several national bodies recommend isolation together with the mother. SARS-CoV-2 has not been detected in human milk and thus breast-feeding should be encouraged, although all the measures required to avoid transmission from the mother are needed.

### Adults

Early in the disease course, adults infected with SARS-CoV-2 may present with fever, alterations in taste and/or smell and mild respiratory or gastrointestinal symptoms (12, 92, 93). Later during disease, a fraction of patients may develop shortness of breath, chest tightness, and palpitations leading to hospitalization (94). Cohorts may differ for age and presence of comorbidities [mainly hypertension, diabetes mellitus, chronic

obstructive pulmonary disease [COPD], coronary heart disease, cerebrovascular disease, and malignancy] leading to variable outcomes. In fact, while a cohort of 1,099 adults with COVID-19 from China, the median age was 47 years and 25% had underlying chronic illness, a cohort of 5,700 patients (median age 63 years) from New York (USA) presented a chronic comorbidity in more than 60% and an Italian one with 1,591 patients (median age 63 years) presented at least one comorbidity in 68% (94–96). While 80% of patients of the Chinese cohort had mild disease, 15.7% had severe disease, the majority of these patients were older than 65 years and those with coexisting morbidities, and 5% were critical, requiring ventilatory or extracorporeal membrane oxygenation (ECMO) support. Another study from China concentrated on a more severe cohort of patients, of whom 54 out of 191 died (12). Nearly half of the patients had underlying comorbidities (30% of the entire cohort had hypertension and 19% had diabetes). Death was associated with older age, higher disease severity score (SOFA), and elevated blood d-dimer on admission. These findings may help to identify patients who will go on to have severe disease. Using data from 169 hospitals in Asia, Europe, and North America, independent risk factors for death were age > 65 years, coronary artery disease, heart failure, cardiac arrhythmia, and COPD (97), a finding that is supported by a recent multicenter US study (98). It has been reported that the prevalence of asthma in patients with COVID-19 is lower than in the geography-matched adults population, and it has been suggested that respiratory allergies might be associated with reduced *ACE2* expression in airway cells (41, 99). Initial data suggested that gender has also been shown to differentially affect the outcome of COVID-19 patients. A small study from China found that men with COVID-19 are more at risk for worse outcomes and death, independent of their age (100), a finding later confirmed by an interim meta-analysis (101).

Recently, it was reported that 12/38 adult patients with COVID-19 had ocular manifestations (e.g., conjunctival hyperemia, chemosis, epiphora, or increased secretions) (102). Guillian-Barre syndrome was also associated with SARS-CoV-2 infection in 5 out of 1,000–1,200 admitted patients in 3 hospitals in Italy after an interval of 5–10 days after illness onset (103). However, the causal relationship remains to be investigated. Large vessel stroke has also been reported to be a presenting symptom of COVID-19 in a small case series in young adults (104).

## Elderly

COVID-19 is severe in older individuals. Death rates have been reported as higher in Italy, Spain, and France in comparison to China, perhaps related to older populations in Europe. These countries differ in the percentages of population over 65 (the age-group most afflicted by infection, 23% in Italy) and life expectancy (e.g., 83.4 years in Italy vs. 76.7 years in China) (105). These demographic differences could partially explain why Italy has a higher overall case-fatality rate CFR (7.2%) compared with China (2.3%). Interestingly, the CFR in Italy and China are similar for age groups 0–69 years, but higher in Italy among >80 years old patients (52% of deaths, 20% CFR), and especially >90 years old (22.7% CFR) (105). However, CFR should be

interpreted with caution as it is affected by testing strategy and capacity and the number tested.

Aging is accompanied by immune senescence and the enhanced tendency to inflammation (106). The chronic increase in inflammatory cytokines may explain the higher tendency for pulmonary fibrosis and clotting dysfunction following infection with SARS-CoV-2, especially in older patients with multiple comorbidities (39, 107), which affect >60% of people >65 years of age (108). Data from 355/2003 (17.7%) Italian patients who died from COVID-19 showed that nearly 50% had ≥3 comorbidities (105). Cardio-respiratory and metabolic diseases were associated with poor prognosis (39). The use of multiple medications and the potential drug-drug interaction might increase the risk of adverse drug effects and thus require a careful evaluation.

Comorbidities, anti-viral and concomitant medication, and COVID-19 appear to be associated with hyperactive delirium, especially in hospitalized patients with pre-existing cognitive impairment (109). As suggested by NICE rapid guidelines and the Canadian Frailty Network, the assessment of all adults for frailty is highly recommended especially at hospital admission, which can guide clinicians in the decision to admit to ICU and in selecting therapeutic choices (110). A grading system has also been reported for US hospitals to provide a framework for making allocation decisions (111). However, the European Geriatric Medicine Society has stated that advanced age should not be a criterion for excluding patients from care (112).

