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Minireview

MINIREVIEW

The past, present and future of RNA respiratory viruses: influenza and coronaviruses

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One sentence summary: Influenza virus and coronaviruses continue to cause pandemics across the globe and here we discuss their common and different properties.

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ABSTRACT

Influenza virus and coronaviruses continue to cause pandemics across the globe. We now have a greater understanding of their functions. Unfortunately, the number of drugs in our armory to defend us against them is inadequate. This may require us to think about what mechanisms to address. Here, we review the biological properties of these viruses, their genetic evolution and antiviral therapies that can be used or have been attempted. We will describe several classes of drugs such as serine protease inhibitors, heparin, heparan sulfate receptor inhibitors, chelating agents, immunomodulators and many others. We also briefly describe some of the drug repurposing efforts that have taken place in an effort to rapidly identify molecules to treat patients with COVID-19. While we put a heavy emphasis on the past and present efforts, we also provide some thoughts about what we need to do to prepare for respiratory viral threats in the future.

Keywords: RNA viruses; coronaviruses; SARS-Cov-2; influenza; chloroquine; serine protease inhibitors; heparan sulfate glycoconjugate

INTRODUCTION

With regularity we face previously unknown strains of virulent respiratory viruses that are life-threatening for large numbers of people. Perhaps the most well known and recent are the pandemics associated with influenza viruses and coronaviruses that have been in contact with humans for millennia.

It is generally thought that the first large outbreak of a respiratory infection with clinical symptoms similar to those of influenza was described in detail by Hippocrates in the year 412 BC as contagious *cough of Perinthus* (Kuszewski and Brydak 2000; Pappas, Kiriaze and Falagas 2008). Next, a detailed written report of an epidemic respiratory disease similar to influenza was noted in England and named *peasant fever* and lasted from 1173 to 1174 (Potter 2001). The first pandemic of influenza was clearly documented in 1580 (Potter 2001; Daly, Gustafson and Kendall 2007). In the 16th century, this infection was named *influenza* (from the Latin *influentia*, influence), as this disease was considered a bad influence from the heavens (Broxmeyer 2006). Since that time, no less than 31 pandemics of influenza have been documented, including 3 in the 20th century and 1 in the 21st century (Kilbourne 2006; Daly, Gustafson and Kendall 2007; Al-Muharrmi 2010) (Table 1).

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Table 1. Influenza pandemics in the last 100 years.

Name of the pandemic	Years	Strain	Number of deaths (millions)
Spanish flu	1918–1920	H1N1	40–50
Asian flu	1957–1958	H2N2	1–2
Hong Kong flu	1968–1970	H3N2	0.5–2
Swine flu	2009–2010	H1N1	0.5

Although a targeted search for pathogens able to produce an epidemic/pandemic of acute respiratory infections started in the late 19th century (Pfeiffer 1893; Olitsky and Gates 1921a,b), it was not until 1933 that the influenza A virus was selected (myxovirus influenza) (Smith, Andrewes and Laidlaw 1933). Influenza B and C viruses were identified in 1940 and 1947, respectively (Francis 1940; Taylor 1949), and the influenza D virus was isolated and characterized recently in 2011 (Hause *et al.* 2013; Ducatez, Pelletier and Meyer 2015).

Coronaviruses are also very common (Suzuki *et al.* 2005; Koetz *et al.* 2006; Sloots *et al.* 2006; Zhao *et al.* 2008) and seem to have been in contact with humans from the earliest of times (Wertheim *et al.* 2013). Until recently, it was thought that coronavirus infections with symptoms of the common cold cause between 15% and 35% seasonal acute respiratory diseases. Children become infected at a rate of five to seven times more often than adults (McIntosh *et al.* 1970; Callow *et al.* 1990; Holmes 2001). In humans, respiratory infections can be caused by two species of α-coronaviruses (229E and NL63) and two species of β-coronaviruses (OC43 and HKU1) (Gaunt *et al.* 2010). In addition, veterinary specialists have known for a long time that coronaviruses cause fatal respiratory and gastrointestinal infections in animals (Pensaert 1999). Coronaviruses were only recently acknowledged as a potential biological hazard as they are a challenge for medicine. In recent decades, new pandemic strains of coronaviruses have often appeared, which are frequently fatal for humans. These include severe acute respiratory syndrome-related coronavirus (SARS-CoV, which occurred from 2002 to 2004), Middle East respiratory syndrome-related coronavirus (MERS-CoV, which was identified in 2012) and most recently the new pneumonia coronavirus (SARS-CoV-2, which is the ongoing outbreak that was identified in 2019) (Table 2). In all cases, these three viruses cause severe bronchiolitis and pneumonia, often with fatal outcomes (Cherry 2004; Ramadan and Shaib 2019; Hui *et al.* 2020).

Human coronaviruses were for the first time isolated from a patient with acute respiratory diseases in 1965 (Hamre and Procknow 1966; Tyrrell and Bynoe 1966). Their characteristic corona seen under the electronic microscope was reflected in the name *coronaviruses* (Tyrrell *et al.* 1975). During the next three decades (until the pandemic strains appeared), the coronaviruses were not of any special interest for most scientists.

It is apparent that pandemic outbreaks of respiratory viral infections represented a danger for humanity in the past, and there are no reasons to believe that they would not repeat in the future. It is as yet impossible to predict the time and place of the start of a new pandemic as well as the virulence of pandemic viral strains. However, there are certain factors that increase the potential for these viruses to spill over from other species (Bobrowski *et al.* 2020; Gomes and Ruiz 2020; Johnson *et al.* 2020).

BIOLOGICAL PROPERTIES OF INFLUENZA VIRUSES AND CORONAVIRUSES

Influenza viruses belong to the orthomyxoviruses family (Orhtomyxoviridae, RNA viruses with segmented genome) and are represented by four monotypic genera: influenza A viruses (*Alpha influenzavirus*), influenza B viruses (*Beta influenzavirus*), influenza C viruses (*Gamma influenzavirus*) and influenza D viruses (*Delta influenzavirus*); each genus contains only one type of eponymous virus. It is understood that only type A viruses have pandemic potential (Bouvier and Palese 2008; Spickler 2016; King *et al.* 2018). Influenza A viruses are further classified into subtypes, depending on the antigenic properties of hemagglutinin (HA; a glycoprotein of the viral envelope that ensures the recognition of target cells and binding of viral particles to the terminal residues of sialic acids of the glycoproteins of plasma membranes of epithelial cells) and neuraminidase (NA; exo-α-sialidase catalyzing the splitting of glycoside bonds of the terminal residues of sialic acids of oligosaccharides, glycoproteins and glycolipids, thus providing release of newly formed influenza virions from the infected cells).

