

EDITORIAL

Pandemics then, now and yet to come

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A pandemic is an epidemic of an infectious disease which has spread across a substantial part of the world and affects a large number of individuals.^[1] Throughout history the world has constantly suffered from pandemics. As humanity started out as hunter gatherers, the interactions with other humans and animals was minimal. However, during history, trade between communities increased, cities developed, the population sky-rocketed and people travelled between communities, all increasing human-human interaction and decreasing the distance between humans and animals. The potential for zoonotic transmission became greater as well as the ability of pathogens to spread in short time periods across large populations and even across continents. In the course of history, endemics and pandemics have constantly plagued humanity.

One of the first reported pandemics is the plague of Justinian (541-543 AD) which started in Egypt and quickly spread beyond the African continent to the Roman Empire and surrounding areas, killing approximately 100 million people.^[2,3] Interestingly, the pandemic spread predominantly through established trade routes sparing isolated Barbarian communities who were not part of these routes. From analysis of dental pulp samples derived from victims of this plague, we have learned that the causative pathogen involved was *Yersinia pestis*, a gram-negative rod-shaped bacterium which since then has plagued the world in an unprecedented manner. *Yersinia pestis* is transmitted by fleas that contract the bacteria when they bite infected rodents. Subsequently, fleas transmit the infection further when they bite other rodents and infect humans when they are bitten. Three forms of the plague may manifest, of which the bubonic form is the most prevalent and lethal form (50-90% mortality). About 800 years later the plague caused a secondary pandemic known as the *black death* which swept through Asia and Europe, again spreading to trade routes, killing 200 million people and a staggering 30% of Europeans. Subsequently, the occurrence of

the plague subsided only to rise again causing major outbreaks in London and Milan in the 17th century. After this, the plague stopped spreading due to circumstances that are incompletely understood. However, even now, isolated outbreaks of the plague are still being reported: between 2010 and 2015, 3248 cases of infection have been reported, especially in Congo, Madagascar and Peru.^[3,4]

A second example of a pathogen that has caused severe pandemics throughout history is *Vibrio cholera*, which was endemic in Asia in the 19th century but was able to spread to other continents as a result of technological innovations, such as steam ships and railways, facilitating transport of people between continents.^[1,5] Cholera is a rapidly dehydrating diarrhoeal illness caused by the cholera toxin, which interacts with the gut causing a dramatic watery diarrhoea. During the 19th and 20th century, a total of seven cholera pandemics occurred. In contrast to *Yersinia pestis*, *Vibrio cholerae* does not have an animal reservoir but is transmitted through water via the faecal-oral route. In 1854, the British physician John Snow famously discovered that the water pumps in Soho were responsible for the major outbreak that was going on at the time, a discovery which may be seen as the birth of medical epidemiology.^[1,6] Due to the enormous improvement in sanitary conditions, cholera is now rare in the Western world. However, in developing countries between 1-4 million people are still being infected yearly. In special circumstances, such as after the 2010 earthquake in Haiti, an island where cholera had vanished a long time before, introduction of a cholera strain (probably by UN Nepalese peacekeepers coming in to aid the Haitians) in a setting of chaos, destruction and decreased sanitation can lead to significant and rapid outbreaks of the disease.^[7]

Next to zoonotic pandemics, such as *Yersinia pestis* and those that spread through water like *Vibrio cholerae*, respiratory

pathogens such as *Influenza* have plagued us throughout history. *Influenza* caused the first major outbreak in the 1500s but the most well-known pandemic occurred in 1918.^[8] At that time the Spanish flu (H1N1 *Influenza*) rapidly spread over the globe causing more than 50 million deaths, which makes it the deadliest virus ever known to man.^[9] *Influenza* primarily infects the lungs and results in severe pulmonary damage which leads to ARDS and increased susceptibility to bacterial superinfection. Interestingly, the pandemic came in three waves, each with a distinct mortality curve with respect to different age groups, and the spread of the virus was greatly facilitated by the living conditions of civilians as well as soldiers during the ongoing First World War. As the virus was respiratory in origin, physicians started to advocate measures now well known to us such as masking, lockdowns, respiratory hygiene and social distancing.^[10] The special ability of *Influenza* to adapt and exchange genes between *Influenza* strains is of great concern and has led to smaller outbreaks of dissimilar strains in recent years. Another group of respiratory viruses, the *Coronaviruses*, have led to serious endemics in recent years. The Severe Acute Respiratory Syndrome (SARS) *Coronavirus* (CoV) outbreak in 2003, originating from bats and palm civets, led to about 9000 infections in 29 countries. Middle East Respiratory Syndrome (MERS)-CoV originated in Saudi Arabia and was shown to have been transmitted by bats and dromedary camels leading to a similar number of cases and deaths as SARS-CoV. Finally, as we all know, we have been experiencing a major pandemic with another *Coronavirus* SARS-CoV-2 which originated in Wuhan, China, and for which the primary origin has not been established with certainty, although it likely originated in bats as well. This pandemic has shaped our lives immensely and has, as of today, resulted in more than 300 million human infections and 5.5 million deaths.

Taken together, pandemics have shaped our history and will most likely keep influencing our lives and the future of humanity. Worldwide overpopulation and the destruction of animal habitats, combined with global warming and increased travel, is a recipe for the increased occurrence and facilitated spread of pandemic pathogens in the foreseeable future. Which pathogen will be responsible for the next outbreak is impossible to ascertain. Most likely it will be a pathogen (such as SARS-CoV-2) which is unknown to us at this time (Disease X). However, it may very well be a pathogen which we already know and which has caused endemics, albeit localised, to date. Because of this, the editorial board of the NJCC has decided that it would be of interest to our readers to highlight in more detail the pathogens that loom in the dark, waiting to find their moment to spread across the world. In the upcoming issues of the Journal, we will therefore select the pathogens of interest, the ones with the largest pandemic potential, and report on their history and potential for pandemic spread. As a blueprint for which pathogens to discuss, we will loosely follow the list of priority pathogens as defined by the World Health Organisation. Among these will be Zika virus, Lassa fever, Nipah virus, MERS, Crimean Congo virus, Ebola virus and Rift valley fever and potentially more to follow. To kick off this series of 'potential pandemic pathogens', in this issue we will highlight the story of Zika virus.^[11] Although this virus does not lead to severe critical illness, which is understandably the main focus of the Journal, it is of special interest due to the unique effects it has on human reproduction through the induction of serious congenital disorders, which made us decide to include it in the list. We hope our readers will appreciate this new series and will find it interesting.

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