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The sudden appearance of SARS-CoV-2

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Introduction

Numerous viral infections have risen in the last decades, causing severe diseases associated with lethality. Diseases have varied in epidemiology and morbidity although people with risk factors such as age, cardiovascular diseases, diabetes, and other chronic diseases have most commonly suffered more serious consequences. The world population is aging and so is the prevalence of noncommunicable diseases. Thus, the potential group of people, who are the most at risk of suffering major consequences if infected by a virus, is vast. One such example is the novel coronavirus (nCoV), identified in Wuhan, China, which was isolated on January 7, 2020, causing severe pneumonia.¹

This chapter analyzes the emergence, first outbreaks outside China, and the epidemiology data and models that has guided public health policies. The period covered in this chapter had included the first notification of cases by China until the declaration of a pandemic by the World Health Organization (WHO) on February 11, 2020. This chapter also describes some of the similarities between this virus and previous coronaviruses (CoVs) like severe acute respiratory syndrome (SARS)-CoV (2002) and middle east respiratory syndrome (MERS)-CoV (2012).

The ancestors: Coronavirus and humans

CoVs, a large family of single-stranded RNA viruses, have been circulating on Earth for centuries. While CoVs are widely detected in bats, other mammals, birds, and reptiles, CoVs are seldom seen in humans causing mainly mild respiratory infections. It was not until the first decade of the twenty-first century with the appearance of the SARS outbreak that their clinical importance was recognized.

Coronaviruses have the largest known RNA genome, with a size of 27–32 kb. The spike glycoprotein (S) protrudes from the surface of the viral particle (hence the

name “coronavirus”) and is responsible for receptor binding and membrane fusion. Therefore, it is believed to represent a key determinant of host range restriction.²

There are four main subgroups of CoVs, namely alpha, beta, gamma, and delta. Human CoVs were first identified in the mid-1960s. Common human CoVs are endemic globally and causing mild respiratory disease are 229E (alpha CoV), NL63 (alpha CoV), OC43 (beta CoV), and HKU1 (beta CoV). They tend to be transmitted predominantly during the winter season in temperate climate countries; they are well adapted to humans, and none have been found to be maintained in an animal reservoir.^{3, 4}

On the contrary, SARS-CoV and MERS-CoV are mostly based on zoonotic reservoirs, with occasional spillover into the susceptible human population, possibly via an intermediate host species. Thus, in the first years of this century, SARS-CoV demonstrated that animal CoVs have the potential to cross over species to humans. In the late 2003, angiotensin-converting enzyme 2 was identified as the receptor of SARS-CoV on the surface of human cells, allowing the spillover into humans.⁵

The index cases of many of these SARS-CoV early case clusters (from November 2002 to January 2003) were food handlers working in restaurants where a variety of exotic animals were slaughtered on the premises.⁶ In February 2003, the Chinese Ministry of Health announced the strange outbreak of an atypical pneumonia in the Guangdong Province of southern China. News of this “mysterious” disease spread fast, as did the disease. During subsequent weeks, the outbreak became self-sustaining, with clusters of transmission in hospitals spilling back into the community. The identification of the SARS-CoV did not happen until almost three months later (April 2003).⁷

SARS spreads rapidly along routes of air travel, affecting 25 countries and territories across five continents, with an estimated 8096 cases and at least 774 deaths (case fatality rate ~ 10%). The outbreak continued until July 2003, when the WHO declared “all known chains of human-to-human transmission of the SARS virus now appear to be broken.”⁸ SARS was less transmittable in the first days of illness, leading patients to be more infectious as they became more symptomatic, providing an opportunity for case detection and isolation to interrupt transmission. However, the higher transmission by severe patients has contributed to transmission in hospitals, especially when they underwent aerosol-generating procedures. The SARS-CoV was also unusually lasting on surfaces, more so than other CoVs or other respiratory viruses, making infection control in hospitals a challenge.⁹ As awareness grew, patients began to be identified and hospitalized earlier in the illness, and as effective infection control modalities were better implemented, it became possible to interrupt transmission in the community and hospitals.¹⁰

The zoonotic source of the virus was identified after the outbreak ended; the investigations led to the detection of the virus in a range of mammalian species available in the wet markets. People working in these markets had a high prevalence of antibodies to SARS-CoV, even without a history of having SARS. SARS-CoV crossed the species barrier into masked palm civets and other animals in live-animal

markets in China; genetic analysis suggested that this occurred in the late 2002. Several people in close proximity to palm civets became infected with SARS-CoV.¹¹

The emergence of SARS in 2003 demonstrated the interconnection of the world and how rapidly a new disease can spread, due to the exponential increase in international travel and trade. That impeded the need to review international mechanisms for monitoring and control of emerging diseases; not only for the four serious infectious diseases included in the original International Health Regulations (IHR) from 1969.¹² In 2005, the World Health Assembly, representing 196 countries, agreed to implement the revised IHR as a commitment to build their capacities to detect, assess, and report public health events under a broader range of public health emergency of international concern (PHEIC). The WHO plays the coordinating role in IHR and, together with technical partners, helps countries to build their capacities to detect and contain public health hazards.

