Virologie 2020, 24 (S1) : E12-E15

Facing challenges with the novel coronavirus SARS-CoV-2 outbreak

Émergence du coronavirus SARS-CoV-2 : faire face à l'épidémie de COVID-19

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On December 31, 2019, Chinese authorities reported a cluster of pneumonia cases in Wuhan, China, most of which included patients who reported exposure to a seafood market selling live animals. Emergence of a new pathogenic zoonotic coronavirus (2019-nCoV) was suspected. By the 12th January 2020, several full genomic sequences were made available by Chinese authorities through the Global Initiative on Sharing All Influenza Data (GISAID) public platform [1] which was initially developed to share sequences and monitor the genetic evolution of influenza viruses. This enabled rapid development of specific RT-PCR methods for detection of 2019-nCoV. The outbreak rapidly evolved, affecting other parts of China. The 13th January 2020, Thailand reported the first imported case from Wuhan. On 27 January 2020, forty-one travel-related cases were confirmed, all coming from China. Twenty-seven cases were imported to Asia, six to North America, five to Oceania, and three to Europe [2]. On 30 January 2020, the Director General of the World Health Organization (WHO) declared the outbreak of 2019-nCoV as a public health emergency of international concern. The first cases in the EU/EEA were confirmed in France the 24th January 2020 at the National Reference Centre (NRC) for respiratory viruses (Institut Pasteur, Paris) and whole genome sequences from two of the first French cases were rapidly shared through the GISAID platform; virus isolates were shared through the European Virus Archive GLOBAL (EVAg) initiative as well [3]. The 12th February 2020, based on its phylogenetic clustering with the SARS coronavirus which spread rapidly in 2002-2003 and other SARS-like coronaviruses, the novel coronavirus was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) [4], while the disease associated with it is now referred to as Coronavirus Infectious Disease 2019 (COVID-19) [5].

Coronaviruses are large, enveloped, positive strand RNA viruses that can be divided into 4 genera: alpha, beta, delta, and gamma, of which alpha and beta CoVs are known to infect humans [6]. Four seasonal human coronaviruses (HCoVs 229E, NL63, OC43, and HKU1) are endemic globally and account for 10% to 30% of upper Respiratory Tract (upper RT) infections in adults. Coronaviruses are ecologically diverse, with the greatest variety seen in bats, suggesting bats as the reservoir for many of those viruses [7]. Peri-domestic mammals may serve as intermediate hosts, facilitating recombination and mutation events with increase of genetic diversity. Sequencing of SARS-CoV-2 has shown that it is highly similar to a known virus from a horseshoe bat (*Rhinolofus affinis*) found in China [8], and to viruses detected or isolated in Malayan pangolins (*Manis javanica*) that might have served as an intermediate amplifying host [9, 10].

Two emerging coronaviruses, SARS-CoV in 2002-2003 and Middle East Respiratory Syndrom (MERS)-CoV in 2012, caused severe respiratory syndrome in humans. Both are thought to have originated from the bat reservoir, after being hosted in their respective intermediate hosts palmed civets and dromedary

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doi:10.1684/vir.2020.0826

Pour citer cet article : van der Werf S, Peltekian C. Facing challenges with the novel coronavirus SARS-CoV-2 outbreak. *Virologie* 2020; 24(S1) : 12-15 doi:10.1684/vir.2020.0826

camels from which they emerged. While in 2003 sustained human-to-human transmission of SARS, along with occasional human super-spreader events, were established, in the case of MERS, recurrent animal-to-human transmission from dromedary camels but limited human-to-human transmission are still occurring in the Middle-East. One of the key determinants for virus'- adaptation to humans is the efficient interaction with their receptors at the surface of the human respiratory epithelium. Circulating SARS-CoV-2 and SARS-CoV have been shown to use ACE2 as a receptor. Of note, amino acid homology at the receptor binding site of the major viral envelope spike (S) protein stresses the ability of closely related viruses from bats and Malayan pangolins to interact with human ACE2 [11, 12]. These results emphasize the need for improved surveillance and research at the animal-human interface for early recognition of animal viruses with highest risk of zoonotic potential.

Since 31 December 2019 and as of 27 February 2020, 82 132 cases of COVID-19 have been reported in the five continents (ECDC data), 477 cases in the EU/EEA/UK and Switzerland. Then, 2 801 deaths were reported, whereof 14 in the EU/EEA/UK and Switzerland. The fact that this virus causes illness, including severe illness resulting in death, with sustained person-to-person spread is an issue, since these factors meet two of the criteria of a global pandemic. As SARS-CoV-2 has been detected in all continents, showing community spread in growing countries, the world moves closer toward meeting the third criteria, i.e. worldwide spread of this virus. Drawing on experience from prior zoonotic outbreaks, as SARS-CoV, MERS-CoV, avian influenza H5NI and H7N9, influenza A(H1N1)pdm09, Ebolavirus disease, public health authorities have initiated preparedness and response activities, to prevent this emergence from becoming a pandemic. Close coordination between clinicians and public health authorities at the local, state, and global levels, as well as the need for rapid dissemination of clinical information related to the care of patients is crucial. In Europe, existing clinical and laboratory networks such as the Platform foR European Preparedness Against (Re-) emerging Epidemics (PREPARE), the French REACTing research institutions network, the Emerging Viral Diseases Laboratory Network (EVD-LabNet) and many others, aligned their strategy to respond to the health threat for European citizens. The clinical protocol initially developed for influenza by the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) and WHO, and adapted in the context of other emerging viruses (MERS-CoV, EBOV, ZIKV) has been adapted to COVID-19. Investigators can collect and store their data in a standardized way to enable pooled data analyses.