## RADIOGRAPHIC FEATURES

Although the diagnosis of COVID-19 is based on the identification of SARS-CoV-2 by PCR, radiological findings are useful complements in the diagnosis and management of COVID-19 pneumonia. However, there is still no consensus for the use of chest radiography or computed tomography (CT) for evaluating patients with suspected COVID-19 pneumonia. The British Society of Thoracic Imaging considers chest radiography as a key decision tool for suspected COVID-19 pneumonia (113). As the predominant pattern seen in COVID-19 pneumonia is ground-glass opacification, detecting COVID-19 pneumonia on chest radiography is likely to be challenging, and is complicated by the presence of comorbidities. The Chinese experience indicates that chest CT is the preferred diagnostic modality for COVID-19 pneumonia (114). The most common CT findings of the COVID-19 pneumonia, ground glass opacification and/or consolidation, mainly reflect diffuse alveolar damage and/or organizing pneumonia, which overlap with non-COVID-19 etiologies (**Figure 2**) (114). Specificity for COVID-19 pneumonia can be increased if its peripheral distribution, fine reticular opacity, and vascular thickening is included (115). There is a correlation between the severity of pulmonary findings on CT and patients outcome (116). Thus, even if not specific, it has been suggested that chest CT could be used as a helpful diagnostic test in the emergency work up of COVID-19, complementing PCR. Chest CT had higher sensitivity for early diagnosis of COVID-19 compared with PCR (117), however, it should be
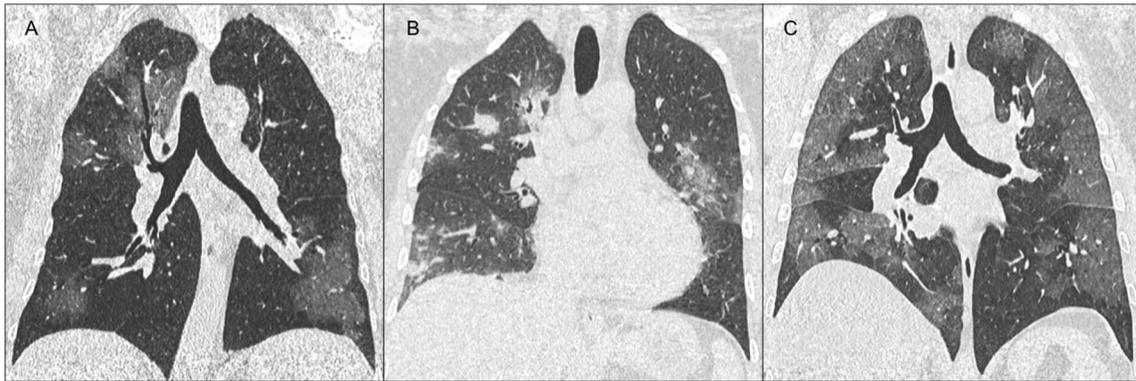
**FIGURE 2** | Representative computed tomography (CT) images of various manifestations of the COVID-19. **(A)** Coronal chest CT images show patchy ground-glass opacities involving both lungs. **(B)** Ground glass may also appear widespread, confluent, and peripherally distributed. **(C)** Consolidation and rounded nodules may be also observed in association with ground glass opacities.

reserved for patients who are not improving or who show worsening respiratory symptoms. It should be noted that 11–15% (sporadically up to ~50%) of patients may have normal chest CT scans up to 2 days after the onset of symptoms (118). The latter findings and the necessary cleaning procedures of both the CT room and personal protection equipment may challenge its integration in the routine work up of COVID-19.

# THERAPEUTIC APPROACH AND INTENSIVE CARE MANAGEMENT

## Pharmacological Treatment

Pharmacological treatment includes drugs targeting key components of the virus entry to alveolar epithelial cells or their reproduction or the host immune system (**Figures 3**, **4**). Lopinavir/ritonavir evaluated in an open label randomized controlled trial in severe cases and late-presenters (median 13 days from symptoms onset), failed to show significant improvement in virologic or clinical response compared to standard of care (140). Gastrointestinal adverse effects including nausea and diarrhea, and drug-drug interaction limit its use in older patients with polypharmacy.

Studies have suggested that the SARS-CoV-2 induces low levels of IFN I and III (36, 37). Recently, a phase-2 open label randomized controlled trial showed that early treatment (median of 4 days from symptoms onset) with the triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin was safe and highly effective in shortening the duration of viral shedding, alleviating symptoms, and reducing cytokine responses, when compared to lopinavir-ritonavir alone in mild to moderate cases (141).
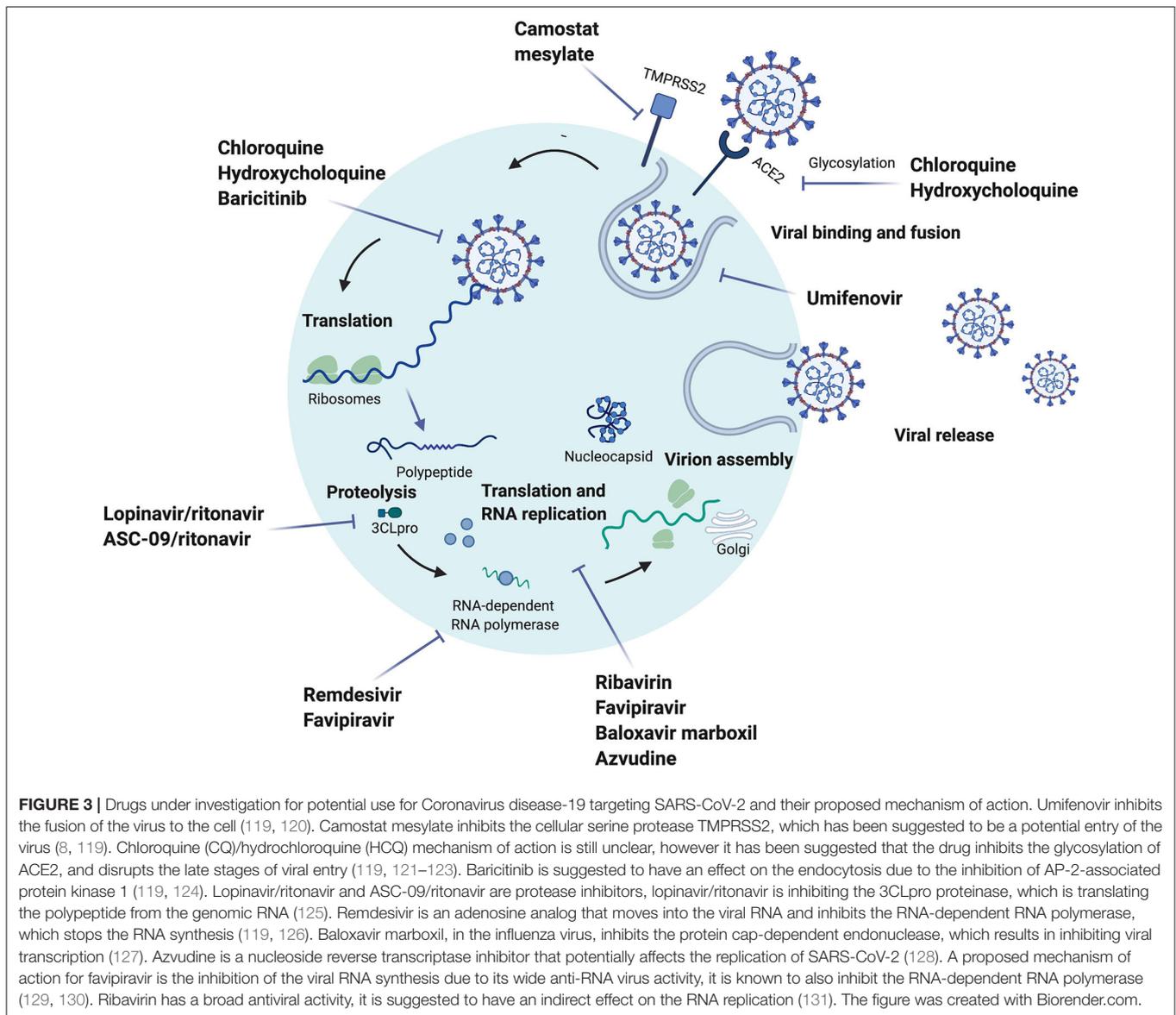
Chloroquine and its alternative hydroxychloroquine showed *in vitro* activity (142). However, available clinical data failed to show a clinical benefit of hydroxychloroquine either as treatment or prophylaxis (143–145) which was confirmed in a recent meta-analysis (146). Cardiotoxicity (e.g., prolongation of QT leading to torsades de pointes) is a well-known adverse effect of these

