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Lessons that can be learned from the SARS-CoV-2 pandemic and their impact on the prophylaxis and treatment development for neglected tropical arboviruses

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In the 21st Century, emergence and re-emergence of infectious diseases is significant and has an increasing importance in global concern of public health. Based on the COVID-19 pandemic and recently reported epidemics, most human pathogens originate in zoonosis. Many of such pathogens are related to viruses that have RNA genomes, which can be presented structurally as a single-strand or double-strand. During the last two decades, a timeline of major RNA viruses emergencies can be exemplified, such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003, influenza A virus (H1N1) pdm09 in 2009, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, Ebola virus (EBOV) in 2013–2016, Zika virus (ZIKV) in 2015 and the SARS-CoV-2 pdm19 in 2019. Even so, prophylactic or therapeutic drugs are unavailable for many RNA viruses circulating. Nonetheless, the COVID-19 pandemic brought considerable scientific advances in accelerating progress regarding prophylaxis, antiviral and drug development, and novel treatments. Regarding RNA virus diseases for humans, arboviruses play an essential and neglected role, constantly reemerging and affecting almost half of the human population, for which no drug has been licensed. Here we review the consolidated RNA viruses' emergence and re-emergence in the 21st Century through available data. Then, we explored valuable lessons gained during the SARS-CoV-2 pandemic and focused on potential epidemiologic updates, prophylaxis, available treatments, and viral drug inhibitors. Finally, we explore arbovirus's significance and the ongoing development of effective vaccines, antiviral drugs, and novel therapeutic approaches as strategies to control these neglected tropical diseases (NTD).

KEYWORDS

zoonotic virus, arboviroses, emerging and reemerging viruses, antiviral drugs, neglected tropical diseases (NTD)

Introduction

Newly emerging and re-emerging infectious diseases (EID) are becoming a more common and significant threat to human and animal health (Plowright et al., 2017; Plowright et al., 2021). Over the twenty-first century, humankind has witnessed the emergence of several zoonotic viruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, influenza A virus (H1N1) pdm09 in 2009, Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, Ebola virus (EBOV) in 2013–2016, Zika virus (ZIKV) in 2015 and the SARS-CoV-2 pdm19 in 2019 (Table 1). Like other microorganisms, viruses can evolve to exploit new niches and adapt to expand the host range, thus crossing species boundaries and infecting new hosts through a well-known viral spillover event (Hui, 2006; Ellwanger & Chies, 2021; Spernovasilis et al., 2022). In the last 2 decades, most outbreaks, epidemics, and pandemics events of spillover were frequently related to zoonotic viruses, already have been circulating before in non-human wild or domestic animal reservoirs (Ellwanger & Chies, 2021). These events significantly challenged global health, security, and economic growth during human history, causing immeasurable cases of morbidity and mortality cases each year (Morens et al., 2004; Wolfe et al., 2007; Sakai and Morimoto, 2022). After the SARS-CoV-2 pandemic, some of the major concerns worldwide are to predict and prevent future events of viral emergence and to know where they will take place in order to apply quick actions to minimize viral spread as a public health priority (Heymann et al., 2015; Becker et al., 2019; Bernstein et al., 2022).

However, actions to reduce such events are yet to be fully established due to the different factors driving the dynamics of spillover, such as climate and environmental changes, global air travel network, population growth and urbanization, anthropogenic activities, demographic changes and migration, and agricultural expansion (Jones et al., 2013; Allen et al., 2017; Wilcox & Steele, 2021; Baker et al., 2022; Mitman, 2022). Based on the SARS-CoV-2 pandemic and what was recently reported in the past outbreaks, most of these viruses have RNA as genetic material as a single-strand or double-strand. This review study aims to explore and consolidate the emergence and re-emergence of RNA viruses in the 21st century through available data. Then, we will explore valuable lessons gained during the SARS-CoV-2 pandemic and focus on potential epidemiologic updates, available treatments, and virus-inhibiting drugs. Finally, we demonstrate the great importance of genomic surveillance of NTD and explore the ongoing development of antiviral drugs, novel therapeutic approaches and strategies for NTD.

Emergence and Re-Emergence of RNA viruses in the 21st century

Historically, epidemics and pandemics of RNA viruses have challenged and directly impacted public health in several countries, raising concerns about the importance of a global epidemiological surveillance system (Devaux, 2012; Khan et al., 2021). It is essential to point out that the origin of RNA viruses is still widely debated as some authors have explained that there might be a possible ancestral origin from a polyphyletic group (Wolfe et al., 2007) evolving from an "ancient virus" (Koonin et al., 2006). RNA viruses generally have small genomes (average size of ~9 kb) with a higher mutation rate per replication cycle than any other organism (Woolhouse, 2002; Domingo, 2010; Holmes, 2010). Viral genetic variation is an important characteristic providing them with an enhanced capability of rapid viral evolution, adaptation, and host range tropism (Moya et al., 2004). Indeed, this higher mutation rate of RNA viruses is a combination of different mechanisms, such as unique point mutations, recombination, and reassortment (Hui, 2006), which together form the viral genetic variation and help shed light on the importance of these organisms in emerging NTD (Hui, 2006; Dolan et al., 2018; Malecela & Ducker, 2021).

Based on the Baltimore classification system, RNA viruses are composed of four main viral categories: double-stranded (dsRNA viruses), positive-sense single-stranded (+ssRNA viruses), negative-sense single-stranded (−ssRNA viruses) and single positive-stranded RNA with DNA intermediate in life-cycle (ssRNA-RT viruses) (Baltimore, 1971; Koonin et al., 2021). Several viruses of NTD have positive single-stranded RNA (+ssRNA) genomes and are divided into distinct viral families with remarkable differences in genomic composition, RNA replication genes, and structural viral particles. However, the steps and mechanisms of +ssRNA virus replication are sufficiently shared within this viral group. Additionally, viral replication happens in the cytoplasm in which the host machinery is used in multiple stages. These common steps of +ssRNA virus replication bring lessons and strategies which can be applied to different viruses in this group, such as antiviral inhibitors and vaccines (Ahlquist et al., 2003). Some examples of viruses of NTD belonging to this group are SARS-CoV, SARS-CoV-2 and many of the arboviruses (ARthropod-BOrne viruses).

In January 2023, according to the list of NTD provided by the World Health Organization (WHO), only Dengue virus (DENV) and chikungunya virus (CHIKV) can be highlighted as single positive-sense RNA ones (Table 1) (Desiree LaBeaud, 2008; Martins-Melo et al., 2018). Nevertheless, many other viruses could be tracked in the category of NTD, as reviewed previously (Maslow, 2019), thus highlighting the importance of these viruses to provide a comprehensive overview of NTD. A summary of the emergence and re-emergence of RNA viruses in the 21st century is listed in Table 1.

Emergence of human highly pathogenic coronaviruses

Coronaviridae is a family of viruses which are initially aimed at epithelial cells from the respiratory and digestive systems. Their genome consists of a single-stranded RNA of positive polarity (+ssRNA), the largest + ssRNA viruses described so far, with sizes ranging from 26 to 32 kilobases (kb). Viral proteases are processed into polyproteins, which encodes 16 non-structural proteins (NsP) to drive essential functions, such as genome replication, inhibition of cellular functions and synthesis of sub-genomic RNA (sg mRNA) (Su et al., 2016). The last part of the viral genome encodes for ORFs responsible for structural proteins, including spike (S), envelope (E), membrane (M) and nucleoprotein (N). Many diseases caused by human

TABLE 1 Emerging and re-emerging viruses which have been reported since 2000.

