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A Flashback to Cholera Outbreaks in Kurdistan region-Iraq

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ABSTRACT

Cholera is a contagious acute diarrheal disease due to ingestion of contaminated water and food with Vibrio cholera, a Gram-negative bacterium that naturally inhabits coastal and estuarine ecosystems. Millions of cholera cases and thousands of deaths are annually reported worldwide. Cholera is endemic in Iraq with every 3-5 years interval. Meanwhile, cholera outbreaks have been reporting in Kurdistan region. However, the epidemiology of the disease has not been investigated. This study comprehensively reviewed the cholera outbreaks in Kurdistan region, depending on the WHO situation reports, online resources and scientific researches. The results showed seven reported cholera outbreaks from 1995 to 2022. The cholera epidemics happened at irregular intervals that makes the prediction of next outbreak difficult. Moreover, the trend of cholera is greatly decreasing from thousands to hundreds of cases throughout the outbreaks and in total about 30 people died. These might be the consequences of effective prevention measures, population health and natural acquired immunity against cholera. It was found that Sulaymaniyah is the most affected governorate in the region. This is probably related to the contamination of the main drinking water resource, little Zab river. Besides, the irrigation of the vegetable fields with untreated sewage could be another cause. Also, both Inaba and Ogawa serotypes of Vibrio cholera, O1, El Tor individually caused the outbreaks. Thus, cholera outbreak will be happening in Kurdistan region, particularly in Sulaymaniyah governorate. This definitely needs more scientific investigations, hoping to tackle the future outbreaks and total eradication of the disease.

Keywords: Cholera, Outbreak, Vibrio cholerae, serotype, Kurdistan.

1. Introduction

Cholera is an acute diarrheal disease that occurs due to the ingestion of contaminated food or water with a bacterium, called *Vibrio cholerae*[1]. Cholera is also characterized by having a sudden onset of acute watery diarrhea, which can cause death after severe dehydration due to water and electrolyte loss[2] The cholera toxin, an enterotoxin produced by pathogenic *Vibrio cholerae*, affects the intestinal cells and causes watery diarrhea, vomiting, leg cramps and dehydration[3, 4]. The clinical manifestations of cholera infection vary from asymptomatic carriers to mild or life-threatening severe diarrhea[5, 6]. The symptomatic patients probably shed 10^{10} and 10^{12} *Vibrio cholerae* per litre of watery stool for 1-2 weeks, whereas the asymptomatic individual, also called carriers, can carry the vibrios for 1-10 days and shed approximately10^3 bacteria per gram of stool into the sewage system. It must be importantly taken into account that symptomatic cholera infection comprises as much as 50%[5, 7]. Out of this, about 10–20% of cholera infections are severe and need medical attention[2].

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Vibrio cholera is a short, motile, comma shaped, facultative anaerobic gram-negative bacterium, which is belonged to the family *Vibrionaceae*[1]. It is serogrouped into over 200 strains based on the differences in the structure of O antigen in the cell wall of the bacterium. Despite the pathogenicity of most of these serogroups to humans, only the O1 and O139 serogroups of *Vibrio cholerae* are known to mainly cause cholera epidemics/outbreaks. The O1 and O139 serogroups are able to produce an enterotoxin[3, 4]. The O1 serogroup strains are mainly related to the endemic and epidemic cholera and are subdivided into two biotypes, classical and El Tor based on their biochemical properties and bacteriophage susceptibility. Furthermore, each of the classical and El Tor biotypes is differentiated into Inaba, Ogawa and Hikojima serotypes[3, 4].

The body immune system efficiently produce antibody against both *Vibrio cholera* s' somatic antigens and enterotoxin. The lipopolysaccharide of cell wall and the B subunit of cholera enterotoxin are the two main immunogenic antigens that protect the infected and vaccinated individuals from subsequent infection[8]. It is recently found that memory B cells, specific to cholera antigens, actively circulate in blood of the infected people. These memory B cells are thought to play an important role in providing prolonged immunity against next exposures[9-13]. Moreover, it was hypothesized that multiple immune responses, including systemic and mucosal antibodies, probably provide a long-term protection against cholera[14, 15].