drugs and should be balanced (147–150). Promising results of a recent phase 2 study exploring the efficacy of a combination of interferon beta-ib, lopinavir-ritonavir, and ribavirin warrant further evaluation (141).

Remdesivir is a broad-spectrum antiviral with potent activity against RNA viruses (151, 152). It reduced viral loads in SARS-CoV-infected mice (151) and has potent *in vitro* activity against SARS-CoV-2 (53). A 10-day course has been shown to be associated with clinical improvement in 36 out of 53 COVID-19 patients (153), but the lack of control group challenges the interpretation of such data. In a recently published RCT, Remdesivir use was not associated with a statistically significant difference in time to clinical improvement compared with placebo among patients with symptom duration of 12 days or less. However, the study was stopped before reaching the pre-specified sample size challenging any definite conclusions (154). A phase 3 study did not show a difference between a 5-day course and a 10-day course but unfortunately lacked a placebo arm to determine its benefit compared to standard of care (155). However, when compared to placebo it was able to show a shortening of time to recovery (156). Tolerability is expected to be good based on its high viral selectivity. Remdesivir has been issued emergency use authorization by the FDA and is being evaluated by the EMA for a conditional marketing authorization.

Interleukin receptor inhibitors like tocilizumab and anakinra have been suggested to curb the cytokine storm (157–159). Drugs like ribavirin, favipiravir, umifenovir, nitazoxanide, darunavir/cobicistat, and IFN-beta are being investigated (157, 160).

The use COVID-19 pharmacological therapies is recommended in the context of clinical trials (143). When designing drug trials it is important to use physiologically-based pharmacokinetic (PBPK) models to select the most appropriate dose likely to be successful (142). Drugs eligible for further evaluation against COVID-19 drug lung concentrations should at least exceed *in vitro* $EC_{90}$ values (161). In addition, the timing of drug administration is another important consideration. WHO is leading a multi-country,