There are 18 known types of hemagglutinin (H1–H18) and 11 identified serotypes of neuraminidase (N1–N11). Therefore, in theory, 198 diverse combinations of these proteins (and thus subtypes of the influenza A virus) are possible (Skehel 2009; Tong *et al.* 2013; Quan *et al.* 2016; Kosik and Yewdell 2019; Zhao *et al.* 2019); of them, >120 combinations have been identified in nature (Tsai and Chen, 2011; Rejmanek *et al.* 2015).

There are eight negative polar segments of RNA genome of the influenza virus that code at least 10 structural and 9 regulatory proteins (Varga *et al.* 2011; Muramoto *et al.* 2013; Hutchinson *et al.* 2014; Vasin *et al.* 2014). Some uncertainty regarding the proteome of the influenza A viruses is related to the fact that, unlike most RNA viruses, the transcription and translation of the genome of these viruses take place in the nucleus and not in the cytoplasm of infected cells. This permits influenza A viruses (Fig. 1A) to use the cellular splicing machinery to form splice variants of viral mRNA(messenger RiboNucleuc Acid). In addition, to widen their proteome, the influenza A viruses are probably using alternative open reading frames.

Most viral proteins are located inside the lipid envelope, while only HA, NA (in the molar relation about 10:1; Mitnaul *et al.* 2000) and M2 proteins, which are built into the virion envelope and present antigenic determinants, are available for immune antibodies (Kosik and Yewdell 2019). HA and NA molecules are highly glycosylated proteins, which give them functional activity and provide for immune evasion by shielding antigenic determinants (Kim *et al.* 2018; York, Stevens and Alymova 2019).

Unlike influenza viruses, coronaviruses are enveloped RNA viruses (with non-segmented positive polar RNA) of the Nidovirales order, Coronaviridae family and Orthocoronavirinae subfamily (Fehr and Perlman 2015). Coronaviral virions have a spherical shape with the typical bulbous projections (Neuman *et al.* 2006; Bárcena *et al.* 2009). The viral envelope is made of a bilipid layer where S, M and E proteins are fixed (Lai and Cavanagh 1997; de Haan and Rottier 2005) (Fig. 1B).

The S protein functions in the form of highly glycosylated 3D complexes (Zheng *et al.* 2018; Parsons *et al.* 2019) provide the interaction of the virion with the receptors of epithelial cells followed by the internalization of the viral genome (Li 2016). The S protein also is known as the spike protein of SARS-CoV-2 which crystal structure described (Wang *et al.* 2020b).

Table 2. Coronavirus epidemics and pandemics in recent years.

Name of the epidemic/pandemic	Years	Strain	Number of deaths (hundreds)
2002–2004 SARS outbreak	2002–2004	SARS-CoV-1	774
2012 Middle East respiratory syndrome coronavirus outbreak	2012–present	MERS-CoV	862
COVID-19 pandemic	2019–present	SARS-CoV-2	(as of 13 January 2020, WHO) 280 431 (as of 9 May 2020, WHO)

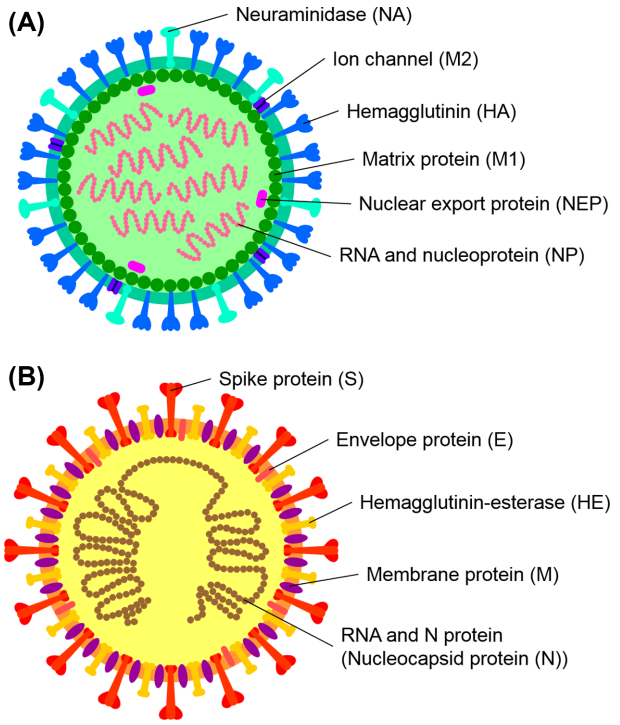


Figure 1. (A) Structural elements of the influenza A virus. **(B)** Structural elements of the coronavirus (based on betacoronavirus subgroup A).

The M protein functions in the form of a dimer with a glycolyzed N-terminal ectodomain (Nal *et al.* 2005) and can be present in two different conformations. The conformers of this glycoprotein ensure the correct assembly and formation of a viral particle (Neuman *et al.* 2011).

The E protein is a transmembrane protein that is present in low quantities and has several functions, namely, in virion assembly, envelope forming and release of a viral particle from the cell. There is indirect evidence that it has the structure of a glycoprotein (Schoeman and Fielding 2019).

The N protein is the only protein present inside the virion; it is responsible for the viral genome packaging (McBride, van Zyl and Fielding 2014).

The fact that deserves particular attention is that the proteins of the envelopes of both influenza A viruses and coronaviruses are made up of glycoproteins.

