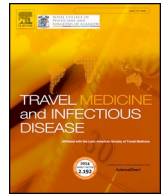




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Going global – Travel and the 2019 novel coronavirus



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Since 2009, the World Health Organization (WHO) has made five declarations of disease outbreaks considered Public Health Emergencies of International Concern (PHEIC): the 2009H1N1 (or swine flu) pandemic, the 2014 polio declaration, the 2014 outbreak of Ebola in Western Africa, the 2015–16 Zika virus epidemic and, as of 17 July 2019, the Kivu Ebola epidemic which began in 2018 [1,2]. Now, on January 30, 2020, after two meetings (the first on January 22 and 23) and a careful assessment of the situation, the Emergency Committee (EC) declared the outbreak of novel coronavirus 2019 (2019-nCoV) in the People's Republic of China a PHEIC [1]. Convened by the WHO Director-General under the International Health Regulations (IHR) (2005), the EC considered exportations to other countries and gave evidenced-based advice to the Director-General to support the final decision. The EC provided public health advice and recommendations in the midst of this outbreak [1].

The zoonotic spillover seen during this outbreak [3] has been previously witnessed with other coronaviruses pathogenic for human beings, four of them causing mild respiratory and intestinal disease, but two previously causing major concerns. The first, is the coronavirus causing the Severe Acute Respiratory Syndrome (SARS-CoV), that emerged as a global outbreak from China between November 2002 and July 2003. That epidemic, resulted in 8098 cases, with 774 deaths (9.6%) reported in 17 countries [4]. In fact, the PHEIC designation was created following an update to the International Health Regulations (2005) after that outbreak.

Only a decade later, in April 2012, in Saudi Arabia, the outbreak of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) affected 24 countries, primarily in the Middle East. The MERS-CoV resulted in over 1200 cases of the virus and over 400 deaths [5].

Both viruses, primarily infect bronchial epithelial cells and type II pneumocytes [6]. However, SARS-CoV uses angiotensin-converting enzyme 2 (ACE2) as a receptor and primarily infects also ciliated bronchial epithelial cells (Fig. 1) [6–10], whereas MERS-CoV uses dipeptidyl peptidase 4 (DPP4; also known as CD26) as a receptor and infects unciliated bronchial epithelial cells (Fig. 1) [6,11–13]. Structural analyses apparently predict that 2019-nCoV uses also the ACE2 as its host receptor (Fig. 1) [9,10,14]. Recent studies suggest that the 2019-nCoV does not use other coronavirus receptors, aminopeptidase N

and DPP4/CD26 [10].

Now, once again, the world faces the emergence of a new pathogen, another coronavirus, with a more important outbreak in terms of number of cases and deaths, compared to SARS-CoV and MERS-CoV [15]. Certainly, the 2019-nCoV represents a big threat to global health, with a growing number of cases, as reported by WHO (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>), requiring coordinated efforts, research and development in counter measures, sharing scientific knowledge and information to mitigate the impact of such situation [16].

After the first cases in Wuhan, Hubei province, the growth of the outbreak was predictable nationally and internationally. Recent data analyses showed that domestic train transportation significantly correlated with the number of imported cases to other provinces in China [17]. But, with Wuhan Airport having non-stop passenger flights scheduled to 113 destinations in 22 countries, in addition to the 78 domestic flights, international imported cases began to occur especially in Asia, but also abroad [18,19]. Furthermore, Beijing Capital International Airport, the largest airport in China, has non-stop passenger flights scheduled to 233 destinations in 54 countries and 127 domestic flights, including four direct routes, just two hours away, in addition to 20 routes with 1 stop, via Jinan, Changzhi, Dongying, and other major cities in China, including the largest city of Shanghai.

Travelers have played a significant role in bringing new cases to other countries, with confirmed ongoing human-to-human transmission [14,20–22], and also transmission from asymptomatic individuals, as has occurred recently in Germany [22,23].