The studies found that acquired immunity against cholera, after infection and vaccination, persists for at least three years[16-19]. The immunity against *V. cholerae* is serogroup and biotype specific[8, 20]. It was concluded that patients with O139 cholera had lower risk of subsequent O139 cholera for three years. It was also found that El Tor cholera provides immunity against next El Tor outbreaks for three years[20]. Moreover, El Tor Inaba serotype provided protection against both El Tor Inaba and Ogawa serotypes, whereas immunity against El Tor Ogawa serotype was only specific to itself[20, 21].

In addition, there has been seven cholera pandemics since 1817[22]. The first to sixth pandemics are caused by classical biotype, whereas the current seventh pandemic, which has been ongoing since 1961, is caused by El Tor biotype[6]. Cholera is endemic in many countries around the world[23, 24]. It is estimated that 1.3 million to 4 million cases of cholera occurs annually worldwide, with an estimated fatality of 21,000 to 143,000[25]. In 2022, Cholera outbreaks has been reported in countries like Pakistan, Cameroon, Tanzania, Malawi, Benin, Somalia, Afghanistan, Bangladesh, Democratic Republic of Congo, Ethiopia, India, Nigeria and Iraq[26-30].

2. History of Cholera in Iraq

Cholera was firstly reported in Basra province of Iraq in 1820[31]. However, it is considered to be endemic in Iraq, after reporting several epidemics of acute watery diarrhea, including cholera, between 1871 to 1917 and 1966 to 1999[31, 32]. Iraq also passed through seven more acute watery diarrhea (including cholera) epidemics in the early years (2003, 2007/2008, 2012, 2015, 2017 and 2022) of the 21st century[27-29, 31, 33-37]. It is predicted that the epidemics of cholera will occurs in Iraq every 3-5 years[33, 34]. Throughout the epidemics, the cases were slightly higher in females than males, adult age group showed higher incidence and the southern governorates were more affected[33]. In addition, both the *Vibrio cholera* O1, El Tor, Inaba and *Vibrio cholera* O1, El Tor, Ogawa were isolated either alone or together in the epidemics of cholera in Iraq[31, 34-36, 38-40].

The main causes of cholera epidemics in Iraq have possibly been the damaged urban infrastructures as a result of series of wars, bad sewage system, malnourished public, mass displacement, global warming, insufficient supply of clean drinking water and poor sanitation[5, 8, 41, 42]. These factors likely kept Iraq being endemic with cholera. In 2022, cholera has been reported in most of the governorates, but Kirkuk, Baghdad and Thi-Qar are the most affected governorates with large number of reported cholera cases. Unfortunately, four people died over the outbreak.

3. Cholera outbreaks in Kurdistan region

Kurdistan region is an autonomous region in the north of Iraq and consists of four governorates, Erbil, Sulaymaniyah, Duhok and Halabja (Figure 1). Kurdistan region has an estimated population of 6,200,000 that roughly constitutes 15% of Iraqi population.

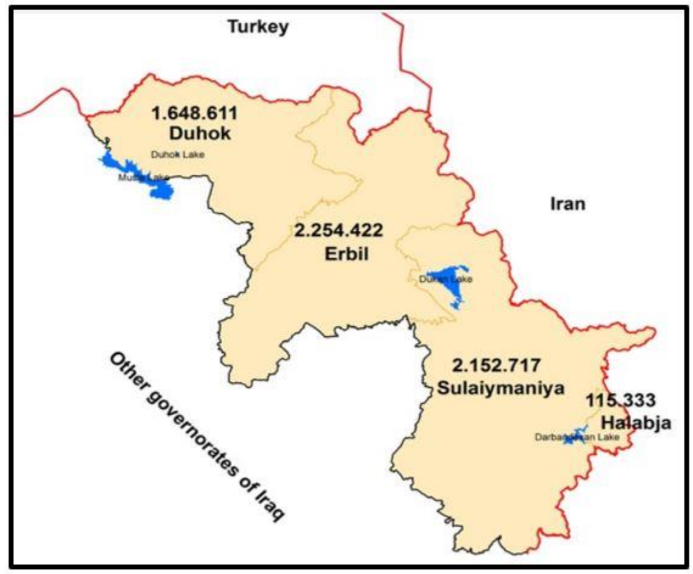

Figure 1: The map of Kurdistan region and its' estimated population in 2020[43].

