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Summary of the coronavirus disease 2019 (COVID-19) update from the 2020 Conference on Retroviruses and Opportunistic Infections, 8–11 March 2020, Boston, USA

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Introduction

The annual Conference on Retroviruses and Opportunistic Infections (CROI) brings together top basic, translational, and clinical researchers from around the world in the ongoing battle against HIV/AIDS and related infectious diseases. CROI 2020 was held 'virtually' for attendees from March 8 to March 11, 2020.

Special session: SS1

Several speakers took part in this special session consisting of web-based presentations on the recent new coronarovirus outbreak at the latest CROI conference. The first presentation was by John T Brooks (Centers for Disease Control and Prevention [CDC], Atlanta, USA) who described the coronavirus disease 19 (COVID-19) global epidemiology and prevention. COVID-19 disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is genetically more closely related to SARS-CoV than MERS-CoV, two human coronaviruses (HCoVs) with high pathogenicity.

SARS-CoV-2 appears to have been first recognised as the cause of human illness in late 2019, even though we do not yet definitely know the exact date and place of its first detection. It is likely to involve a cross-species transmission from an animal reservoir such as bats. Most, but not all, of the early cases were linked to a wet market in the city of Wuhan in Hubei province [1]. Cases in early 2020 were diagnosed in people with no known exposure to this market and had presumably been infected through person-to-person contact which amplified the outbreak.

Epidemiologists increasingly use modelling to better understand where an infectious disease outbreak may arise on a global scale in order to assess the contextualised risk and vulnerability index of each country, and to strategically direct and preposition preparedness and response resources [2]. Although modelling can be helpful, widespread and rapid dissemination in our hyperconnected world, as was seen with COVID-19, creates real-time challenges for these analyses. As of 4 March 2020, COVID-19 had spread worldwide with remarkable speed and large foci had developed outside China, in Italy, South Korea, Iran, Japan, as well as on the Diamond Princess Cruise Ship (Figure 1, [3]). On 25 February, reported cases outside China exceeded those reported in China, and as of 04 March reported deaths outside China exceeded those reported in China (Figure 2) [3].

In terms of clinical epidemiology, there is no particular set of signs or symptoms that can reliably discriminate COVID-19 from other respiratory viral illnesses, including influenza. The median incubation period is currently estimated to be 4–6 days (range 2–14) with most people recovering spontaneously with the help of supportive care. However, severe complications, including pneumonia as well respiratory and multiorgan system failure may lead to death [4–7].

In terms age distribution of persons affected by COVID-19, data from the largest China surveillance report to date shows that most of them are middle-aged adults [8]. More recent data suggest that children are as equally susceptible to COVID-19 as adults [9], but Chinese paediatric cases were probably under reported because of milder symptoms than adults and therefore decreased likelihood of children presenting for clinical care or if they had come to care they may not have been recognised as having COVID-19 [8]. Adults aged >60 years experience a more severe COVID-19 illness and are more likely to die, as reflected by case fatality rates (CFR) [8]. A number of factors can affect the CFR, such as the geographical location, local healthcare systems, group of persons affected by COVID-19, number of people tested and the efficiency of diagnosis and management of COVID-19. The most seriously ill people with the highest risk of death tend to be tested first in disease outbreaks. As more persons with less severe disease are tested, the increasing number of cases diagnosed include more survivors and therefore the CFR decreases. The number of deaths depends on how quickly an illness is recognised and the quality of its management, and increases when there is insufficient life-sustaining supportive care. All things considered, the CDC's current best estimate of COVID-19 CFR lies between 0.5 and 3.5% as compared with seasonal influenza of about 0.1%, suggesting that it might be 5–35 times more deadly. However, the presenter stated that most COVID-19 illnesses tended to be mild and generally patients recovered spontaneously with some level of supportive care, especially children and middle-aged adults.

