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New endemic and pandemic pathologies with interhuman airborne transmission through ear, nose and throat anatomical sites

Nuove patologie endemiche e pandemiche con trasmissione aerea interumana attraverso siti anatomici di orecchio, naso e gola

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SUMMARY

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has once again stigmatised the importance of airborne pathogens and their clinical, social and public health impact. Respiratory viruses are transmitted between individuals when the pathogen is released from the upper airways or from the lower respiratory tract of an infected individual. Airborne transmission is defined as the inhalation of the infectious aerosol, named droplet nuclei which size is smaller than 5 mm and that can be inhaled at a distance up to 2 metres. This route of transmission is relevant for viral respiratory pathogens, including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS)-CoV, influenza virus, human rhinovirus, respiratory syncytial virus (RSV) and other respiratory virus families that differ in viral and genomic structures, susceptibility of a population to the infection, severity, transmissibility, ways of transmission and seasonal recurrence. Human respiratory viruses generally infect cells of the upper respiratory tract, eliciting respiratory signs and symptoms, sometimes without the possibility to differentiate them clinically. As seen by the current Coronavirus Disease 2019 (COVID-19) pandemic, human respiratory viruses can substantially contribute to increased morbidity and mortality, economic losses and, eventually, social disruption. In this article, we describe the structural, clinical and transmission aspects of the main respiratory viruses responsible for endemic, epidemic and pandemic infections.

KEY WORDS: SARS, MERS, SARS-CoV-2, COVID-19, H1N1, RSV, pandemic, health system

RIASSUNTO

L'attuale pandemia di SARS-CoV-2 ha ancora una volta stigmatizzato l'importanza dei patogeni respiratori e il loro impatto clinico, sociale e di salute pubblica. I virus respiratori si trasmettono tra gli individui quando l'agente patogeno viene rilasciato dalle vie aeree superiori o dal tratto respiratorio inferiore di un individuo infetto. La trasmissione per via aerea è definita come l'inalazione di particelle aereosolizzate infette di dimensioni inferiori a 5 mm, che può essere inalato a una distanza fino a 2 metri. Questo modo di trasmissione è rilevante per gli agenti patogeni respiratori virali, tra cui il coronavirus della sindrome respiratoria acuta grave (SARS-CoV), la sindrome respiratoria del Medio Oriente (MERS)-CoV, il virus dell'influenza, il rinovirus umano, il virus respiratorio sinciziale (RSV) e altre famiglie di virus respiratori che differiscono per strutture virali e genomiche, suscettibilità delle popolazioni all'infezione, gravità, trasmissibilità, modi di trasmissione e ricorrenza stagionale. Questi virus respiratori umani generalmente infettano le cellule del tratto respiratorio superiore, suscitando segni e sintomi respiratori, a volte senza la possibilità di essere differenziati clinicamente. Come evidenziato dall'attuale pandemia di COVID-19, i virus respiratori umani possono sostanzialmente contribuire ad aumentare la morbilità e la mortalità, con un notevole impatto sociale ed economico. In questo articolo, descriviamo gli aspetti strutturali, clinici e di trasmissione dei principali virus respiratori responsabili di infezioni endemiche, epidemiche e pandemiche.

PAROLE CHIAVE: *SARS, MERS, SARS-CoV-2, COVID-19, H1N1, RSV, pandemia, sistemi sanitari*

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Introduction

The current SARS-CoV-2 pandemic has once again stigmatised the importance of airborne pathogens and their clinical, social and public health impact. Respiratory viruses are transmitted between individuals when the pathogen is released from the upper airways or from the lower respiratory tract of an infected individual [1]. Actually, pathogen droplets released from respiratory events are the primary means of dispersion and transmission of organisms that colonise or/and infect the upper airways. During breathing, talking, singing, shouting, coughing and sneezing, individuals harbouring pathogens in the upper airways may produce small saliva particles (droplets) and aerosols containing those pathogens [2-4]. Airborne transmission is defined as the inhalation of the infectious aerosol, named droplet nuclei which size is smaller than 5 mm and which can be inhaled at a distance of up to 2 metres. This way of transmission is relevant for viral respiratory pathogens, including severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS)-CoV, influenza virus, human rhinovirus, respiratory syncytial virus (RSV) and other respiratory virus families that differ in viral and genomic structures, susceptibility of the populations to the infection, severity, transmissibility, ways of transmission and seasonal recurrence.