Kurdistan region experienced seven epidemics of acute watery diarrhea, including 8354 confirmed cases of cholera, in 1995, 1998, 1999, 2007, 2012, 2015 and 2022 (Table 1 and Figure 2). It seems that cholera outbreaks occur in a varied inter-epidemic period. Although, this makes prediction difficult, the next cholera outbreak may happen in 2025 or beyond. The intervals of these epidemics could be determined by the environmental related factors (such as high temperature, drought conditions and density of *V. cholerae* reservoirs such as phyto- and zooplankton)[44-47], the bacterial related factors (serotypes and enterotoxin production)[3, 4] and population related factors (such as health, wellbeing, immunity and size of tourism). There are evidences that the acquired immunity against cholera lasts at least three years[16-19]. So, this long term immunity presumably determines the intervals of the subsequent outbreaks and prevents annual epidemic of cholera in the region.

It was also found that the confirmed cholera cases comprise a fraction of the total acute watery diarrhea cases throughout the epidemics in Kurdistan Region (Table 1). This may suggest that the main focus of the health system is on the identification of *Vibrio cholerae*, while the other possible causative agents of acute watery diarrhea have not been paid attention.

Table 1: The data of acute watery diarrhea epidemics, including cholera in Kurdistan region of Iraq.

Cholera outbreak	Acute watery diarrheal cases	Confirmed cholera cases	No. of death
1995[48-50]	More than 500	309	3
1998[48, 49]	Unknown	1492	4
1999[49]	Unknown	4299	More than 6

2007[51, 52]	Nearly 5,000	1441	14
2012[35]	More than 6,000	266	4
2015[53-55]	Unknown	27	0
2022[27-29, 37, 40]	2364	520	0

The cholera positive samples were initially confirmed in Iraqi central public health laboratory, Baghdad.

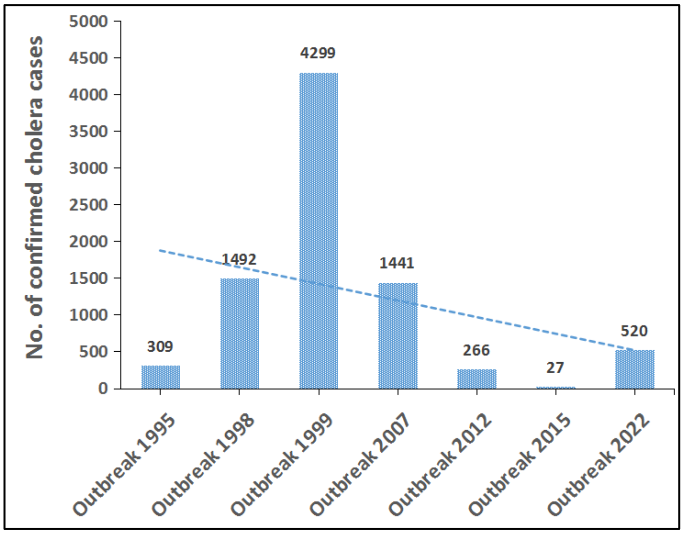

Figure 2: The trend of cholera outbreaks in Kurdistan region.