An influenza virus enters a cell during a process that involves several steps. A critically important moment in the lifecycle of an influenza virus is the recognition of the specific cellular receptors that are glycoproteins or glycolipids containing a terminal α2,6- or α2,3-sialic acid in the glycan (Leung *et al.* 2012; Byrd-Leotis, Cummings and Steinhauer 2017). When viral HA binds sialic glycoproteins or glycolipids on the plasma membrane of an epithelial cell, this results in the initiation of several mechanisms of endocytosis that quickly lead to the formation of endosomes, each of which contains a viral particle (Chardonnet and Dales 1970; Matlin *et al.* 1981; Kartenbeck, Stukenbrok and Helenius 1989; Rojek, Perez and Kunz 2008; Nanbo *et al.* 2010; Watanabe, Watanabe and Kawaoka 2010; Boulant, Stanifer and Lozach 2015).

The next step of the internalization is the release of the viral genome (RNA segments) into the cellular cytoplasm; this phase depends on the activity of Na^+/K^+-ATPase located in the endosomal membrane, which functions as a proton pump. Na^+/K^+-ATPase is responsible for the acidification of the internal environment of endosomes/lysosomes (to pH 5.0) (Cain, Sipe and Murphy 1989). The acidification of the internal endosomal medium, i.e. the accumulation of protons (H^+) inside the endosomes, helps the tetramers of the M2 protein of the viral envelop to realize its potential as a protonophore (Sugrue and Hay 1991; Pinto, Holsinger and Lamb 1992; Manzoor, Igarashi and Takada 2017). When hydrogen ions enter a viral particle, it mediates conformational changes and decomposition of the structural components of the viral envelope, which finally leads to an increase in the lability of its genome (Shibata *et al.* 1983; Yoshimura and Ohnishi 1984). However, the fusion of the viral envelope membrane and the endosomal membrane, which releases the RNA genome of the virus into the cellular cytoplasm, is possible only with the participation of the viral HA after the previous proteolytic processing with serine (secretory trypsin-like) proteases (Klink *et al.* 1975; Lazarowitz and Choppin 1975; Tashiro *et al.* 1987; Steinhauer 1999; Kido *et al.* 2008).

The translocation of RNA segments of the influenza viral genome from the cytoplasm to the nucleus is necessary for their replication, during which viral mRNA exits the nucleus to synthetize viral proteins in the cytoplasm. The viral self-assembly takes place at the apical surface of the plasma membrane of epithelial cells, where HA and NA molecules are concentrated (Samji 2009; Dou *et al.* 2018).

The process of internalization of coronaviruses is determined by the functional activity of the S protein (widely known as the spike protein) of the viral envelope. The S protein of a coronavirus is a highly glycosylated supramolecular structure that enables the fixation of viral particles on the plasma membrane of epithelial cells, followed by the release of their RNA into the cellular cytoplasm (Li 2016; Watanabe *et al.* 2020). Each S protein has two receptor-binding domains located on its S_1-subunit; these domains interact with either specific proteins or sialoglycans of the epithelial cells (Li 2012; Shahwan *et al.* 2013; Hulswit *et al.* 2019). For example, MERS-CoV preferentially binds the $\alpha_{2,3}$-bonded sialic acid (and to a lesser degree the $\alpha_{2,6}$-bonded sialic acid) (Li *et al.* 2017). It seems that SARS-CoV-2 has the same affinity for the $\alpha_{2,3}$-sialic acid conjugates (Ou *et al.* 2020).

After that, the internalization of the viral genome may proceed by endocytosis of the virion (which is in many respects

a similar process to the internalization of the influenza viruses) or by the fusion of the membrane of a coronaviral envelope with the plasma membrane of an epithelial cell, without the formation of endosomes (directly on the plasma membrane). In any case, the release of the viral RNA into the cellular cytoplasm is preceded by the proteolytic (provided by serine proteases) cleavage of S_1-subunit and modulation of the S_2-subunit of the S protein (Bosch *et al.* 2003; Belouzard, Chu and Whittaker 2009; Simmons *et al.* 2013; Heurich *et al.* 2014; Zumla *et al.* 2016).

In the cytoplasm of an epithelial cell, the viral RNA genome functions as mRNA, where the complex of replication and transcription is responsible for both RNA genome replication and synthesis of mRNA of structural viral proteins (Sola *et al.* 2015; Nakagawa, Lokugamage and Makino 2016). After the posttranslational glycosylation in the Golgi apparatus cisternae (Nal *et al.* 2005; Tseng *et al.* 2010), newly synthesized coronaviral proteins enter the cytoplasm and ensure the self-assembly of viral particles. The latter particles migrate to the cellular membrane inside the cisternae and are released from the cell by exocytosis (Fehr and Perlman 2015; Lim *et al.* 2016).

Taking into account the importance of serine proteases, glycoproteins and glycolipids in the lifecycle of influenza viruses and coronaviruses, it seems logical to suggest that the factors that modulate the profile of glycosylation of proteins and lipids of epithelial cells and viruses, as well as control the activity of serine proteases on the epithelial lining of respiratory ways, may significantly limit the virulence of influenza viruses and coronaviruses and represent therapeutic drug targets.

GENETIC EVOLUTION OF INFLUENZA A VIRUSES AND CORONAVIRUSES

When influenza viruses circulate in their natural reservoirs, they are characterized by high genetic variability that is reflected in the formation of quasi-subtypes (immunologically different antigenic variants) of type A viruses (Barbezange *et al.* 2018). This biological characteristic is called antigenic drift (Taubenberger and Kash 2010) and it is explained by the fact that RNA-dependent RNA-polymerase of influenza viruses does not have an active corrective site (Steinhauer, de la Torre and Holland 1989; Cheung *et al.* 2014), which results in a high frequency of point mutations in the process of RNA genome replication (300 times higher than during the replication of bacterial DNA genome) (Drake 1993). Another distinctive characteristic is the high mutational tolerance of glycoproteins of viral envelopes, i.e. the ability of HA and NA to maintain their functional activity in case of significant changes in the primary structure of the polypeptide chain (Thyagarajan and Bloom 2014; Visher *et al.* 2016).

An important and prevalent phenomenon in the evolution of influenza A viruses is so-called antigenic shift (Holmes *et al.* 2005; Dugan *et al.* 2008). The antigenic shift is the interchange of RNA segments of viral genome that code the HA and/or NA structure in case of simultaneous infection of a cell by several strains of the influenza A virus (Taubenberger and Kash 2010). It is the antigenic shift that permits new subtypes of influenza A virus to overcome cross-species barriers (Scholtissek *et al.* 1978; Garten *et al.* 2009).