A key component of pandemic preparedness is the deployment of diagnostic capacity. First of all, diagnostic testing for SARS-CoV-2 was developed and implemented quickly in specialized laboratories, largely relying on the long-standing and well-structured WHO Global Influenza Surveillance and Response System (GISRS). These in-house and accurate diagnostic tests were shared worldwide, through the WHO website and transferred to additional laboratories by NRCs and WHO COVID-19 reference laboratories [13-15]. Essential positive controls and specificity panels were provided through the European Virus Archive GLOBAL (EVAg) initiative [16]. Availability of primers/probes, positive controls and personnel were the main implementation barriers, suggesting that the challenges faced by specialized laboratories when responding to emerging events are at a structural level [17]. Parallel to the extension of the epidemic and identification of cases in new countries, diagnostic capacities were deployed in first-line hospital laboratories who manage COVID-19 patients before rolling-out to additional hospital laboratories. However, if the outbreak turns into a pandemic, this capacity would be rapidly limited. Efforts of NRCs would then refocus to reference activities like confirmatory testing, laboratory surveillance including virus characterization, provision of reference materials and advice, while general testing for SARS-CoV-2 would shift to hospital laboratories and medical laboratories that currently do not have this capacity. These circumstances drive the need for approved commercial diagnostic kits compatible with hospitals and medical laboratories' equipment and routine practices. Considering occurrence of viral mutations that may lead to potential false negative results, performance of available tests should be monitored. Also, challenges pertaining to availability of reagents and controls, transport of specimens for testing (delays, cold chain, availability of accredited carriers), biosafety issues etc. need to be considered. Finally, with regard to remote territories and Low-and-Middle-Income Countries (LMICs) showing vulnerable health care systems, a key research priority is to develop rapid Point-of-Care (PoC) tests for COVID-19 which would enable faster detection of infected cases, remove the need for specialized laboratories, and help improving our ability to control the spread of the virus.

Global efforts are currently focused on containing the spread and mitigating the impact of this virus. Identification and isolation of COVID-19 cases, contacts tracing and quarantine measures have been applied in order to interrupt chains of transmission and to prevent establishment of sustained community transmission. According to the local and global evolution of the epidemic, that can show either a limited number of cases, contained clusters or generalized transmission into the community, rapid adaptation of

infection-control measures and diagnostic algorithms are required. These measures may be further modified by public health authorities, depending on the updated knowledge and risk assessment to efficiently control the outbreak.

Since the first confirmed cases, studies on modelling the epidemic, estimating its size, transmissibility and severity have been carried out. But there are still many unanswered questions, such as who is most at risk of developing severe symptoms, how transmissible is SARS-CoV-2, what is the contribution of mild or asymptomatic cases. Answering these questions is challenging in the early stage of any emerging infectious disease outbreak, and evidence needs to be developed through a series of linked studies that are difficult to conduct during a vast outbreak [18]. So far, it appears that the Case Fatality Rate (CFR) of COVID-19 is lower than that of SARS and MERS; mild clinical symptoms or asymptomatic infections could be more frequent in cases of COVID-19 [19]. For SARS and MERS, viral load is highest in the lower Respiratory Tract (lower RT) and transmission mainly occurs after the onset of symptoms, which contributed to the effective control of the SARS outbreak in 2003. Conversely, for COVID-19, currently available data indicate that SARS-CoV-2 is detected in the upper Respiratory Tract (upper RT), early in the course of infection or even before disease onset, resulting in major challenges for case detection and isolation strategies to control this outbreak. Regarding the basic reproduction number (R0) of SARS-CoV-2, several estimates have been released, based on (i) specific clusters, (ii) evaluation of the epidemiology of infection in travelers and their contacts, (iii) modelling of the formal notifications. While there is considerable heterogeneity in these estimates, there is consensus that the current R_0 is in the range of 2 to 3, reflecting the expanding epidemic.

Besides infectious disease modelling that will help to predict transmission and inform health authorities to plan response, setting-up patients' cohorts and clinical trials are priorities to inform case's management. Under careful watch of the WHO, clinicians are now testing a range of COVID-19 therapies, including HIV and anti-influenza antivirals [20]. In addition, determination of the kinetics of virus shedding in diverse body compartments (upper RT, lower RT, stool, blood . . .) and follow up of the immune responses, both in relation with severity of the disease, will be crucial to inform pathogenesis and virus transmission, and lay the ground for vaccine development. Genetic and phenotypic characterization of SARS-CoV-2 through *in vitro* and *in vivo* studies are needed as well, to identify antigenic, virulence, and possible resistance traits for rapid risk assessment purposes.

A lot of research needs to be carried out to gain insights into the molecular mechanisms underlying the pathogenesis of this novel virus and develop diagnostic, prevention and treatment tools. On 11-12 February the WHO, in collaboration with GloPID-R (the Global Research Collaboration for Infectious Disease Preparedness), brought together researchers to assess the current level of knowledge about COVID-19, identify the research needed to end the current outbreak, and help prepare for future outbreaks. The 2-day forum was convened in line with the WHO R&D Blueprint – a strategy for developing drugs and vaccines before epidemics, and accelerating R&D while they are occurring [21] Immediate and longer-term research priorities were identified to draw the WHO roadmap and implement comprehensive targeted research actions for a robust global response. Alongside with this researcher's global commitment, investments supported by political will and private-sector's involvement are needed to mobilize necessary resources for immediate start of critical research and foster capacity building in the most vulnerable nations.

Conflicts of interest : none.

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