These human respiratory viruses generally infect cells of the upper respiratory tract, eliciting respiratory signs and symptoms, sometimes without the possibility to differentiate them clinically. As seen by the current COVID-19 pandemic, human respiratory viruses can substantially contribute to increase morbidity and mortality, economic losses and, eventually, social disruption [5].

Methods

To carry out this narrative review we searched PubMed, Scopus, Google Scholar, EMBASE, Cochrane Library, and WHO websites from 1950 to January 2022 to identify articles discussing structural, clinical and transmission aspects of the main respiratory viruses responsible for endemic, epidemic and pandemic infections.

The chain of transmission for pathogens transmitted through the airborne route: the case of COVID-19

Predicting changes in the spread of COVID-19 requires understanding of the interaction between natural processes, such as host immunity, and interventions such as physical distancing. A framework for natural processes is provided by the coevolution of hosts and viruses. Although it is early in the co-evolutionary history of SARS-CoV-2 and the human host, complementary theoretical insights into the dynamics of host-pathogen interactions are becoming relevant, e.g., the possibility of endemic equilibria [6].

Drivers of disease dynamics can be conceptualised as a sequence of rings in a chain of infection which, in turn, relates to the life cycle of the pathogen and present different opportunities for intervention. The first link in the chain of infection is the pathogen itself. SARS-CoV-2 is an RNA virus, with the potential for high rates of mutation and recombination and therefore a high diversity of genotypes [7]. Mutations may contribute to enhancement of viral proliferation and infection as well as escape from host immune attack [8].

The chain of infection can be interrupted at the point of the reservoir, including other hosts (primary, intermediate) and the wider environment. Currently there is no evidence of animal reservoirs for SARS-CoV-2, and therefore no ongoing transfer to humans, other than from the original hypothesised primary host (bats) in China. SARS-CoV-2 can survive in the abiotic environment with half-lives of up to nine days, depending on the nature of the substrate and the temperature [9]. Coronaviruses can persist in aqueous solutions for several weeks, again with a strong inverse correlation with temperature [10]. Various disinfectants are effective at inactivating the virus and therefore the abiotic environment is a potential target for disruption of COVID-19 dynamics [11].

The third ring is represented by the transfer of the virus between human hosts, which has been the main target of control measures, including use of masks, reduction of social activities, contact tracing, quarantine and physical/social distancing. As with other viruses transmitted through the respiratory route, SARS-CoV-2 is primarily transmitted by droplets, airborne route and contact with contaminated surfaces and fomites (which in turn relate to the properties of the abiotic environment), and by aerosol formation during invasive respiratory procedures. Some concern has been raised by the respiratory shedding of virus which peaks at the end of the first week after infection, just before and as symptoms are developing [12]. Although testing of convalescent COVID-19 patients has provided evidence for persistent RNA shedding, there is no suggestion of chronic carriers of SARS-CoV-2.

The last ring of the chain of infection is represented by the characteristics of the susceptible human host. Host determinants are an important ring in the chain of transmission for infectors and infectees. Indeed, for infectors, tissue and cellular tropism for virus replication can be important determinants for contagiousness and transmission of res-

piratory viruses. Whereas SARS-CoV replicates mainly in epithelial cells of the alveoli, SARS-CoV-2 replicates predominantly in upper respiratory ways and in the bronchial epithelium, thus explaining its more efficient transmission [13]. The Omicron variant of SARS-CoV-2 appears to be more efficient in transmission because tropism for the epithelial cells of the otolaryngological anatomic sites seems higher than for the Wuhan and Delta variants [14]. As a consequence, host nasal or throat viral shedding is an important determinant for contagiousness and transmission.

For influenza A virus, however, otolaryngological site viral shedding alone seems does not completely explain household transmission [15]. Other factors have been hypothesised, including the presence of superspreaders, and presymptomatic shedding. For SARS-CoV-2, levels of viral shedding seem to be similar between presymptomatic and symptomatic infected individuals, thus determining a silent presymptomatic transmission and a consistent fraction of infected individuals from asymptomatic COVID-19 individuals [16,17].

Another important point is the fact that pre-existing immunity and vaccination can "modulate" viral shedding from infectors [18-20]. In the recent forth wave of the COVID-19 pandemic, highly sustained by Omicron, boostering by a third vaccine administration can partly explain the higher rate of asymptomatic or paucisymptomatic SARS-CoV-2 infected individuals, who manifest only congestion, runny nose and sore throat. Passive immunisation in early infected COVID-19 patients has been shown to decrease the rate of hospitalisation for COVID-19 in acute and intensive care units [21]. Similarly, new antivirals have been introduced in clinical practice to decrease the viral load in early infected individuals [22]. Fully vaccination coverage, new vaccines and monoclonal antibodies targeted against new variants are probably the main steps to reduce the burden of susceptible hosts.