1. Europe

Following the first reports of cases of 2019-nCoV, cases have now been detected in many countries in Europe, including Germany, France, Italy, Russia, United Kingdom, Spain, Finland, and Sweden. As this is an emerging, rapidly evolving situation with ongoing outbreak investigations, the European Centers for Disease Control (ECDC) is closely monitoring this outbreak and providing risk assessments to guide European Union (EU) Member States and the EU Commission in their response activities [24]. The ECDC has developed multiple documents

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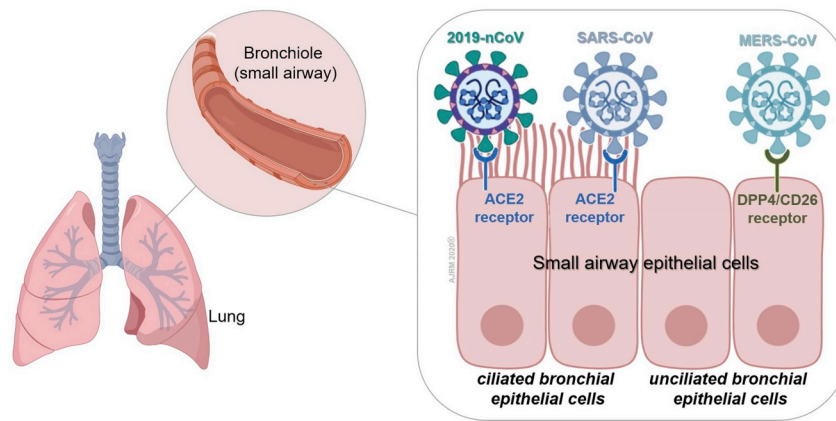


Fig. 1. Differences between bronchial epithelial cells infected and known receptors for SARS-CoV, and MERS-CoV and the potential receptor for 2019-nCoV.

in response, including technical reports, statements, risk assessments, algorithms, among others, related to diagnosis, management, and prevention [25–30].

2. United Kingdom

Travel patterns between the UK and China are well established; in an analysis of air travel from cities in China to international destinations in 2019, nine of the ten cities receiving the highest volumes of arriving passengers were in Asia, with London (UK), ranking 10th [18]. Of the 62.9 million tourist arrivals to China in 2018, the majority of these would have been from the Asia Pacific Region, but an estimated 4% were from Europe [31], and a large proportion of the latter would have been from the UK where an estimated 393,532 UK residents travelled to China [32].

China is also the world's largest spender on international tourism, with around 10% of China's 1.4 billion residents travelling internationally (WTO). In 2018, 391,380 visits would have been to the UK [32].

With the scale of travel between the UK and China, UK travel health professionals are used to advising those travelling to China. However, the outbreak of 2019-nCoV with the evolving epidemiological picture has added some complexities; rapidly changing case numbers, travellers exporting cases, shifting government advice based on logistics rather than public health risk, and media scare stories to name but a few.

In common with many other countries, UK travel health advice and public health messaging has been changing repeatedly since late December 2019 to early January 2020 with the first reports of a cluster of pneumonia cases in Wuhan, China [33], to the present day when 24,554 cases have been confirmed globally. Currently, Public Health England's (PHE's) assessment of the impact of the disease is moderate, and based on limited available information on the transmission of the disease, the risk to the UK population is considered moderate [34].

The UK's Foreign and Commonwealth Office (FCO) advises against all travel to Hubei Province, and all but 'essential travel' to the rest of mainland China [35]. For those already in China, it advises that those that are able to leave the country should do so [35]; with the developing situation, and the suspension of flights by some airlines to and from mainland China it may become harder to access departure options over the coming weeks. Indeed, in light of the severity of travel restrictions in Hubei Province, and difficulty accessing medical assistance, the FCO assisted the departure for those who were in Hubei Province [36].

