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Review Article

The COVID-19 pandemic – How many times were we warned before?

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ABSTRACT

Infectious diseases are known to act in both predictable and unpredictable ways, which leads to the notions of emerging and reemerging infectious diseases. Emerging diseases with their disastrous consequences might be surprising and unpredictable, but they could be foreseen. For instance, some emerging diseases and recently the coronavirus disease 2019 (COVID-19) were the reason for papers published by the World Health Organization (WHO) and other researchers addressing the likely pathogens causing future outbreaks, according to the reports of the WHO in 2016 and 2018. Although it might seem like a wisdom in retrospect, several studies had already indicated possible future outbreaks caused by coronaviruses. Announcements, which may be viewed as “warnings,” appeared since the emergence of the first coronavirus-related outbreak caused by severe acute respiratory syndrome coronavirus (SARS-CoV) in the winter of 2002–2003 and a later outbreak caused by the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012–2013. Therefore, we were curious to review the medical literature prior to the COVID-19 pandemic with an aim to enumerate and evaluate studies addressing and warning against future outbreaks, and surprisingly pandemics, of members of coronaviruses. Interestingly, we found numerous studies that correctly predicted the current pandemic of COVID-19. While this part is highly interesting, how authorities reacted and prepared for warnings, if any, and how will they get prepared for the next warnings are our main messages. Taking these points into serious consideration will certainly aid in analyzing reports regarding possible future outbreaks as well as in developing various strategies for prevention and coping with such epidemics.

1. Introduction

As the pandemic of coronavirus disease 2019 (COVID-19) continues to emerge worldwide with no country being spared [1], scientists and researchers are relentlessly looking for the origin of SARS-CoV-2 [2]. However, previous outbreaks of coronaviruses, particularly the SARS epidemic that emerged in 2002 [3] and later the MERS outbreak in 2012 [4], might in fact be viewed as a warning of future human coronaviruses-related pandemics. The close resemblance of the viral genome structures of SARS-CoV-2 and SARS virus (SARS-CoV) [5] makes the assumption more accurate.

Coronaviruses with the subfamilies or genera designated as Alpha, Beta, Gamma, and Delta belong to the large family named “Coronaviridae” [6]. While not all the genera are human pathogens, human coronaviruses are mainly respiratory pathogens that cause a wide range of respiratory-related symptoms and diseases [7]. In addition, coronaviruses have shown through history, particularly in the last decades, their ability to mutate while passing through various species, eventually

resulting in human pathogens responsible for several outbreaks such as SARS and MERS and even large pandemics as the COVID-19 pandemic [8]. A review of the medical literature long before the current pandemic of COVID-19 showed that a pandemic could emerge in the future caused by mutant members of the Coronaviridae, particularly those derived from bats [9]. Moreover, the characteristics of bat-derived coronaviruses and their ability to infect new species leading to human pathogens were previously reported [10].

In a timeline fashion and by dividing the time periods from the outbreak of SARS in 2002 to that of MERS in 2012 and then from MERS to the current COVID-19 pandemic, we reviewed the medical literature in terms of previous “warnings” or more precisely “predictions,” “announcements,” and reports of possible and probable future pandemics caused by members of the Coronaviridae family. The frequency of mention of those statements, the evidence presented, and the response of international organizations such as the World Health Organization (WHO) were analyzed and presented. The “pre-COVID-19” papers and studies concluding those aspects were viewed as warnings, and thus,