From the side of infectees, tissue-specific expression of viral receptors angiotensin-converting enzyme 2 (ACE-2) [23] or glycosylation and glycan expression in the upper and lower respiratory tract may determine not only the most prevalent clinical manifestations, but also may affect contagiousness, as the case of virus-laden aerosols infecting predominantly the nasal cavity [23].

Human genetic factors can also influence susceptibility to SARS-COV-2, including effects via blood group, HLA genotypes and fibroblasts. The major genetic risk factor for severe SARS-CoV-2 infection and hospitalisation seems to be related to variations on human chromosome 3. Finally, the role of innate immunity against COVID-19 is under study, since exposure to microbial signals and to cytokines trains myelomonocytic cells with enhanced effector function against microbial agents.

Below we describe the structural, clinical and transmission aspects of the main respiratory viruses responsible for endemic, epidemic and pandemic infections.

Coronaviruses

Coronaviruses (CoVs), enveloped positive-sense RNA viruses, were isolated for the first time in 1960 as disease-causing agents in humans. There are four genera (alpha, beta, gamma, and delta), with alpha and beta receiving the most attention due to their propensity to cross animal-human boundaries and to cause relevant human diseases.

There are seven known beta human Coronaviruses (HCoVs), including Severe Acute Respiratory Syndrome (SARS)-CoV (SARS-CoV), Middle East Respiratory Syndrome (MERS)-CoV (MERS-CoV), SARS-CoV hCoV-HKU1, and hCoV-OC43, as well as hCoV-NL63 and hCoV-229E from the genus alfa.

The coronaviruses hCoV-HKU1, hCoV-OC43, hCoV-NL63 and hCoV-229E cause asymptomatic or moderate respiratory and gastrointestinal infections, accounting for 5-30% of common colds [24]. However, attention to this family of viruses only began with the first global outbreak caused by the SARS-CoV in 2002. To date, only three highly pathogenic and lethal hCoVs are known, namely SARS-CoV, MERS-CoV and SARS-CoV-2 [25]. In this section we will summarise structural, transmission and clinical findings of this family of viruses.

SARS and MERS

SARS was the first new disease of the 21st century of global interest. The virus was first identified in Foshan, Guangdong Province, China, in mid-November 2002. However, only in February 2003 did the virus spread to Hong Kong, and through international air travel it rapidly spread worldwide [26]. The association of the first SARS-CoV patients with wild animal markets in Guangdong strengthens the hypothesis that SARS-CoV emerged from wild animals (including palm civets) sold at these markets [27]. To confirm this, a CoV strain with a homology similarity of almost 99.9% was isolated from palm civets at wild animal markets able to pass their hosts to humans causing human-to-human transmission [28]. Also, as epidemiological criteria supporting this hypothesis, almost 80% of SARS-CoV patients claimed to have had contact with palm civets during the sporadic occurrence in Guangdong [29]. Furthermore, other authors found that farmed palm civets were free of SARS-CoV, while those sold in animal markets showed high IgG levels for SARS CoV [30]. This corroborates the role of palm civets in the origin of disease.

SARS-CoV is both contagious and virulent. Moreover, due to its incubation period of up to 10 days, it can be spread worldwide by asymptomatic carriers travelling worldwide with no symptoms [31]. By the end of the pandemic in June 2004, there were 8422 cases worldwide with 916 deaths (11% mortality rate) [32]. In Table I, we summarise the main findings.

The virus is spread from person to person through droplets produced by coughing and sneezing. In addition, infection can spread through contact with contaminated droplets on surfaces [33]. Fortunately, numerous studies have shown that regularly used disinfectants such as Clorox, 75% ethanol and fixatives such as formaldehyde and paraformaldehyde cause the virus to lose its infectivity [34].

In September 2012, eight years after the first SARS-CoV outbreak, a new Coronavirus classified as MERS-CoV (Middle East Respiratory Syndrome) was identified in Saudi Arabia [35]. The first MERS cases were reported in Jordan in April 2012, but it was confirmed only later [36]. So far, all MERS infections have been linked to travel or stays in or around the Arabian Peninsula. Most MERS-CoV cases have been reported in Middle Eastern countries, including Saudi Arabia, the United Arab Emirates, Qatar, Oman, Kuwait and Iran [35].