Unlike other RNA viruses, the coronavirus genome replication involves RNA-dependent RNA-polymerase that has 3′-exonuclease corrective activity (Smith, Sexton and Denison 2014). With the objective of immune evasion in humans and maintenance of the genotype in the *Homosapiens* population, as has been demonstrated for the coronaviral strain HCoV-OC43, coronaviruses also maintain the antigenic drift (Ren *et al.* 2015). In addition, the genome of coronaviruses uses RNA–RNA recombination for its evolution (Keck *et al.* 1988; Huang *et al.* 2016; Forni *et al.* 2017). Homologous RNA recombination represents a redistribution of the genetic material by interchange of RNA segments in the conditions of co-infection (Makino *et al.* 1986; Lai 1990; Lai and Cavanagh 1997). In addition to evasion from the host immune reactions, RNA recombination lets coronaviruses change the profile of virulence and tissue affinity as well as overcome cross-species barriers (Haijema, Volders and Rottier 2003; Stavrinides and Guttman 2004).

High genetic and phenotypic variability of influenza A viruses and coronaviruses can lead to a situation where these pathogenic agents obtain resistance to specific therapeutics as well as to the sudden appearance of new virulent pandemic strains.

PANDEMIC RESPIRATORY VIRAL INFECTIONS AND THE PROBLEM OF PNEUMONIA

The influenza pandemic in 1918–1920 became the most fatal disease-related event in human history (to date), which resulted in the death of >50 million people (Johnson and Mueller 2002). The mortality during pandemics of influenza and coronaviral infections is largely associated with pneumonia (Morens, Taubenberger and Fauci 2008; Metersky *et al.* 2012; Yin and Wunderink 2018; Al-Baadani *et al.* 2019). Primary viral pneumonias are often complicated by bacterial co-infection as they transform to viral-bacterial and bacterial pneumonias (Oswald, Shooter and Curwen 1958; Bisno *et al.* 1971; Palacios *et al.* 2009; Gill *et al.* 2010; Martín-Loeches *et al.* 2011; Cillóniz *et al.* 2012). The statement by Louis Cruveilhier expressed in 1919 is still common in expert circles: 'The influenza awards a sentence, and it is bacterial flora that carries it out' (Cruveilhier 1919).

The clinical picture of severe viral respiratory infections often presents with symptoms of primary viral pneumonia. The development of primary viral pneumonia in case of a viral respiratory infection is probably related to co-expression of glycoproteins and glycolipids that contain glycans with terminal $\alpha_{2,3}$-linked sialic acid (which plays the role of respiratory virus receptor), and to the transmembrane serine protease TMPRSS2 (which itself plays a role in proteolytically activating viral HA and S protein) of the epithelial cells of alveoli and bronchioles (Ibricevic *et al.* 2006; Shinya *et al.* 2006; Kumlin *et al.* 2008; Bertram *et al.* 2010; Limburg *et al.* 2019; Tortorici *et al.* 2019).

The vulnerability to bacterial co-infection during respiratory viral pandemics is associated with multiple factors: virus-induced dysbiosis and disruption of barrier function of the epithelial lining of respiratory airways (Pittet *et al.* 2010; Ellis *et al.* 2015; Nita-Lazar *et al.* 2015; Hanada *et al.* 2018; Sencio *et al.* 2020); virus-induced dysfunction of effector immune cells (McNamee and Harmsen 2006; Small *et al.* 2010; Ghoneim, Thomas and McCullers 2013; Sun and Metzger 2014) and immunosuppressive activity of cytokines in relation to antibacterial immunity (Cao *et al.* 2014; van der Sluijs *et al.* 2004; Shepardson *et al.* 2019); and virus-associated dysfunction of alveolar-capillary barrier (McAuley *et al.* 2007; Henkel *et al.* 2010; Short *et al.* 2016; Kamal, Alymova and York 2018) and suppression of activity of ion channels that are responsible for the absorption of fluid from the alveolar lumen (Carlson *et al.* 2010; Peteranderl *et al.* 2016; Brand *et al.* 2018).

Pneumonias associated with respiratory viral infections are an independent factor in disease severity and mortality (Maruyama *et al.* 2016; Ishiguro *et al.* 2017). This means that the main problem of severe viral infections, in the past as well as in the present, has been the problem of viral, viral-bacterial and secondary bacterial pneumonias.

ANTIVIRAL THERAPY

The biology of influenza viruses and coronaviruses inevitably leads to the appearance of new pandemic strains; it is impossible to predict the moment of their development, genomic variability and antigenic properties. This means that pandemics of new respiratory infections will always start in the absence of immune prophylactics and treatments. This underlines the necessity of prior research and development of treatments for the prevention and treatment of respiratory viral infections and in particular for coronaviruses and influenza A viruses. Several antiviral drugs that will be described herein are presented in Table 3.

The nature of RNA viruses suggests that systemic interferon alfa-2b might be effective as non-specific background therapy, taking into account the weakened state of patients. The efficacy of topical interferon solutions is doubtful, but they may be considered in case of local symptoms (rhinitis, pharyngitis etc.). Usage of systemic interferon inducers such as tilorone and cycloferon (Ekins *et al.* 2020; Ekins and Madrid 2020) may result in secondary immunosuppression 10–14 days later, which can lead to another infection. Background antiviral therapy also includes targeted agents that affect enzymes of the viral genome replication; this includes oseltamivir, and the most potent (but also most toxic of this group) ribavirin, as well as other novel targeted antiviral medications. Anti-replicative activity has been observed for inosine pranobex (Sliva, Pantzartzi and Votava 2019), a purine derivative that is active against influenza A and B viruses.

The current knowledge of the viral nature and pathogenetic properties of the infectious process allows us to consider the possibility of using adjuvant agents, the efficacy of which has been observed in different studies (Ekins, Lane and Madrid 2020).

It is well known that serine proteases participate in the process of internalization of coronaviruses and influenza A viruses into the epithelial cells (Simmons 2013; Garten *et al.* 2015). The activity of trypsin-like proteinases in the upper respiratory tract significantly depends on the activity of inhibitors of secretory leucoproteinases and in the lower respiratory tract it depends on the surfactant (Kido *et al.* 2004). Therefore, therapeutics that induce the expression of inhibitors of secretory leucoproteinases and surfactant may significantly inhibit the multicyclic replication of RNA viruses (including influenza and coronaviruses).