Almost a decade later of the SARS-CoV, a new CoV emerged in Saudi Arabia in 2012, subsequently named MERS-CoV. MERS-CoV is a beta-coronavirus, like the SARS-CoV. It causes severe pneumonia as well as renal failure. Index cases have originated in the Arab Peninsula (Jordan, Qatar, Saudi Arabia, and the United Arab Emirates), while travel-associated cases have been diagnosed in the European Union, North Africa, Asia, and the USA. The receptor for MERS-CoV has been identified to be dipeptidyl peptidase IV, which is expressed in the human respiratory tract and is conserved across many species, including bats.¹² This virus, originated from bats, uses camels and dromedaries as intermediary hosts; and, although the outbreak declined over the time, the risk of new cases is still considered to exist as the animal reservoir persists.¹³ By the end of December 2019, 27 countries reported a total of 2502 laboratory-confirmed cases of MERS, including 861 associated deaths (case–fatality rate: 34.4%); the majority of these cases were reported from Saudi Arabia (2106 cases, including 783 related deaths, case–fatality rate: 37.2%). Reported cases are classified as primary (direct spillover from camels) or secondary (human-to-human transmission, mostly healthcare workers); the proportion between those categories changed over the time, in the period July–December 2019, 33% were primary cases, 6% were secondary cases, and 31% of unknown contact history. As in SARS-CoV, human-to-human transmission of MERS-CoV occurs mainly associated with healthcare.¹⁴ The predominance of nosocomial transmission is probably due to the fact that higher virus shedding (high viral loads in respiratory tracts) occurs after the onset of symptoms when most patients are already seeking medical care.¹⁵ As an example, in the period 2013–2019, approximately 20% of the cases of MERS were healthcare workers in Saudi Arabia.¹⁶

Affected countries reduced the global threat of MERS by addressing knowledge gaps about transmission, enhancing surveillance, and strengthening the ability to detect cases early and contain outbreaks through improved infection prevention and control measures in hospitals. Preventing international spread and sustained transmission has been improved by local policies, better prevention and control measures in hospitals, restriction of camel movement in affected areas, stronger and more comprehensive investigations of cases and clusters, and improved communication.¹⁷

Unfortunately, neither the SARS nor the MERS outbreaks yield to solid clinical data on the efficacy of treatment regimens. This evidence was urgently needed for the treatment of MERS, as well as to prepare for nCoVs that may emerge, as it was demonstrated with SARS-CoV-2.

While MERS has not caused the international panic seen with SARS, the emergence of this second, highly pathogenic zoonotic human CoV illustrates the threat posed by this viral family. In 2017, the WHO placed SARS-CoV and MERS-CoV on its Priority Pathogen list, to accelerate research and the development of vaccines and antivirals against CoVs.¹⁸

Emergence of SARS-2 CoV

On December 31, 2019, a cluster of cases of pneumonia of unknown etiology—a surveillance definition after the SARS outbreak—were detected in Wuhan City, Hubei Province of China. Patients exhibited symptoms of viral pneumonia including fever, difficulty breathing, and bilateral lung infiltration in the most severe cases. Bronchoalveolar samples from these patients were positive for pan-Beta coronavirus (real-time PCR assays).¹⁹ As of January 20, 2020, 282 confirmed cases of this nCoV have been reported from four countries including China, Thailand, Japan, and the Republic of Korea.²⁰

The novel virus was named as Wuhan CoV or 2019 nCoV (2019-nCov) by the Chinese researchers. The International Committee on Taxonomy of Viruses Coronaviridae Study Group has studied the classification of the new virus and named it as “SARS-CoV-2.”²¹ The disease name (which in many cases is different from the virus name) has been designated as coronavirus disease 2019 (COVID-19) by the WHO. The “19” in COVID-19 stands for the year (2019) that the virus was first seen. The virus name was announced by the WHO on February 11, 2020.²²

The critical factor for an emergent virus is its pandemic potential. Efficient human-to-human transmission is a requirement for a large-scale spread. The proportion of patients with mild symptoms is another important factor that determines the ability to identify infected individuals and to prevent the transmission of the virus. Identification of transmission chains and subsequent contact tracing are further complicated when several individuals remain asymptomatic or mildly symptomatic.²³

Genetic studies: Looking for the origin

In less than a month, the nCoV was identified, isolated, and sequenced by the Chinese scientists. The complete viral genome sequences from the initial patients showed a sequence identity of 99.98%.²⁴ This level of viral genomic identity isolated from different human subjects is unusual for an RNA virus that has been circulating for a long time in the human population. This observation suggests a recent single spillover event from an animal source into humans.

Genetic sequencing of the Wuhan coronavirus offers clues to its origins and spread. With regards to its origin, the alignment of the full-length genome sequence of the SARS-CoV-2 and other available genomes of Beta CoV showed the closest relationship was with the bat SARS-like CoV strain BatCov RaTG13 (identity match 96%) and suggest multiple outbreak sources of transmission.²⁵

Nine months after the detection of SARS-CoV-2, laboratories all over the world have sequenced the genomes of more than 5000 strains and have made them publicly available.²⁶ This phylogeny (Fig. 1) shows evolutionary relationships of SARS-CoV-2 viruses from the ongoing nCoV COVID-19 pandemic; and an initial emergence in Wuhan, China, in November–December 2019 followed by sustained human-to-human transmission leading to sampled infections. Although the genetic relationships among sampled viruses are quite clear, there is uncertainty surrounding estimates of specific transmission dates and in reconstruction of geographic spread.