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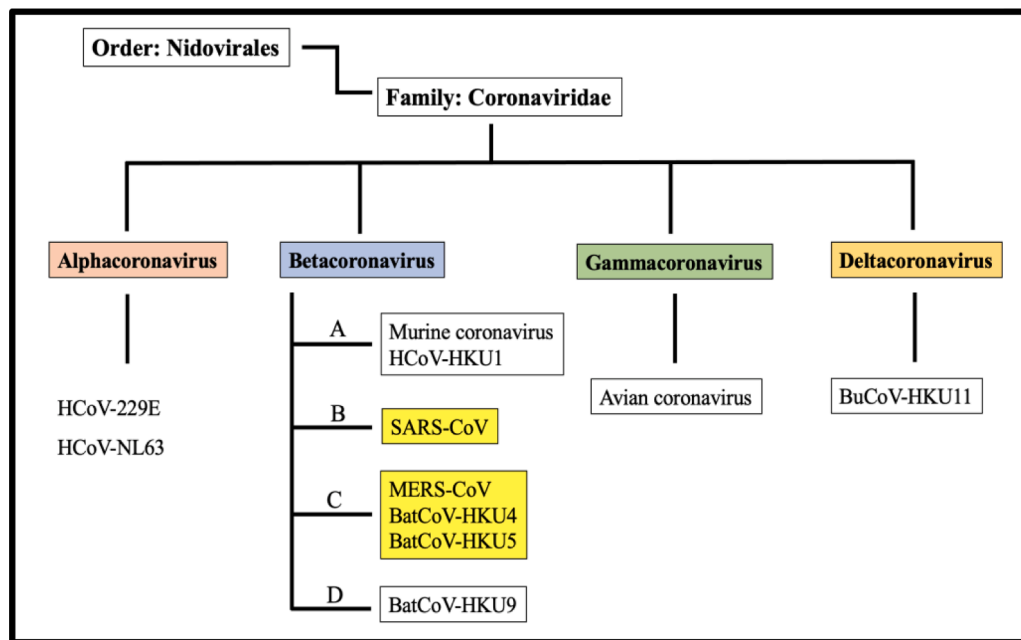


Fig. 1. The family “Coronaviridae”. SARS and MERS are highlighted in yellow.

how many times we were warned before was the aim of our study.

1.1. The family of coronaviruses

The Coronaviridae along with Arteriviridae, Mesoniviridae, and Roniviridae are families belonging to the Nidovirales order. The Coronaviridae family consists of 4 subgroups: Alpha, Beta, Gamma, and Delta coronaviruses (Fig. 1) [11]. All viruses in the Nidovirales order are non-segmented positive-sense RNA viruses having some of the largest described RNA genomes, with some members having up to 33.5 (kb) genomes [12]. Members of the Nidovirales order are also known to have a highly conserved genomic organization with the following features: a large replicase gene preceding structural and ancestry genes, unique enzymatic activities encoded within a large replicase-transcriptase polyprotein, expression of many nonstructural genes by ribosomal frame-shifting, and expression of downstream genes by synthesis of 3' nested subgenomic mRNAs [13]. The differences in the members of the order lie in the numbers, types, and sizes of structural proteins. Such differences constitute the alterations in structure and morphology of the nucleocapsids and virions [7].

Initially, coronaviruses were believed to cause mild, self-limited respiratory infections in humans; however, the SARS outbreak proved that coronaviruses are capable of causing more severe respiratory symptoms [14]. Of the 4 established human coronaviruses, two originated from alphacoronaviruses, while the remaining two from betacoronaviruses. Interestingly, these viruses were isolated nearly 50 years ago [15–17]. It is important to note that Betacoronavirus is the genus from which SARS and MERS evolved.

1.2. Animal origin of human pathogenic coronaviruses

Retrospectively, epidemiological data showcased that the index case of SARS had contact history with game animals. Following that, serological studies revealed a higher prevalence of anti-SARS-CoV IgG antibodies in animal traders as compared to that in the general population [18]. Among animals in live markets, a racoon dog and masked palm civets (*Paguma larvata*) were initially highlighted for displaying SARS-CoV-like viruses almost identical to SARS-CoV [19]. Moreover, killing all masked civets in the markets resulted in a halt in reporting of SARS-CoV [20]. Wild or farm civets with no exposure to the animal

markets were predominantly negative for SAR-CoV [21]. This indicated that masked civets are a potential augmenting intermediate host for SARS-CoV but are not likely to be the natural reservoir for the virus. Furthermore, 80% of the variety of species in the Guangzhou animal markets were shown to manifest anti-SARS-CoV antibodies [22]. The potential for these organisms to be an amplifying intermediate should not be ignored as all of these seem to be the final hosts for SARS-CoV [18].