Family	Genus	Genomic structure	Virus	Reservoir in nature	Vector in nature	EIDs	References
Arenaviridae	*Mammarenavirus*	A) (−)ssRNA	CHPV	Rodents	-	2003, 2019	Delgado et al., 2008; Toledo et al., 2021
			GTOV			2006, 2021	Fulhorst et al., 2008; Rodríguez-Morales et al., 2021
			JUNV			1950–2022	Enria et al., 2008; Gómez et al., 2011; Gallo et al., 2022
			LASV			1965–2022	Fichet-Calvet & Rogers, (2009); Raabe et al., 2022
			LCMV			2012–13, 2021	Vilibic-Cavalek et al., 2021; Aaron et al., 2022
			MACV			2005, 2006–08, 2010	Patterson et al., 2014a; Patterson et al., 2014b
Caliciviridae	*Norovirus*	(+)ssRNA	NV	Humans	?	1972–2022	Lee and Pang, (2013); Chen et al., 2022
	Sapovirus		SV	?		2004–20	Oka et al., 2015; Becker-Dreps et al., 2020
Coronaviridae	*Betacoronavirus*	(+)ssRNA	MERS-CoV	Bats	-	2012–2022	da Costa et al. (2020)
			SARS-CoV1	?		2002	
			SARS-CoV2			2019-?	
Filoviridae	*Ebolavirus*	(−)ssRNA	EBOV	?	?	2013–16, 2018, 2022	Malik et al. (2023)
	Marburgvirus		MARV			2004, 2022	Araf et al. (2023)
Flaviviridae	*Flavivirus*	(+)ssRNA	DENV	Humans	Mosquitoes	2003, 2006, 2010–21	Sirisena et al. (2021)
			JEV	Birds, pigs		1924–2009, 2021–22	Erlanger et al., 2009; Waller et al., 2022
			KFDV	NHP	Ticks	2002–17	Munivenkatappa et al. (2018)
			OHFV	Rodents		2022	Wagner et al. (2022)
			SLEV	Birds	Mosquitoes	2005, 2011–20	Diaz et al. (2018)
			WNV			2000, 2007, 2010–13, 2015–19, 2022	Chancey, (2015); Howard-Jones et al., 2023
Flaviviridae	*Flavivirus*	(+)ssRNA	YFV	NHP	Mosquitoes	2000–08, 2013, 2016–20	Chippaux & Chippaux, (2018); Sacchetto et al., 2020
			ZIKV			2007, 2013–14, 2016, 2018	Pielnaa et al. (2020)
	Hepacivirus		HCV	Humans	-	1965–2019	Yang et al. (2023)
Hantaviridae	*Orthohantavirus*	A) (−)ssRNA	ANDV	Rodents	-	2002	Martinez et al. (2005)
			APV			2014	Bellomo et al. (2021)
			SNV			2000–14, 2017–18	Torres-Perez et al., 2010; Drebot et al., 2015; Kofman et al., 2018; Tobolowsky et al., 2019
Hepadnaviridae	*Orthohepadnavirus*	dsDNA	HBV	Humans	-	1980–2021	Ott et al., 2012; Dekker et al., 2021
Hepeviridae	*Orthohepevirus*	(+)ssRNA	HEV	Humans, pigs	-	2001–14, 2016	Khuroo & Khuroo, (2016); Aslan & Balaban, (2020)

(Continued on following page)

TABLE 1 (*Continued*) Emerging and re-emerging viruses which have been reported since 2000.

Family	Genus	Genomic structure	Virus	Reservoir in nature	Vector in nature	EIDs	References
Orthomyxoviridae	*Alphainfluenzavirus*	(−)ssRNA	IAV	Birds	-	2002–16, 2021–22	Khandaker et al., 2011; Wang, 2021; Wille and Barr, 2022
	Betainfluenzavirus		IBV			2001, 2005–16	Yang et al. (2018)
	Gammainfluenzavirus		ICV			2002, 2005, 2012	Sederdahl & Williams (2020)
Nairoviridae	*Orthonairovirus*	A) (−)ssRNA	CCHFV	Ticks	Ticks	2009–10, 2018, 2021–22	Portillo et al., 2021; Shaikh et al., 2022
Paramyxoviridae	*Morbillivirus*	(−)ssRNA	HMPV	Humans	-	2001–04	Sloots et al. (2006)
			MeV			2016–19	Hübschen et al. (2022)
	Henipavirus		HeV	Bats		2016, 2019	Yuen (2021)
			NiV			2001, 2003, 2007–08, 2014–15, 2018, 2021	Skowron et al. (2021)
Phenuiviridae	*Phlebovirus*	A) (−)ssRNA	RVFV	Livestock	Mosquitoes	2000, 2006–08, 2016	Wright et al. (2019)
Picornaviridae	*Hepatovirus*	(−)ssRNA	HAV	Humans	-	1990–2019	Migueres et al. (2021)
Poxviridae	*Orthopoxvirus*	dsDNA	MPXV	NHP, Rodents	?	2017–22	Beer & Rao, (2019); Kumar et al., 2022
Sedoreoviridae	*Rotavirus*	dsRNA	RV	Humans	-	2000–13	Tate (2016)
Retroviridae	*Lentivirus*	(+)ssRNA	HIV	?	-	1975–2022	Brazier et al. (2023)
Togaviridae	*Alphavirus*	(+)ssRNA	CHIKV	NHP	Mosquitoes	2005, 2013–14, 2018, 2022	Dennehy, (2017); Silva et al., 2018; de Souza, (2023)
			EEEV	Birds		2019	Corrin et al. (2021)

(−): negative-sense strand (+): positive-sense strand A): ambisense genome; ANDV: andes orthohantavirus; APV: alto paraguay orthohantavirus; CCHFV: Crimeian-Congo hemorrhagic fever orthonairovirus; CHIKV: chikungunya virus; CHPV: chapare mammarenavirus; DENV: dengue virus; dsDNA: double-strand DNA; dsRNA: double-strand RNA; EBOV: zaire ebolavirus; EEEV: eastern equine encephalitis virus; GTOV: guanarito mammarenavirus; HAV: Hepatovirus A; HBV: Hepatitis B virus; HCV: Hepacivirus C; HeV: hendra henipavirus; HEV: Orthohepevirus A; HIV: human immunodeficiency virus; HMPV: human metapneumovirus; IAV: Influenza A virus; IBV: Influenza B virus; ICV: Influenza C virus; JEV: japanese encephalitis virus; JUNV: junin mammarenavirus; KFDV: kyasanur forest disease virus; LASV: lassa mammarenavirus; LCMV: lymphocytic choriomeningitis mammarenavirus; MACV: machupo mammarenavirus; MARV: marburg marbugvirus; MERS-CoV: Middle East respiratory syndrome-related coronavirus; MeV: measles morbillivirus; MPXV: monkeypox virus; NHP: non-human primates; NiV: nipah virus; NV: norwalk virus; OHFV: omsk hemorrhagic fever virus; RV: rotavirus; SARS-CoV: Severe acute respiratory syndrome-related coronavirus; SLEV: saint louis encephalitis virus; SNV: sin nombre orthohantavirus; ssRNA: single-strand RNA; SV: sapporo virus; WNV: west nile virus; YFV: yellow fever virus; ZIKV: zika virus.

coronaviruses (HCoVs) are widely dispersed worldwide. Most of the HCoVs known until the 20th century were related to mild respiratory diseases, such as common flu symptoms (Lai & Cavanagh, 1997; McIntosh & Perlman, 2015; Su et al., 2016).

Based on the sequences available in the public databases and protein conservation, the *Coronaviridae* family (CoVs) can be divided into four genera: alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV (Lai & Cavanagh, 1997; Su et al., 2016). Currently, seven different strains of HCoVs can cause respiratory tract infections, namely,: two alphaCoV strains (HCoV_229 E and HCoV_NL63) and five betaCoV strains, of which two are from group A (HCoV_HKU1 and HCoV_OC43), two from group B (SARS-CoV and SARS-CoV-2) and one from group C (MERS-CoV) (Jacobs et al., 2020). Fortunately, many HCoVs are seasonal viruses circulating endemically in the human population for several decades, thus commonly causing mild respiratory infections depending on each individual's immune response (Su et al., 2016). However, prior to SARS-COV-2, we had the emergence of two highly pathogenic coronaviruses, that is, SARS-CoV and MERS-CoV (Ksiazek et al., 2003; de Wit et al., 2016).

The first cases of SARS-CoV were identified in Foshan, a city in Guangdong Province, China. The disease was characterized by high fever, cough, myalgia, headache, shortness of breath and respiratory distress as late symptoms of the disease progressing quickly to an "atypical pneumonia" (de Wit et al., 2016; Lu et al., 2020; Paules et al., 2020). The outbreak spread rapidly to 29 countries in different continents. The pandemic ended in July 2003, with 8,096 reported cases and 774 deaths, notably being the first pandemic of this century (de Haan & Rottier, 2005; de Wit et al., 2016; Hua et al., 2020). Other highly pathogenic coronavirus emerged after almost 10 years, the MERS-CoV in 2012, which caused a cluster of severe cases of pneumonia in Jeddah, Saudi Arabia (Hijawi et al., 2013). Similarly, to SARS-CoV, the MERS-CoV infection can be asymptomatic or evolve into a wide range of symptomatic clinical cases. The most significant clinical symptoms are fever, abdominal pain, and in some cases, diarrhea, whereas the most severe cases are characterized by progressive acute pneumonia

(Hilgenfeld & Peiris, 2013; Zhu et al., 2020; Cascella et al., 2023). MERS-CoV spread from the Middle East to twenty new countries in distant continents. In 2016, 2,521 cases and 624 deaths were reported, with the death toll recently increasing to 866 deaths (Alyami et al., 2020; Dhama et al., 2020; Ahmad, 2022).