Viral sequences could identify any genetic changes that might have helped the virus make the jump from animals to humans, and signs that the virus has gained further mutations that are enabling it to spread more efficiently in humans. For instance, the transmission rate of SARS-CoV-2 is higher than SARS-CoV, and the reason could be genetic recombination event at S protein of SARS-CoV-2. The single N501T mutation in SARS-CoV-2's Spike protein may have significantly enhanced its binding affinity for the human angiotensin-converting enzyme 2 protein.²⁷

Primary reservoirs and hosts of SARS-CoV-2: A market full of wildlife

The source of the SARS-CoV-2 is still unknown, although the initial cases have been associated with the Huanan Seafood Wholesale Market, Wuhan, China. The live animals are frequently sold at the Huanan Seafood Wholesale Market such as bats, frogs, snakes, birds, marmots, and rabbits.²⁸ Environmental samples taken from this market in December 2019 tested positive for SARS-CoV-2, further suggesting that the market in Wuhan City was the source of this outbreak or played a role in the initial amplification of the outbreak, but no specific animal association has been identified.^{29–31}

Genetic sequencing suggests that the SARS-CoV-2 is related to CoVs that circulate in bats, including SARS and its close relatives. Probably, the lineage giving rise to SARS-CoV-2 has been circulated unnoticed in bats for more than 40 years. SARS-CoV-2 itself is not a recombinant of any sarbecoviruses (the viral subgenus containing SARS-CoV and SARS-CoV-2) detected to date, and its receptor-binding motif, important for specificity to human angiotensin-converting enzyme 2 receptors, appears to be an ancestral trait shared with bat viruses and not one acquired recently via recombination.³²

Besides bats, other mammals can transmit these viruses and, similarly to SARS, SARS-CoV was most likely to spread to humans by mammals. Claims were made but were not substantiated that snakes or pangolins³³ were intermediate hosts for

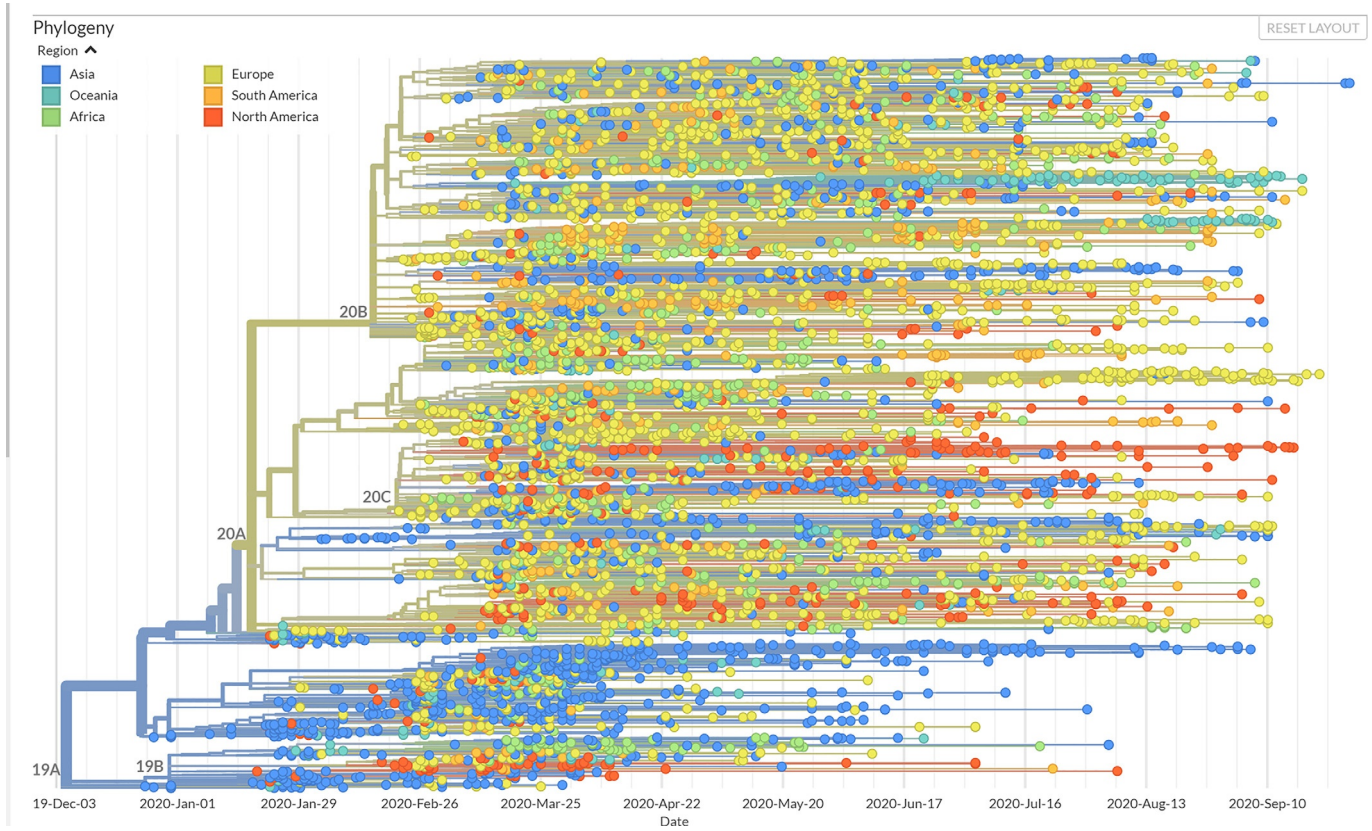


FIG. 1

Genomic epidemiology of nCoV. Phylogenetic tree as of September 2020.

Credit: <https://nextstrain.org/ncov/global>.

creating the coronavirus by recombination events.³⁴ Researchers are currently working to identify the source of 2019-nCoV including possible intermediate animal vectors.

In addition to investigations on the possible intermediate host(s) of SARS-CoV-2, there are also a number of studies underway to better understand the susceptibility of SARS-CoV-2 in different animal species. Current evidence suggests that humans infected with SARS-CoV-2 can infect other mammals, including dogs, cats, ferrets, and farmed mink.^{35–38} However, it remains unclear if these infected mammals pose a significant risk for transmission to humans.