In the early outbreaks from 1998 to 2007, large number of cholera cases was confirmed. This may be related to the bad situation of the country's infrastructures and population's health and wellbeing, due to the long-term international economic sanction in 1990s. Interestingly, the number of cholera cases was greatly reduced in the later outbreaks of 2012 and 2015, whereas it is again increased in 2022. Although the trend of cholera cases is greatly descending overtime, cholera outbreak will still be reporting (Figure 2). This probably evident that improved sanitary and effective prevention measures efficiently protected the Kurdish population in the last three outbreaks. Besides, the lack of the natural acquired immunity against cholera resulted in high case number in the early outbreaks. These early subsequent exposures presumably created a protective level of immunity and reduced the cholera cases in the later outbreaks of 2012, 2015 and 2022 (Figure 2). Regarding the death toll, out of 8354 patients about 30 deaths were reported in all the seven outbreaks in Kurdistan region (Table 1). This suggests that the fatality of cholera is probably limited by standard medical treatment, good health and wellbeing, and natural acquired immunity against cholera.

The cholera outbreaks were also investigated in the governorates of Kurdistan region. It was found that Sulaymaniyah governorate is greatly affected by cholera, and followed by Erbil and Duhok governorates (Figure 3). Halajab was initially a district in Sulaymaniyah governorate until it was approved to be an independent governorate in 2014. So, the cholera cases in Sulaymaniyah governorate include Halabja cholera cases throughout the outbreaks of 1995 to 2012. No cholera cases were reported in Halabja governorate in the outbreaks of 2015 and 2022 (Figure 3).

The large-scale outbreaks reported from 1998 to 2007, after this the number of cholera cases tremendously decreased in all governorates, but Sulaymaniyah recently suffered and passed the last outbreak of 2022. Fortunately, the trends showed that cholera cases are sharply reducing overtime, except in Sulaymaniyah the trend stays high (Figure 3). The reported cholera cases, in Erbil and Duhok governorates in the outbreak of 2015, may be due to hosting a large number of internally displaced people and Syrian refugees during war with Islamic State Iraq and Syria (ISIS). The differences in the reported cholera cases among the Kurdistan governorates might depend on the procedure of prevention measures, rate of water resource contamination and size of tourism.

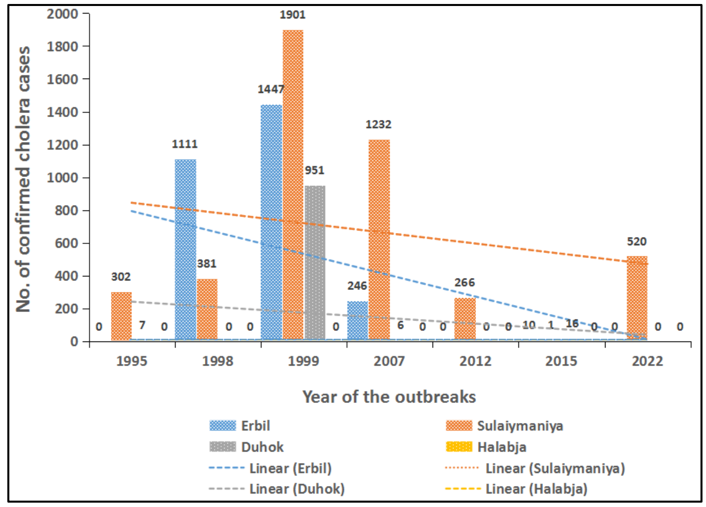

Figure 3: The trend of cholera outbreaks in the governorates.

4. The serotypes of *Vibrio cholerae* in Kurdistan region

The serotypes of *Vibrio cholera* that caused the outbreaks in Kurdistan region are reviewed. It was found that both Inaba and Ogawa serotypes of *Vibrio cholera* O1, El Tor were isolated in the outbreaks (Figure 4). The serotype Ogawa was prevalent in the outbreaks of 1995, 1998, 1999, 2012 and 2022[35, 40, 48-50]. In contrast, only the outbreaks of 2007 and 2015 were caused by the Inaba serotype[51-55]. Such interconversion between serotypes may be adjusted by the natural acquired immunity in the population against cholera, which was suggested to persist for at least 3 years[16-19]. It was found that the natural acquired immunity induced by Inaba serotype protects the population from annual outbreaks by both Inaba and Ogawa serotypes, but Ogawa serotype only protects against its' homologous serotype[18, 20, 21]. This immunity effect can obviously be observed in the extended inter-epidemic periods between 2007 (Inaba) to 2012 (Ogawa) and 2015 (Inaba) to 2022 (Ogawa) outbreaks. However, narrower inter-epidemic periods were noticed after the outbreaks of 1995 (Ogawa), 1998 (Ogawa) and 2012 (Ogawa) (Figure 4). The reason of long interval between 1999 (Ogawa) and 2007 (Inaba) is the tight restricted movement between Kurdistan region and former Iraqi government before 2003. Thus, understanding the pattern of seroconversion between outbreaks and the longevity of body immunity after infection is very important in the preparedness of control and prevention of cholera in Kurdistan region.

