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Feature Article

History of Coronaviruses: Why is it Important in the Context of COVID-19?

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Abstract

Coronaviruses have been around since time immemorial. However, their relevance in the context of human diseases is relatively new, spanning hardly over half a century. In this short span of time, we've learned much about these viruses, but there is still much more to learn. It is said that *"history repeats itself"*. This adage can't be more true than in the case of coronavirus outbreaks. History has taught us that epidemics, such as SARS and MERS are capable of threatening our lives repeatedly. And now, with the emergence of the COVID-19 pandemic, which is causing devastation across the globe, history has again shown that it can repeat itself. The present review traces the history of coronaviruses from pre-biblical times till modern times and tries to put it in the context of the ongoing COVID-19 pandemic.

Key words: History, coronavirus, SARS, MERS, COVID-19, SARS-CoV-2.

Introduction

Coronaviruses are so-called because they look like a crown (Latin: *"corona"* = *"crown"*) due to the spike proteins that protrude from their surface. The history of coronaviruses can be traced back to pre-biblical times. The origin and evolution of viruses are measured by a technique known as phylogenetic analysis. The approximate time of origin of viruses is estimated using the so-called *most recent common ancestor* (MRCA) calculation. Based on the MRCA, the first coronaviruses originated around 8000 BC, although some other models indicate that these viruses could have originated 55 million years ago or even earlier. If this is true, then it may be presumed that these "prehistoric" coronaviruses co-evolved with bats, which are considered to be the natural host or reservoir of coronaviruses. The four types of coronaviruses – alpha, beta, gamma, and delta – are believed to have originated around 2400 BC, 3300 BC, 2800 BC, and 3000 BC, respectively, thereby making the betacoronaviruses the oldest of the clan [1].

Discovery of Animal Coronaviruses

In the modern era, coronaviruses were first detected in animals and birds, prior to detection in humans. The earliest evidence of the existence of coronaviruses came in the 1920s when there was an outbreak of respiratory infections among domestic chickens in North America. This initial investigation was followed by a series of discoveries that eventually established the existence of coronaviruses in the animal kingdom [2].Coronaviruses have since then been reported in multiple animal species, including mice, rats, rabbits, cats, dogs, pigs, calves, and turkeys.

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Discovery of Human Coronaviruses

Human coronaviruses were first reported in 1965 when Dr. David Tyrrell and Dr. Malcolm Bynoe succeeded in culturing a unique common cold virus, which they designated as B814 [3]. This was the first human coronavirus to be discovered. This discovery was made at the Common Cold Unit, of which Dr. Tyrrell was then the Director (Figure 1). The Common Cold Unit is located in the city of Salisbury in the county of Wiltshire in the southwest of England.

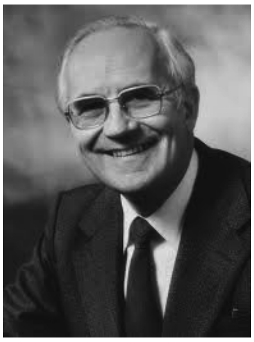

Figure 1: Dr. David Tyrrell, MD, FRCP, FRCPath, CBE, FRS

Concurrently, other discoveries were being made in the US. For example, at the University of Chicago, Dr. Dorothy Hamre and Dr. John Procknow isolated and cultured a similar novel coronavirus, which they designated as 229E [4]. The following year, in 1967, Scottish virologist Dr. June Almeida captured the very first electron microscopic (EM) images of these and related coronaviruses [5]. In fact, the first EM image was that of the coronavirus designated as OC16. This coronavirus was so-called because it was isolated in organ culture (OC = organ culture).Even though the image was taken more than 50 years ago, the club-shaped spike proteins on the surface of the viral particles are still clearly visible (Figure 2). The distinctive crown-like appearance of this and related viruses led to the coining of the term "coronavirus". This was later officially accepted as a separate genus [6].

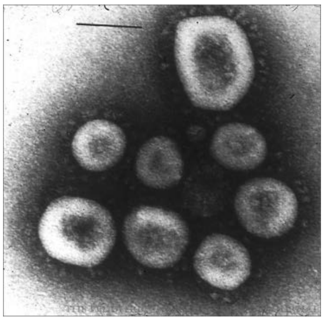

Figure 2: OC16 – First electron microscopic image of a coronavirus

Ongoing seroepidemiological studies revealed new information on human coronaviruses. For example, it was found that in temperate regions of the globe, coronavirus infections occurred more during winter and spring than during summer and autumn. It was also revealed that coronaviruses accounted for more than 35% of total respiratory viral infections. Moreover, it was estimated that 15% of all adult colds were caused by coronaviruses [7]. The summary of the discovery of human coronaviruses is presented in Table 1.