Later, investigations identified similar coronavirus in bats, SARS-related *Rhinolophus* bat CoV HKU3 (SARSr-Rh-BatCoV HKU3), and Chinese horseshoe bats [23]. The horseshoe bats display anti-SARS-CoV antibodies alongside the genomic sequences of SARSr-Rh-BatCoV HKU3 [24,25]. The latter with other bat coronaviruses were shown to share 88–92% nucleotide sequence homology. In fact, these studies constitute the basis for the notion that bats could potentially be the host for emerging human pathogenic coronaviruses.

Similarly, phylogenetic cluster analysis showcased MERS-CoV belonging to the same group as bat CoV-HKU4 and CoV-HKU5. Like bat CoV-HKU4, MERS-CoV utilized the dipeptidyl peptidase 4 (DPP4) for the entry of virus into cells [26]. Studies highlighted RNA-dependent RNA polymerase sequences of MERS being phylogenetically similar to those in bat Beta-CoV obtained from Africa and Europe [27,28]. Studies in the Middle East and Africa illustrated dromedary camels to be seropositive for MERS-CoV-specific neutralizing antibodies [29,30]. Moreover, MERS-CoV isolated from nasal swabs of dromedary camels was identical to the one found in humans. This further supported the theory addressing camels as the definite reservoir of MERS [31]. In this regard, experimentally infected camels showed mild infection and massive viral shedding of MERS-CoV [32]. It is important to underline that camels shed MERS both through respiratory and fecal routes. Surprisingly, the majority of confirmed cases had no history of camel contact, which served to identify human-to-human transmission as the main source of infection or showcase the possibility of another route involving a currently unknown species [33].

Interestingly, SARS-CoV-2 shows more than 96% homology with bat CoV RaTG13 identified in *Rhinolophus affinis* bats [34]. However, the variations between SARS-CoV-2 and RaTG13 are significant to establish a parental relationship. This does not necessarily deny bats being the intermediate host for SARS-CoV-2, but it highlights that there could be another potential animal host, most likely among the species found in

Table 1

A summary of the reports and papers addressing and warning against future outbreaks related to coronaviruses.

Author	Date	Conclusion (“Warnings”)
WHO [47]	2003	Status of SARS-CoV outbreak – outlined major takeaways for the future from the outbreak.
Snell et al. [48]	2004	Highlighted the potential for SARS-CoV to cause future pandemics.
Tapper et al. [49]	2006	Underlined SARS as an emerging viral disease and a public health concern.
Woo et al. [50]	2009	Emphasized interspecies jumping as a mechanism with which new coronaviruses can cause outbreaks.
Chan et al. [61]	2012	Urged authorities to not rule out MERS’ potential for a SARS-like pandemic.
Ge et al. [64]	2013	Isolation of a live SARS-like coronavirus from bat, which is capable of invading human cells through the ACE2 receptor.
Graham et al. [65]	2013	Suggested that the human orthologue receptors might be naturally recognizable for several bat coronaviruses.
Menachery et al. [66]	2015	Demonstrated that a SARS-like coronavirus in bats has potential to infect humans by using the ACE2 receptor.
WHO [67]	2015	R&D Blueprint initial list of pathogens: preparing the priority pathogen list for the first time. SARS-CoV and MERS-CoV were present in the list.
WHO [69]	2016	Plan of action for R&D Blueprint: the methodology of preparing the priority pathogen list was finalized.
Hu et al. [71]	2017	Three new SARS-CoVs capable of using human ACE2 for cell entry were identified.
WHO [70]	2017	R&D Blueprint list of pathogens updated: SARS-CoV and MERS-CoV maintained their position in the list.
WHO [54]	2018	Status of MERS-CoV outbreak: issued warnings and precautions against the emergence of new MERS outbreaks.
WHO [72]	2018	(R&D) Blueprint list of pathogens update: SARS-CoV and MERS-CoV still retained their place.
Wang and Anderson [74]	2019	Bat-borne viruses, among them coronaviruses, carry the highest risk for the emergence of new outbreaks.
Wong et al. [75]	2019	Bats are the major host for zoonotic transmission of viruses to humans. Wildlife wet markets and restaurants in southern China are the potential places for the next transmission of bat coronaviruses to humans.
Fan et al. [76]	2019	It is reported that 10% of bats in China were positive for SARS-associated CoV nucleotide, and among all the coronaviruses they carry, some of the coronaviruses can use human ACE2 receptor for cell entry. The authors claimed that China is the most probable place for future coronavirus outbreaks.