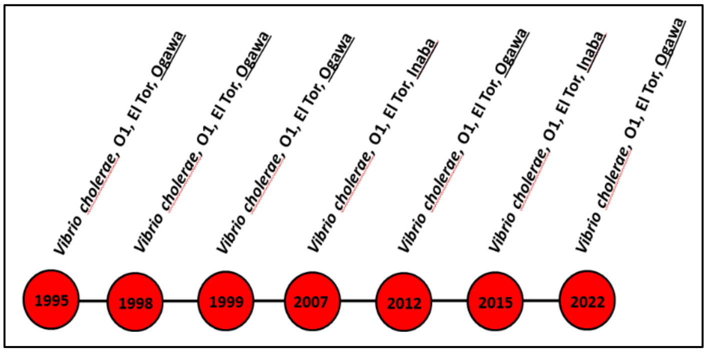

Figure 4: The *Vibrio cholerae* isolates across the cholera outbreaks in Kurdistan region.

5. Possible causes of Cholera outbreaks in Kurdistan region

Kurdistan region has three lakes of Dukan, Duhok and Darbandikhan that are used as the sources of drinking water in the region (Figure 1). Sewage and industrial rubbish are often directly drained into the major rivers without filtration. This contaminates the main sources of drinking water, particularly Dukan and Darbandikhan, in the region.

It is known that the pathogenic *Vibrio cholera* serogroup O1 naturally inhabits and routinely isolated from the coastal and estuarine ecosystems[45]. The studies in Uganda and northwest Ohio/USA recently isolated non-O1/non-O139 serogroups of *Vibrio cholerae* from fresh water lakes and rivers, whereas the toxigenic *Vibrio cholera* serogroup O1was not detected[56, 57]. In contrast, other studies reported the isolation of *Vibrio cholera* serogroup O1 in the estuarine freshwater in Beira/Mozambique and freshwater lakes of Republic of Georgia during summer season[58, 59]. This may also depend on the geographical location of the lake, the climate of the country[44, 47], the natural reservoirs of the bacterium[60] and additionally the season in which the water samples were investigated[58].

It was assumed that the source of cholera outbreak in Sulaimaniya governorate is little Zab river in Dukan district[35]. However, the Kurdistan lakes are reservoirs and their fresh water is unlikely to permanently support the growth and persistence of *Vibrio cholerae* serogroup O1 (Figure 4). Thus, how *Vibrio cholera* serogroup O1 arrives Kurdistan region is still controversial. Finding out the initial source of cholera outbreaks would have a great implication to prevent and eradicate the disease in Kurdistan region.