Quercetin has such properties. In the micromolar range, in addition to antioxidant effects, it can chelate metals of mixed valency (Gholampour and Saki 2019), stimulate the expression of antioxidant enzymes (Chen *et al.* 2017), provide direct reduction of free radicals of fatty acid residues of phospholipids and oxidized forms of vitamin E (Ozgen, Kilinc and Selamoglu 2016; Chepur *et al.* 2020), inhibit the activity of serine proteases (Xue *et al.* 2017; Jo *et al.* 2019) and shield the active center of HA of the influenza A virus (Wu *et al.* 2015), which gives it a wide range of antiviral effects (Zakaryan *et al.* 2017). However, in our opinion, this compound is highly promiscuous and not a good drug candidate.

Ambroxol (trans-4-[[(2-amino-3,5-dibromophenyl)methyl] amino]cyclohexanolhydrochlo-ride) also deserves attention as an additional antiviral agent (Yang *et al.* 2002). The *in vitro* inhibitory effects of ambroxol on influenza virus were described in 2014 (Yamaya *et al.* 2014). The spectrum of pharmacological activity of ambroxol, in addition to its mucolytic effects (Rogers 2007), includes antibacterial and anti-biofilm effects (Lu *et al.* 2010; Li *et al.* 2011; Cabral-Romero *et al.* 2013; Cataldi *et al.* 2014); the ability to serve as chemical chaperones (Bendikov-Bar *et al.* 2013; Sanchez-Martinez *et al.* 2016), modulate surfactant secretion (Yang *et al.* 2002; Seifart *et al.* 2005), provide anti-inflammatory (Gibbs *et al.* 1999; Beeh *et al.* 2008; Gupta 2010) and antioxidant action (Nowak *et al.* 1994; Stetinová, Herout and Kvetina 2004); and the ability to locally (in the respiratory airways) stimulate the secretion of IgA and IgG (Yang *et al.* 2002) as well as to provide a local anesthetic effect (Kern and Weiser 2015). Due to these diverse effects and high oral bioavailability (Jauch *et al.* 1978), ambroxol may be included in a list of medications used for the treatment of viral pneumonias.

An important role in the pathogenesis of respiratory infections is being played by the virus-induced oxidative stress (Schwarz 1996; Lin *et al.* 2006; Liu *et al.* 2017; Khomich *et al.* 2018). Xanthine oxidoreductase has an important role in the appearance of the symptoms and complications of virus-associated pneumonias. Xanthine oxidoreductase is a cytosolic enzyme of purine catabolism (Frederiks and Vreeling-Sindelarova 2002; Agarwal, Banerjee and Banerjee 2011) and its activity strongly increases in hypoxic conditions (Poss *et al.* 1996; Terada *et al.* 1997; Linder *et al.* 2003) as well as under the influence of proinflammatory mediators and cytokines (Page *et al.* 1998; Brandes *et al.* 1999). In pathological conditions, xanthine oxidoreductase is released from the cells to the blood (predominantly in oxidase form; Spiekermann *et al.* 2003) and fixates at the luminal surface of the plasma membrane of endothelial cells in the area of the inflammation by physical/chemical interaction with glycosaminoglycans (Akaike *et al.* 1990; Adachi *et al.* 1993; Rouquette *et al.* 1998). Xanthine oxidoreductase located on the cytoplasmic membrane of endothelial cells produces a superoxide anion radical in the process of purine oxidation, and at the same time may redux nitrite and nitrate anions to the nitrogen oxide ($NO^{\bullet}$) at another active site (Jansson *et al.* 2008; Cantu-Medellin and Kelley 2013), i.e. it can recycle this vasodilating agent. Local production of the prooxidative complex ($O_2^{-\bullet}$, H_2O_2, $NO^{\bullet}$, $ONOO^{-}$) is potentially very dangerous, especially in the vascular bed of the lungs. Nevertheless, the attempts of using allopurinol, an inhibitor of xanthine oxidoreductase (Pacher, Novorozhkin and Szabo 2006; George and Struthers 2009), for the treatment of influenza A virus-induced pneumonia in daily doses of 5–50 mg/kg have failed. Allopurinol has not shown any effects on the evolution and outcomes of the viral infection (Dolganova and Sharonov 1997). Lack of therapeutic effect in this case is associated with the fact that after the inhibition of (Mo-Co)-containing center of the enzyme by allopurinol, the NADH-oxidative and nitrite-/nitrate-reductive activities of xanthine oxidoreductase, which are realized at the FAD-dependent site of the enzyme, were not affected (Harris and Massey 1997; Doel *et al.* 2001; Boueiz, Damarla and Hassoun 2008). As there are still no approved medications able to inhibit the FAD-dependent activity of xanthine oxidoreductase, administration of heparin seems feasible as prophylaxis of pulmonary embolism with the objective of the desorption of xanthine oxidoreductase from the cytoplasmic membrane of endothelial cells (Povalyaev 2014; Obi *et al.* 2019).

Another significant source of the active forms and metabolites of oxygen during respiratory viral infections is mitochondria (To *et al.* 2020). Melatonin is a mitochondrial antioxidant (Reiter *et al.* 2017) with anti-inflammatory and immunomodulatory activity and has noticeable positive effects on the evolution and outcomes of viral infections under experimental conditions (Srinivasan, Mohamed and Kato 2012; Silvestri and Rossi 2013; Tan *et al.* 2014; Huang *et al.* 2019; Zhang *et al.* 2020). Melatonin is also widely used to promote sleep, so this may be undesirable in an antiviral during the daytime.

Table 3. Chemical structures of selected drugs described in this review.