There were 2578 laboratory-confirmed cases of Middle East respiratory syndrome (MERS) from 2012 to 2018. Larger outbreaks occurred in South Korea in 2015 and Saudi Arabia in 2018, with fatality rates of 34.3% in both cases [37].

MERS-CoV is a zoonotic virus that infects people through direct or indirect contact with ill dromedary camels, according to several studies [35,37]. MERS-CoV has been confirmed in dromedaries in the Middle East, Africa and South Asia [38]. The virus's origins are unknown, although based on the examination of multiple viral genomes, it is thought to have originated in bats and been transferred to camels at some point in the distant past.

Both SARS and MERS have an average incubation period of 5-days, and 95% of patients who develop symptoms within 13 days after exposure. In both infections, cough, asthenia, headache, fever, cold, cough and myalgia are common symptoms [39,40]. Also, diagnostic confirmation with a nasopharyngeal molecular swab with real-time Polymerase Chain Reaction (RT-PCR) can be facilitated by accurate history, which enhances the possibility of infection [41,42]. MERS patients have a higher radiological involvement (90-100%) than SARS patients (60-10%). This is linked to a higher need for intensive care and a higher incidence of acute respiratory distress syndrome (ARDS) in MERS patients than with SARS [43,44]. The fatality rate for MERS, which is around 34%, is consistently higher than the 9.6% mortality rate for SARS.

Diabetes, hypertension, renal failure and neoplasia are among the comorbidities that worsen the condition in both SARS and MERS patients. Furthermore, different studies have revealed that older age and male sex are risk factors of poor outcome for both diseases [43,44].

Table I. Main characteristics of SARS-CoV, MERS, SARS-CoV2, VRS and H1N1.

	SARS-CoV	MERS	SARS-CoV-2	RSV	H1N1
First isolation	16 November 2002, Foshan, China	4 April 2012, Zarqa, Jordan	7 December 2019, Wuhan, China	1955, United States	1918, United States
Family	Betacoronavirus, lineage B	Betacoronavirus, lineage C	Betacoronavirus, lineage B	Paramyxoviridae	Orthomyxoviridae
Host receptor	ACE2	DPP4 or CD26	ACE2	CX3CR1	Sialic acid
Reservoir and origin	Palm civets	Dromedary camels	Unclear	Chimpanzees	Pigs
Genome	RNA	RNA	RNA	RNA	RNA
Mode of transmission	Respiratory droplet, Contact	Respiratory droplet, Contact	Respiratory droplet, Contact	Respiratory	Respiratory droplet, Contact
Mortality rate	9.6%	34.3%	4.4%	< 1%	0.03-0.8%
Diagnosis	rRT-PCR	rRT-PCR	rRT-PCR	EIA	rRT-PCR
Blood test results	Lymphopenia and leukopenia	Lymphopenia, thrombocytopenia	Lymphopenia, thrombocytopenia, leukopenia, LDH	Lymphopenia, AST,ALT, PCR	Lymphocytosis and leukopenia
Long sequalae	Yes	Yes	Yes	No	No
Vaccine	No	No	Yes	No	Yes

ACE2: Angiotensin-converting enzyme 2; DPP4 or CD26: Dipeptidyl peptidase-4 (DPP4), also known as CD26 (cluster of differentiation 26); CX3CR1:C-X3-C Motif Chemokine Receptor 1; RNA: Ribonucleic acid; rRT-PCR: Reverse transcription polymerase chain reaction; EIA: enzyme immunoassay; SARS: Severe acute respiratory syndrome; MERS: Middle East respiratory syndrome; SARS CoV2: Severe acute respiratory syndrome coronavirus 2; VRS: Respiratory syncytial virus; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PCR: polymerase chain reaction.

Furthermore, follow-up studies on SARS and MERS patients have showed that long-term sequalae occur in nearly 20-60% of individuals with asthenia, chronic tiredness, reduced lung function and worse quality of life at two years after infection [44-46]. Anxiety, post-traumatic stress disorder and impaired performance at work are also reported in 20% of MERS and SARS patients [47,48].