the Wuhan seafood wholesale market, where many of the initial COVID-19 cases were located [35]. Recent studies presented a potential association with endangered small mammals known as Pangolins (*Manis javanica*) [36].

1.3. The 2002–2003 SARS outbreak

SARS was the first global outbreak of the 21st century with the first case reported in Foshan, China, in November 2002 [32]. The main symptoms of the disease were those mimicking influenza or atypical pneumonia, including fever, dry cough, malaise, myalgia, and headache [37]. Gastrointestinal symptoms and asymptomatic infections were also documented [38,39]. SARS-CoV caused mortality in some patients by progressing to pneumonia and respiratory failure [40]. The early cases were among people in the food industry and medical professions [41]. Infection occurred through either direct or indirect contact with patients. Until February 2003, the human-to-human transmission occurred only in mainland China. However, a physician, originally from Guangdong Province, who traveled to Hong Kong on February 21, 2003, while being infected with SARS-CoV transmitted the disease to 10 people in the hotel. Infected individuals spread the outbreak further to Hong Kong, Singapore, Canada, and Vietnam, leading to tertiary cases [42].

Following the spread, the WHO was notified by the end of February 2003. As a result, the WHO issued a global alert in March 2003 and established an international network of laboratories to reveal the etiological agent of the disease. A previously unrecognized coronavirus, SARS-CoV, was identified as the causative agent by April 2003 and subsequently sequenced by several laboratories [43]. The rapid sequencing of the virus with the help of cutting-edge molecular techniques and global efforts enabled to develop highly specific diagnostic tests and to track the pandemic [44]. By the beginning of the summer of 2003, SARS-CoV had spread to over 30 countries, causing 8096 reported cases and 774 deaths with a case fatality rate of approximately 10% [16]. China* and Hong Kong were the hot spots of the outbreak reporting most of the cases within the first 8 months of the outbreak. The WHO declared the pandemic is over in July 2003. Four additional cases were reported until late 2004, but none of them caused mortality or secondary spread [45].

In terms of origin, since the beginning of the outbreak, several studies have been conducted to reveal how SARS-CoV originated. Due to early epidemic studies indicating an animal origin, the efforts were focused on detecting SARS-CoV-like viruses among wildlife animals [45]. In 2003, Guan et al. [19] isolated SARS-CoV for the first time from Himalayan palm civets (HPCs) and a raccoon dog from a live animal market in Guangdong, China. At the same time, Li and colleagues [46] identified the metalloproteinase, angiotensin-converting enzyme 2 (ACE2) receptor as the functional receptor for SARS. The authors demonstrated that S proteins of SARS-CoVs isolated from infected civets and humans were capable of binding to human ACE2. Following these findings, the research community raised the question of whether civets are the natural reservoir or amplifying host. In 2005, two groups showed independently that horseshoe bats in the genus *Rhinolophus* are the natural reservoir of SARS-like coronaviruses [23,25]. Consequently, the medical community assumed that SARS-CoV originated from bats and was transmitted to humans via an intermediate host. To summarize, the features of SARS-CoV and the sequencing of its whole genome, the identification of the host receptor responsible for virus entry, the molecular characteristics of viral-host interaction, and studies for the development of diagnostic assays and vaccine candidates have been well documented.