**FIGURE 3 |** Drugs under investigation for potential use for Coronavirus disease-19 targeting SARS-CoV-2 and their proposed mechanism of action. Umifenovir inhibits the fusion of the virus to the cell (119, 120). Camostat mesylate inhibits the cellular serine protease TMPRSS2, which has been suggested to be a potential entry of the virus (8, 119). Chloroquine (CQ)/hydrochloroquine (HCQ) mechanism of action is still unclear, however it has been suggested that the drug inhibits the glycosylation of ACE2, and disrupts the late stages of viral entry (119, 121–123). Baricitinib is suggested to have an effect on the endocytosis due to the inhibition of AP-2-associated protein kinase 1 (119, 124). Lopinavir/ritonavir and ASC-09/ritonavir are protease inhibitors, lopinavir/ritonavir is inhibiting the 3CLpro proteinase, which is translating the polypeptide from the genomic RNA (125). Remdesivir is an adenosine analog that moves into the viral RNA and inhibits the RNA-dependent RNA polymerase, which stops the RNA synthesis (119, 126). Baloxavir marboxil, in the influenza virus, inhibits the protein cap-dependent endonuclease, which results in inhibiting viral transcription (127). Azvudine is a nucleoside reverse transcriptase inhibitor that potentially affects the replication of SARS-CoV-2 (128). A proposed mechanism of action for favipiravir is the inhibition of the viral RNA synthesis due to its wide anti-RNA virus activity, it is known to also inhibit the RNA-dependent RNA polymerase (129, 130). Ribavirin has a broad antiviral activity, it is suggested to have an indirect effect on the RNA replication (131). The figure was created with Biorender.com.
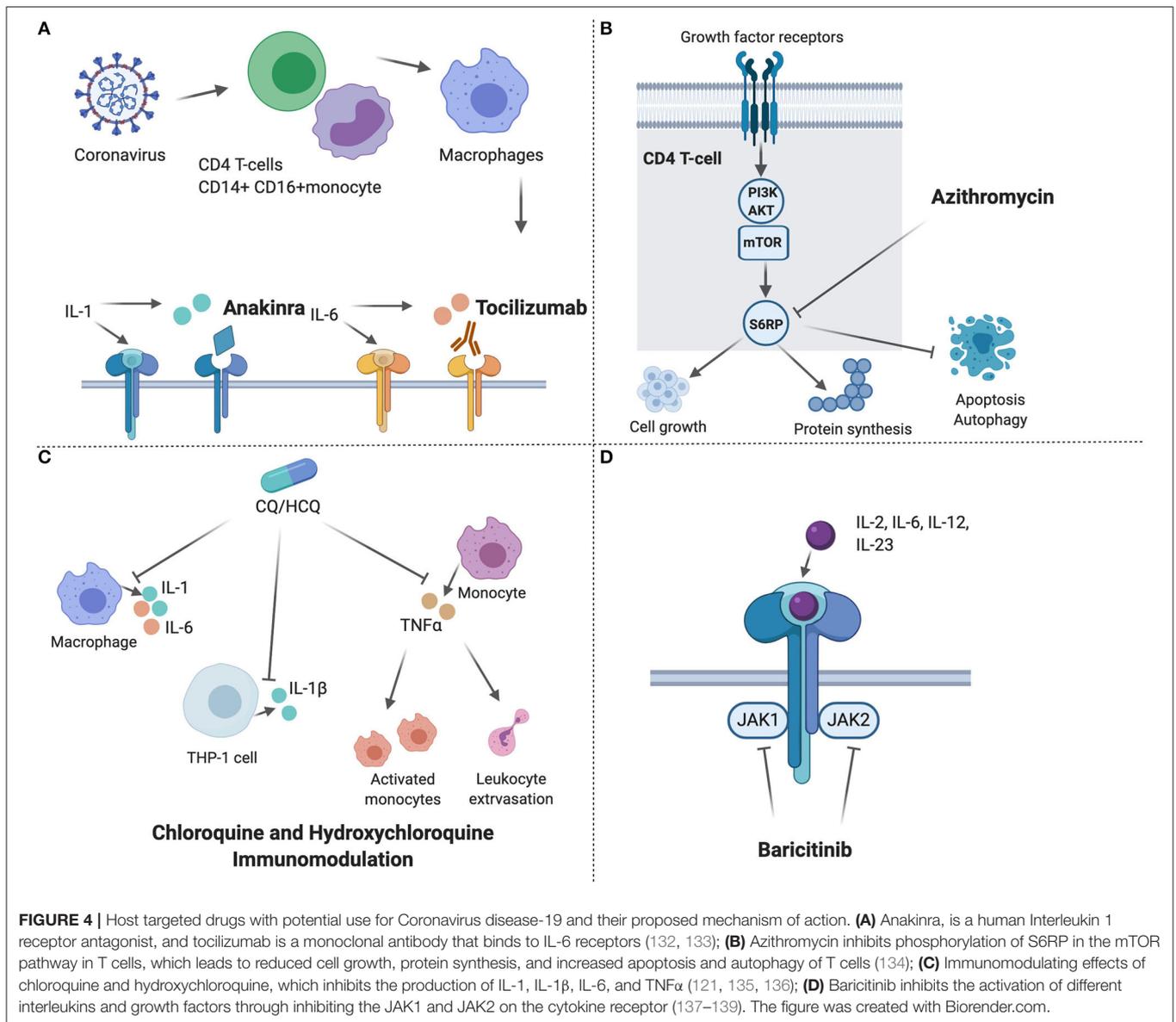
randomized trial comparing standard of care with remdesevir, lopinavir/ritonavir, lopinavir/ritonavir, and IFN-beta1a, or chloroquine/hydrochloroquine (solidarity trial).

## Intensive Care Management

The COVID-19 pandemic is having a highly significant impact on ICUs (162). Early data from China (163) reported that 5% of all COVID-19 patients required ICU admission and the CFR of patients with ARDS was 54% (164). Patients admitted to the ICUs with ARDS present with a severe form of the disease and require mechanical ventilation and 5% required ECMO. Data from Italy on 1,591 patients admitted to the ICU in the Lombardy region showed that of 1,403 patients with available data on comorbidity, 709 (68%) had at least one comorbidity and 509 (49%) had hypertension. Patients older than 64 years old had a

higher mortality rate than patients younger than 63 years old, 36 vs. 15%, respectively (96).

The Surviving Sepsis Campaign recommendations provide guidance on the management of adults with COVID-19 in the ICU and these guidelines grade the evidence and provide best practice statements where evidence is lacking (165), such as: the use of fit-tested FFP2 respirators for personal protection of healthcare workers, the use of negative pressure rooms for patients having aerosol generating procedures, and the performance of endotracheal intubation by experienced personnel to avoid nosocomial spread of SARS-CoV-2. Areas where no recommendation was made include the use of helmet non-invasive ventilation or the therapeutic use of antivirals, chloroquine or hydrochloroquine, interferon gamma, anakinra, and tocilizumab. One important area of controversy is the use of corticosteroids for ARDS. Although steroids have been

**FIGURE 4 |** Host targeted drugs with potential use for Coronavirus disease-19 and their proposed mechanism of action. **(A)** Anakinra, is a human Interleukin 1 receptor antagonist, and tocilizumab is a monoclonal antibody that binds to IL-6 receptors (132, 133); **(B)** Azithromycin inhibits phosphorylation of S6RP in the mTOR pathway in T cells, which leads to reduced cell growth, protein synthesis, and increased apoptosis and autophagy of T cells (134); **(C)** Immunomodulating effects of chloroquine and hydroxychloroquine, which inhibits the production of IL-1, IL-1β, IL-6, and TNFα (121, 135, 136); **(D)** Baricitinib inhibits the activation of different interleukins and growth factors through inhibiting the JAK1 and JAK2 on the cytokine receptor (137–139). The figure was created with Biorender.com.

recommended for patients with ARDS (165), their use should be individualized and is preferable in settings with clinical trial capacity (143, 166). ARDSNet guidelines recommend against the routine use of corticosteroids in patients with ARDS. However, the recent SSC COVID-19 guidelines recommend their use in COVID-19 patients with ARDS (weak evidence) although without full agreement from all panel members. Guidance for the management of critically ill adults with COVID-19 is outlined (**Panel 1**).