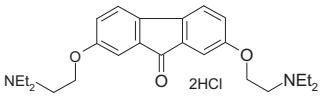
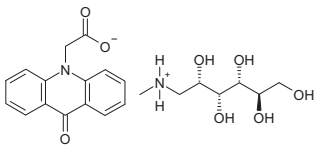
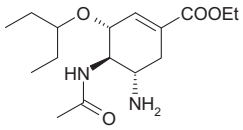
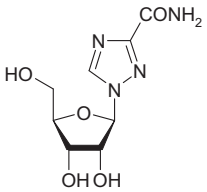
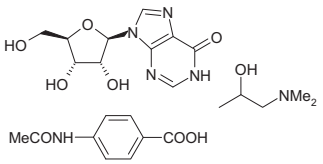
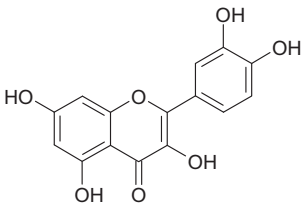
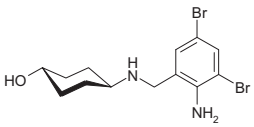
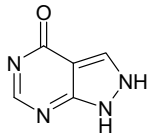
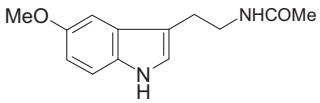
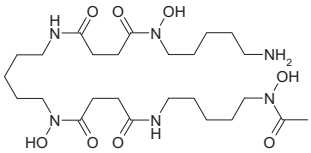
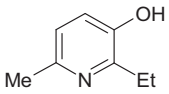
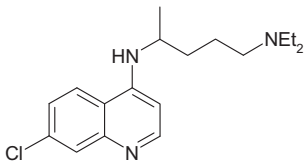
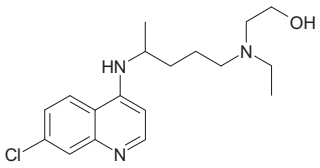
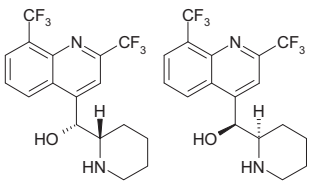
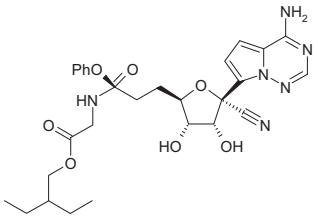
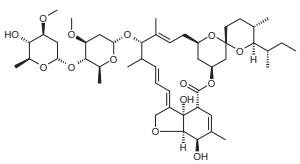
INN	Chemical structure	Brand name	Key reference
Tilorone		Amixin, Lavomax	Ekins *et al.* 2020; Jeon *et al.* 2020
Meglumine acridine acetate		Cycloferon	Ekins *et al.* 2020
Oseltamivir		Tamiflu	Neupane *et al.* 2020
Ribavirin		Copegus, Rebetol, Ribasphere, Vilona, Virazole	Neupane *et al.* 2020
Inosine Pranobex		Methisoprinol	Sliva, Pantzartzi and Votava 2019
Quercetin			Zakaryan *et al.* 2017
Ambroxol		Muciclar, Mucosolvan, Mucobrox, Mucol, Lasolvan, Mucoangin, Surbronc, Brontex, Ambolar, Lysopain	Yang *et al.* 2002; Yamaya *et al.* 2014
Allopurinol		Allohexal, Allosig, Milurit, Alloril, Progout, Ürikoliz, Zyloprim, Zyloric, Zyrik and Aluron	Pacher, Novorozhkin and Szabo 2006; George and Struthers 2009

Table 3. Continued

INN	Chemical structure	Brand name	Key reference
Melatonin			Reiter *et al.* 2017
Deferoxamine		Desferal	Borg and Schaich 1986; Klebanoff *et al.* 1989; Dulchavsky *et al.* 1996; Niihara *et al.* 2002; Francisco *et al.* 2010
Mexidol		Emoxipine, Emoxypin, Epigid	Pavelkina, Yerovichenkov and Pak 2010
Chloroquine		Chloroquine FNA, Resochin, Dawaquin, Lariago, Delagil	Jeon *et al.* 2020; Jin *et al.* 2020; Liu *et al.* 2020
Hydroxychloroquine		Plaquenil, Hydroquin, Axemal, Dolquine, Quensyl, Quinoric, Immard	Liu *et al.* 2020
Mefloquine		Lariam	
Remdesivir		GS-5734	Lu 2020; Wang *et al.* 2020a; Zhang *et al.* 2020
Ivermectin		Stromectol	Caly *et al.* 2020

The superoxide anion radical may act on organic and inorganic compounds, depending on their chemical properties, as an oxidant ($E_0O_2^{-\bullet}/H_2O_2$ +0.89 V) or a reductant ($E_0O_2/O_2^{-\bullet}$ −0.16 V) (Wood 1987, 1988). The reductive properties of the superoxide radical is produced in the area of inflammation during viral pneumonias. This may occur via reduction of ferric ions after their release from complexes with biomacromolecules. For example, iron in a molecule of ferritin is represented by Fe^{3+} ions, which under the influence of the superoxide anion radical transforms into Fe^{2+} and leaves the aforementioned protein (Biemond *et al.* 1984; Bolann and Ulvik 1987). In the presence of free ferric ions and partially reduced forms of oxygen, the conditions are created for a kind of *catalytic reactor* for redox catabolic production of prooxidants, especially very toxic hydroxyl radicals (Morris, Earl and Trenam 1995). This condition of a biological system is extremely dangerous because in the presence of free ferric ions, biological fluids lose their antibacterial properties (Bullen, Ward and Rogers 1991; Griffiths 1991; Sritharan 2006). The elimination of free ferric ions from the biological media of a body is a life/death issue in case of viral pneumonias. There were earlier attempts to use available complexones (for example, deferoxamine) to bind ferric ions during viral pneumonia; contrary to the expected, not only did they show no positive effects on the pathological process, but they also led to increased mortality (Dolganova and Sharanov 1997). The explanation of this paradox is that deferoxamine (desferal) has approximately the same affinity constant for ferric ions as siderophores of microorganisms (Hallaway *et al.* 1989; Askwith, de Silva and Kaplan 1996); for this reason, it is unable to limit the availability of Fe^{3+} for pathogenic organisms (Kim, Park and Shin 2007; Cassat and Skaar 2013). At the same time, it seems that ferric ions chelated by deferoxamine do not completely lose their ability to redox transformation and thus support the reactions of Fenton and Osipov (Borg and Schaich 1986; Klebanoff *et al.* 1989; Dulchavsky *et al.* 1996; Niihara *et al.* 2002; Francisco *et al.* 2010).