Respiratory secretions are the main mode of COVID-19 transmission through respiratory droplets. Transmission from people who are pre-symptomatic or have asymptomatic infection is possible, but its contribution to the overall number of infections appears to be small at this time. The amount of viral shedding from the respiratory tract is greatest at the time of symptoms and then declines. High-risk groups include people with medical comorbidities and older people, who are at increased risk for severe illness and death (CFR>5%, with diabetes, cardiovascular disease or chronic respiratory disease). No data are yet available for people who are immunocompromised due to medical treatment, or people living with HIV. Pregnancy data seem reassuring with a similar mortality rate between women with and without COVID-19.

Ralph S Baric (University of North Carolina Chapel Hill, USA) presented virological insight to coronaviruses (CoV). These viruses have a long history of cross-species transmission, starting around 100–800 years ago, with four major coronavirus-related events emerging in the last 20 years, including SARS-CoV in 2003, MERS-CoV in 2012, a swine acute diarrhoea syndrome coronavirus (SADS-CoV) in 2012 and SARS-CoV-2 in recent months. Major

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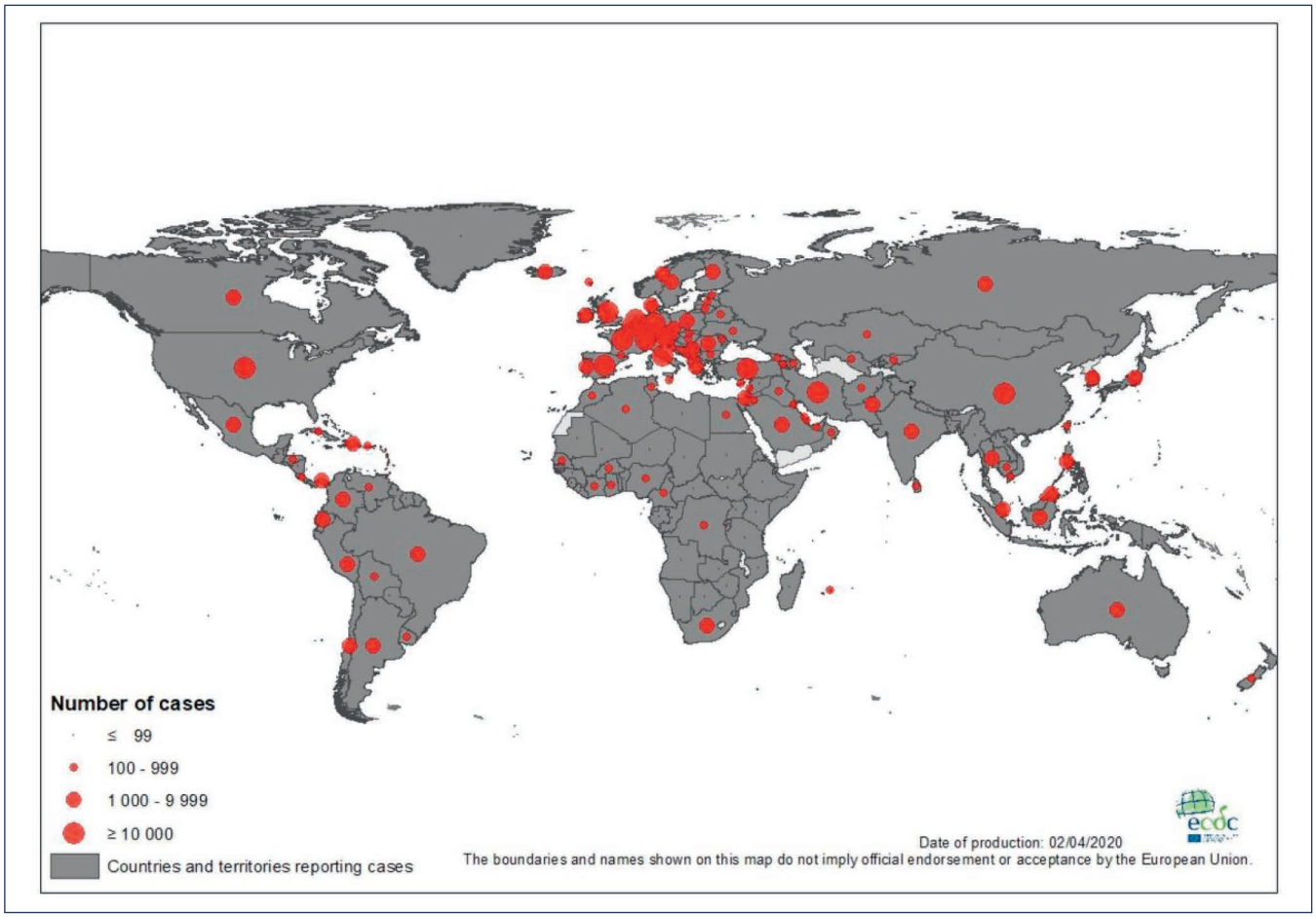