## PUBLIC HEALTH RESPONSE

### Case Definition

The initial WHO case definitions for COVID-19 consider suspected, probable, and confirmed cases and requests national authorities to report both probable and confirmed cases (**Panel 2**). Case-based reporting is done daily, and aggregated data are sent to the WHO on a weekly basis. Selected health conditions, which may predispose people to COVID-19 (e.g., pregnancy, cardiovascular diseases, and immunodeficiency) are reported, and whether the patient is a health care worker.

The case definitions are established to verify that individuals with the highest risk of acquiring the disease are tested. This helps in providing early isolation and avoids further transmission of SARS-CoV-2. History of exposure is reported to document transmission patterns in the communities and 14 days is considered as the incubation period to cover a relatively large confidence interval (168). Therefore, history of travel in the last 14 days and the list of country/countries where the individual is traveling from are also reported. Once community transmission has been documented, case definitions require modification and should be based on the most common symptoms. It was recently

**PANEL 1 |** Recommended management of patients admitted to intensive care unit with Coronavirus disease-19.

- Indication for admission is severe respiratory failure due to pneumonia and acute respiratory distress syndrome with or without shock.

- If the patient is not intubated, perform a trial with non-invasive mechanical ventilation* (preferred option) or high-flow nasal cannula (alternative option, if non-invasive mechanical ventilation is not available) (4–6 h). HFN is preferred due to its better tolerance.
- If the patient does not respond, intubate the patient by skilled personnel with maximal precautions.
- Obtain an endotracheal aspirate for bacterial and fungal stains and culture and for PCR viral detection.

- Use protective mechanical ventilation according to Surviving Sepsis Campaign (SSC) recommendations.
- Use prone position if the patient has a PaO2/FiO2 ratio equal or lower than 100 (12 h minimum).
- Consider ECMO when refractory hypoxemia despite prone position.
- Manage shock according to SSC recommendations.

- In patients with ARDS administer prednisone or methyl prednisolone (SSC, weak recommendation).
- In patients with persistent high D-dimer levels (>3,000 U/mL) consider anticoagulation and rule out pulmonary thromboembolism.
- Do not withhold antibacterial treatment.
- Continue or change anti-COVID-19 treatment according to hospital protocols and published evidence.

*Non-invasive mechanical ventilation with Helmet commonly used in intensive care units in Italy.*

**PANEL 2 |** World Health Organization Coronavirus disease-19 (COVID-19) case definitions (as updated March 16, 2020).

**Suspect case:**
A patient with acute respiratory illness [fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness of breath)], AND with no other etiology that fully explains the clinical presentation AND a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days prior to symptom onset.
**OR**
A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID- 19 case in the last 14 days prior to onset of symptoms.
**OR**
A patient with severe acute respiratory infection (fever and at least one sign/symptom of respiratory disease (e.g., cough, shortness breath)) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

**Probable case**
A suspect case for whom testing for COVID-19 is inconclusive (as reported by the laboratory).

**Confirmed case**
A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs, and symptoms.

*Based on World Health Organization case definition (as updated March 16, 2020) (167).*

shown that the prevalence of SARS-CoV-2 among patients that would have missed risk-based testing was ~5% among adults with flu-like symptoms in California (169).

**PANEL 3 |** Infection control and containment measures considerations specific for SARS-CoV-2 infection.

- The capacity of SARS-CoV-2 to survive up to several hours on surfaces requires careful disinfection measures and additional hygiene precautions (e.g., wearing gloves for exposed individuals, washing hands frequently, preventing contact of hands with mouth, and eyes) (179).

- The specific features of SARS-CoV-2, which spreads very rapidly with a short incubation time as to infect exponentially thousands of individuals in all age groups (162), calls for the implementation of specific containment measures.

- The containment approach is usually based on case isolation and quarantine (which includes contacts) in early stages, with contact tracing of infected individuals. More stringent measures to limit the speed of the infection curve and to ensure a more diluted pressure on health services include social distancing (e.g., keeping at least one meter between individuals), limitations of internal movement and reduction of social activities, including a "stay home" approach (e.g., home-work encouraged, movement allowed for essential services/medical needs/food purchasing), closure of schools, bar, restaurants, cinemas, and similar activities, and in some cases closure of borders and creation of isolated "red zones" (179, 180).

- Prompt and adequate communication to the general public and training of health care workers are essential components of the COVID-19 response.