By the end of December 2019, the third highly pathogenic coronavirus was identified in the central hospital of Wuhan, a densely populated city in the central province of Hubei, China. The new HCoV was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its phylogenetic proximity to SARS-CoV (Zhou et al., 2020; Santacroce et al., 2021). This new HCoV could induce systemic symptoms in the severe cases, such as dry cough, fever, fatigue, respiratory pneumonia, and potentially fatal cardiorespiratory failure (Hong et al., 2020; Shi et al., 2020; Zhou et al., 2020; Hay et al., 2022). The disease caused by SARS-CoV-2 was subsequently named coronavirus disease 2019 (COVID-19). Due to the rapid spread of SARS-CoV-2, WHO declared a new pandemic in March 2020. In March 2023, there were 680 million reported cases with 6.8 million deaths, thus being the most significant pandemic of the 21st century (Dorsett, 2020; Bigoni et al., 2022; Cascella et al., 2023).

Neglected tropical diseases: arboviruses on the move

Much of what has been observed in the scientific efforts and advances for the new pandemic coronavirus was not observed during the last decades for a considerable number of viral outbreaks of NTD occurring each year in tropical and subtropical regions (Wilder-Smith et al., 2017). Over 500 arboviruses have been identified, with 150 viruses being known to cause human disease (Young, 2018), and belonging to families such as *Flaviviridae* (genus *Flavivirus*) and *Togaviridae* (genus *Alphavirus*), including the order of *Bunyaviridae* (families of *Nairoviridae, Peribunyaviridae* and *Phenuiridae*) (Simmonds et al., 2017; Chen et al., 2018; Young, 2018; Abudurexiti et al., 2019). Most of those outbreaks are related to arboviruses which are cyclically transmitted to a mammalian host through the bite of hematophagous insects (Go et al., 2014; Weaver et al., 2018; Young, 2018). The geographic distribution of these arboviruses is restricted to the ecological parameters related to their transmission cycles (Gubler, 2001; Tajudeen et al., 2022), but a considerable increase of cases was observed in endemic regions as most countries are middle-income ones and have low investments in research (Tajudeen et al., 2022).

The genera *Flavivirus* and *Alphavirus* are arboviruses most known for causing disabling fever syndromes worldwide, which significantly burden worldwide public health and the global economy as well (Go et al., 2014). Several studies highlight the importance of DENV as the most prevalent arbovirus disease, which can be found in the co-circulation of multiple serotypes (i.e., hyperendemic) in several tropical countries of South America, Asia and Africa. In fact, CHIKV and ZIKV have recently expanded their geographical boundaries into the New World (Marcondes & Ximenes, 2016; Rodrigues Faria et al., 2016). In the last decade, South America and Caribbean regions reported endemic infections of CHIKV (2013–2014) (Rodrigues Faria et al., 2016) and epidemic infections of ZIKV (2015–2016) (Marcondes & Ximenes, 2016). Additionally, sporadic outbreaks of Mayaro virus (MAYV) were reported in rural areas of Central and South America (Figueiredo & Figueiredo, 2014; Acosta-Ampudia et al., 2018), including a recently reported re-emergence of yellow fever virus (YFV) in Brazil (2016–2019) (Cunhados et al., 2019).

Other studies have pointed out the possibility of the geographical spread of West Nile virus (WNV), Japanese encephalitis virus (JEV) (Simon-Loriere et al., 2017), and Rift Valley fever virus (RVFV) (Freire et al., 2015), as well as several human cases of Saint Louis encephalitis virus (SLEV) (Heinen et al., 2015) and Oropouche virus (OROV) (Mourão et al., 2009). Unfortunately, in contrast to SARS-CoV-2, a few licensed vaccines are available, and still today, there is no specific antiviral drug to treat infections caused by arboviruses. Figure 1 highlights the global spread of emerging and re-emerging arboviruses in the 21st century (Figure 1A) and lists the number of reported cases in the world (Figure 1B) and in America (Figure 1C).

Flavivirus

Flaviviruses comprise the epidemic viruses DENV, ZIKV, WNV, YFV, and JEV (Simon-Loriere et al., 2017), all belonging to a diverse viral genus with close phylogenetic relationships and similar biological cycles (i.e., virus-vector-host interaction). The viral particles of *Flaviviruses* are enveloped and share an icosahedral structure of 40–60 nm (Zhang, 2003; Mackenzie, 2005). These viruses have a genome size of approximately 11 kb, which encodes a single polyprotein by its ORF and is flanked by two non-coding regions (5′and 3′) (Chambers et al., 1990). The polypeptide consists of approximately 3,400 amino acids, which are further cleaved into three structural proteins, namely, capsid protein (C), precursor membrane protein (prM) and envelope protein (E), and into seven non-structural proteins (NS1-NS5) (Chambers et al., 1990).

Alphavirus

Togaviridae is a smaller family comprising only one genus, *Alphavirus,* and also includes the epidemic viruses CHIKV and MAYV (Chen et al., 2018). This genus comprises a small group of viruses with diversity in molecular and antigenic classification (Strauss & Strauss, 1994). *Alphaviruses* are enveloped viruses with a diameter ranging from 65–70 nm and an icosahedral capsid. Their genome is approximately 10–12 kb in length (Azar et al., 2020) and has an architecture organized into two ORFs. The first ORF encodes for four non-structural proteins (nsPs) accounting for the replication of the virus' genetic material through the formation of RNA replicase complexes, which act in the evasion of the immune responses. The genes of the second ORF encode for structural proteins named C (capsid), E1 and E2 (envelope glycoproteins 1 and 2) as well as E3 and 6 K peptides (Kril et al., 2021).

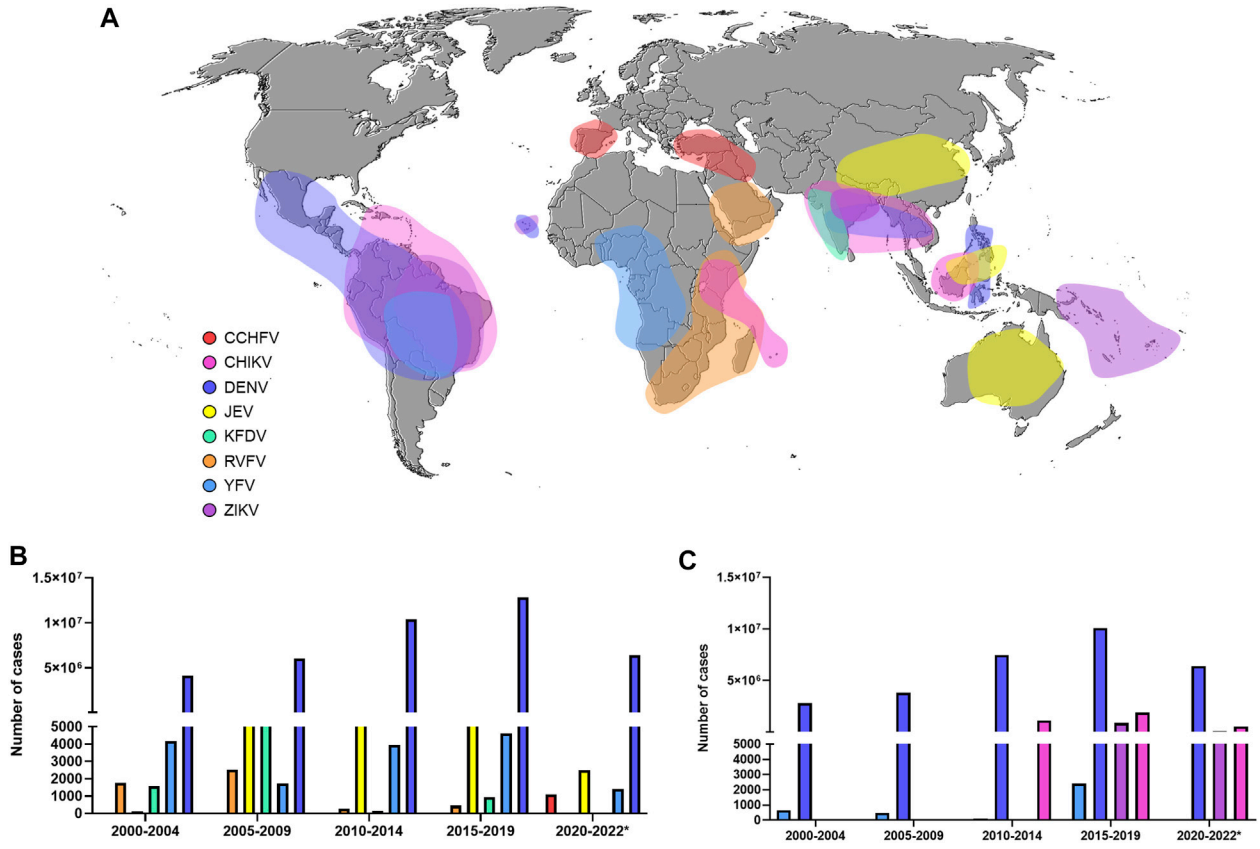

FIGURE 1
Global burden of *Flavivirus* and *Alphavirus* infections **(A)** Map showing arbovirus-reported outbreaks in the 21st century **(B)** The number of cases of some arbovirus diseases worldwide (data provided from WHO) **(C)** The number of cases of some arbovirus diseases in America (data provided from PAHO). CCHFV: Crimean-Congo hemorrhagic fever virus. CHIKV: Chikungunya virus. DENV: Dengue virus. JEV: Japanese encephalitis virus. KFDV: Kyasanur forest disease virus. RVFV: Rift Valley fever virus. YFV: Yellow fever virus. ZIKV: Zika virus.

