Abstract

Background: Cholera has been an endemic disease in the Islamic Republic of Iran. According to surveillance system records and historical documents, cholera epidemics have led to thousands of mortalities throughout the country in past centuries.

Aims: The aim of this study was an overview of cholera disease during the last five decades (1965–2014) and the epidemiological features of the last large-scale outbreaks in the Islamic Republic of Iran.

Methods: In this descriptive study, cholera incidence data provided by the National Surveillance Database were extracted and significant fluctuating trends were tested using Cochran-Armitage test by Winpepi software, during 1965–2014. To realize the most associated factors of cholera incidence in the outbreaks, adjusted Odds Ratios (AORs) were computed by means of ordinal logistic regression using STATA, version 11.

Results: Analysis of data has revealed a tremendous decrease of incidence trends from 19.7/100 000 to 0.01/100 000, with nine cholera epidemics that occurred with 5–6 year intervals during 1965–2014. Younger age groups (15–44 years) and inhabitants in urban areas have been more vulnerable to cholera in recent epidemics. However, the virulence of pathogens as well as case fatality rates have not changed during the last three epidemics.

Conclusion: Burden of cholera disease in terms of case load has been dramatically reduced
during 1965–2014. Furthermore, the epidemiological feature of cholera with regard to transmission route, place of inhabitant, age, immigration, mortality and antimicrobial resistance has changed considerably in recent epidemics. While the number of epidemic regions has diminished, some areas are still susceptible to cholera outbreaks.

Keywords: Cholera, epidemiology, outbreak, epidemic, Iran


Received: 20/05/18; accepted: 14/11/18

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Introduction

Cholera is a severe and acute diarrhoea disease that Robert Kokh discovered when identifying Vibrio cholerae as its etiologic agent in 1883 (1). The association of cholera disease with drinking water supplies contaminated with sewage was discovered during the cholera outbreak in London, United Kingdom (2). If dehydration and electrolyte imbalance are properly compensated for, the prognosis of cholera disease will be favourable in most patients, otherwise it results in potentially high rates of mortality (3,4). Environmental investigation of the pathogen and its interaction with susceptible hosts as well as other organisms makes the dynamics of cholera disease much more complex (5). According to the World Health Organization (WHO) report in 2018, an estimated 95 000 people die due to cholera and 2.9 million are affected every year (3). Moreover, cholera epidemics have been recognized as a major health problem in recent decades with large outbreaks in Haiti and the Dominican Republic in 2012 (6,7).

Emerging new pathogenic variants in many African and Asian countries, which have a mixture of phenotypic and genotypic traits of classical and El Tor biotypes, are greater challenges in the global fight against cholera (8). The Islamic Republic of Iran, as a middle-income country, is
experiencing case notification of cholera on a small scale annually. Although 90% of cholera cases have been reported from Afghanistan and Pakistan, and a more recent epidemic in Yemen in 2017 (9–11), cholera is considered an endemic disease in the Islamic Republic of Iran, where the National Cholera Surveillance System is one of the oldest data collecting programmes in the country and was originally planned after the substantial El Tor cholera epidemic in 1965. According to surveillance system records and historical documents, cholera epidemics have claimed thousands of mortalities over the past centuries throughout the country (12).

However, the epidemiological features of cholera have changed dramatically in the Islamic Republic of Iran since 1965 and this study aimed to address the socio-demographic characteristics and their relationship with variations in transmission routes through the past three epidemics in 1998, 2005 and 2011.

**Methods**

**Study setting and population characteristics**

The Islamic Republic of Iran is located in the south-west region of Asia with an area landmass of 1 630 207 km2, and a population of approximately 80 million. This country borders Turkey, Iraq, Azerbaijan, Armenia, Turkmenistan, Afghanistan and Pakistan, and the country is divided into 31 provinces. At the time of this study, urban inhabitants make up 69% of the population (13).

**Cholera surveillance system**

The Cholera Surveillance System is operated by the Iranian Department of Food and Waterborne Disease in the Center for Communicable Disease Control (CCDC). Any suspicious case with mild to severe diarrhoea attending hospitals (public/private), clinics and health centres (urban/rural) are included in a free-of-charge stool culture screening programme. In addition, all travelers arriving from east and west neighbouring endemic countries (based on WHO reports) in the Islamic Republic of Iran by land or sea are screened for cholera at border health posts, especially during July–December. Diagnostic as well as treatment centres are obliged to immediately notify the Department of Food and Waterborne Disease in the CCDC of any confirmed case of cholera based on laboratory certification via the district health centre.