## Infection Control

Traditionally, infection prevention and control principles are based on a hierarchy of administrative, environmental, and personal protective measures (masks for infectious patients and respirators for airborne agents to protect health care workers and visitors) (170). This approach has been well-summarized for tuberculosis (170), but has also been suggested for COVID-19 (171, 172). While N95/N99/FFP2/FFP3 masks are recommended to protect health care workers and other exposed individuals in the workplace, there is debate on the use of surgical masks (173, 174). Although there is agreement on the use of surgical masks to limit the spread of droplet nuclei for symptomatic patients under isolation, there is an ongoing dialogue for the potential mass use of surgical masks to limit the community spread of COVID-19 in early stages infection and from asymptomatic individuals (171–175). Arguments against this have been raised, based on the potential false sense of protection this can generate and the potential risks of moisture retention, long mask re-use, and limited filtration capacity (176). Studies performed on influenza confirm that surgical masks are up to 3 times more effective in reducing droplet transmission than home-made masks (176, 177). The interim WHO guidance (5 June 2020) on the use of masks in the context of COVID-19 states that the use of masks by healthy people in the community is not supported by high quality evidence. However, governments should encourage the general public to wear masks in specific situations and settings (178). Specific infection control considerations for COVID-19 are detailed in **Panel 3**.

## Country-Specific Responses

On March 18 2020, the WHO Regional Office for Europe issued a statement (181) summarizing the situation of Europe as under the "Four Cs" scenarios of the outbreak: (1) no

case; (2) first case; (3) first cluster; and (4) first evidence of community transmission. The pandemic is progressing at different speeds and at different times in different countries, depending on demographics and other factors (e.g., population mixing, migration, and international travel). However, the basic actions to be undertaken under each scenario are the same. These include strict measures to interrupt human-to-human transmission including active case-finding followed by rapid diagnosis and isolation with immediate physical distancing and travel-related (e.g., travel restrictions and border closure) measures (182, 183).

Surveillance is critical in understanding the progression of the pandemic. Rapidly establishing sensitive surveillance and widespread testing ensures that cases are identified promptly and effective contact tracing is in place in the early stages when there are only a small number of cases. As the outbreak progresses, seroprevalence studies can help in estimating infections in communities, the extent of spread of asymptomatic transmission, the role different age groups might be playing in enhancing transmission, and the acquisition of population immunity.

The WHO recommended that countries: (1) prepare and be ready; (2) detect, protect, and treat; (3) reduce transmission; and (4) innovate and learn, while protecting vulnerable people. Herein, we describe public health responses and lessons learned from several countries identified because of the caseload, the strategic importance, and direct experience within the writing committee.

## China

After the major outbreak was recognized, the city of Wuhan was cordoned off on January 23 2020 (184). However, around 5 million people had already left Wuhan during the peak transport period before the Chinese New Year. An extreme form of social distancing and compulsory mask-wearing in public places were undertaken all over the country to block human-to-human transmission (173, 185). These measures appeared to eliminate most of the transmissions with unclear links in the community, and many of the subsequently observed cases then appeared in clusters, mostly involving families (76). Intensive case-finding and isolation were undertaken together with contact tracing and quarantine of contacts and other high-risk groups using big data and artificial intelligence. The spread of COVID-19 was rapidly brought under control outside the province of Hubei, allowing for the staged resumption of essential economic activities with modification of the work process and environment to minimize person-to-person contact.

More than 1,800 health care workers were infected in Hubei, mostly occurring early in the overwhelmed hospitals with severe shortages of personal protective equipment in Wuhan (76). Successful confinement of massive outbreaks of COVID-19 to Wuhan and other cities of Hubei allowed for the timely channeling of disaster response capacity of the country to these seriously affected areas. Hospital capacity was rapidly expanded with reinforced manpower and personal protective equipment to accommodate all patients with severe disease. New intermediate care facilities were rapidly constructed and manned by rescue teams from other parts of the country to care for the much

larger number of patients with milder disease. Effective triage of patients according to their treatment needs maximized the health care capacity and throughput to accommodate all subsequent patients in an environment safer for themselves, their families, the health care staff, and the community.

## Italy

The epidemic in Northern Italy took place about 4 weeks after that in China, while other European countries followed Italy with a delay of 7–10 days. Italy started creating a closed "red zone" around the municipalities initially experiencing the outbreaks. The "red zone" was then extended to entire Regions (Lombardia, Veneto, part of Emilia Romagna) and then to the entire country. Movement restrictions, closure of schools, and other social aggregation sites were implemented early, although people's compliance was suboptimal initially. An extraordinary effort was conducted to increase the number of ICU beds and to procure masks, respirators, and ventilators, which, in the early phases, were lacking. The response was coordinated by the Civil Protection which is well-organized in Italy to ensure a rapid response to earthquakes. The situation has improved significantly since the end of March 2020.

Several countries followed this approach while others followed slightly different ones (**Table 1**).

## Other Experiences

The UK response has been based on (186) (1) contain (detect early cases, follow-up close contacts); (2) delay (slow the spread, lower the peak impact); (3) research; and (4) mitigate (provide the best care for cases, support hospitals to maintain essential services, ensure ongoing support for ill people in the community, and minimize the impact of the disease on society, public services, and economy). Early on it was thought that by "slowing spread" rather than "suppression," the peak could be pushed into the summer when there is less pressure on the health service. However, it became clear that this approach was not going to be successful given the level of spread already within the population. Thus, the government rapidly moved to a strategy of "suppression" in line with the responses of other countries. The study that predicted that the National Health Service would be overwhelmed if a mitigation strategy continued was pivotal in the change of the UK approach (187). This approach raised discussions in the UK and beyond (188).

In Sweden, travels were discouraged but not prohibited, schools partially closed, bars and restaurants continued to operate. Sweden has chosen one of the most liberal approaches seen in Europe, with many measures being of a suggestive, recommended, or non-compulsory character. This approach differs from that of other countries in Europe, and was associated with a relatively high cumulative case incidence and mortality. After 4 months from the epidemic onset, the overall mortality rates are approaching normal levels in most of the affected countries, following a period of a substantial excess mortality, which was also observed in UK, Italy, Spain, and Belgium.