Table 1: Timeline of Discovery of Human Coronaviruses

Year of Discovery	Country of Discovery	Details of Discovery
1965	UK	B814 – first human coronavirus to be discovered
		Discovered by Tyrrell and Bynoe at the Common Cold Unit in Salisbury, Wiltshire, UK
		Isolated from a boy with a cold
1966	USA	229E discovered by Hamre and Procknow at the University of Chicago, USA
		Isolated from a medical student with a cold
1967	USA	OC43 and OC16 discovered by scientists at the National Institute of Allergy and Infectious Diseases (NIAID), USA
		Termed *"OC"* because these viruses were grown in *"Organ Culture"*
		OC43 had a similar morphology to B814
1967	UK	First images of B814, 229E, OC16, and OC43 taken by EM
		Viral particles were of medium size (80-150 nm)
		Covered with *"club-shaped surface projections"* (now called *"spike proteins"*)

Recently Discovered Human Coronaviruses

The last two decades have seen the discovery of several new human coronaviruses. The first of these is the severe acute respiratory syndrome coronavirus (SARS-CoV), which was behind the SARS outbreak. SARS-CoV has now been renamed as SARS-CoV-1, to distinguish it from SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19). SARS-CoV-1 emerged in 2003 from Yunnan Province in China [8, 9]. This was the first instance where a virus *"jumped"* from its natural animal reservoir (bats) to humans via an intermediate host (civets). Seroepidemiological studies revealed that animal handlers who slaughter wild animals in the food markets were the first to be infected with the virus, before spreading to the general population [10]. This outbreak soon reached epidemic portions and rapidly spread to other countries. During the epidemic, SARS spread to 29 countries in Asia, Europe, North America, and South America. There was a total of 8,096 cases and 774 deaths [11]. At that time, SARS was the biggest coronavirus epidemic in recorded human history. This could be considered as a *"wake-up call"* for bigger ones to follow.

In 2004, van der Hoek and colleagues from the Erasmus University Medical Center in Rotterdam, Netherlands, discovered the human coronavirus NL63 (NL = Netherlands) [12]. This virus was isolated from a very young girl, aged just 7 months, who was suffering from a respiratory infection. Phylogenetic analysis revealed that NL63 was similar to 229E and transmissible gastroenteritis virus that affects pigs. The researchers identified another variant of the same virus, which they termed NL. The following year, Esper et al. (2005) discovered a respiratory coronavirus in New Haven, Connecticut, USA, which they named HCoV-NH (NH = New Haven) [13]. They detected this virus in respiratory samples of infected children less than 5 years of age, who exhibited cough, runny nose, breathing problems, and other symptoms of respiratory infection. Phylogenetic analysis indicated the HCoV-NH resembled NL63 and NL. Further research revealed that HCoV-NH could cause Kawasaki disease, an inflammatory disease in children, characterized by rashes, glandular swelling, and sometimes cardiovascular problems. In the same year, Woo et al. (2005) from Hong Kong University (HKU) discovered a novel respiratory virus from an aged man in his seventies, who exhibited fever and cough [14]. They used reverse-transcription polymerase chain reaction (RT-PCR) to amplify the novel genetic sequence. They named this novel coronavirus HKU-1. Besides Hong Kong, this virus was subsequently found in other countries also, including Australia, France, and the US [15].

After a gap of 7 years in 2012, another novel coronavirus emerged, this time in Saudi Arabia. This was named Middle East respiratory syndrome coronavirus (MERS-CoV) and was first detected in a man with pneumonia and kidney failure. This virus, like SARS-CoV-1, spread from bats to humans. But this time, instead of civets, the intermediate hosts were dromedary (one-humped) camels. Initially, there were no reports of human-to-human transmission. But later on, this was reported from France, Germany, UK, Tunisia, Qatar, Jordan, UAE, and Saudi Arabia, among several other countries. The MERS epidemic affected a total of 27 countries, with 2,494 cases and 858 deaths. This was the last major coronavirus epidemic, prior to the current COVID-19 pandemic, which started on 31 December 2019. It should be noted that SARS-CoV-2 is the only coronavirus to cause a global pandemic. A summary of the recently discovered human coronaviruses discussed above is presented in Table 2.

Table 2: Recently Discovered Human Coronaviruses

Virus	Place of Discovery	Year of Discovery
SARS-CoV-1	Yunnan, China	2003
NL63 / NL	Amsterdam, Netherlands	2004
HCoV-NH	New Haven, Connecticut, USA	2005
HKU-1	Hong Kong	2005
MERS-CoV	Saudi Arabia	2012
SARS-CoV-2	Wuhan, China	2019

The transmission of these and other coronaviruses from their reservoir hosts (bats or rodents) to humans via their respective intermediate hosts are presented in Figure 3. Notably, the intermediate hosts for a couple of these viruses, including SARS-CoV-2, are yet to be definitively established.