In contrast, 2-ethyl-6-methyl-3-hydroxypyridine succinate (mexidol, emoxipine) has noticeable iron chelating activity (Andrusishina *et al.* 2014), antioxidative activity (Voronina 2001) and the ability to inhibit serine proteases and matrix metalloproteases (Akhmedov, Budylgin and Dolgikh 2010). Mexidol has many such biological effects and has been proposed for the effective use as a supportive agent in the treatment of pneumonia (Ilyashenko *et al.* 2001; Luzhnikov *et al.* 2006) and viral infections (Pavelkina, Yerovichenkov and Pak 2010).

In clinical practice, chloroquine has been widely used as a safe, effective and affordable medication for more than seven decades (since 1947; Solomon and Lee 2009). It is used in the forms of phosphate, hydrochloride and sulfate for the following indications: treatment and prevention of malaria (Mengesha and Makonnen 1999; Bello, Chika and Bello 2010; Waqar, Khushdil and Haque 2016); treatment of leprosy (Meinão *et al.* 1996; Bezerra *et al.* 2005; Gordon *et al.* 2018); as an anti-inflammatory agent in patients with rheumatoid arthritis (Augustijns *et al.* 1992; Schrezenmeier and Dorner 2020); treatment of antiphospholipid syndrome (Tektonidou *et al.* 2019); treatment of Sjogren's syndrome (Vivino *et al.* 2016; Shivakumar *et al.* 2018; Lee *et al.* 2019); treatment of amoebic hepatitis and hepatic abscesses (Sodeman *et al.* 1951; Cohen and Reynolds 1975); cancer treatment as sensitizing agent (Solomon and Lee 2009; Maycotte *et al.* 2012; Kimura *et al.* 2013); and treatment of metabolic syndrome (Kastan, Semenkovich and Schneider 2008; McGill *et al.* 2019) and inflammatory diseases of bacterial nature (in synergy with antibiotics (Crowle and May 1990; Feurle *et al.* 2012; Jagadeesh, Saivisveswar and Revankar 2014; Son and Chung 2014).

Chloroquine and its many analogs (such as hydroxychloroquine etc.) have properties of weak acidic amines in unprotonated form as they easily permeate cellular membranes (Chinappi *et al.* 2010) and after the protonation accumulate in closed cellular compartments with acidic pH (i.e. endosomes or lysosomes) (Vincent *et al.* 2005). The level of chloroquine in such compartments may be >100 times higher than its concentration in the cell (de Duve *et al.* 1974). Chloroquine may stay in the isolated intracellular compartments for hundreds of hours (Schrezenmeier and Dorner 2020). Accumulating in endosomes/lysosomes, chloroquine shifts the pH to alkali (Homewood *et al.* 1972; Ohkuma and Poole 1978; Al-Bari 2017) and inhibits diverse ATPases, including H^+-ATPase (V-ATPase), which defines the acidification of the environment of endosomes and cisternae of the Golgi apparatus (Chandra *et al.* 1992; Bhattacharyya and Sen 1999; Holliday 2017). It is possible that these many phenomena define the blockade of the release of RNA genome of influenza viruses from the lipoproteins of their envelopes (Shibata *et al.* 1983), which results in the inhibition of viral replication (Ooi *et al.* 2006; Di Trani *et al.* 2007). The ability of chloroquine to inhibit the acidification of endosomes that contain respiratory viruses, and thus to block the release of their RNA genomes and following replication, may partially explain its antiviral activity. Chloroquine also has high antiviral activity against not only influenza A viruses (internalized in the endosomes) but also coronaviruses (Keyaerts *et al.* 2004; Vincent *et al.* 2005; Ooi *et al.* 2006; Yan *et al.* 2013; de Wilde *et al.* 2014; Kearney 2020), which are almost exclusively internalized by membrane fusion, i.e. without the formation of endosomes (Matsuyama *et al.* 2005).

Of the three types of biological aperiodic polymers (nucleic acids, polypeptides and carbohydrates), aperiodic polymers of carbohydrates (glycans and oligosaccharides) have the highest information capacity, due to their structural properties. This ensures high specificity of ligand–receptor interactions of oligosaccharide conjugates. But the structure of glycans in the eukaryotic genome is coded indirectly. Oligosaccharides are synthetized in the cisternae of Golgi apparatus with the support of secondary protein matrices that form functional heterogenic associations (conveyor lines) of glycosyltransferases (Chepur *et al.* 2019). Obviously, the spatial structure of such matrix protein molecules and thus their affinity to the enzymes of glycan synthesis may quickly and significantly change under the influence of the dynamics in the pH and oxidative-reductive potential in the cisternae of Golgi apparatus.

For this reason, it is important that chloroquine is able to change the redox status of a cell (Giovanella *et al.* 2015) and decrease the concentration of protons (increase the pH) in the cisternae of Golgi apparatus by suppression of ATPase activity, including H^+-ATPase (Reaves and Banting 1994; Hassinen *et al.* 2011). The function of the Golgi apparatus that is considered most sensitive to pH changes is the synthesis of aperiodic oligosaccharides (Kellokumpu 2019). A pH increase by 0.2 inside the Golgi apparatus is associated with a disruption in terminal $\alpha_{2,3}$-sialylation of both N-linked and O-conjugated glycans (Rivinoja *et al.* 2006, 2009). It seems that aberrant glycosylation after the decrease in acidity of intraluminal environment of Golgi complex cisternae is associated with pH-induced changes in the topology/location of glycosyltransferases in multienzyme complexes of aperiodic oligosaccharides synthesis.

As all participants of the interaction between human cells and respiratory RNA viruses (glycoproteins and glycolipids) are

richly decorated by glycans with terminal sialic acids, which are recognized by the viral particles as specific receptors, the chloroquine-induced disruption of the processes of sialylation/glycosylation of cellular and viral participants of this interaction is reflected in its antiviral effects.