Figure 1. Geographical distribution of COVID-19 cases worldwide. Source: European Centre for Disease Prevention and Control [3].

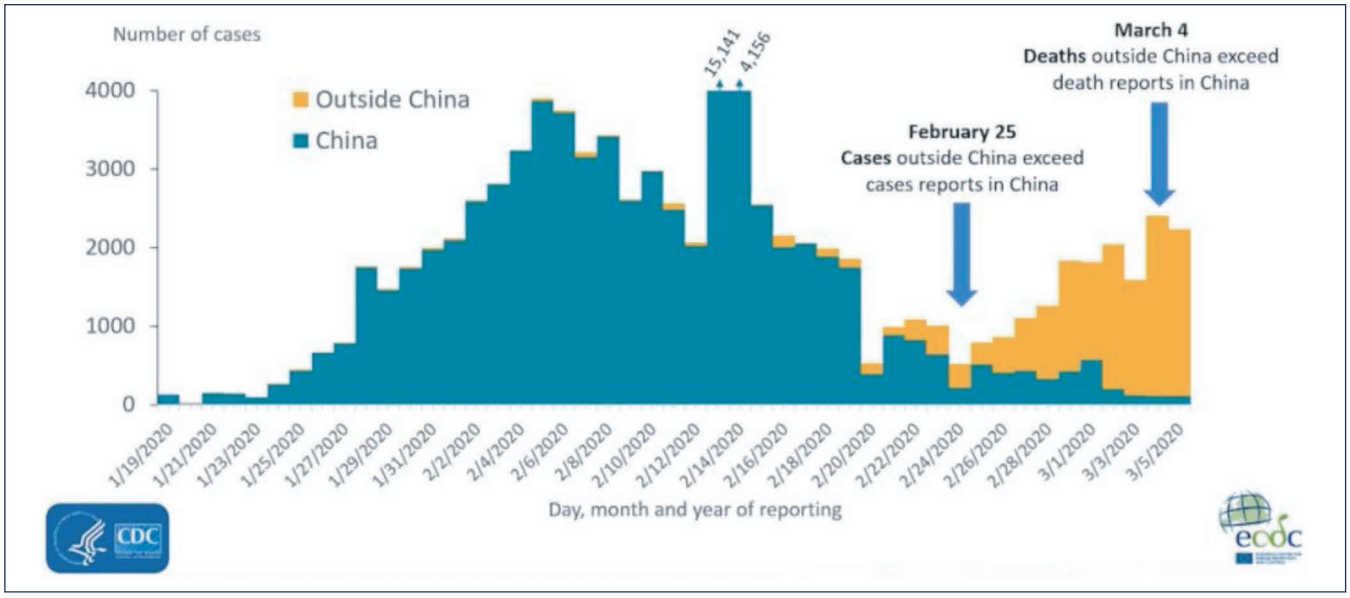

Figure 2. Distribution of COVID-19 cases in accordance with the applied case definitions in the affected countries, as of 05 March 2020. Source: European Centre for Disease Prevention and Control [3].

drivers of CoV evolution include a mutation rate influenced by environmental changes, high rates of RNA recombination, as well as surface glycoprotein plasticity.