The source of origination and mechanisms of zoonotic transmission are important to be determined in order to develop preventive strategies to contain the infection; from prevention of additional zoonotic exposures/risk exposure, infection prevention and control measures, nonpharmacological measures, and the development of vaccines in adequate animal models.

Human-to-human transmission

Initially, most of the early COVID-19 patients in China had an epidemiological link with the Wuhan market: they may have visited the wet market where live animals were sold or may have used infected animals or birds as a source of food. However, none of the exported cases had contact with the market, and early epidemiological studies showed that there was an exponential increase in the number of cases beginning in the late December 2019 clearly suggesting the human-to-human spreading capability of this virus since the middle of that month.^{39, 40} To identify the transmission mechanism is extremely relevant for the implications in infection prevention precautions and to determine the specific measures and efforts to reduce transmission would be required to control outbreaks.

The transmission mechanism among humans was early identified as respiratory. The human-to-human spreading of the virus occurs in close contact with an infected person, exposed to coughing, sneezing, respiratory droplets, or aerosols. These particles can penetrate the human body via inhalation through the nose or mouth initiating their replication in the mucosa cells of the respiratory tract.^{41, 42} Contact transmission (direct contact with an infected subject or indirect contact, through hand-mediated transfer of the virus from contaminated fomites to the mouth, nose, or eyes) is considered very likely, given consistent findings on environmental contamination in the vicinity of infected cases and the fact that other coronaviruses and respiratory viruses can transmit this way. However, there are no specific reports that have directly demonstrated fomite transmission. People who touch potentially infectious surfaces often have close contact with the infectious person, making the distinction between respiratory droplet and fomite transmission difficult to discern. Lastly, indirect transmission through fomites is considered possible, although, so far, transmission through fomites has not been documented.³⁶

Infection is understood to be mainly vectored via large respiratory droplets containing the SARS-CoV-2 virus. Transmission through aerosols (droplet nuclei that remain infectious when suspended in air over long distances and time) can occur during medical procedures that generate aerosols. WHO, together with the scientific community, has been actively discussing and evaluating whether SARS-CoV-2 may also spread through aerosols in the absence of aerosol generating procedures, particularly in indoor settings with poor ventilation. There is no evidence of aerosol transmission in the absence of aerosol generating procedures.⁴³

As SARS-CoV-2 has been found in the fecal samples, the possibility of fecal–oral (including waterborne) transmission needs to be considered. A scoping review showed that the virus is less stable in the environment and is very sensitive to oxidants, like chlorine, and temperature (the titer of infectious virus declines more rapidly at 23°C–25°C than at 4°C).⁴⁴ There is no current evidence that human coronaviruses are present in surface or groundwater bodies or are transmitted through contaminated drinking water.

Virus transmissibility and R_0 estimations

Early epidemiological records in China suggest that up to 85% of human-to-human transmission occurred in family clusters. Healthcare workers became infected with an absence of major nosocomial outbreaks and some supporting evidence that some healthcare workers acquired infection in their families.³⁷ These findings suggest that close and unprotected exposure is required for transmission by direct contact in the immediate environment of those with infections.

Continuing reports from outside China suggest the same means of transmission to close contacts and persons who attended the same social events or were in circumscribed areas such as office spaces or cruise ships.^{38, 45} Therefore, it looks like that transmission rates are higher in closed settings than in open air ones.

Transmissibility is measured by two parameters: secondary attack rate and basic reproduction number (R_0). Attack rate has been measured in different settings, such as attendees of a religious event (estimated attack rate 38%–78%) or children attending summer camp (estimated attack rate 44%).^{46, 47} SARS-CoV-2 spread efficiently in both settings, resulting in high attack rates among persons in all age groups. Asymptomatic infection was common and potentially contributed to undetected transmission.

R_0 is considered as one of the most valuable parameters to predict the evolution of an epidemic, useful to answer questions about how fast the disease will spread or estimating other response parameters such as the number of hospital beds needed. Its value has important implications for predicting and measuring the effects of pharmaceutical and nonpharmaceutical interventions. R_0 has been extremely difficult to estimate at the beginning of the pandemic because of the underreporting of asymptomatic and mild cases. This parameter is often calculated as a fixed property of a pathogen, based on the mode of transmission; but R_0 also depends on the behavior (i.e., how often people come into contact with one another) that can differ drastically

between countries, cities, or neighborhoods. For instance, the European Center for Disease Prevention and Control and other researchers, initially estimated the R_0 for COVID-19 to be between 2 and 3 as per the epidemiological data from China.^{48, 49}

However, soon other studies estimated R_0 using multiple methods and reported large-scale outbreak with R_0 equal to 6.47 [95% confidence interval (CI) 5.71–7.23] or 5.7 (95% CI 3.8–8.9) indicating higher transmission of COVID-19. That highlights the importance of active surveillance, contact tracing, quarantine, and early strong social distancing efforts to stop transmission of the virus.^{50, 51}

Controversies about transmission

People without symptoms

Once the human-to-human mechanism transmission was clear, another major discussion over transmission was whether—and how extensively—people without symptoms can infect others.³⁹ Infected persons without symptoms could play a significant role in the ongoing pandemic, but their relative number and effect have been under discussion. As early as February 2020, it was evidence that people infected with SARS-CoV-2 who did not develop symptoms of COVID-19, but whose viral load was similar to that of symptomatic cases, suggesting a potential for transmission.^{52, 53} If such asymptomatic cases are common and these individuals can spread the virus, then containing its spread will be much more difficult. In that context, the proportion of asymptomatic persons who tested positive for SARS-CoV-2 infections was estimated to account for approximately 40%–45%, and they can transmit the virus to others for an extended period, perhaps longer than 14 days.⁴⁰ These are people fully asymptomatic, not the ones who will develop symptoms later on (presymptomatic). Research has shown that people become infectious before they start feeling sick, during that presymptomatic period. The difficulty of distinguishing asymptomatic persons from those who are merely presymptomatic is extremely an obstacle in epidemiological or clinical studies, leading to acknowledge the possibility that some of the proportions of asymptomatic persons are lower than reported, as those who are presymptomatic cases.