Alongside the FCO's advice on decisions to travel, the UK's National Travel Health Network and Centre (NaTHNaC) provides travel health advice. This advice is available directly on its website TravelHealthPro (<https://travelhealthpro.org.uk/>), or where more specialist advice is needed - through a dedicated phone advice line for healthcare

providers. In addition to pre-existing travel health information for travel to China, TravelHealthPro has produced news items to help travellers keep pace with the evolving nature of this outbreak; particularly important when this outbreak has coincided with the national holiday of Chinese New Year, when large numbers of UK travellers will have planned to visit China. Outbreak information is updated daily so that data on cases to other countries can also be tracked. These resources appear to be reaching a large audience - with pageviews to the TravelHealthPro website hitting a new record of 80,000 in one day, and pageviews of the China-specific advice page increasing by over 400% - from 9000 views in January 2019, to over 45,000 in January 2020 [unpublished data]. Anecdotally calls to the advice line regarding the outbreak have also increased and this trend is likely to continue as 2019-nCoV cases increase in travel destinations out with China. These early signals of high public concern can help frontline clinical staff in their preparations for potentially similar increases in consultations, and the resources and capacity building this may require.

The importance of timely, accurate and context-specific risk communication during public health emergencies is increasingly being recognized, particularly with rapid changes in how people consume media. The WHO has produced useful guidance on communicating risk in such situations, which draws on experiences from previous PHEIC [37]. Good risk communication allows people to know from trusted sources in real-time the risks they may face, and any protective measures they can take to help minimise this.

UK communications are providing advice to both the public and health professionals that covers a range of eventualities including asymptomatic travellers returning from Wuhan, symptomatic travellers returning from elsewhere in China, and those who have had contact with a confirmed 2019-nCoV case. The advice includes specific details around self-isolation and who to contact [38].

Box 1 shows the accompanying more general advice about reducing spread of respiratory viruses [39] and Box 2 UK advice for asymptomatic and symptomatic travellers returning from China.

A blog run by Public Health England (PHE) is a good example of real-time risk communication as it allows readers to post questions which have then been answered by the blog editor the same day. For example, a question posed about the use of masks for the UK public received a same day response that there is little evidence of their widespread benefit from use outside of clinical settings, and people concerned would do better to prioritize good personal, respiratory and hand hygiene [34].

Good risk communication from official organizations helps travel health providers communicate and navigate risk with their clients. Consistency with in-country guidance will help reduce uncertainty and rumor. In rapidly changing outbreak situations such as this, travel health providers must be aware of where to get the latest official guidance, and be able to direct travellers to getting relevant local

Box 1

General UK advice for preventing the spread of respiratory viruses.

- Wash your hands often with soap and water for at least 20 seconds. Use an alcohol-based hand sanitizer that contains at least 60% alcohol if soap and water are not available. This is particularly important after taking public transport.
- Avoid touching your eyes, nose, and mouth with unwashed hands.
- Avoid close contact with people who are sick.
- If you feel unwell, stay at home, do not attend work or school.
- Cover your cough or sneeze with a tissue, then throw the tissue in a bin.
- Clean and disinfect frequently touched objects and surfaces in the home and work environment.

guidance. **Box 3** provides a checklist for travel health providers to help guide consultations where there are concerns surrounding the coronavirus outbreak.

3. United States

In the United States, the U.S. Centers for Disease Control and Prevention (US CDC) are closely monitoring the situation in China, but also at home, with reported cases in Chicago, Illinois; San Benito, California; Santa Clara, California; Los Angeles, California; Boston, Massachusetts; Tempe, Arizona; Orange, California; and Seattle, Washington. As a consequence, the US CDC have also developed a pack of technical documents for healthcare professionals, including interim guides for the evaluation of patients under investigation for 2019-nCoV, for the prevention and control recommendations for patients with confirmed 2019-nCoV or patients under investigation for 2019-nCoV in healthcare settings, as well as guidance for implementing home care of people not requiring hospitalization for 2019-nCoV, among others [40].

4. Latin America

Many countries in other regions have not yet confirmed cases, but the number of suspected cases increases continuously showing that all territories and regions are at risk. This is the case in Latin America, which has increased cultural and population mobility with China as well as with Asia in general [41–43]. Intense travel traffic with countries that have already received confirmed cases of 2019-nCoV is seen, as is the case for United States and Spain. In this context, heightened preparedness and response is necessary in order to mitigate the impact of the introduction of this new coronavirus, as has been already doing the Latin American Society for Travel Medicine (SLAMVI) in this region [15].