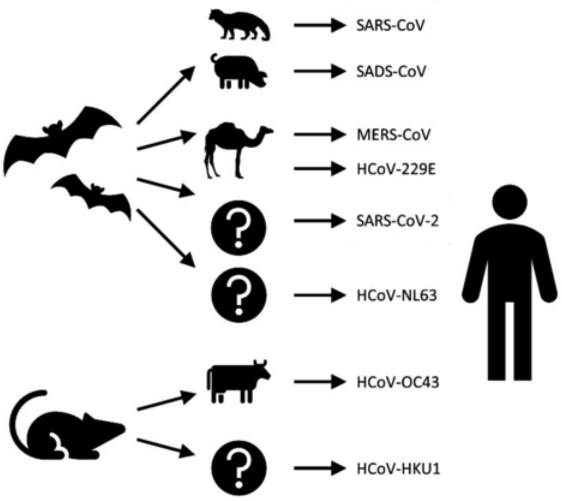

Figure 3: Origins of human coronaviruses and their possible intermediate hosts
[SADS: Swine Acute Diarrhea Syndrome;
HCoV: Human coronavirus]

Discovery of SARS-CoV-2 and Emergence of the COVID-19 Pandemic

The prelude to the discovery of SARS-CoV-2 and the emergence of COVID-19 involved the reporting of a cluster of atypical pneumonia cases on 31 December 2019 from the city of Wuhan in the Hubei Province of China. The COVID-19 pandemic has now affected all continents, with recent spread to hitherto unaffected Antarctica too. This is the fifth and undoubtedly the biggest pandemic since the Spanish Flu, which occurred in 1918. Other pandemics that followed the Spanish Flu (1918) include the Asian Flu (1957), Hong Kong Flu (1968), and Pandemic Flu (2009), which killed 50 million, 1.5 million, 1 million, and 300,000 people respectively. In comparison, COVID-19 has already killed over 2 million people [16].

As of 24 January 2021, SARS-CoV-2 has infected 99.4 million people and killed 2.1 million people across 219 countries and territories around the world [17]. SARS-CoV-2 is highly transmissible, with its basic reproduction number (Ro) varying anywhere between 1.5 and 7. Its mortality rate is around 1%, which is 10-times higher than influenza viruses. Hence, the virus spreads very fast and it's a killer! It is believed that SARS-CoV-2 is transmitted from bats to humans via pangolins, which are presumed to act as intermediate hosts. However, the identity of the intermediate host is yet to be unequivocally established. An international team of scientists, assembled by the World Health Organization (WHO) is currently investigating this aspect in Wuhan, China [18].

Table 3: Characteristics of Major Zoonotic Coronavirus Strains

	SARS-CoV-1	**MERS-CoV**	**SARS-CoV-2**
Disease	SARS	MERS	COVID-19
Outbreaks	2002-2004	2012, 2015, 2018	2019-2021 (ongoing pandemic)
Epidemiology			
Date of first case	November 2002	June 2012	December 2019
Location of first case	Shunde, China	Jeddah, Saudi Arabia	Wuhan, China
Countries affected	29	27	219
Average age (years)	44	56	56
Sex ratio (M : F)	0.8 : 1	3.3 : 1	1.6 : 1
Cases	8,096	2,494	102 million (as of 30.01.2021)
Deaths	774	858	2.2 million (as of 30.01.2021)
Case fatality rate (%)	9.2	37	2.2
Major Symptoms			
Fever (%)	99-100	98	87.9
Dry cough (%)	29-75	47	67.7
Dyspnea (%)	40-42	72	18.6

What has the history of coronaviruses taught us?

From the foregoing discussion, it is clearly evident that in the case of pandemics, the old adage *"history repeats itself"* holds true. Keeping aside the four flu pandemics, which are not caused by coronaviruses, there have been two major epidemics (SARS and MERS) and one pandemic (COVID-19), which is currently ongoing. Between the SARS and MERS epidemics, history took 9 years to repeat itself, while between MERS and COVID-19, it took just 7 years. Ever since the SARS epidemic, scientists around the world anticipated that a global pandemic was a real possibility. The WHO Director-General Dr. Tedros Adhanom Ghebreyesus warned about this when he assumed office in 2017. Even Bill Gates prophesied about this as far back as 2015. This anticipation led to the setting-up of the Coalition for Epidemic Preparedness Innovations (CEPI), whose sole purpose is to develop innovative vaccine platform technologies in case a pandemic happens to emerge. In fact, the prior assembly of the various vaccine platforms enabled the development of the COVID-19 vaccines at such a record-breaking speed – the fastest in medical history!

So, what's in store for us in the future? Will there be another pandemic? History has taught us that there could indeed be another one. In the words of Dr. Michael Ryan, the Executive Director of WHO's Health Emergencies Program, *"the next pandemic could be an even bigger one"*. But will it occur within our lifetimes? Who can tell?

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