Children and transmission

Currently, the extent to which children contribute to transmission of SARS-CoV-2 overall remains unclear. The contribution of children at the total of cases and deaths is minimal (1.7% of cases and less than 1% of the deaths).^{54–56} On the other hand, evidence is limited regarding the prevalence of SARS-CoV-2 infections in children, but it appears to be lower for younger children (e.g., under 12 years old) compared to the adult population (above 18 years old) and teenagers (13–19 years old).^{41–43} Despite the high viral load detected in children, their contribution to transmission is not clear,

as the evidence suggests that most cases in children result from household exposures, and transmission among children and staff in educational settings is low.⁵⁵

Contact tracing provides an accurate estimate on transmission. In South Korea, tracing of 59,073 contacts of 5706 index patients detected COVID-19 in 11.8% of household contacts. In children, the highest COVID-19 rate (18.6% [95% CI 14.0%–24.0%]) was found for household contacts of school-aged children (10–19) and the lowest (5.3% [95% CI 1.3%–13.7%]) for household contacts of children aged 0–9 years in the middle of school closure. These data suggest that children younger than 10 years transmit the virus to others in the household much less often than adults do, but the risk is not zero.⁴⁴

Transmission is influenced by many other factors as well, such as droplet production, physical environment (air flow, temperature, and humidity), susceptibility of the exposed person, transmission greatly influenced by activities, and social behavior patterns. In summary, the degree to which age alone, regardless of symptoms, affects viral load, and thus, the infectiousness of COVID-19 remains unclear.

In conclusion, although the rise in cases probably reflects an increase in testing, the dramatic jump seen in many countries is concerning. The researchers are struggling to accurately model the outbreak, and to predict how it might unfold, because the case report data are incomplete (date of starting of symptoms and proportion of asymptomatic cases).

Early dissemination—The first outbreaks

Once human-to-human transmission was documented by the first epidemiological studies, it was clear that the transmissibility of the virus was high. In its early stages, the epidemic doubled in size for every 7.4 days.⁵⁷ In this section, it describes the local and international COVID-19 dissemination until the declaration of pandemic by WHO (March 11, 2020).

China

About the dynamics of the transmission in China, the WHO Joint Mission (February 16–24, 2020) informed on the transition from early cases identified in Wuhan are believed to have acquired the infection from a zoonotic source, as many reported visiting or working in the Huanan Seafood Wholesale Market.⁵¹ However, early in the outbreak, the cases generated human-to-human transmission chains that seeded the subsequent community outbreak. The dynamics of transmission radiated from Wuhan to other parts of Hubei province and China. On January 23, 2020, Wuhan city was locked down—with all travel in and out of Wuhan prohibited—and movement inside the city was restricted with the purpose of preventing further transmission. Within Hubei, the implementation of control measures (including social distancing) reduced the community force of infection, resulting in the progressively lower incident reported case counts.

Given Wuhan's transport hub status and population movement during the Chinese New Year, infected individuals quickly spread throughout the country and were particularly concentrated in cities with the highest volume of traffic with Wuhan.⁵¹

Based on the epidemiological official data, the published literature, and on-site visits in Wuhan (Hubei), Guangdong (Shenzhen and Guangzhou), Sichuan (Chengdu), and Beijing, the Joint WHO China Mission team made the following epidemiological observations on the demographic characteristics of the 55,924 laboratory-confirmed cases reported as of February 20, 2020. The median age was 51 years (range from 2 days to 100 years old; interquartile range 39–63 years old) with the majority of cases (77.8%) aged between 30 and 69 years. Among the reported cases, 51.1% were male, 77.0% were from Hubei, and 21.6% were farmers or laborers by occupation.

The data are similar to the first series of cases published by the Chinese Center for Disease Control and Prevention.⁵⁸ By February 11, 2020, a total of 72,314 individuals diagnosed with COVID-19 were included in the analysis. Among them, 44,672 cases (61.8%) were confirmed, 16,186 cases (22.4%) were suspected, 10,567 cases (14.6%) were clinically diagnosed, and 889 cases (1.2%) were asymptomatic. Most of the confirmed cases ($N = 44,672$) were aged 30–69 years (77.8%), male (51.4%), farmers or laborers (22.0%), and diagnosed in the Hubei Province (74.7%). Most patients reported Wuhan-related exposures (85.8%) and were classified as mild cases (80.9%). The lethality rate was estimated to be around 2.3% (confirmed cases). Of all the age groups, the patients in the ≥ 80 years age group had the highest case fatality rate at 14.8%. The case fatality rate for males was 2.8%, and for females, it was 1.7%. While patients who reported no comorbid conditions had a case fatality rate of 0.9%, patients with comorbid conditions had much higher rates—10.5% for those with cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, and 5.6% for cancer.

In the first WHO Situation Report on the nCoV, dated January 20, 2020, there were reports of confirmed cases from three countries outside China: Thailand, Japan, and South Korea.⁵⁹ These cases had all been exported from China, with no documented local transmission outside China yet.