Lessons from SARS-CoV-2

Real-time genomic data and evolution

During the SARS-CoV-2 pandemic, unprecedented efforts and studies performed by the international scientific community and health agencies generated public knowledge on SARS-CoV-2. Consequently, numerous sequenced viral genomes became available in public databases, such as GenBank and GISAID. In fact, more than 14 million genetic sequence data (GSD) are deposited in the GISAID database (Khare et al., 2021), and this number continues to increase. Analysis of GSD was performed almost in real-time, which has profoundly affected the management of the SARS-CoV-2 pandemic. Additionally, it made it possible to generate epidemiological (Faria et al., 2021; Naveca et al., 2022), genetic, and phylogenetic studies (Cunhados et al., 2019; Nunes D. A. F. et al., 2022), with enhancing precision to provide a wide range of information, which in turn enabled more effective actions to face the pandemic (Chen et al., 2022). In such a scenario, the importance of WHO was also highlighted as a reference center providing a genomic guide to help laboratories worldwide carry out DNA sequencing given the extreme relevance of these data and possible impact on public health (Jacot et al., 2021; Brito et al., 2022).

Currently, the genomic databases of SARS-CoV-2 GSD can be classified into public-domain and public-access databases, which differ from each other in terms of access restrictions. In the public-domain database, GSD can be accessed without registration or identification (Cochrane et al., 2016). On the other hand, identification is needed to access a public-access database, such as GISAID, and manipulate GSD in order to supervise the use of information. Moreover, it is possible to credit researchers who contributed by depositing GSD into databases (Elbe & Buckland-Merrett, 2017; Shu & McCauley, 2017; Shu & McCauley, 2017; Khare et al., 2021).

Analysis of GSD made it possible to infer that SARS-CoV-2 originated from a zoonotic source, like most viruses affecting humans (Holmes et al., 2021), and similarly to SARS-CoV, had its pandemic epicenter traced to a wild animal market (Guan et al., 2003). However, despite all efforts, the specific intermediate host of SARS-CoV-2 still needs to be determined. Its genetic proximity to the bat SARS-CoV-like coronavirus (BatCoVRaTG13), with a nucleotide similarity of ~96%, is still the closest one to that of zoonotic coronaviruses reported in the first outbreak region (Paraskevis et al., 2020). Nevertheless, despite the high percentage

of genetic similarity between SARS-CoV2 and RaTG13, there is a divergence in part of the genome encoding for the receptor-binding domain (RBD), which is an essential role in the connection between spike protein and angiotensin-converting enzyme 2 (ACE2), the receptor of human cells where the virus binds (Andersen et al., 2020).

Many studies have suggested that pangolins (*Manis javanica*) are possible intermediate hosts of SARS-CoV-2 because of the high sequence similarity with the viral RBD (~97.4%) found in coronaviruses isolated from these animals (Zhang et al., 2003; Lam et al., 2012; Zhou et al., 2020; Malik et al., 2023), implying a possible origin of SARS-CoV-2 through recombination (Wong et al., 2020). However, the hypothesis of homoplasy, which suggests that similarities between SARS-CoV-2 and other SARS-CoV-2-like coronaviruses have arisen independently through convergent evolution rather than ancestry, has yet to be fully discarded (Tang et al., 2020).

SARS-CoV-2 has an evolutionary rate of 1.15×10^{-3} substitutions/site/year, which differs slightly from the substitution rates of other highly pathogenic hCoVs, such as SARS-CoV ($0.80–2.38 \times 10^{-3}$) and MERS-CoV ($0.63–1.12 \times 10^{-3}$). However, the two viral strains of SARS-CoV-2, A and B lineages, left China and diversified into several new variants, possibly due to deletion events (Candido et al., 2020; Tang et al., 2020; Rambaut et *al.*, 2021; McCarthy et al., 2021). SARS-CoV-2 variants have been identified and named in different ways by GISAID, Nextstrain and Pango (Alm et al., 2020). As a standardization attempt, in May 2021, WHO suggested a new nomenclature based on the Greek alphabet, which covers some of the main variants and has been extensively used ever since (Papanikolaou et al., 2022). Among the new variants, the most worrying ones have been classified by the Centers for Disease Control and Prevention (CDC) as well as by WHO based on their mutational characteristics, transmissibility, pathogenicity, and ability to evade the immune system, the so-called variants of concern (VOC) (CDC, 2021).

In December 2022, the latest emerging VOC was named Omicron, which appeared in South Africa (Kirola, 2021; Tegally et al., 2022) and spread worldwide (Mohapatra et al., 2022). Evidence of an increased transmission of Omicron variant, including risk or mortality, pointed to mutations in RBD and nucleocapsid (N) regions (Andreano et al., 2020; Plante et al., 2020; Tegally et al., 2020; Xie et al., 2021; Andreata-Santos et al., 2022). The Omicron-related strains (BA.2, BA.4 and BA.5) carry numerous mutations, particularly in the S gene, which encodes for spike protein (Hussain et al., 2020; Wu et al., 2020; Zhou et al., 2020; Hanifa et al., 2022; Papanikolaou et al., 2022; Takashita et al., 2022; Tegally et al., 2022). Although this is already well-established in the literature, the mechanisms underlying these mutations have not been fully characterized. It is established, however, that directional positive selection pressure drives the accumulation of mutations in the SARS-CoV-2 genome, resulting in more non-synonymous mutations affecting the virus' adaptability (Martin et al., 2021; Andreata-Santos et al., 2022; Nunes D. R. et al., 2022). The spike protein plays a crucial role in the virus tropism and its entry into host cells by binding to the ACE2 receptor, thus also being the most immunogenic viral protein (Li 2016; Hoffmann et al., 2020).

As a result, the spike protein has been used as the central target region in many vaccines and serological tests (Galipeau et al., 2020; Sandbrink & Shattock, 2020; Infantino et al., 2021; Kyriakidis et al., 2021). Thus, the emergence of new variants carrying mutations throughout the genome, but with greater intensity in the spike region, has raised the question of how it would impact the efficiency and effectiveness of vaccines and serological tests. This issue is still being carefully evaluated.

Currently available treatments and viral drug inhibitors

Tested therapeutic options are available to date for SARS-CoV-2, including antiviral drugs. The National Institutes for Health (NIH) in the United States has frequently published guidelines for treating COVID-19, including a classification of drugs for use by different individuals as authorized by the Food and Drug Administration (FDA). Based on a wide range of clinical manifestations and considering the patient's age, some medicines were recommended, such as ritonavir-boosted nirmatrelvir (Paxlovid), remdesivir, molnupiravir and bebtelovimab (Murakami et al., 2022; Niknam et al., 2022).

One of the most evident lessons from the COVID-19 pandemic is the extensive and rapid antiviral drug repurposing by using high-throughput screening methods with numerous research groups (Chen, 2020; Rodon et al., 2021; Hamed et al., 2022). The RNA-dependent RNA polymerase (RdRp) enzyme is one of the main therapeutic targets of viral drugs (Wang et al., 2020). Two drugs aimed at RdRp are currently used to control SARS-CoV-2 infection, namely, remdesivir and molnupiravir (Kabinger et al., 2021). As the first drug to be approved for the treatment of COVID-19, remdesivir was also endorsed for children's treatment (Young, 2021; Chera & Tanca, 2022), whereas the above-mentioned drugs are only authorized for emergency use (Atluri et al., 2022). Remdesivir is a nucleotide analogue which prevents the synthesis of viral RNA in coronavirus infection when incorporated as a substrate by RdRp (Gordon et al., 2020; Kokic et al., 2021).