In the US, testing became free for all on March 16 2020 but, initially, there were limited numbers of tests available. Movement of individuals was discouraged while domestic travel

**TABLE 1** | Country specific non-pharmaceutical public health interventions.

| Country | Domestic lockdown/closure of borders | Travel restrictions (internal) | Schools/Universities closed | Mass gatherings prohibited | Sport events stopped | Restaurants/bars/pubs closed | Other |
|---|---|---|---|---|---|---|---|
| Argentina | All country: March 16 | All country: March 19 | All country: March 19 | All country: March 19 | All country: March 19 | All country: March 19 | Initial compulsory quarantine for all citizens till June 7; some flexibility since May 24 in less affected areas |
| Australia | Partial: February 1 Total: March 20 | Australians must avoid all non-essential domestic travel. March 22 | Schools closed March 24–30; don't bring kids to school, only kids allowed of critical professions. Universities open but all face to face teaching online since March 23. | >500 since March 13 >100 since March 17 >2 since March 20 (exemption for specific situations; wedding 5, funeral 10) | Sport events stopped related to >500 participants March 15 Grand Prix Melbourne | Restaurants/bars March 22; expanded restrictions for other businesses on March 26 | Gradual reopening since May 15 |
| Austria | All country: March 16 | Partial: March 11 | All: March 16 | All: March 16 | All: March 16 | All: March 16 | Easing of lockdown as of May 1; restaurants can reopen on May 15 and hotels on May 29 |
| Belgium | All country: March 16 | All country; March 16 (but ongoing if parents work) | All country: March 16 | All country: March 16 | All country: March 16 | All country: March 16 | EU parliament in video-conference, economic support package. Easing of lockdown rules as of May 18 |
| Brazil | Partial: March 18 All country: March 30 | Partial: March 17 | Partial: March 16 | Partial: March 13 | All country: March 16 | Partial: March 18 | "Stay home" recommended but not compulsory; Restrictions differ from state to state; some flexibility in less affected areas |
| Canada | Partial: March 16 | Not yet | Partial: March 16 | Partial: March 16 | Partial: March 16 | Not yet | Some provinces begin to slowly relax lockdown restrictions as of May 4 |
| Chile | All country: March 17 | 90 Sanitary checkpoints throughout the country limiting travel of ill individuals between specific areas: April 1 | All country: March 16 | All country: March 20 | All country: March 20 | All country: March 20 | Alternating quarantines of communities/cities beginning March 25 National emergency declared March 18 Lockdown from May 15 in the capital and metropolitan region |
| Denmark | All country: March 11 | All country: March 11 | All country: March 11 | All country: March 11 | All country: March 11 | All country: March 11 | Gradual reopening from April 15 (some private primary and secondary schools) May 11 (additional primary schools, shops) Phase 3 (from June 8): Almost all remaining blocking restrictions in the country will be removed |
| EU | Closure of external borders: March 17 | Internal circulation of essential good encouraged by the EU authorities | Recommended | Recommended | Recommended | Recommended | No official document on heath measures |

*(Continued)*

**TABLE 1 |** Continued

| Country | Domestic lockdown/closure of borders | Travel restrictions (internal) | Schools/Universities closed | Mass gatherings prohibited | Sport events stopped | Restaurants/bars/pubs closed | Other |
|---|---|---|---|---|---|---|---|
| France | Partial; early March All country: March 17 | Partial: early March All: March 17 | All: March 16 | All: March 16 | All country: March 16 | All country: March 16 | Second round of voting canceled. The second round of local elections has been suspended, along with the government's reform agenda Gradual reopening from May 11 (primary schools and most businesses); lockdown measures will be further eased from June 2; Paris and its surrounding region will have a more gradual reopening |
| Germany | Local: mid-March (initial areas affected) All Country: March 16 | All country: March 16 | Partial: March 13 All: March 16 | All: March 16 | All country: March 16 | Partial country: March 16 | "Landers" to decide when limiting closing bars/restaurants Gradual reopening from April 20 (commercial spaces under 800 sq meters, car dealerships, bike shops, and book stores); some schools gradually open from May 4; no big groups and no meeting with multiple people from different households until June 5 |
| Hong Kong | Most borders with Mainland China: February 8 | Quarantine +/– refusal of entry for selected country or epidemic areas: late February to early March Delay all non-essential: March 6 Quarantine: Europe—March 17 All countries: March 19 Refusal of entry or transit of non-Hong Kong residents: March 25 | All schools and universities closed: January 29 | Advice against gatherings: late January Prohibit public gatherings > 4 persons for 14 days: March 29 | Major sport events stopped: late January | Strong advice against large dinner gatherings: late January Seating < half capacity; tables 1.5 m apart; not > 4 persons per table; mask when not eating; alcohol sanitizers and temperature check for 14 days: March 28 Progressive closure of entertainment facilities for 14 days: March 28 to April 1 Closing bars and pubs: April 3 | Advice to stay home if possible and self-initiated masking in public places: late January Stopping non-essential government services and civil servants working at home if possible: 29 Jan to 1 March and again from 23 March Gradual reopening from May 4 |
| Italy | Partial: February 24 All country: March 8 | Partial: February 24 All country: March 8 | Partial: February 24 All country: March 8 | Partial: February 24 All country: March 8 | Partial: February 24 All country: March 8 | Partial: February 24 All country: March 8 | Economic support package Gradual reopening from May 4 |

