Respiratory viruses crossing the species barrier and emergence of new human coronavirus infectious disease

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ABSTRACT
In the context of the current pandemic caused by the new coronavirus SARS-CoV-2, it is essential to note that a new human respiratory virus has been identified almost every year in the last two decades. This brief summary outlines the airborne respiratory viruses discovered among the human population in recent years and their pandemic potential. The focus falls on the coronaviruses: cell interaction, cross-species and human transmission.

ARTICLE HISTORY
Received 11 September 2020
Accepted 23 October 2020

KEYWORDS
Respiratory viruses; crossing species barrier; coronaviruses

Introduction
Most of the emerging human respiratory viruses likely originate from animal or avian representatives, acting as a reservoir for these pathogens, and spread efficiently among the human population through adaptive mutations. The specific etiological role of the newly proven respiratory viruses deserves attention because, in addition to the common acute respiratory diseases, they can cause severe respiratory diseases in children and adults. More often than not the delays in their detection are due to a combination of the impossibility to work with modern diagnostic methods in remote areas and/or lack of systematic search for some less common pathogens.

The phenomenon of newly emerging human viruses and its underlying mechanisms, social and healthcare implications have been well acknowledged [1–3] with a particular focus on Influenza A virus [4], SARS-CoV [5] and most recently SARS-CoV-2 [6, 7]. Against the backdrop of the current COVID-19 pandemic, in this mini-review, we provide an overview of some notable cases of human respiratory viruses to illustrate the role of viral host jumps as a natural phenomenon in the emergence of new infectious diseases in the past 20 or so years.

Human respiratory viruses: social relevance and pandemic potential
The identification of ‘newly’ discovered respiratory viruses provokes growing interest among specialists in infectious diseases, virology and molecular biology. Studies on the pathogenesis of this viral group continue to be relevant as more scientific data are accumulated on the mode of transmission from animals to humans. Since 1997 (Table 1), a dozen human respiratory viruses have been registered: human metapneumovirus (HMPV); the coronaviruses SARS-CoV, NL63 and HKU1; human bocavirus (HBoV); polyomaviruses KI, WU and Merkel cell polyoma virus (MCPyV). Other viruses such as Reston ebolavirus (RESTV), Middle East Respiratory Syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) continue to be monitored with concern due to their unclear behavior and the mortality rate they lead to. As a cause of severe respiratory diseases in humans, the occurrence of the influenza viruses A(H5N1) and A(H1N1) in a possible pandemic potential should be recalled, while the Torque teno virus (TTV) – given its worldwide distribution and possible airborne droplet transmission – continues to arouse uncertainty.

Respiratory viruses crossing the species barrier: a natural phenomenon that needs careful monitoring
The ability of viruses to cross the species barrier is not a new trend. Rather, it is a natural phenomenon caused by environmental and anthropogenic factors...
that has been known to occur for thousands of years. For example, the virus that causes measles in humans (*Measles virus* - MV) originated from the cross-species transmission of *Rinderpest virus*, which is the causative agent of cattle plague, resulting from the domestication of cattle [22, 23]; while *Canine distemper virus* (CDV) affecting animals in canidae and mustilidae families leads to respiratory symptoms and high mortality rate in monkeys [24].

Evidence of crossing the interspecies barrier has been found only in some of the human viruses mentioned in Table 1. For example, the 1997 avian influenza outbreak (the so-called Bird Flu) was caused by the highly pathogenic avian influenza A(H5N1). This outbreak provided the first modern-day evidence of direct respiratory virus transmission from chickens to humans without any other intermediate animal host [8]. Thus, inducing severe and fatal diseases in humans, A(H5N1) poses a serious threat to humanity due to the possible danger of becoming a pandemic virus again through mutations or recombination [25]. The 2009 swine flu pandemic involved the H1N1 influenza virus. This new strain resulted from the reassortment of bird, swine and human flu viruses together combined with a Eurasian pig flu virus [19]. An unusual and characteristic feature of this pandemic was the impact on children and young people, while adults over the age of 60 were spared. An interesting fact remained the clinically severe course of illness in Mexico and North America, while in other parts of the world A(H1N1) passed as mild flu symptoms among healthy people.

Outbreaks caused by Reston ebolavirus (RESTV) have been reported in primates and pigs, while in humans the disease is asymptomatic [26]. For the period 1989-1996, several RESTV outbreaks have been described among monkeys in the Philippines or imported into the United States and Italy from the Philippines [27]. Specific RESTV antibodies have also been shown in humans who have had direct contact with these monkeys, although there were no symptoms of the disease. Studies have concluded that direct and close contact with infected monkeys leads to the transmission of RESTV to humans [28]. In 2008, RESTV was first demonstrated in pigs in the Philippines. The virus has been isolated in several pig farms with increased mortality caused by the Porcine Reproductive and Respiratory Syndrome virus (PRRSV). RESTV was thought to exist in the form of co-infection with the virus causing the underlying disease. Interestingly, workers from these pig farms responded by seroconversion (formation of IgG antibodies) [26]. This fact proved the ‘transmission’ of the virus to humans, and the most probable way for transmission to occur remains through airborne aerosol and through infected animal body fluids. Another hypothesis could be that co-infection with PRRSV facilitates the transmission of RESTV in pigs. Based on the above, we must carefully monitor the behavior of these viruses for the future.