1.4. Following the SARS outbreak

2003

On May 20, 2003, the WHO issued a report called “SARS: Status of the outbreak and lessons for the immediate future” [47]. In this report, the WHO warned that SARS could remain a threat for a variety of reasons such as:

- (1) SARS epidemiology is poorly understood, and diagnostic tests are limited, thereby making early detection difficult.
- (2) Difficulty of isolation and quarantine.
- (3) Coronaviruses are notorious for high mutation rates with an increased potential for outbreaks in the future.
- (4) Difficulties with vaccine development.

The WHO also identified the following concerns:

- (1) Inadequate surge capacity in hospitals and public health systems.
- (2) Healthcare providers themselves being the victims of the disease.
- (3) Shortage of expert staff to coordinate national and global responses to a rapidly evolving public health emergency.
- (4) In some cases, the need for hasty construction of new facilities; in other cases, hospitals being closed.
- (5) The power of poorly understood infectious diseases to incite widespread public anxiety and fear, social unease, economic losses, and unwarranted discrimination.

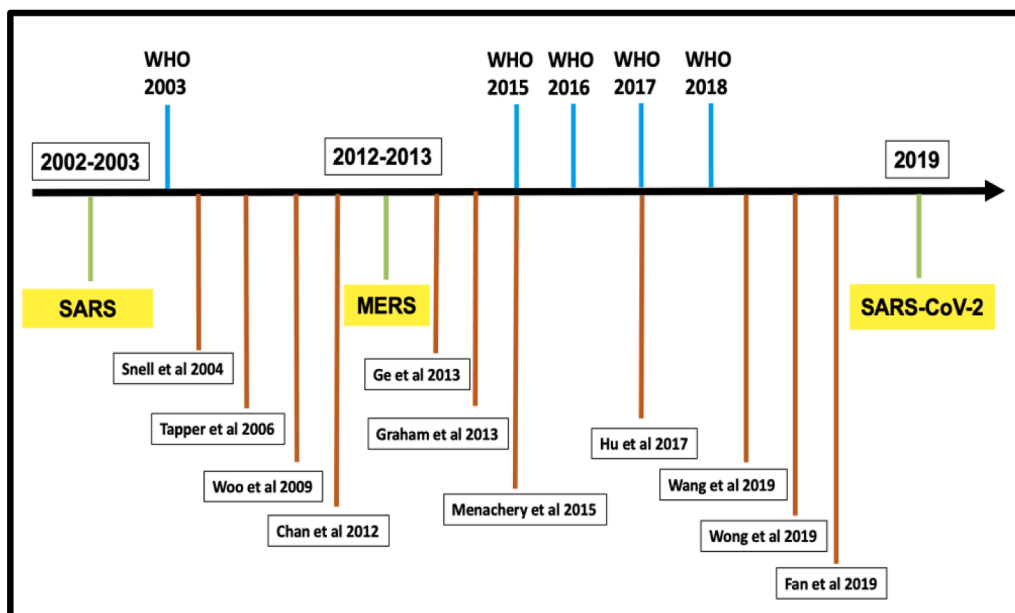


Fig. 2. Reports in correlation with coronavirus outbreaks in a timeline from 2002 until 2019. WHO: World Health Organization.

2004

In June 2004, Snell [48] wrote that despite optimism regarding the novel respiratory viruses at that time, infections such as SARS and influenza still pose a risk. The study also highlighted the importance of areas of intensive livestock and marketing in propagating such infections. The author emphasized that because of the low infectivity of SARS, the epidemic could have been far more devastating if SARS showed more transmission rates.

2006

SARS was addressed as an emerging infectious disease alongside other pathogens in a study on emerging viral diseases and infectious disease risks published in March 2006 [49].

2009

Woo and colleagues [50] published an article titled “coronavirus diversity, phylogeny and interspecies jumping.” In their study, the authors showed that prior to the SARS outbreak, there were only 10 complete coronavirus genomes available. In contrast, by 2008, the number increased to 26 genomes. The genomes included human coronaviruses, bat coronaviruses, and coronaviruses native to other mammals. The study underlined rapid interspecies jumping of coronaviruses and the presence of more closely related coronaviruses among more distant organisms. The paper emphasized that interspecies jumping from zoonotic outbreaks could potentially reach humans and cause a devastating outbreak.