SARS-CoV-2

The SARS-CoV-2 pandemic began when a significant number of atypical pneumonias were reported in December 2019 in Wuhan, China [49]. Within weeks, a new coronavirus was isolated: SARS-CoV-2. After only few months, the virus had spread to 114 countries and on March 11th, 2020, the WHO declared SARS-CoV-2 as a global pandemic [50]. To date, exactly 2 years after the start of the pandemic, more than 390 million cases with more than 5.7 million deaths are reported [51]. No country in the world is virus free, with significant direct and indirect impact on mortality and control of other communicable and non-communicable diseases, due to a major impact on health services, with outpatient services severely disrupted [52,53].

SASR-CoV-2 is a single-stranded RNA virus with positive polarity (28-32 kb). The virus has four structural proteins: Spike (protein S), which allows the virus to bind to the membranes of the host cells, Envelope (protein E) and Membrane (protein M) combine to form the Nucleocapsid (protein N) capsid, which holds the genome. The S-glycoprotein is what determines the virus' specificity for respiratory epithelial cells; in fact, it is known that SARS-CoV-2 can bind the ACE-2 receptor, which is expressed by cells in the capillaries of the lungs [54,55].

The specific origin of the new coronavirus is unclear, and no theory has been ruled out. A possible zoonotic aetiology has been postulated by several ideas proposed in early investigations (such as SARS and MERS) [56]. In particular, Bungarus multicinctus, a highly venomous snake trafficked in the Wuhan wet market, was suspected by several scientists to be the source of the disease. Since most of the first affected people worked in that market, it was suspected that an early strain of the virus had arrived and spread to the province and adjacent territories. However, another zoonotic option might be the Malaysian pangolin, which is also sold in the Wuhan market [57-59].

It is known that SARS-CoV-2 has more of an indirect cytotoxic action than direct cytotoxicity. In fact, the action of the virus is decoded in this triple activity:

1. cytokine storm: dysregulated or overactive immune responses can cause significant systemic damage. In the patient's lung tissue and peripheral blood, mononuclear cells such as neutrophils and monocytes release high amounts of pro-inflammatory cytokines such as interleukin-6, interleukin-1 and tumour necrosis factor, which are linked to disease severity and death [60,61];
2. hypoxaemic respiratory failure: some of the distinctive clinical features found in individuals with COVID-19 include the direct cytotoxic effects of the virus and the virus-induced reduction in surfactant levels, resulting in atelectasis. The pulmonary derangement of the disease is characterised by hypoxaemia, which occurs without any indication of respiratory distress ('silent hypoxemia') [62];
3. COVID-19-related hypercoagulability: the cytokine storm and virus-induced endothelial dysfunction work together in this process with a significant risk of thrombosis in lungs or extrapulmonary areas [63,64].
4. SARS CoV-2 has a 5-day incubation period, like SARS-CoV and MERS, with clinical features ranging from asymptomatic to severe patterns, where interstitial pneumonia evolves into ARDS causing high mortality [65]. Currently, the mortality rate is of about 4%, but the global scenario for this disease is changing with the start of the vaccination campaign in December 2020 [66] and the appearance of new virus variants.

Going beyond the acute phase, there is increasing evidence about long COVID syndrome, with symptoms related to COVID-19 persistent for 12 weeks after the acute infection episode. In particular, asthenia, myalgia, reduced working capacity can persist in 30-60% of cases [67]. Also, anxiety and depression related to previous SARS-CoV-2 infection appear to be frequent [68].

In addition, multiple variants of the Wuhan type (Alpha, Delta, Gamma, Mu, Zeta, Omicron, and many more) have been identified in the last two years of the pandemic [69,70], which has an influence on both clinical management and global health policy, which we will not address in this paper.

H1N1

H1N1 influenza was first isolated in military troops during the 1918-1919 pandemic in the United States. One third of the world's population was affected, around 50 million people died globally, of whom about 675,000 in the United States [71]. Subsequent outbreaks of H1N1 swine flu were recorded in the United States in 1976 and more recently in April 2009, when a reassortant triple strain of influenza (H1N1) caused 2000 deaths in Mexico [72].

Influenza viruses are very unstable RNA viruses and can be found in wild animals as reservoirs, allowing genetic mutations and reassortments [73]. Currently circulating in humans as seasonal influenza, H1N1 and H3N2 [74] are subtypes of influenza A that originated in birds and pigs [75].

Until 1979, these strains had been the only one present in Europe isolated from pig farms and with a clear lineage relationship to the 1918 pandemic virus [75]. Subsequently, since the 1980s, new strains of H1N1 swine influenza have been isolated, such as the H1avN1 virus, showing rapid and persistent adaptation in mammals [76]. Subsequent viral reassortments led to the development of different genotypes such as H1N2 (H1huN2) with a higher capacity for gene reassortment and spreading [77].