### Indeed, coronaviruses cause epidemics

The potential of coronaviruses to cross the species barrier has been known since the 1960s–1970s, with a hypothesis that the 1889–1890 pandemic was caused by cross-species transmission of *Bovine coronavirus* (BCoV) to humans [29]. The first representatives of the *Coronaviridae* family were isolated in the early 1930s, namely: the virus causing infectious bronchitis in poultry (IBV) [30] and the one causing transmissible gastroenteritis in swine [31]. Later, in the 1960s, another two human respiratory viruses known as human coronaviruses (HCoVs) and murine hepatitis virus (MHV) were classified in separate groups, Alpha- and Betacoronaviruses. The research into the family of

| Table 1. Identification of ‘newly’ discovered respiratory viruses causing human infectious diseases sorted by years. |
|---------------------------------------------------------------|
| Respiratory virus name                                      | Abbreviation | Year | Reference |
| Influenza virus A – Bird Flu                                 | A(H5N1)      | 1997 | [8]       |
| Torque teno virus                                            | TTV          | 1997 | [9]       |
| Human metapneumovirus                                       | HMPV         | 2001 | [10]      |
| Severe Acute Respiratory Syndrome coronavirus               | SARS-CoV     | 2003 | [11]      |
| Human coronavirus NL63                                       | HCoV-NL63    | 2004 | [12]      |
| Human coronavirus HKU1                                       | HCoV-HKU1    | 2005 | [13]      |
| Human bocavirus                                              | HBoV         | 2005 | [14]      |
| Kl polyomavirus                                              | KIPyV        | 2007 | [15]      |
| WU polyomavirus                                              | WUPyV        | 2007 | [16]      |
| Merkel cell polyoma virus                                   | MCPyV        | 2008 | [17]      |
| Reston ebolavirus                                            | RESTV        | 2009 | [18]      |
| Influenza virus A – Swine Flu                                | A(H1N1)      | 2009 | [19]      |
| Middle East Respiratory Syndrome coronavirus               | MERS-CoV     | 2012 | [20]      |
| Severe Acute Respiratory Syndrome coronavirus-2             | SARS-CoV-2   | 2019 | [21]      |
Coronaviruses over the following 40 years was conducted mainly because of the serious economic losses resulting from respiratory and gastrointestinal diseases in domestic animals. Among other reasons was that they are suitable and easy models to study viral pathogenesis. This all changed in 2002, when a new human disease emerged – Severe Acute Respiratory Syndrome (SARS) caused by a coronavirus (SARS-CoV) [32].

**Coronaviruses: structure and virus–cell interactions**

The members of family *Coronaviridae*, order *Nidovirales*, have pleomorphic viral particles sized 120–200 nm and a helical nucleocapsid of 20 nm in diameter. Their form is spherical, but also irregularly and pimple-shaped bugles of 30–220 nm have been described. Peplomers with a length of 10–12 nm and filamentous forms can reach more than 500 nm in size [33]. The viral RNA is a continuous linear strand of positive polarity (which makes it infectious), about 30 kb long, with a sedimentation coefficient of 60–70S and molecular weight of 4–5 × 10^6. The viral RNA plays the role of mRNA to initiate the translation of the replicate by a mechanism known as ribosomal frameshift. This one-nucleotide shift is programmed in two elements: 5'UUUAAAC-3' (identical in all coronaviruses) and a pseudoknot (Ω) located downstream of the first element (5'UUUAAAC_Ω_3') [34]. Next, the replication/transcription complex forms; it contains transmembrane helices associated with cellular membrane remodeling in order to form a convoluted membranes, double-membrane vesicles and vesicle packets that are continuous with the endoplasmatic reticulum. The expression and assembly of the complex lays the ground for viral RNA synthesis, encoding spike (S-S1 and S2), envelope (E), transmembrane (M), nucleocapsid (N) and, in some members, hemagglutinin-esterase (HE). In addition to the genes encoding these structural proteins, the genome contains two open reading frames encoding a replicase [35].

Typically, coronaviruses infect just one or several closely related hosts. The main factor that determines the range of host species and the tissue tropism of coronaviruses is the interaction between the viral S protein and its corresponding host-cell receptor. There are two mechanisms for virus–cell interaction to occur: through expression of a specific receptor in non-permissive cells of a heterologous type, which makes these cells susceptible to the coronavirus; or through alteration of an S protein ectodomain, which changes the species specificity or the tissue tropism of the virus [35].