The mechanism by which SARS-CoV emerged in 2002 in China provides insight for SARS-CoV-2. The closest relative to SARS is a bat virus called WIV-16 which is about 97–98% identical to the epidemic SARS strains. Bat viruses were either transmitted directly from these animals to humans, or alternatively via civets as intermediate hosts. Dr Baric's hypothesis is that most emerging viruses pre-exist as large heterogeneous pools of related viruses (pre-pandemic strains) in bats that can display spike glycoprotein variation by up to 35% and then emerge from zoonotic reservoirs to infect humans and cause a large number of cases globally. SARS-CoV-2 is about 78% identical to the original SARS-CoV that emerged in 2003. Both belong to the known group of 2B

Table 1. Updates and comparisons of SARS-CoV-2 and SARS-CoV and MERS-CoV

Characteristics	Coronavirus		
	SARS CoV	MERS CoV	SARS-CoV 2
Outbreak period	2003–2004	2012–present	Dec 2019–present
Initial site of isolation	Guangdong province, China	Saudi Arabia	Wuhan, China
Countries (*n*)	29	27	178*
Cases (*n*) (mortality)	8096 (9.6%)	2494 (~34%)	952 171* (3.4%)**
Reservoir (intermediate host)	Bats (palm civet)	Bats (dromedary camels)	Bats (likely a zoonosis)
Incubation period (days)	2–7 (range 2–21)	2–7 (range 2–14)	2–14 (mean 5–6)
Infectivity, rho (number of patients infected from one individual)	1.8–2.5	0.3–1.3	3 (2.4–3.8)
Super spreaders	Yes	Yes (common)	Yes (many examples)
Asymptomatic/mild	No	Rare	Yes/yes

Adapted from presentation by RS Baric. (Datasources: WHO, CDC, ECDC, NHC, DXY, 1point3acres, Worldometers.info, BNO, state and national government health departments, and local media reports).
* Number of cases updated from Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University as of April 2nd, 2020 at 1:40 pm [15].
** Datasource: WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020 [10].

SARS-like CoV poised for human emergence. They use human hACE2 receptor for entry and can grow in primary human airway epithelial cells causing an acute respiratory distress syndrome with an age-related disease severity. When the spike glycoprotein variation rate reaches about 10% these viruses can escape existing immune therapeutics (hmAb) or vaccines developed for previous CoV.

Table 1 shows updates and comparisons between SARS-CoV-2 and SARS-CoV and MERS-CoV. The average mortality rate globally is around 3.4% with age-stratified mortality rates: 14.8% for those aged >80 years, 8.0% for those aged 70-79 years, 3.6% for those aged 60–69 years, 1.3% for those aged 50–59 years, 0.4 for those aged 40–49 years, 0.2% for those aged 10–30 years and 0% for those aged 0–9 years [10]. These age and comorbidity statistics were provided by two sources: Report of the WHO-China Joint Mission published on 28 February by the World Health Organization (WHO) [11], which is based on 55,924 laboratory confirmed cases and an article by the Chinese CDC released on 17 February 2020, which is based on 72,314 confirmed, suspected, and asymptomatic cases of COVID-19 in China as of 11 February 2020 and was published in the *Chinese Journal of Epidemiology* [8]. It is crucial to know that the WHO–China report notes that '*The Joint Mission acknowledges the known challenges and biases of reporting crude CFR early in an epidemic*' [11].

Phylogenetic relationships between the group 2B coronaviruses show that SARS-CoV-2 represents a new clade compared to classic SARS-CoV, with a 25% difference in its genome compared to these other viruses, which may explain why SARS-CoV immune therapeutics (hmAb) and vaccines may fail or be incompletely effective against this new pathogen. It highlights the need for drug and vaccine development. There are currently no approved drugs, immune therapeutics or vaccines that have shown efficacy in randomised trials against any group 2B CoV. Experimental drugs include remdesivir (GS-5734, Gilead), which is a ribonucleoside inhibitor that causes chain termination during ARN synthesis [12,13]. It has been tested *in vitro* against COVID-19 and *in vivo* studies are in process.