Crucial for the pathogenesis of the virus is the HA protein, which is capable of drift and anti-hygienic shifts due to the flexibility of the viral RNA-dependent RNA polymerase [78]. Indeed, previous pandemics are thought to have been caused by changes in the HA protein, including reassortments and mutations between animals and humans. Clinically, influenza has a short incubation period of about 2 days (range, 1-5 days). The clinical presentation may range from moderate to severe patterns, with fever, cough, bacterial overinfection and, in severe circumstances, acute respiratory distress syndrome (ARDS) and acute respiratory failure [79].

The H1N1 virus is now a common human flu virus with low mortality rate (0.03-0.8%), which is related to comorbidities and age of patients [80]. The use of the 2009 H1N1 influenza virus vaccine has recently been approved, with positive implications for pandemic containment, patient outcomes and maintenance of healthcare systems [81].

Respiratory syncytial virus, RSV

The human respiratory syncytial virus (RSV) is an enveloped, non-segmented negative-strand RNA virus of family *Paramyxoviridae* able to cause respiratory tract infections especially in children with a seasonality between December and February and between April and May [82,83]. It was first isolated in chimpanzees in 1955 and subsequently in infants with severe pulmonary disease [83].

The clinical presentation varies from mild infection of the upper respiratory tract or otitis media to severe and life-threatening involvement of the lower respiratory tract [84]. The most common form in infants is bronchiolitis, with a hospitalisation rate of about 3%. Preterm delivery, chronic lung disease of prematurity, low birth weight, Down syndrome together with other chromosomal abnormalities, and neuromuscular dysfunction are also risk factors for RSV-related hospitalisation or worsening of the condition and admission to the critical care unit [85]. RSV symptoms peak around day 5 and usually improve after 7-10 days. Due to the prolonged recovery of the ciliated cells, the cough may last for up to four weeks [86]. The diagnosis of acute bronchiolitis is clinical and microbiological based on presentation with typical respiratory signs and symptoms, which may be accompanied by lethargy, irritability and poor nutrition. Nasopharyngeal washes or tracheal secretions are better specimens for confirming RSV than nasal swabs, although nasal swabs are the most widely used due to their convenience. Because of the short timeframe (less than 30 minutes), low cost and objective end point, enzyme immunoassay is the quick detection test most used. A chest X-ray may show a radiological image of pneumonia, with enhancement of the bronchial pattern. In addition, especially in children admitted to intensive care, concomitant battery overinfection is frequent. The mortality rate is low, below 0.5/0.8%, but with higher mortality in low-income countries due to the scarcity of resources and neonatal intensive care [87,88].

Conclusions and recommendations

In the last 20 years we have experienced three different Coronavirus pandemics with progressively greater spread and impact on life and health systems, and learned to live with RSV and H1N1 epidemics.

Some reflections can be drawn from this:

- training on epidemic preparedness and response must be an integral part of the educational and cultural background of health workers in order to always be prepared for what is no longer a sporadic or episodic event;
- a One Health approach, with high respect for nature and animals, is the basis for the prevention of infectious diseases. Deforestation, the use of exotic animals as food or medicine and intensive animal husbandry may be at the root of current pandemics and responsible for future ones;
- the indirect impact on other diseases cannot be neglected. Health systems must have plan to avoid disruption of diagnostic and therapeutic pathways;
- team working should be central in the health section. Respiratory pathogens require a strong co-operation of different specialists: infectious diseases specialists, microbiologists, ENT specialists, pulmonologists and epidemiologists. Only thinking system-wide and working together will it be possible to tackle current and future pandemics;
- vaccination is proving to be one of the most successful strategies in the fight against SARS-CoV-2. Allowing vaccination worldwide, including in low-income countries, is necessary for justice but also to avoid the emergence of new variants;
- development of therapeutic strategies is a key pillar to improve the outcome of our patients;
- developing cost-effective point-of-care tests can be crucial for widespread diagnosis in remote areas, more investments are needed on this field;

- long-term effects on patients and healthcare personnel must be constantly monitored;
- strengthening networks of molecular genomics laboratories worldwide is indispensable for nipping future epidemics in the bud.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

FDG and NP conceived the idea. Both authors reviewed the literature, drafted the manuscript, critically revised, and approved the final version before submission. Both authors have read and agreed to the published version of the manuscript.

Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirments of the World Medical Association's Declaration of Helsinki.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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