For instance, HCoV-OC43 and BCoV bind to N-acetyl-9-O-acetyleneuraminic acid on permissive cells and induce hemagglutination activity [36–38]; MERS-CoV spike protein receptor-binding domain (RBD) in complex with the receptor DPP4 plays a role in glucose metabolism, incretin degradation, T cell activation, chemotaxis modulation, cell adhesion and apoptosis [39]. Once translocated to the cell membrane, Glucose Regulated Protein 78 (GRP78) can mediate the entry of SARS-CoV-2 in the cell. This may be the reason for the future circulation of the virus among certain species of apes that can be a source of infection for humans [40]. On the other hand, inhibiting the interaction that occurs between the virus spike protein and the host cell receptor GRP78 would probably decrease the rate of infection [41]. And last, similarities between SARS-CoV and SARS-CoV-2 have identified key
interactions between the virus spike protein and its host receptor angiotensin-converting enzyme 2 (ACE2), which regulate the cross-species and human-to-human transmission [42].

The human diseases caused by the four coronaviruses that were known up to 2002, HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1, are associated with development of mild respiratory symptoms [43, 44], in contrast to SARS and MERS, which are caused by infection with ‘new’ coronaviruses. Genetic, serologic and virologic analyses have shown that all coronaviruses infecting humans have originated from farm animals, bats or rodents, with various and potential intermediate hosts, such as lamas, camels, civets, pangolins or cattle [45, 46]. Since coronavirus infections are zoonotic, understanding their zoonotic origin is a key factor in combating them.

Cross-species and human transmission of coronaviruses

Several examples of crossing the species barrier can be mentioned (Figure 1). (A) Free-range pig farming enables direct contact with bats (including alimentary) This has possibly facilitated Rhinolophus bat coronavirus HKU2 (Rh-BatCoV-HKU2) to cross the species barrier and adapt to pigs, leading to the emergence of a new strain named swine acute diarrhea syndrome coronavirus (SADS-CoV), which – as its name suggests – causes acute diarrhea syndrome in pigs [47]. (B) The process of adaptation of BCoV to the human body and the emergence of human enteric coronavirus (HECV) was likely associated with the domestication of cattle. Cattle have played a key role as an intermediate host in the evolution of murine coronaviruses and the emergence of respiratory Human coronavirus HCoV-OC43 [48]. Some authors have reported a very close genetic relationship between HCoV-OC43 and BCoV, but weaker than the one between HECV and BCoV [29]. This is probably due to the possibility of a co-infection or super-infection to develop (by the alimentary route through ingestion of dead rodents) and of genetic material to get exchanged between murine coronaviruses and BCoV. Thus, one of the generated reassortments could have resulted in the emergence of HCoV-OC43. (C) Rat coronavirus (RCoV) is also considered an ancestor of Human coronavirus HCoV-HKU1, albeit with an unknown intermediate host [48], which is not necessary to have been present because humans come into immediate, everyday life contact with the primary host.

Bats, species engulfed in mysticism, have been used in folk medicine since 3500 BCE to prepare various decoctions for treatment and prophylaxis of trichiasis, depilation, snake bites, sleep prevention and so on [49, 50]. In China, in addition to the application of bat products per os in traditional Chinese medicine, there are also traditions in cuisine associated with the consumption of other wild animals as well [51]. Pangolin meat and blood are used in rheumatism, to ‘unblock’ the meridians and improve the eyesight [52]. It is this species, with Pangolin-CoV circulating in it, which is considered the intermediate host of the newly emerged SARS-CoV-2 [53], likely having originated from bat BetaCoV (Figure 1) (D). What is more, bat coronaviruses cause asymptomatic infections in their natural hosts. Some authors suggest that SARS-CoV-2 did not spread directly from pangolins to humans [54]. Moreover, SARS-CoV-2 shares about 89% identity with bat SARS-like-CoVZXC21, 82% with human SARS-CoV [55] and 50% with MERS-CoV [56]. This reflects the multitude of unknowns in the environmental circulation of the virus. This, as well as the above, is a precondition for bypassing the primary non-specific defense of the human body, thus allowing direct contact of coronaviruses with susceptible cells. All these have contributed to the cross-species transmission of bat and other coronaviruses, and to the emergence of coronavirus diseases in humans.

All the above shows that the biological potential of coronaviruses has arisen owing to the anthropogenic activity providing opportunities for humans to come into contact with these viruses. Accumulating knowledge about coronaviruses and other infectious agents that have plagued humankind over the past 30 years guides us toward revealing the origin and evolution of viruses: a common origin and emergence of new species (quasispecies) as a result of anthropogenic activity.

Conclusions

This mini-review aims to emphasize the fact that almost every year new respiratory diseases caused by ‘new’ or unknown viruses and viruses that we know well can cause serious health problems. The COVID-19 pandemic is a typical example, and it surprises even the greatest experts in the infectious diseases and public health field. We cannot, and should not, assume that viruses we have known so far will not return with even greater force in the future. Rather, we must be prepared for these events with continuous research, development of new diagnostic tests,
antiviral agents and vaccines with the participation of specialists from different countries around the world.

Disclosure statement
No potential conflict of interest was reported by the authors.

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