1.5. The 2012–2013 MERS outbreak

In June 2012, a novel coronavirus was isolated from the sputum of a 60-year-old man who had died from acute pneumonia in Jeddah, Saudi Arabia [37]. Due to its geographical appearance alongside severe respiratory symptoms, the isolated coronavirus was named as the Middle East respiratory syndrome coronavirus (MERS-CoV). MERS-CoV infection manifested as flu-like symptoms such as fever, myalgia, dry cough, malaise, and headache, similar to that* of SARS-CoV. However, the infection could progress to pneumonia with acute respiratory distress syndrome, septic shock, and multiorgan failure with high mortality rates [51]. Asymptomatic infection was also documented [52]. According to the MERS situation update report issued by WHO in February 2022, a total of 2585 cases were reported globally and 890 of them died with a case-fatality rate of 34.4%, which is more than three times of the fatality

rate of the SARS epidemic [53]. In contrast to SARS, the outbreak of MERS has not disappeared completely as new cases are still being reported in a continuous but slow manner, according to the report.

Even though the MERS epidemic reached more than 20 countries since its first discovery, the virus was endemic in Arabian Peninsula, and 80% of cases have occurred in Saudi Arabia [54]. In fact, the epidemiology of MERS infection showed a slow and continuous transmission in Arabian Peninsula with occasional flare in cases and limited outbreaks in different regions other than Arabian Peninsula. Because MERS-CoV infects humans through zoonotic transmission and human-to-human transmission is rare, the outbreaks are mostly limited to the Gulf region [55]. Nevertheless, secondary outbreaks of MERS were reported in other countries by travel, such as the outbreak in South Korea in 2015 [56]. These outbreaks, however, claimed to be caused by human-to-human transmission among household contacts and in healthcare settings [57]. In the case of the 2015 outbreak in South Korea, a single infected traveler spread the disease to healthcare professionals and other patients in the hospital, resulting in more than 180 hospital-related reported case [58].

The complete genome of MERS-CoV was sequenced and published in November 2012 [26]. In 2013, Raj et al. [59] identified the dipeptidyl peptidase 4 (DPP4; also known as CD26) as a functional receptor for MERS-CoV. Phylogenetic analysis of the novel virus revealed high similarity with the bat Betacoronaviruses: BtCoV-HKU4 and BtCoV-HKU5. Since the contact between bats and humans is not very likely in Arabian Peninsula, other intermediate hosts were considered. In this regard, the MERS-CoV has been isolated primarily from the nasal swabs of dromedaries in the Middle East, thus showing that camels are a potential source of MERS-CoV infection [60]. The researchers suggested that MERS-CoV originated in bats and were transmitted to camels in the past and then eventually transmitted to humans. However, MERS-CoV has never been isolated from bats; hence, the origin of the virus could not be fully revealed.

1.6. Following the MERS outbreak

2012

Chan and colleagues [61] concluded that MERS-CoV, called HCoV-EMC at that time, is less transmissible than SARS-CoV, but urged healthcare authorities to remain alert and not to rule out a SARS-like

pandemic.

Based on the WHO recommendations at the time, Saudi Arabia issued no Hajj travel restrictions for the Hajj in October 2012 and issued recommendations only for proper hand hygiene and cough etiquette [62].

2013

In February 2013, the WHO issued a global alert and response update urging international communication regarding MERS infections and reporting all cases to the WHO [63].

In the same year, Ge et al. [64] isolated a live SARS-like coronavirus from bat which was capable of using ACE2 receptors for cell entry in humans, civets, and Chinese horseshoe bats. The authors provided the clearest evidence on the origin of SARS-CoV in bats by that time. Additionally, they highlighted the importance of developing pathogen discovery programs to detect high-risk wildlife groups and hotspots of disease emergence.