On January 30, 2020, the WHO has declared this first outbreak of nCoV in China a PHEIC.⁴⁶ This is a formal declaration of “an extraordinary event which is determined to constitute a public health risk to other states through the international spread of disease and to potentially require a coordinated international response,” formulated when a situation arises that is “serious, sudden, unusual, or unexpected,” which “carries implications for public health beyond the affected state’s national border” and “may require immediate international action.”⁴⁷ Under the 2005 IHR, states have a legal duty to respond promptly to a PHEIC. As this is a new coronavirus, the global community should demonstrate solidarity and cooperation, in compliance with Article 44 of the IHR (2005), in supporting each other on the identification of the source of this new virus, its full potential for human-to-human transmission, preparedness for potential importation of cases, and research for developing necessary treatment. Under Article 43 of the IHR, States Parties implementing additional

health measures that significantly interfere with international traffic (refusal of entry or departure of international travelers, baggage, cargo, containers, conveyances, goods, and the like, or their delay, for more than 24h) are obliged to send to WHO the public health rationale and justification within 48h of their implementation.

During the following weeks, several countries implemented entry screening measures for arriving passengers from China. Soon, several major airlines suspended their flights from and to China.⁴⁸

Travel restrictions were issued to impede or slow down transmission in a number of countries. As mentioned, on January 23, 2020, Wuhan City was locked down—with all travel in and out of Wuhan prohibited—and movement inside the city was restricted. The major problem for airport control would be that about 64% of the infected travelers were presymptomatic at arrival, as estimated per Monte Carlo simulation.⁴⁹ Therefore, travel restrictions are insufficient to contain the global spread of COVID-19, as it was later on demonstrated. With most cases arriving during the asymptomatic incubation period, rapid contact tracing would be essential both within the epicenter and at importation sites to limit human-to-human transmission outside of mainland China. Modeling suggested that sustained 90% travel restrictions modestly affect the epidemic trajectory unless combined with a 50% or higher reduction of transmission in the community.⁵⁰

In less than 8 weeks, the overall number of cases reported as of March 10, 2020 was 113,702 confirmed cases with 4012 deaths. Of those, in China, there were 80,924 confirmed cases with 3140 deaths, while outside of China 32,778 confirmed cases with 872 deaths. About 109 countries/territories/areas have reported the confirmed cases of COVID-19. The most affected countries after China were the Republic of Korea (7513), Iran (7161), and Italy (9172) (Figs. 2 and 3). The WHO risk assessment at national, regional, and global level was very high.

Asia

After the announcement of 41 confirmed COVID-19 cases in Wuhan City, China on January 11, infected patients were identified in Thailand on January 8 and 13.⁵¹ According to the cases' history, the two imported COVID-19 cases described were not directly linked, yet their genomes were identical. They had no direct link to the Huanan Seafood Wholesale Market, but their genomes were identical to four sequences from Wuhan collected on December 30, 2019, indicating potential wider distribution in the city.

The first imported case of COVID-19 in Japan was reported on January 3, with laboratory confirmation on January 16th, and notified the WHO.⁵⁹ The patient did not visit the seafood market. However, he potentially had close contact with pneumonia patients during his stay in Wuhan, raising the possibility of human-to-human spread. Both Thailand and Japan are among the top three Wuhan air travel destinations, according to a study on travel patterns and public health preparedness in light of the new threat.