Zunyou Wu (Chinese Center for Disease Control and Prevention, Beijing, China) gave an overview of the early events of the SARS-CoV-2 pandemic. The first three cases of COVID-19 were confirmed between 27 December 2019 and 1 January 2020 and an alert was raised by the local health authority with the closure of the Huanan Seafood Market in Wuhan [8]. As of 7 January, SARS-CoV-2 was identified and the first PCR kits were sent to Wuhan. As of 23 March, Wuhan and 15 other cities were 'shut down'. It only took 42 days for the virus to spread from 14 counties in 1 province to >1600 counties in 31 provinces. The majority (84%) of confirmed cases outside Hubei were explained by either a Wuhan-related exposure, or a close contact from a confirmed case, which suggests a low level of community transmission outside Hubei. No meaningful differences in age distribution of COVID-19 cases were observed between sexes. The majority (94%) of patients were adults between the ages of 20 and 79 years.

Underlying medical conditions such as hypertension, diabetes, cardiovascular (CV) or lung disease were seen in a high proportion of critical cases (5%). Virus shedding is highest early in the course of disease and can occur 24–48 hours prior to symptom onset. It is usually detected for 7–12 days in mild/moderate cases and >2 weeks in severe cases. The virus can be isolated from faeces, however, there is no present epidemiologic evidence of faecal–oral transmission. Patients who recover can remain PCR positive after symptoms have resolved.

Regarding transmission dynamics, 75–85% of clusters were family-based, and while household attack rates were around 10% early in the outbreak, they decreased to 3% after fast isolation. Transmission in closed settings such as health facilities, nursing homes or prisons was not a major driver of transmission in China. Dr Wu highlighted that, as SARS-CoV-2 is a new virus, we do not have pre-existing immunity, treatment or a prophylactic vaccine to control it. According to the presenter, China has implemented strong public health measures in order to confront this new epidemic.

Anthony S Fauci (National Institute of Allergy and Infectious Diseases [NIAID], Bethesda, USA) highlighted research NIAID implemented in response to COVID-19 since Chinese researchers released the draft genome of the Wuhan pneumonia virus [14]. Basic research is facilitated by the availability of viral isolates and reagents by the Biodefense and Emerging Infections Research

Resources Repository (BEI Resources) which is a World Reference Center for Emerging Viruses and Arboviruses. Diagnostics are obviously of critical importance and, even if there have been some delays in this domain, we should alleviate regulatory requirements and allow wider availability. CDC has developed an rRT-PCR test that can diagnose SARS-CoV-2 in respiratory and serum samples from clinical specimens for the public health sector.

Potential agents against SARS-CoV-2 include remdesivir (nucleotide analogue) which has shown promising results against coronaviruses in animal models, Kaletra (lopinavir/ritonavir) (protease inhibitor) and interferon-beta, which have been used as investigational agents against other coronaviruses, as well as other broad-spectrum antivirals such as chloroquine and monoclonal antibodies. There are, as of 3 March 2020, >261 records for COVID-19 in the WHO's International Clinical Trials Registry Platform. A National Institute of Health Clinical Trial of remdesivir is about to start. Vaccine platform technologies are also in development, especially using an mRNA vaccine candidate expressing the COVID-19 viral spike protein (NIAID Vaccine Research Center collaborating with Modern and the Coalition for Epidemic Preparedness Innovations, CEPI).

Coronavirus vaccine research is moving at record speed and approximatively only 2–3 months will be needed from sequence selection to the first human injection. Dr Fauci stated that this is a rapidly evolving field and we look forward to meeting the challenge of what would be a very important impact on global health and this evolving epidemic as we live through it in real time.

Conflicts of interests

The authors declare no conflicting interests.

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