Furthermore, Graham and colleagues [65] in a paper titled “a decade after SARS,” summarized various strategies for coping and controlling emerging coronaviruses. The authors illustrated that several bat coronaviruses might be naturally able to enter human cells by recognizing the human orthologue receptors. The authors claimed that the growing density of human population made interaction with wild animal habitats easier. According to the study, an increase in the average age of the population and the number of immunocompromised patients facilitate the emergence of future coronavirus outbreaks. The importance of developing efficient strategies for rapid diagnosis and treatment and the development of vaccines against emerging coronavirus infections were addressed and emphasized.

2015

In 2015, Menachery and colleagues [66] demonstrated the potential pathogenicity of SARS-like coronavirus, SHC014-CoV, which circulated in Chinese horseshoe bat populations. The authors created a chimeric virus by merging SHC014-CoV spike protein with mouse-adapted SARS-CoV backbone. The chimeric viruses efficiently bind to human ACE2 receptor orthologs and replicated in primary human airway cells, eventually achieving *in vitro* titers equivalent to the epidemic strains of SARS-CoV. The study concluded that SARS-like coronaviruses that are capable of entry into human cells through ACE2 receptors pose a great risk for the emergence of new coronavirus outbreaks.

By the end of the same year, 2015, a group of WHO experts met in a workshop in Geneva to prepare an initial list of the top emerging pathogens likely to cause severe outbreaks in the near future. Among other viruses listed, highly pathogenic emerging coronaviruses relevant to humans such as SARS and MERS-CoV were mentioned [67]. The list was prepared under the platform of the research and development (R&D) Blueprint, which was established by WHO to increase preparedness for future epidemics. According to the R&D Blueprint, the WHO works to develop R&D roadmaps for each pathogen in the priority list. This list is updated regularly, where the last version mentioned COVID-19 as the first issue to deal with, alongside SARS and MERS-CoV [68].

2016

The WHO convened to declare a plan of action to support and elaborate on R&D Blueprint. During the meeting, infectious disease epidemics were addressed as a clear and persistent risk to global health and economy [69]. The members recognized the importance of research as an essential weapon in the fight against any epidemic. Most importantly, the methodology of preparing the priority pathogen list was determined in the meeting. The methodology employed Delphi technique, questionnaires, multi-criteria decision analysis, and expert review to identify relevant pathogens likely to cause future outbreaks.

2017

In January 2017, the WHO R&D Blueprint meeting was conducted to review the list of priority diseases. Virologists, bacteriologists, vaccinologists, public and animal health professionals, and infectious disease clinicians gathered to update the pathogen list based on the tailored

prioritization methodology that was established in 2016. Unsurprisingly, SARS and MERS-CoV maintained their places in the updated version of the list [70].

In November 2017, Hu et al. [71] carried out a 5-year surveillance of SARS-related coronaviruses (SARSr-CoVs) in a cave inhabited by multiple species of horseshoe bats in Yunnan Province, China. Three new SARSr-CoVs capable of using human ACE2 receptors for cell entry were identified. The authors warned that recombination within the species inhabiting the cave may lead to future emergence of SARS-like outbreaks.

2018

In 2018, the WHO issued a report titled “MERS Global Summary and Assessment of Risk” [54]. In this report, the WHO warned against the emergence of new MERS outbreaks and provided preventive recommendations. The most urgent needs mentioned to prevent large MERS-CoV outbreaks were as follows:

- 1 To develop a better understanding of the transmission of MERS-CoV from animals and environmental sources to humans.
- 2 To identify risk factors for human or environmental infection in the workplace and health care settings.
- 3 To improve community studies and surveillance for community-acquired pneumonia.

In the same year, R&D Blueprint updated the priority list for pathogens based on the same methodology mentioned earlier [72]. Again, highly pathogenic emerging coronaviruses relevant to humans, including SARS-CoV and MERS-CoV, were present among the six other diseases in the list [73]. The prioritization criteria were mainly based on human transmissibility, medical countermeasures, disease severity, and human/animal interface.