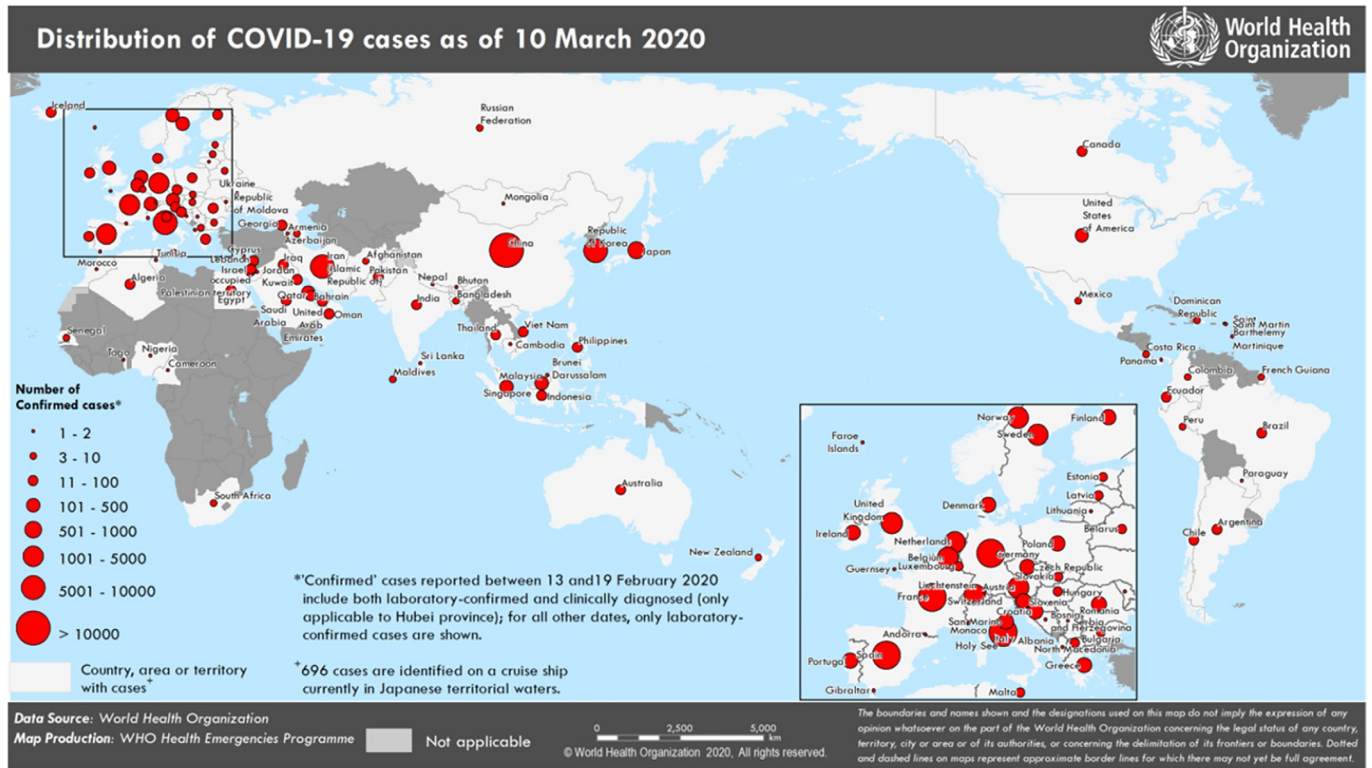


FIG. 2

Countries, territories with reported confirmed COVID-19 cases as of March 10, 2020.

Source: WHO Credit: WHO.

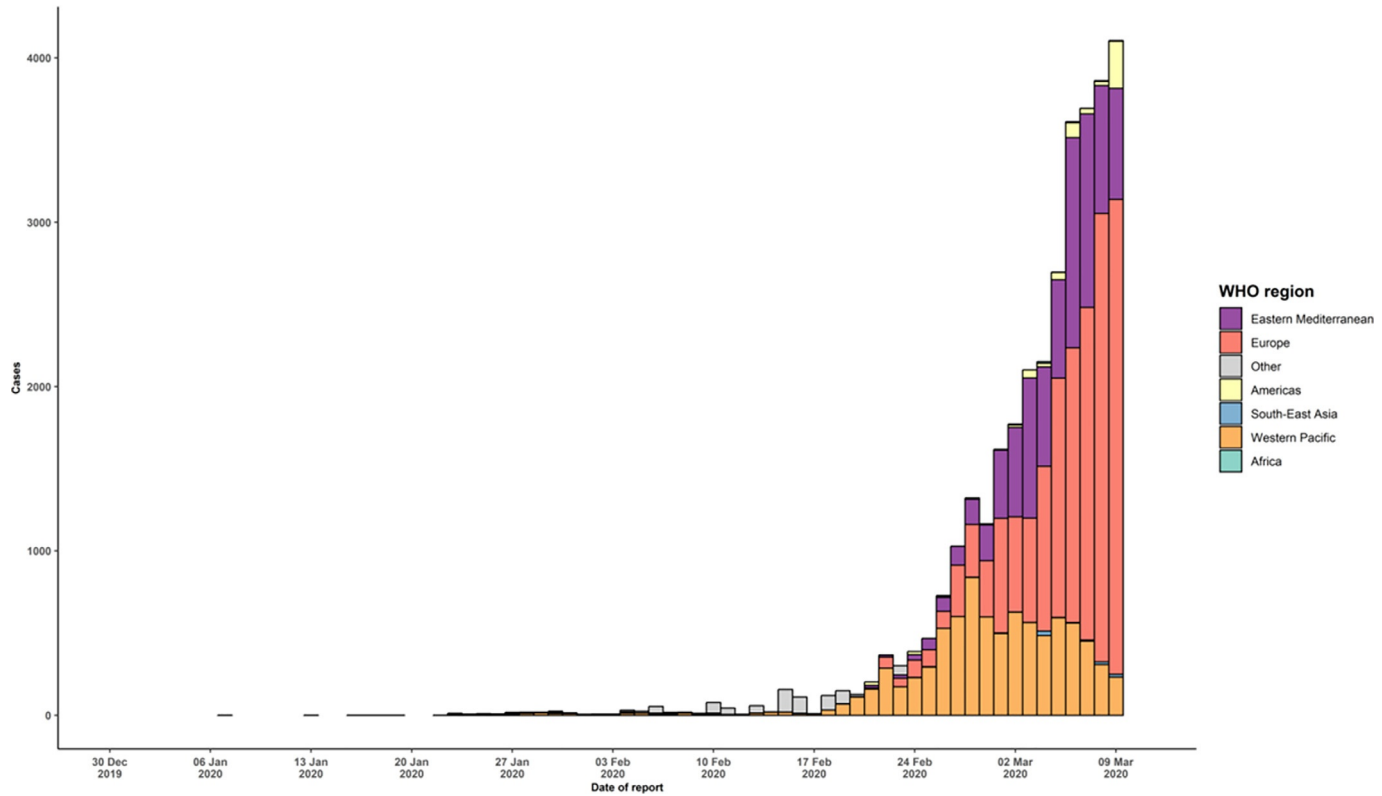


FIG. 3

Epidemic curve of confirmed COVID-19 cases ($N = 32,778$) reported outside of China, by date of report and WHO region with complete days of reporting through March 10, 2020.

Credit: WHO.

In Korea, 28 confirmed cases of COVID-19 had been reported as of February 14, since the first case was confirmed on January 20, 2020. Of these, 16 cases were imported into the country (57.1%) and 10 were believed to be secondary cases of infections originating in Korea; in the other 2 cases, the route of transmission remained undetermined.⁶⁰ At that point, these COVID-19 cases originating in Korea have been reported to be index cases imported from abroad, and resultant first-generation and second-generation cases.

Europe

The first infections in Europe occurred between January 16 and 24 by a group of 30 tourists from Wuhan visiting Italy, Switzerland, and France. The first European case was reported in France on January 24, 2020. This case had a travel history to China. In Germany, cases were reported on January 28, related to a person visiting from China.