The participation of glycans in viral adhesion and proliferation are extremely important. A wide array of viruses, including coronaviruses (Milewska *et al.*, 2014, 2018; Szczepanski *et al.* 2019), use a common heparan sulfate-dependent mechanism of the attachment to a cellular membrane. Inhibitors of this attachment could therefore prevent and treat infections. The N,N′-bisheteryl derivative of dispyrotripiperasine, pyrimidine dispirotripiperasinium, became the first synthetic small molecule (Schmidtke, Wutzler and Makarov 2004; Novoselova *et al.* 2017) broad spectrum inhibitor of the replication of viruses of different families that use heparan sulfate to attach to and/or enter a host cell. The inhibition is via mimicking the binding of specific structural parts of heparan sulfate. This investigational class of compounds opens new opportunities for the inhibition of the process of viral transmission, for example, by using them to prevent infection by herpes simplex virus type I.

A method of prevention and treatment of aspiration pneumonias and ventilator-associated pneumonias may be adapted for virus-associated pneumonias. The method involves hypoosmotic (to 200–250 mM) conditioning of red blood cells (RBCs) of autogenic blood in a solution of a broad-spectrum antibiotic, with the addition of dimethyl sulfoxide (DMSO) and heparin. This approach avoids hemolysis and uses autogenic RBCs as an intravenous depot for the delivery of antibiotics to the area of inflammation (pneumonia), where the tonicity of blood is normalized due to swelling. DMSO increases the fluidity (decreases the microviscosity) and permeability of cellular RBC membranes, which helps to deliver antibiotic into the cell. A proposed dose of DMSO (0.3–0.4 ml) does not affect morphology or functional properties of blood cells (Gurtovenko and Anwar 2007). In addition, DMSO inhibits the activation of proinflammatory transcription factors NF-κB, AP-1 and expression of adhesion molecules ICAM-1 (Chang, Albarillo and Schumer 2001), blocks transcription of the IL-1, IL-6, IL-8 genes, as well as activation of the inflammasomes NLRP3 (Ahn *et al.* 2014; Elisia *et al.* 2016), and has noticeable antioxidant activity in extremely low concentrations (Jia *et al.* 2010; Sanmartín-Suárez *et al.* 2011).

From the earliest days of the current outbreak of SARS-CoV-2, there has been considerable focus on drug repurposing. A bibliometric analysis of drug repurposing has described the many FDA-approved drugs that have been tested for other indications. This analysis highlighted chloroquine as one of the most repurposed drugs as it has been tested against hundreds of diseases (Baker *et al.* 2018). Not surprisingly, chloroquine has also been identified by several groups (in China, South Korea and the United States) (Jeon *et al.* 2020; Jin *et al.* 2020; Liu *et al.* 2020) to have micromolar activity against SARS-CoV-2. Remdesivir, which had previously failed in clinical trials for Ebola (Mulangu *et al.* 2019) but had also recently shown activity against MERS in rhesus macaques (de Wit *et al.* 2020), was tested *in vitro* against SARS-CoV-2 and shown to be active. Both these drugs (and closely related analogs) are already in many clinical trials globally. There are numerous other drugs proposed, including a broad array of nucleoside analogs, neuraminidase inhibitors, peptides, RNA synthesis inhibitors, anti-inflammatory drugs as well as traditional Chinese medicines (Lu 2020; Wang *et al.* 2020a; Zhang and Liu 2020). In just a few months, many papers and preprints have described one or more molecules with *in vitro* data against the virus. To date, there are likely >100 drugs that have been tested and described with *in vitro* IC_{50} data in cells from these studies (Caly *et al.* 2020; Choy *et al.* 2020; Jeon *et al.* 2020; Jin *et al.* 2020; Liu *et al.* 2020; Yamamoto *et al.* 2020). These cover large natural product molecules like ivermectin (Caly *et al.* 2020) through to an array of small molecules that are primarily lysosomotropic drugs (Weston *et al.* 2020). Most of these studies use Vero cells for testing and this animal cell type may not be an ideal. We await seeing how the wider use of human cells may impact the discovery of other inhibitors of this virus. Additionally, some of these molecules identified may be impractical due to off-target effects or not being able to be used at concentrations similar to their original indication.

CONCLUSIONS

Respiratory RNA viruses are anthropozoonotic infectious pathogens that have natural reservoirs and form dynamic genetic pools. Such a genetic pool suggests the interchange or spillover of genetic material between the genomes of familial RNA viruses of humans and animals. This inevitably leads to the appearance of new, highly virulent strains of pathogens and it is impossible to predict the moment of such appearance and antigenic properties of these strains. This means that epidemics of new respiratory RNA viral infections will always begin in the absence of medications for their immune-mediated prevention or treatment. This underlines the necessity of continuing to perform research and development of antivirals and other therapeutic drugs that could be used in the treatment of respiratory RNA viral infections. This review has focused on the past and present efforts at addressing these viruses. Clearly, our future will be very much defined by such viral outbreaks if we are not able to identify broad-spectrum antivirals or vaccines. Looking at the past research may provide some important clues as to how we can identify such therapeutics. The reliance on a single magic bullet for every disease may be unrealistic and we therefore need to consider the combination of diverse antiviral treatments as we currently do for HIV and HBV. Considering molecules that are traditionally not considered 'antivirals' may also be critical to open our eyes to accessing additional targets and mechanisms. Host-targeted mechanisms may also be of interest such as those that stimulate the immune system. Clearly, we are seeing many drugs that are lysosomotropic; while long-term use of such molecules may be detrimental, short-term use may prevent viral entry and protect the individual. There is certainly much more research that can be performed to understand how combinations of drugs for these respiratory viruses may work together. While interest in antiviral research and development has apparently languished for decades, the COVID-19 may permanently change that. If we continue to ignore such viruses, the cost will be unimaginable and continue to hold back human progress. We will now see a rebirth in interest and perhaps significant investment in developing antivirals. For years, there have been few major drug companies dominating this field. What we have seen with viruses should also serve to remind us that we also face great pressures such as drug resistance for other classes of drugs like antibiotics. This review should remind us that we need to be ready for the next outbreak and that means having a plentiful supply of drugs that can potentially address any new virus we are faced with. A relatively small investment in this science could pay big dividends for the future in preventing catastrophic pandemics, limiting the global financial depressions that result and providing a degree of security for humanity. We cannot

neglect these or other viruses for they provide other insights that could ultimately be useful in healthcare and beyond.

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