As a result of a broad collaborative effort, the US Food and Drug Administration (FDA) approved the brand-name drug of Veklury (remdesivir) on 22 October 2020, as being the first drug for the treatment of COVID-19 (Al-Ardhi et al., 2022; Niknam et al., 2022). Despite its approval, there are controversies regarding its efficacy. The Solidarity Therapeutics Trial, conducted by WHO, showed no improvement in the overall mortality rate of hospitalized COVID-19 patients treated with remdesivir compared to standard care. In contrast, another study on adaptive COVID-19 treatment trial (ACTT-1), sponsored by the National Institute of Allergy and Infectious Diseases, demonstrated that remdesivir reduced recovery time by 5 days in hospitalized COVID-19 patients compared to standard care, but did not significantly reduce mortality (Beigel et al., 2020). Thus, the use of remdesivir for COVID-19 treatment remains controversial, but it has undoubtedly played an essential role in the fight against the pandemic (Okoli et al., 2021).

As for molnupiravir, a slightly different mechanism of action is observed. Molnupiravir is first converted into β-D-N4-hydroxycytidine ribonucleoside and subsequently into ribonucleoside triphosphate (NHC-TP) through the catalytic activity of the enzyme kinase. When incorporated by RNA polymerase, NHC-TP leads to a significantly increased number of

errors in the viral genetic material, thus generating an erroneous mechanism (Donovan-Banfield et al., 2022), and consequently making viral replication unfeasible (Agostini et al., 2019; Kabinger et al., 2021; Kamal et al., 2022).

Other antiviral drugs have been used to inhibit viral proteases, thereby interfering with the SARS-CoV-2 replication cycle. For example, Paxlovid inhibits viral proteases, which are crucial for the replicative cycle of SARS-CoV-2 (Cannalire et al., 2022;; Marzi et al., 2022), by combining the action of two drugs: Nirmatrelvir and Ritonavir. Nirmatrelvir is a newly developed drug by Pfizer which can bind to the viral protease and prevent its catalytic activity. On the other hand, Ritonavir functions by slowing down the metabolism of Nirmatrelvir to increase its efficiency (Ahmad et al., 2021; Marzi et al., 2022).

Other available treatments for COVID-19 are the anti-SARS-CoV-2 monoclonal antibodies, which can be used depending on the severity and risk factors. Tixagevimab and cilgavimab (AZD7442), two human monoclonal antibodies (mAbs), have been designated for complement blockade of SARS-CoV-2 infection by inhibiting the attachment of the SARS-CoV-2 spike protein. These antibodies have the ability to prevent the virus from attaching to the cell surface receptor (ACE2) by binding to two distinct regions of the spike protein, namely, tixagevimab, which recognizes the receptor-binding domain (RBD) and cilgavimab, which targets the N-terminal domain (NTD) (Stuver et al., 2022; Focosi et al., 2023). FDA approved this pre-exposure prophylactic drug in October 2022, given the continuous emergence of new SARS-CoV-2 variants. After previously being tested in a phase III double-blind trial involving 5,197 participants during the emergence of VOCs, the promise of reducing the incidence of symptomatic COVID-19 was demonstrated (Kertes et al., 2023).

AZD7442 was originally indicated for individuals who did not have an adequate immune response or who had contraindications to vaccination (Akinosoglou et al., 2022). However, the neutralizing ability as a consequence of escape mutations acquired by the new SARS-CoV-2 variants led to its removal from the recommended drugs by the FDA (Focosi et al., 2023; Suribhatla et al., 2023).

Prophylaxis and treatments for *flavivirus* and *alphavirus* diseases: New therapeutic approaches

Despite the importance of the epidemics of arboviruses regarding severe illnesses, no specific drugs or therapies are currently approved for their treatment. However, some strategies in the development and reposition of drugs for the treatment of SARS-CoV-2 can be used for arboviral infections. These main strategies can be classified into the following categories: antiviral drugs, vaccine development and gene therapies (Idrees & Ashfaq, 2013; Bishop, 2015; Gao et al., 2019; Poland et al., 2019; Dong & Dimopoulos, 2021).

Antiviral drugs

Viral protease inhibitors represent a promising class of drugs for controlling and treating arboviral infections. Drugs such as atazanavir, boceprevir, and lopinavir/ritonavir can inhibit viral protease activity, thus preventing the cleavage of proteins essential for maturation of virions, leading to a significant reduction in viral load (Anderson et al., 2009). These inhibitors have a well-established history of use against human immunodeficiency virus (HIV) and hepatitis C virus (HCV), being further approved for treating SARS-CoV-2 infections, although only ritonavir and Paxlovid (nirmatrelvir and ritonavir) remain in use by FDA (11 May 2023) (Lv et al., 2015; Wang et al., 2021; Narayanan et al., 2022).

In recent years, much information on the structure and function of proteins has been generated, such as NS2, NS3, and nsP3, which are essential proteases for cleavage and maturation of virions for many arboviruses belonging to the *Flavivirus* and *Alphavirus* genera, respectively (Nitsche, 2019; Hucke & Bugert, 2020). Thanks to these collaborative efforts, it has been possible not only to design molecules capable of inhibiting the proteolytic activity of these enzymes (Ivanova et al., 2021;; Nunes D. A. F. et al., 2022), but also to investigate drug replacement for arboviruses (Ding et al., 2022).

Indeed, the use of nelfinavir as an inhibitor of HIV and HCV proteases in the replication of DENV and CHIKV has been previously described. In the study by Bhakat et al., the drugs used as inhibitors of HIV and HCV proteases were screened based on their structural similarity to compounds of interest. Although the transition from *in silico* to *in-vivo* studies revealed promising initial results, such inhibition was accompanied by high levels of toxicity (Bhakat et al., 2015; Boldescu et al., 2017).

A more recent screening of FDA-approved drugs identified telmisartan and novobiocin as promising candidates, and they were used as protease inhibitors against chikungunya virus. Telmisartan is an antihypertensive drug aimed at blocking the angiotensin receptor, whereas novobiocin is an approved antibiotic aimed at inhibiting the ATPase activity of bacterial DNA gyrase. By using molecular modeling was demonstrated that these drugs interact with the chikungunya virus nsP2 protein and confirmed *in vitro* their inhibitory activity (Figure 2) (Tripathi et al., 2020). Although these findings demonstrate the potential of drug replacement strategies and exploration of protease inhibitors for possible treatments for arboviruses, no protease inhibitor has been approved yet for these viruses.

Another promising drug class for antiviral therapy is the nucleoside/nucleotide analogs, with remdesivir being the most recent example (Kokic et al., 2021). Sofosbuvir was the first drug of this class and was initially developed for the treatment of HCV. It is orally administered and consists of a uridine molecule connected to a phosphoramidite group through an ester bond. After absorption, sofosbuvir undergoes hepatic metabolism to be converted into an active form through hydrolysis and phosphorylation (Figure 3A). This active form is a nucleotide analog aimed at inhibiting the HCV RNA-dependent RNA polymerase NS5B, ultimately blocking the viral RNA synthesis (Figure 3B) (Bhatia et al., 2014; Keating, 2014).

Indeed, the GDD (Gly-Asp-Asp) motif is a highly conserved site found in flaviviruses and which has been identified as the binding site for sofosbuvir (Figure 3C) (Yap et al., 2007). This drug has shown success in both *in vitro* studies with dengue virus and clinical

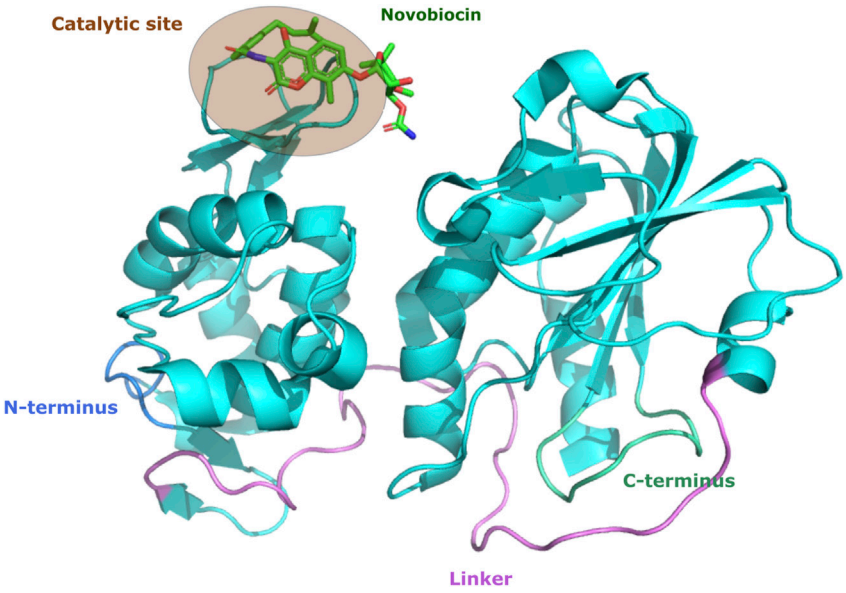

FIGURE 2
Structural representation of CHIKV nsP2 bound to the protease inhibitor. CHIKV nsP2 protein (cyan cartoon) highlighting the active site of novobiocin (green stick). The figures of protein structure were made with the PyMOL Molecular Graphics System, Version 2.0 Schrödinger, LLC.

trials with yellow fever virus, thus highlighting its potential for therapeutic applications (Figure 3D) (Gan et al., 2018; Mendes et al., 2019; Siqueira-Batista et al., 2019).