In the WHO European Region, COVID-19 surveillance was implemented on January 27, 2020. As of February 21, nine European countries reported 47 cases. Among 38 cases studied, 21 were linked to two clusters in Germany and France, 14 were infected in China.⁶⁴ The median age of the case was 42 years; 25 were male. Late detection of the clusters' index cases delayed isolation of further local cases. As of March 5, there were 4250 cases. The analysis of early cases, we observed transmission in two broad contexts: sporadic cases among travelers from China (14 cases) and cases who acquired infection due to subsequent local transmission in Europe (21 cases).⁶⁴

As of March 2, the European Center for Diseases Prevention and Control reported about the increasing number of countries with widespread community transmission around the world and in Europe, and these are exporting cases with subsequent transmission to previously unaffected areas. Only 9 days later, as of March 11, all the European countries were affected, reporting a total of 17,413 cases and 711 fatalities. Italy represented 58% of the cases ($N = 10,149$) and 88% of the fatalities ($N = 631$).⁵²

Iran

Iran reported its first two CoV cases on February 19, 2020. The virus may have been brought to the country by a traveler to China. Less than a week later, the country reported to WHO 61 COVID-19 cases and 12 related deaths. Iran borders are crossed each year by millions of religious pilgrims, migrant workers, and others. As of March 1, 2020, Iran had reported 987 novel (COVID-19) cases, including 54 associated deaths. At least six neighboring countries (Bahrain, Iraq, Kuwait, Oman, Afghanistan, and Pakistan) had reported imported COVID-19 cases from Iran. Researchers and modelers used air travel data and the numbers of cases from Iran imported into other Middle Eastern countries to estimate the number of COVID-19 cases.⁵³

The national authorities reported an increasing number of new cases and deaths, reaching 8042 cases and 291 deaths on March 11.⁶¹

America

<https://www.cdc.gov/mmwr/volumes/69/wr/mm6918e2.htm>.

<https://www.contagionlive.com/news/most-early-new-york-covid-19-cases-came-from-europe>.

USA early transmission

Latin America

Caribbean

In light of this situation, Pan American Health Organization's Alert in January 16, 2020 recommended the Member States to strengthen surveillance activities to detect any unusual respiratory health event.⁶⁵ Health professionals should be informed about the possibility of the occurrence of infection caused by this virus and the actions to be implemented in case of a suspected case.

Transmission in cruises

Cruise ships are often settings for outbreaks of infectious diseases. The spread of SARS-CoV-2 in cruise ships, in particular in the Diamond Princess, provided very rich information on the transmission and characterization of the clinical spectrum, in particular of the asymptomatic cases. On February 5, 2020, in Yokohama, Japan, a cruise ship hosting 3711 people underwent a 2-week quarantine after a former passenger was found with COVID-19 post-disembarking. At the end of the quarantine, 634 persons on board tested positive for SARS-CoV-2. It was estimated that each infected passenger infected 11 others. On March 10, 7 deaths caused by the virus were registered. The estimated asymptomatic proportion was 17.9% (95% CI 15.5%–20.2%).⁵⁴

During the initial stages of the COVID-19 pandemic, the Diamond Princess was the setting of the largest outbreak outside mainland China. Many other cruise ships have since been implicated in the SARS-CoV-2 transmission, such as the Grand Princess cruise ship. As of March 17, confirmed cases of COVID-19 had been associated with at least 25 additional cruise ship voyages. More than 800 cases and 10 deaths of laboratory-confirmed COVID-19 cases occurred during outbreaks on these cruise ship voyages until the end of March 2020.⁵⁵

From outbreak(s) to pandemic

Since the WHO declared this first outbreak of nCoV a “PHEIC” on January 30, there were increasing reports globally informing on the local transmission in multiple locations, without reported travel history to areas reporting community transmission and without epidemiological links to known cases. Several countries implemented entry screening measures for arriving passengers from China, and soon, several major airlines suspended their flights from and to China, although these public health measures did not prevent the dissemination of the virus across the globe. Events and

locations that involve social interaction or institutional contact have been related to the development of COVID-19 clusters, including workplace interactions, religious events, festivities, health and social care settings, and travel. Transmission events were reported in hospitals, with COVID-19 cases identified among healthcare workers and patients as well as in long-term care facilities.⁵⁶ Considering the global spread with the local transmission, the Director General of the WHO declared COVID-19 as a global pandemic on March 11, 2020.⁶²

The spread of the virus was exponential. Despite of the Chinese government efforts meeting the international standards in terms of isolation of suspect cases, diagnosis and treatment and educational campaigns, only 2 months after the notification of the first COVID cases through IHR, as of March 1, 2020, the local transmission was reported in 13 countries outside of China such as South Korea, Japan, Singapore, Australia, Malaysia, Vietnam, Italy, Germany, France, the United Kingdom, Croatia, San Marino, Iran, the United Arab Emirates, and the United States of America.⁶³ The most worrisome evidence was the local transmission documented in multiple locations and extensively, without direct or indirect epidemiological link to China. Only 10 days later, as of March 11 more than 118,000 cases of COVID-19 were reported worldwide in 114 countries, with 4291 fatalities.^{63,64} By then, it was clear that the world was entering a new phase of the global outbreak. Efforts to restrict the COVID-19 virus to China had failed, and in some countries, the focus had to turn towards mitigation rather than containment, as they try to slow the spread of the infection to stop hospitals all being overwhelmed at once. At that point, the WHO made the declaration of pandemic. Nevertheless, describing the situation as a pandemic did not change WHO's assessment of the threat posed by this virus, nor did the WHO recommendations and technical support to the countries change.

This expanding epidemic has been a stress test for existing health systems, including those of industrialized countries. It has also provided further motivation to strengthen fundamental research in trans-species viral infections and on potential zoonosis impacts, particularly from bats, under changing environmental conditions.

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