1.7. The pre-COVID-19 period

The year 2019, the year COVID-19 emerged, was surprisingly the year important papers were published addressing a possible emergence of a large outbreak related to coronaviruses, months before the pandemic started. These are summarized as follows:

- In February 2019, Wang and Anderson [74] stated that bats are one of the richest virus reservoirs among mammals in terms of viral diversity, physiological variations in their body temperature, diverse habitats, and dietary preferences. The authors speculated that future outbreaks are more likely to develop from bat-borne viruses by assessing the spillover risk of the new strains of bat viruses related to ones that caused outbreaks in humans before. They concluded that among all bat viruses, coronaviruses pose the highest risk of emerging new outbreaks because of its great genetic diversity, large RNA genome carrying high mutation chance, and its previous spillovers to humans and animals.
- In February 2019, Wong and colleagues [75] listed features of bats making them the number one suspect of zoonotic transmission of viruses to humans. In their article, the authors stated that bats have the second largest number of species among all mammals. According to the authors, the great genetic diversity of bats enables them to harbor a large variety of viruses enhancing the chance of interspecies virus transmission. Furthermore, the flying capability of bats enables them to transmit the viruses they harbor to long distances and to different species. The authors focused on the interspecies jumping of bat coronaviruses and pointed out the wildlife wet markets and restaurants in Southern China as a potential location for the next bat to human spillover events. Finally, the authors suggested more detailed and comprehensive surveillance of risky geographical areas to predict and prevent future coronavirus outbreaks in humans.
- Fan et al. [76] published a paper on viral diversity, reservoir hosts, and the geographical distributions of bat coronaviruses in China in

March 2019, 9 months before the first reported SARS-CoV-2 case. To the best of our knowledge, this is the last study or “warning” against a possible outbreak before the COVID-19 pandemic started. The authors reported that 10% of bats in China were positive for SARS-associated CoV nucleotide, and some of the viruses which they carry can use ACE2 receptor for entry to the human cells as SARS-CoV. In their paper, the authors warned against a potential spillover of the SARS-CoV-resembling bat coronaviruses to humans where China could be the source of a new emerging outbreak.

A summary of the reports and papers addressing and warning against future outbreaks related to coronaviruses is presented in Table 1. Similarly, in a timeline presentation, the leading papers and reports are illustrated in Fig. 2.

2. Conclusion

Previous warnings against a future outbreak of members of the coronaviruses were numerous and generated by independent researchers as well as by the WHO and the R&D Blueprint forum. For instance, the importance and valuable efforts made by the R&D Blueprint under the WHO, their meetings, list of priority pathogens, and the messages concluded cannot be overemphasized. The WHO 2003 report regarding the SARS epidemic almost perfectly applies to the COVID-19 pandemic that emerged 17 years later, in terms of concerns and need of actions. Unfortunately, the calls of the WHO for increased medical infrastructure, hospital capacity, and adequate supply of PPE remained largely unanswered from the original SARS epidemic. The response for such calls and warnings were in fact very few to absent. This leaves no surprise of how unprepared countries have been in dealing with the pandemic of COVID-19, in terms of hospital and intensive care unit (ICU) beds, mechanical ventilators, and platforms for possible vaccine candidates, among others. Taking into considerations the reports issued through the years is of huge importance in coping with infection-related human disasters such as the COVID-19 pandemic. Similarly, close monitoring over emerging pathogens likely to cause human outbreaks along with investing in vaccine development would save very valuable lives and time. Among the unanswered questions following COVID-19, with regard to the preparedness for future pandemics, “have we understood the lesson?” and “will we be better prepared for the next time?” require urgent answers.

CRedit authorship contribution statement

Naim Mahroum: Supervision, Writing – review & editing. **Isa Seida:** Writing – original draft, Software. **Sevval Nil Esirgün:** Writing – original draft. **Nicola Luigi Bragazzi:** Conceptualization.

Declaration of Competing Interest

The authors declare no competing interests.

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