This class of drug was quickly recognized as a promising tool against epidemic viruses, and the subsequent refining of the most efficient nucleotides led to the identification of remdesivir, later described as the most effective drug against emerging viruses such as SARS-CoV, MERS-CoV and Ebola virus (Malin et al., 2020). As for SARS-CoV-2, this strategy has also shown promising results against arboviruses, as already demonstrated in preclinical studies on remdesivir and molnupiravir (Konkolova et al., 2020; Chera & Tanca, 2022; Extance, 2022; Vangeel et al., 2022). However, further studies are required to establish these drugs' efficacy in treating patients with arboviral infections.

mRNA vaccines

In recent years there has been a marked shift regarding vaccines, treatments and control of arbovirus-borne diseases, as demonstrated by the launch of the Global Arbovirus Initiative (Simpson, 1972; Rocha et al., 2018; Balakrishnan, 2022), due, in part, to the growing emergence of these viruses. Arboviruses are responsible for roughly 30% of all emerging infectious diseases (Jones et al., 2008; Soldan & González-Scarano, 2014). Despite their significance, there are still limited options of vaccines or effective antiviral therapies for most arboviruses, including *flavivirus* and *alphavirus* genera (Carvalho & Long, 2021).

Only four arbovirus vaccines have been currently approved by WHO and FDA for use, namely, dengue virus vaccine (Tully & Griffiths, 2021), Japanese encephalitis virus vaccine (Amicizia et al., 2018), yellow fever virus vaccine (Gordon Frierson, 2010), and tick-borne encephalitis virus vaccine (Wikel, 2018; Nygren et al., 2022). The available vaccines can be categorized into inactivated (TBEV) and live attenuated (YFV, JEV, DENV) ones. The latter category may use chimeric viruses, as demonstrated by the DENGVAXIA vaccine for DENV and one of the three vaccines available for JEV (Collins & Metz, 2017). However, the COVID-19 pandemic has presented the opportunity to use a new technology (Klein, 2022), which has been under development over the last 30 years, the so-called mRNA vaccines (Verbeke et al., 2019). The mRNA-based vaccines are usually encapsulated by a lipid particle to allow the delivery of coding RNA into the cytoplasm, where the ribosomes will translate it into a protein. As demonstrated in the case of SARS-CoV-2, mRNA vaccines elicit both humoral and cellular responses. Host cells express viral proteins which are recognized by B-cell-produced antibodies, thus preventing viral entry into the cell. Furthermore, these vaccines may also induce robust $CD8^+$ T-cell-based immune responses involving apoptosis in the infected cells (Pardi et al., 2018; Rijkers et al., 2021). There is also the possibility of modifying the mRNA to increase stability (Sahin et al., 2014) or prevent immune response to the exogenous RNA molecule, as in the case of the SARS-CoV-2 Pfizer-BioTech vaccine, where uridine was modified into a pseudo-uridine (Dolgin, 2021).

This type of vaccine has several benefits, such as excellent safety, better stability and the possibility of increased absorption. Indeed, this platform allows vaccines to be optimally developed and produced at a shorter time than any other platform (Pardi et al., 2018; Chaudhary et al., 2021; Dolgin, 2021). The mRNA vaccines have immense potential for use in combating NTD. This technology is already being applied in preclinical studies for vaccines against several arboviruses, including Zika, chikungunya and dengue viruses (Chaudhary et al., 2021; Wollner et al., 2021; Ge et al., 2022). Moderna has developed an mRNA sequence by using the mRNA platform which encodes a

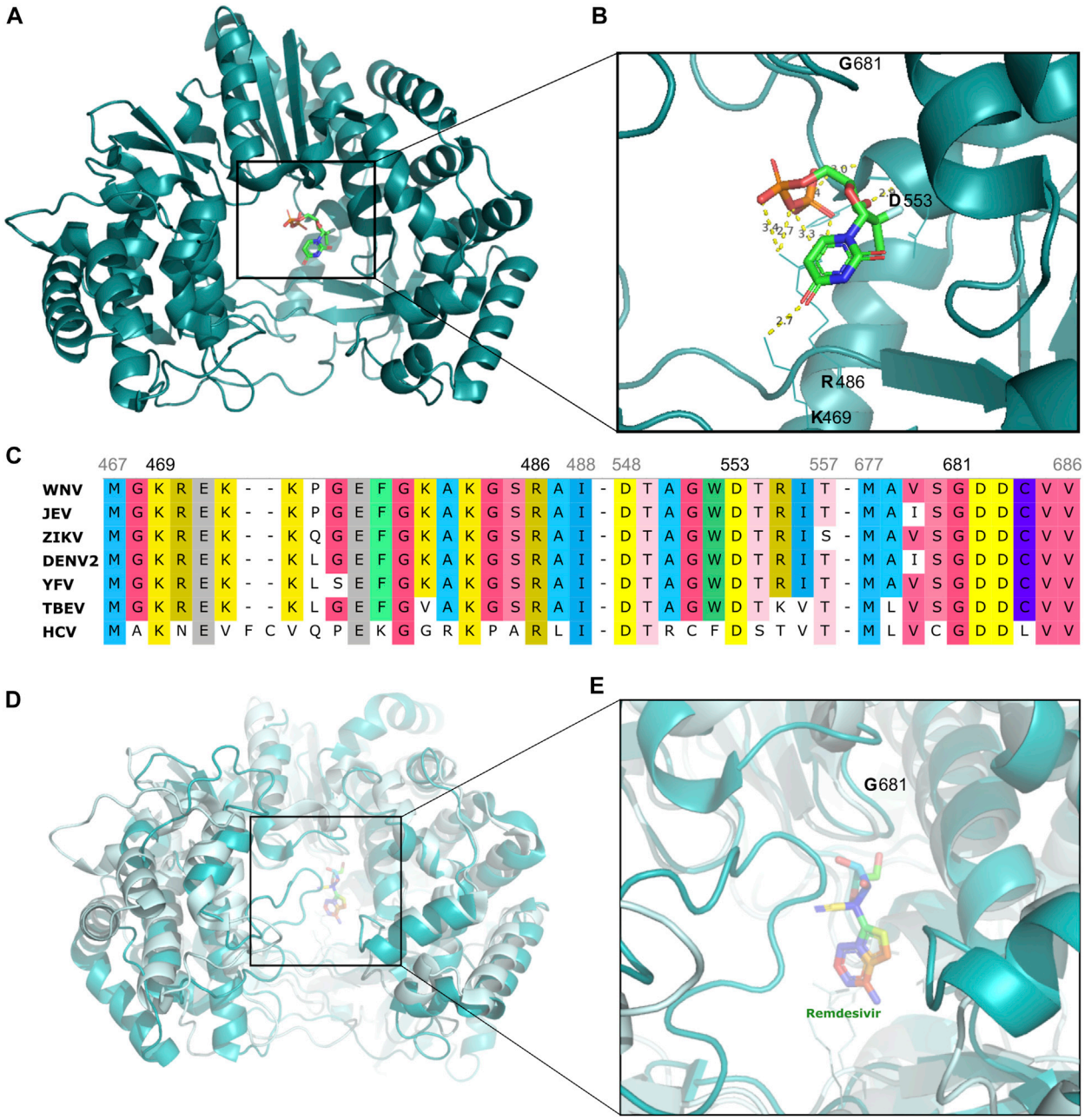

FIGURE 3
Structural representation of Flavivirus (HCV, DENV) proteins, highlighting the site of binding of select drugs that illustrate one of the most effective strategies against arboviruses **(A)** HCV NS5-RNA-dependent-RNA-polymerase domain (teal cartoon) structure interacting with sofosbuvir (multicolored stick), depicted in greater detail in **(B)** highlighting critical amino acid residues (K469, R486, D553) forming polar contacts with sofosbuvir, as well as the G681 residue which is the starting of GDD motif, the drug's active site **(C)** Amino acid sequence alignment of NS5 region from flaviviruses (WNV, JEV, ZIKV, DENV2, YEV, TBEV, and HCV) highlighting some of the most conserved protein regions, including the GDD motif and sites of polar contacts with sofosbuvir/NS5 **(D)** Structural overlay of NS5 from HCV (palecyan cartoon) and DENV (teal cyan cartoon) with remdesivir (multicolored stick) **(E)** Detail of structural similarity between DENV and HCV virus proteins. **(F)** CHIKV nsP2 protein (cyan cartoon) highlighting the active site of novobiocin (green stick).

membrane protein fused to the envelope protein (prM-E) (Richner et al., 2017). The mRNA sequence encoding the prM-E protein is an immunogenic strategy successfully explored for fighting ZIKV, thus demonstrating the induction of high levels of specific and neutralizing antibodies (Larocca et al., 2016; Pardi et al., 2017; Richner et al., 2017).