It is already mentioned that cholera is endemic in Iraq and several outbreaks were reported in the Iraqi governorates[27-29, 31, 33-36]. Also, the history of cholera starts in Basra governorate that located in the south of Iraq and borders the Arabian gulf [31]. The spread of cholera is possible between the neighbouring governorates by the movement and travelling of asymptomatic carriers, who comprise as much as 50% of the cholera cases[5]. The reviewed WHO reports showed that the source of cholera outbreaks in Kurdistan region is likely Iraq. The cholera outbreaks in 1999, 2003, 2015 and 2017 initiated in the middle and southern governorates of Iraq[31, 34, 39, 53, 61]. Again, the cholera outbreak in 2007 first happened in Kirkuk and then reported in Suliaymaniya and Erbil governorates[51, 52]. In the outbreak of 2022, Kirkuk, Baghdad and Thi-Qar have been the most affected governorates[37]. These indicate that the Kurdistan outbreaks originated from the other Iraqi governorates and spread possibly through the movement and travelling of tourists. The tourists, who may be carriers or recently recovered, more likely shed the *Vibrio cholera* into the sewage system and then into the streams and rivers at the touristic areas. Moreover, Sulaymaniyah and Kirkuk governorates usually depend on little Zab River as a main source of drinking water in Dukan and Dubz districts respectively (Figure 5). The contamination of little Zab River in Dukan, an attractive touristic district, causes cholera outbreak in Sulaymaniyah and Kirkuk, and then circulates in the neighbouring governorates. Therefore, cholera outbreak is more possible in these two governorates, if the contaminated water of the river is not treated well at the water treatment plants. In addition, it is observed that the domestic and urban sewage is used by farmers to irrigate the ready to use vegetables. This presumably increased the scale of the epidemics of acute watery diarrhea, including cholera in Kurdistan region.

Figure 5: The map of lakes and rivers in Kurdistan region and northern governorates of Iraq. The red dashed line is the possible direction of cholera circulation.

Climate also plays a key role in the rise of cholera epidemics. It was found that temperature is an accessory environmental factor[44, 47]. According to the reviewed data[27-29, 35, 37, 48, 49, 51-55], the onset of cholera outbreaks in Kurdistan region mostly happened in summer months (Figure 6), when the temperature usually rises to above 40 C°. In the meantime, the Iraqi tourists usually visit Kurdistan region in summer and it is likely to spread the disease in the region. Furthermore, a study observed correlation between low- precipitation and incidence of cholera infection[47]. Kurdistan Region has suffered severe drought due to low seasonal rainfalls. The shortage of drinking water supply also made people depend on non-chlorinated water of wells and tankers. This probably increased the incidence of diarrhea outbreak, including cholera, in the region. Thus, the above observations should be taken into account during annual preparedness for tackling the expected cholera outbreak in Kurdistan region.

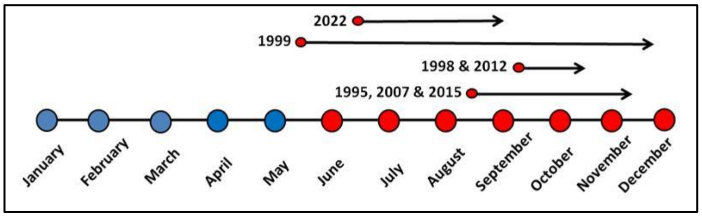

Figure 6: The onset of cholera outbreaks in Kurdistan region.

Conclusion

Cholera is an infectious diarrheal disease that spreads quickly and threatens the life of vulnerable people. It is endemic in the middle and south of Iraq, where movement and travelling among the governorates presumably lead to the spread of the disease. A cholera outbreak has recently been reported in Kurdistan region in 2022. However, there was not a comprehensive study to address the situation of past and present cholera outbreaks in Kurdistan region. Investigation of the outbreaks is very important to tackle and respond rapidly to the future outbreaks. It was found that seven cholera outbreaks were reported in Kurdistan region since 2022, and the next outbreak may expectedly happen in the summer of 2025 or in the years later. Fortunately, the trend of cholera cases is declining throughout the first to the last outbreak and the fatality of the disease is very low. It was also found that all the cases of acute watery diarrhea are not cholera, suggesting that *Vibrio cholerae* has been the main focusing pathogen, whilst the other causative agents of acute watery diarrhea have not been paying attention. Besides, statistical analyses were limited due to unknown cases of acute watery diarrhea in some of the outbreaks and no data was available about estimated Kurdistan population size in the years of the outbreaks. Thus, efficient prevention measures are still required to keep minimizing the size of future outbreaks and even eradicate the disease in the region. This definitely needs more scientific investigations, including epidemiology, bacteriology and immunology of cholera disease.

Conflict of interests

None

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