Box 2

UK advice for asymptomatic and symptomatic travellers returning from China.

Guidance for asymptomatic UK travellers returning from Hubei Province in the last 14 days:

- Immediately stay indoors and avoid contact with other people as you would with the flu.
- Call NHS 111 [a national non-emergency telephone number] to inform them of your recent travel to the area.

Guidance for symptomatic UK travellers returning from elsewhere in China, Hong Kong, Japan, Macao, Malaysia, South Korea, Singapore, Taiwan or Thailand in the last 14 days:

- If develop symptoms of cough, fever or shortness of breath, you should immediately:
- Stay indoors and avoid contact with other people as you would with the flu.
- Call NHS 111 to inform them of your recent travel to the country.

Both groups for 14 days after returning to the UK:

- Don't go to work, school or public areas.
- Where possible, avoid having visitors to your home, but it's ok to have food/medicine dropped off on your behalf.
- Don't use public transport or taxis.
- Where possible, contact a friend or family member to take your children to school.

5. Perspectives

No specific treatment for 2019-nCoV infection is currently available [40]. The clinical management includes prompt implementation of recommended infection prevention and control measures and supportive management of complications, including advanced organ support if indicated [40]. Cases in Vietnam, Thailand and United States [22,44], have been reported where patients received antivirals, such as remdesivir [44], among other drugs including oseltamivir; clinical trials of antivirals and vaccines are ongoing for MERS-CoV and one controlled trial of ritonavir-boosted lopinavir monotherapy for 2019-nCoV (ChiCTR2000029308) [45], at the Wuhan's Jin Yintan Hospital [46] is in progress. In a historical control study [14,47], the combination of lopinavir and ritonavir among SARS-CoV patients was associated with substantial clinical benefit (fewer adverse clinical outcomes). Saudi Arabia initiated a placebo-controlled trial of interferon beta-1b, lopinavir, and ritonavir among patients with MERS infection [14,48,49]. In the first case of 2019-nCoV in the USA, the administration of remdesivir was considered for compassionate use based on the case patient's worsening clinical status. Certainly, randomized controlled trials are needed to determine the safety and efficacy of remdesivir and any other investigational agents for treatment of patients with 2019-nCoV infection [44].

As has been recommended by the WHO, basic preventive measures against the new coronavirus, should be applied. Scientific information and evidence regarding multiples aspects of this outbreak and the virus change every day. Research papers and preprints are appearing every day as researchers worldwide respond to the outbreak [50]. As occurred with SARS-CoV and MERS-CoV, their epidemics stimulated a significant increase in scientific production in the world, including the most affected countries [16]. Clear communication, information and updated resources, for public health, infectious diseases and travel medicine practitioners are useful as most of these are constantly renewed with

Box 3

Checklist for travel health providers to help guide consultations surrounding 2019-nCoV.

- Travellers should be aware of the latest official departing country advice about travel and the impact this may have on travel insurance coverage and medical repatriation costs in case of ill health from any cause.
- Travellers should contact any travel agents or airlines to get the latest advice on any local travel restrictions or local authority guidance for preventive measures.
- Vulnerable travellers (such as the elderly or those with co-morbidities) should be aware of their potentially increased risk of severe and possibly fatal infection.
- Travellers should be advised to keep up to date with local or departing country advice throughout their trip as it has the potential to rapidly change.
- Travellers should be aware that there may be enhanced screening/monitoring at entry and exit ports.
- Travellers should be aware of returning country advice as to whether they need to self-isolate for a set period even if asymptomatic, and where to get help if they feel unwell within a set period of returning (often 14 days).

cutting-edge knowledge useful for evidence-based decisions to deal now [15], and in the upcoming weeks and months with this new emerging pathogen of world concern, the 2019-nCoV.

Declaration of competing interest

None.

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