Surface proteins, such as spike of SARS-CoV-2, E2-E1 of chikungunya and prM-E of Zika and dengue viruses, are commonly chosen as targets for mRNA vaccines not only because they are the surface protein allowing the entry of the virus, but also because they elicit a robust immune response. Proteins E and prM are the two main targets of monoclonal antibodies in *Flaviviruses* (Rey et al., 2018; Slon-Campos et al., 2018; Chaudhary et al., 2021; Wollner et al., 2021; Ge et al., 2022).

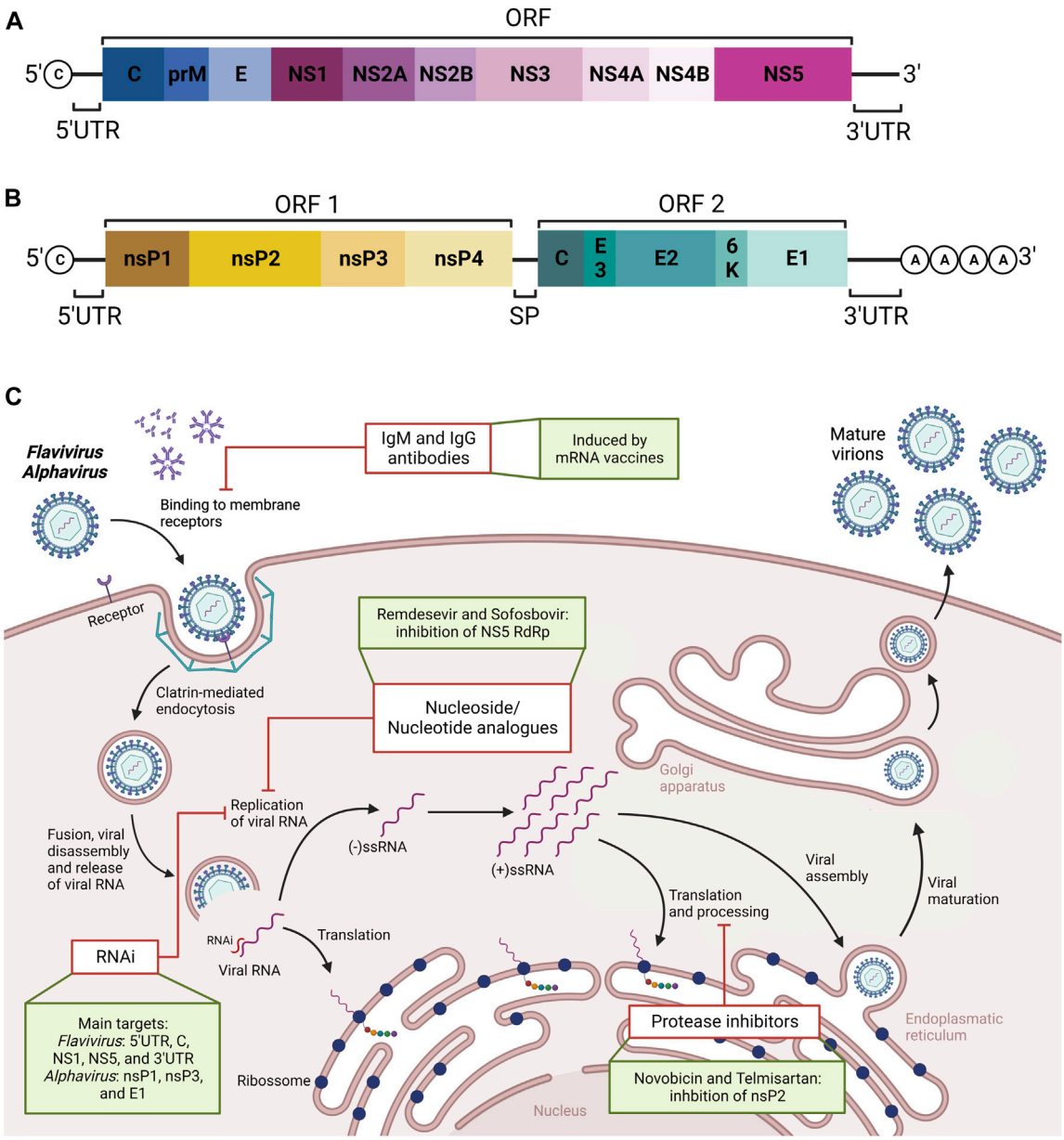

FIGURE 4
Schematic representation of genome organization of *Flavivirus* **(A)** and *Alphavirus* **(B)**, and summary of new therapeutic approaches against *Flavivirus* and *Alphavirus* diseases **(C)**. The viral genome of *Flavivirus* consists of an open reading frame (ORF) between two untranslated regions (UTR). From the ORF, all viral proteins are generated, which are non-structural (NS1-5) and structural (C, M, and E) proteins. The viral genome of *Alphavirus* consists of two ORFs separated by a subgenomic promoter (SP). From the first ORF, the non-structural proteins (nsP1-4) are generated, while the structural proteins (C, E1 and E2) are generated by the second ORF. In addition, a summary of viral infection cycle of *Flaviviruses* and *Alphaviruses* in eukaryotic cells is represented. The first step involves the virion particles containing structural proteins and RNA genomic material. The box highlights the possibility of blocking viral entrance by using neutralizing IgM and IgG antibodies induced by mRNA vaccines. The second step involves the release of viral genome traffic from early endosomes. Next, RNA replication can be blocked either by using analogue nucleoside, the growing such as remdesevir and sofosbovir, to be incorporated by the RNA-dependent RNA polymerase (RdRp) enzyme into which is then incorporated into the growing RNA strand or using RNA interference (RNAi) specific for target locations of the viral genome, leading to genome degradation. The following steps, such as translation, can be inhibited by blocking both structure and function of nonstructural proteins, which are essential proteases for virion cleavage and maturation. Examples of such protease inhibitors include novobicin and telmisartan. Created with Biorender.com.

RNA interference

The RNA interference (RNAi) is a cellular mechanism present in several eukaryotic organisms aimed at decreasing the expression of specific genes by the use of molds of small non-coding RNAs (sncRNAs) with approximately 20–30 nucleotides as a template complementary to mRNA. This pathway is specific and conserved between species and, in theory, can be used to silence the expression of any gene of interest (Agrawal et al., 2003). Physiologically, RNAi acts in biological processes such as cell development and

TABLE 2 RNAi-based antiviral therapy for SARS-CoV2, *Flavivirus* and *Alphavirus*.