*(Continued)*

**TABLE 1** | Continued

| Country | Domestic lockdown/closure of borders | Travel restrictions (internal) | Schools/Universities closed | Mass gatherings prohibited | Sport events stopped | Restaurants/bars/pubs closed | Other |
|---|---|---|---|---|---|---|---|
| Mexico | Partial: March 20 (with USA) | Not yet | Partial: March 17 (some private schools and some universities) All country: March 20 | March 24 | March 16 (soccer matches) | Partial: many closed by not mandatory at the federal level | Body temperature check at mass gathering/airports March 23: maintain the healthy distance 16 March: all workers from the federal government non-essential activities were stopped, home work was suggested Gradual reopening from May 18 (for hundreds of counties) and from June 1 (the rest of the nation) |
| Netherlands | Not yet. Belgium closed the border | Partial: March 16, asked not to leave the country Since April 9, 14 days quarantine if return from specific countries/places | Yes, since March 16. Universities closed until September | All country: March 16 | All country: March 16 | All country since March 16. | Churches with Max 30 persons (funerals). Gradual reopening from May 11 |
| Norway | All country: March 16 | All country: March 20. (Exceptions for special services allowed). | All country: March 12 | All country: March 16 | All country: March 16 | Restaurants Partial Bars closed. March 16. | Gradual reopening from April 20 (kindergartens and some health specialists); Partial reopening of high schools and universities, hair, massage, and beauty salons from April 27; major events canceled through at least June 15. |
| Poland | All country: March 14 | Partial: March 14 | Partial: March 14 | Partial: March 14 | Partial: March 14 | Partial: March 14 | Gradual reopening from April 20 (parks, forests); from May 4 (hotels, shopping centers, and cultural institutions); from May 6 (nurseries and preschools); elections on May 10 canceled; from May 28 (restaurants, salons, and sports facilities) |
| Portugal | Not yet | Partial: March 13 | All: March 13 | Partial: March 13 | Partial: March 13 | Not yet | Gradual reopening from May 4 (medical and dental clinics, hair salons, small shops); from May 18 (bars, cafes, restaurants, daycare centers, museums, palaces, national monuments, art galleries, and high schools for senior students) |
| Russian Federation | All country: March 16 | Partial, from some countries | All: March 21 | Not yet | Not yet | Not yet | Contact tracing (contacts of test positives) Easing of restrictions from May 11 |
| Spain | All country: March 16 | All country: March 16 | All country: March 16 | All country: March 16 | All country: March 16 | All country: March 16 | Gradual reopening from May 4, with four phase de-escalation measures depending on the on-going progress across the different regions |
| Sweden | Partial: March 17 (traveling highly discouraged) | Partial: March 16 Partial: March 19 (Internal travel discouraged not forbidden) | Partial: March 16 (high schools and universities only; not compulsory education) | All country: March 16 (>500 persons) | All country: March 16 | Not yet | Economic support package. Stay home policy recommended March 16. |

*(Continued)*

**TABLE 1** Continued

| Country | Domestic lockdown/closure of borders | Travel restrictions (internal) | Schools/Universities closed | Mass gatherings prohibited | Sport events stopped | Restaurants/bars/pubs closed | Other |
|---|---|---|---|---|---|---|---|
| Switzerland | All country: March 16 | All country: March 16 | All country: March 16 | Partial: March 16 | All country: March 16 | All country: March 16 | Gradual reopening from April 27 (some shops, hair-dressers); from May 11 (primary and lower secondary schools, restaurants, museum, libraries, sports facilities) |
| United Kingdom | All country: March 23 | Reduction of social activities recommended (March 16) All country: March 23 | All: March 20 | All country: March 20 | All country: March 20 | All country: March 20 | "Stay home" recommended 20 March but not compulsory Lockdown started on March 23; easing of lockdown measures from May 13 |
| United States of America | All country: March 16 | Partial: March 16 | Partial: March 16 (e.g., New York) | Partial: March 16 (>50 persons) | Partial: March 16 | Partial: March 17 (e.g., New York) | Free cost testing from March 16 At the end of March, 42 states were under stay-at-home orders Restrictions differ from state to state; States are reopening differently, starting with Alaska from April 24 |

*All dates refer to the year 2020.*

was still allowed. Massive testing was performed in the US and strict quarantines were imposed in large cities with different approaches from State to State (**Table 1**).

## FUTURE PERSPECTIVES

The future pandemic course will depend on the early implementation, massive diagnosis, and contact tracing/isolation in addition to broad restrictions leading to significant and prolonged physical distancing. Nevertheless, considering that sufficient population immunity will be required to definitely control the virus in the upcoming years (unless it were to mutate to a less virulent, competing virus), which will require several years of manageable levels of viral infection, introducing, and retreating social restrictions proving most effective, can be envisioned for the near future [187]. Fast track drug development and repurposing of available drugs should be informed initially by *in vitro* data to support activity, PBPK data to inform dose selection, and well-designed, prospective randomized-controlled trials powered to detect a clinically meaningful outcome.

Safe and effective vaccines would be the most suitable solution generating the required population immunity to stop virus circulation. Vaccine development is in progress, both by pharmaceutical companies and research institutions. On the website of the WHO, a draft landscape of a growing number of COVID-19 candidate vaccines can be found. Most vaccines are still in the preclinical phases of the development, but some of them are already in Phase I clinical trials [189, 190]. Previous preclinical studies with vaccine candidates for SARS and MERS demonstrated the induction of neutralizing antibodies, but a possibility for enhanced disease had been seen in some vaccinated animals after challenge with the wild-type virus [191], and in experimental models [191, 192]. Potential vaccines will need to be carefully studied, the duration of immunity assessed, and the potential for enhanced vaccine disease will need to be carefully evaluated over time. Importantly, from here on, the inevitable threat of new emerging coronaviruses [193] will have to be confronted earlier. China acted well, but too late, and the virus spread in weeks to the rest of the world, which in turn also acted too late, with few exceptions; and some countries continue to do so. Preparing for new events will require coordinated efforts between epidemiologists, clinical and basic science researchers, and artificial intelligence experts; the time is now. Hot spots for new coronavirus emergence need to be monitored continuously to detect severe human cases very early on. In this new post COVID-19 era, transparency and collaboration will be critical to confront future pandemic threats.

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