Virus	Target locations	RNAi	Summary of the results observed	Reference
SARS-CoV2	M, N, S	siRNA	• *In silico*: 6 siRNAs were designed using bioinformatics tools and effectively inhibited their respective targets in prediction tools	Ayyagari (2022)
	5′UTR, RdPd, Helicase		• *In vitro*: decreased viral titer in Vero cells	Idris (2021)
			• *In vivo*: reduced viral titers in the lungs, lower clinical scores, and weight loss in K18-hACE2 mice (the effect was lost after 6 days)	
	5′UTR		• *In vitro*: decreased viral titer in Vero cells infected with SARS-CoV2, SARS-CoV2 Alpha Variant, and SARS-CoV1	Tolksdorf et al. (2021)
Flavivirus				
DENV	NS1, NS5	siRNA	• *In vitro*: inhibits viral replication of DENV-2, DENV-3, DENV-4 in Vero cells	Paul et al. (2014)
	C, CprM, NS1, NS3, NS5		• *In vitro*: the siRNA target against the capsid gene successfully inhibits DENV-1, DENV-2, DENV-3, and DENV-4 replication in BHK-21 cells	Prakash et al. (2021)
	5′UTR, Structural region, 3″UTR		• *In vitro*: reduction of DENV-2 RNA copies and viral particles in Vero transfected with siRNA targeting the structural proteins region of the genome	Raheel et al. (2015)
	5′UTR, C, E, NS3, NS5, 3′UTR		• *In vitro*: decreased viral titer in Huh-7 cells infected with DENV-1, DENV-2, DENV-3, and DENV-4	Stein et al. (2011)
			• *In vivo*: inhibition of DENV-2 infection in AG129 mice	
	C, E, NS1, NS5	amiRNA	• *In vitro*: inhibition of DENV-2 infection in BHK-21 cells	Xie et al. (2013)
JEV	NS5	shRNA	• *In vitro*: decreased viral titer in HEK293A, Vero, PS, and N2a cells • *In vivo*: reduced viral titer in FvB/J mice brains and increased survival rate from infection	Anantpadma & Vrati (2012)
	3′UTR	amiRNA	• *In vitro*: decreased intracellular viral RNA and infectious viral particles in N2a cells	Sharma et al. (2018)
WNV	C, prM, E, NS1, NS3, NS4A/B, NS5, 3′UTR	shRNA	• *In vitro*: decreased viral titer in Vero cells	Anthony et al. (2009)
	E	siRNA	• *In vitro*: inhibition of viral replication in Vero cells • *In vivo*: decreased viral load in Balb/c liver, spleen, and brain, and increased survival	Bai et al. (2005)
	NS2A, NS5	amiRNA	• *In vitro*: decreased viral titer in Vero cells	Karothia et al. (2020)
	NS5	siRNA	• *In vitro*: inhibition of viral replication in Vero cells	Ong et al. (2006)
	C, NS2B, NS4B	shRNA	• *In vitro*: inhibition of viral replication in Vero cells transfected with shRNA anti-C	Ong et al. (2008)
	C, prM, E, NS5	siRNA	• *In vitro*: inhibition of viral replication in HTB-11 cells	Yang et al. (2008)
YFV	E, NS1, NS5	shRNA	• *In vitro*: decreased viral titer and NS4 expression in Vero cells • *In vivo*: increased the survival of Balb/c mice and attenuated meningitis and central nervous system lesions after intracerebral inoculations of YFV and shRNAs	Pacca et al. (2009)
ZIKV	5′UTR, C, prM, NS2B, NS3, NS4A, NS4B, NS5, 3′UTR	siRNA	• *In silico*: 20 siRNAs were designed using bioinformatics tools, and their efficacy against ZIKV and other flaviviruses were verified in prediction tools	Giulietti et al. (2018)
	3′UTR		• *In vitro*: decreased viral load in C6/36 cells	Perez-Mendez (2020)
Alphavirus				
CHIKV	nsP3, E1	siRNA	• *In vitro*: inhibition of viral replication in Vero cells for 48 h	Dash et al. (2008)
	nsP1, C, E1	shRNA	• *In vitro*: decreased viral titer in HeLa, RD, and BHK-21 cells	Lam et al. (2012)
			• *In vivo*: increase in survival of C57BL/6 mice infected	
	nsP1, E2	siRNA	• *In vitro*: inhibition of viral replication in Vero E6 cells	Parashar et al. (2013)
			• *In vivo*: administering of siRNAs after the infection reduced the viral load in the serum and other tissues and improved the inflammatory condition in muscle tissues	
	nsP1, nsP2, nsP3, C	amiRNA	• *In vitro*: inhibition of viral replication in Vero cells	Saha et al. (2016)
VEEV	nsP4		• *In vitro*: inhibition of viral replication in BHK-21 cells	Bhomia et al. (2013)

(Continued on following page)

TABLE 2 (*Continued*) RNAi-based antiviral therapy for SARS-CoV2, *Flavivirus* and *Alphavirus*.

Virus	Target locations	RNAi	Summary of the results observed	Reference
	nsP1, nsP2, nsP3, nsP4, C, E1	siRNA	• *In vitro*: decreased viral titer in HEK-21 cells	Haikerwal (2022)
	nsP1, nsP4, E1		• *In vitro*: decreased viral titer in BHK-21 cells	O'Brien (2007)

amiRNA: artificial microRNA; C: capsid protein; CHIKV: *chikungunya virus*; DENV: *dengue virus*; E: envelope protein; JEV: *japanese encephalitis virus*; M: membrane protein; N: nucleocapsid protein; NS/nsP: non-structural protein; RdPd: RNA-dependent polymerase; S: spike protein; SARS-CoV: *Severe acute respiratory syndrome-related coronavirus*; shRNA: short hairpin RNA; siRNA: small interfering RNA; UTR: untranslated region; VEEV: *venezuelan equine encephalitis virus*; WNV: *west nile* virus; YFV: *yellow fever virus*; ZIKV: *zika virus*.

differentiation, and in some animals (e.g., mosquitoes), it participates in the immune response against viral genetic material (Siomi & Siomi, 2009; Wang, 2021). In fact, RNAi has been studied as a therapeutic platform for treating various genetic diseases, cancers and antiviral therapy (Sidahmed et al., 2014; Kristen et al., 2019; Kara et al., 2022). These molecules can be quickly designed, synthesized and tested in several *in vitro* and *in vivo* trials (Agarwal et al., 2022).

By recognizing specific sequences of the viral genome, these molecules can prevent the replication of the virus and the translation of viral proteins without affecting the host's gene expression (Ketzinel-Gilad et al., 2006). Considering their therapeutic applications, three types of RNAi stand out, namely, microRNAs (miRNAs), small interfering RNAs (siRNAs) and short hairpin RNAs (shRNAs) (Agarwal et al., 2022). Although the miRNA pathway occurs through the expression and processing of non-coding regions of the cell's genome, the siRNA pathway relies on detecting double-stranded RNAs inside the cell. There are currently several tools and techniques allowing the design and insertion of artificial RNAs (e.g., amiRNAs and siRNAs) into the cell environment (Agarwal et al., 2022). Also, shRNAs are synthetically designed and delivered as expression plasmids or bacterial/viral vectors.

COVID-19 pandemic has made coronaviruses the most urgent targets for developing antiviral drugs, including exploring the RNAi platform. This methodology was used *in vivo* and *in vitro* to prevent SARS-CoV-2 dissemination (Table 2) (Donia & Bokhari, 2021; Talukder & Chanda, 2021). Studies with the development of RNAi directed against the 5′UTR region of the viral genome (Idris, 2021; Tolksdorf et al., 2021), including other genome regions such as RNA polymerase (RdRp) and Helicase (Hel) proteins (Idris, 2021) were rapidly conducted (Table 2). They reported a reduction in viral loads *in vitro* and *in vivo*, showing that this technique can be a good strategy for arbovirus infections and considering the complex host-pathogen and vector-pathogen interactions (Gubler, 2002). Several *in vitro* and *in vivo* studies with different *flavivirus* and *alphavirus* genera (Table 2) have demonstrated a significant viral load reduction by several RNAi designed against non-structural and structural protein genome regions (Pacca et al., 2009; Parashar et al., 2013; Haikerwal, 2022) or even terminal genome regions (Stein et al., 2011). These studies develop and test approximately 6–10 RNAi aimed at various genome locations, with 2-3 molecules having a significant inhibitory activity (Table 2) ranging from 80%–90%. A common point in many of these studies is the use of tests combining siRNAs, which showed an additive effect on the inhibition of replication of different viral strains (O'Brien, 2007).

Nowadays, no clinical trials use RNAi against SARS-CoV2 or *flavivirus* and *alphavirus* genera. However, the use of this technology in treating other emerging viruses, such as HIV and EBOV, has succeeded in different stages of clinical trials, demonstrating its potential in treating viral diseases (Setten et al., 2019). Although there is still much to be done in the development of these therapeutic approaches, mainly regarding cost and time of action of the molecules in the organism (which can also influence the price of the treatment), the promising results presented by these studies show that this new therapeutic approach is excellent in the treatment of these diseases.

Conclusion

Herein, we reviewed the literature regarding the research for prophylaxis and treatment development for SARS-CoV-2 and Neglected Tropical Diseases (NTD), focusing mainly on arboviruses (Figure 4). Efforts to combat the SARS-CoV-2 pandemic have opened new perspectives regarding strategies that can be used to expand the treatment, therapy, and immunization for other RNA viruses. The review also indicates which approaches were used and currently appear to be the most promising ones—for example, inhibitory replication drugs like nucleoside analogs and protease inhibitors. Moreover, developing mRNA vaccines against the SARS-CoV-2 virus demonstrates enormous efficacy and great vaccine candidates. Since few vaccines can suppress most epidemic arboviruses, this would be an excellent strategy as it has already started on clinical trials for zika, chikungunya, and dengue viruses. Also, the recent design and development of new therapy using RNAi for the most critical arboviruses was reviewed, some of it within promising results targeting distinct *flavivirus* and *alphavirus* RNA conserved regions. Ultimately, antiviral treatments and vaccines are crucial for improving public health and preventing future arbovirus epidemics in tropical and subtropical areas.

Author contributions

DRN and CTB conceptualized the work. DRN and DBML performed the graphical analysis, Table and Figures. DRN, DBML, RAS, LMRJ and CTB wrote the manuscript and corrected the final version. All authors have read, edited and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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