All confirmed cases are cross-checked by stool cultures and serotyping in national reference laboratories. As part of the National Cholera Surveillance System, V. cholerae sensitivity to antimicrobials should be assessed annually. Furthermore, a round of active case investigation by health staff is conducted among people who have had a history of close contact with index cases, after which records are entered into a national electronic database. These records
Data source, statistical procedures

In this descriptive study, cholera incidence data provided by the National Surveillance Database during the last five decades (1965–2014), and coverage data of accessibility to safe drinking water based on WHO definition (14) of sanitation in CCDC, were extracted for 1965–2014. The national census data in six periods over 1965 to 2011 were used to estimate incidence rates and consequential trends. For analysis of linear trend of cholera incidence rates, Cochran-Armitage test by Winpepi software was used. Any unexpected increase/departure from a linear trend based on Cochran-Armitage test in number of cases of cholera incidents in the mentioned period was considered as an outbreak. Data of the past three outbreaks are disaggregated by province. To realize the most important determinants of cholera incidence in the outbreaks, adjusted Odds Ratios (AORs) were computed using STATA version 11, by means of ordinal logistic regression. This method takes into account the effect of exposure(s) over the three levels of an ordered outcome (outbreaks in 1998, 2005 and 2011), and yields an OR summarizing effect(s) across given exposure levels. P-value of ≤0.05 was considered significant.

Results

Analysis of cholera incidence in the Islamic Republic of Iran during 1965–2014 revealed a tremendous decrease of incidence trends from 19.7/100 000 in 1965 to 0.01/100 000 in 2014 (P = 0.0001), with nine cholera epidemics having occurred with 5–6 year intervals (Figure 1). The highest incidence rate of cholera was in 1970 with 66.7/100 000 population.

Figure 2 demonstrates the frequency of cholera cases by province in the last three epidemics in the country. Twenty-one provinces reported at least one outbreak during the period 1998–2014. Five provinces in the north and central plateau regions experienced the last three outbreaks.

Figure 3 indicates coverage rate of accessibility to safe drinking water as well as sanitation in the past four decades. The number of households with access to drinking water and sanitation have increased dramatically, the gradient of the slope for increasing accessibility to sanitation is not similar, and number of inhabitants in south-east regions who did not have access to sanitation is at least 20%.
Figure 4 shows the incidence rate of cholera in the country that has fallen during the past three outbreaks, primarily in the north and south-east regions in recent years. While inaccessibility of safe drinking water was prominent in the 1998 outbreak as a whole, consumption of raw vegetables that were cultivated by sewage was the main route for cholera transmission in the northern region in 2005 and 2011. Moreover, the main route for disease transmission in the south-east region in 2011 was consumption of unsafe drinking water.

As indicated in Table 1, cholera transmission season in the Islamic Republic of Iran begins in July and extends to December every year. Comparison of the most recent epidemic (2011) against the former (1998 and 2005) has revealed that cholera incidence has been decreasing from July to December, and the proportion of cases in 2005 and 2011 reduced earlier (July–October) compared to 1998. Generally, the number of cholera cases has decreased in older age groups (> 65 years) in the last epidemics (2005, 2011) versus 1998. Women were equally affected as men in the latest epidemic (2011) versus the two previous epidemics. Comparison of urban with rural populations showed odds likelihood of cholera cases having decreased in rural areas to 37%, and urban populations were more likely to be affected in the past two epidemics compared with 1998. Iranians made up the majority of cholera cases in all three epidemics. In line with no change in hospitalization rates in all three past epidemics, cholera case fatality rates were not changed. Although there has been a switching pattern between Inaba and Ogawa as dominant serotypes during the last three epidemics, the latter serotype was more isolated in the most recent epidemic.

**Discussion**

Cholera incidence distribution during past epidemics has been characteristically different over time. While the burden of cholera disease in terms of case load has been reduced in recent years and the number of epidemic regions has diminished, five provinces have been susceptible in all three epidemics. Moreover, evidence on the transmission mechanism in the past three epidemics has revealed different routes within and between affected regions. Accordingly, inaccessibility of safe drinking water in affected areas in 1998 and in the south-east region in 2011 was indicated as the main route of transmission, while consumption of raw vegetables contaminated by sewage in the northern region was more prominent in the 2005 and 2011 epidemics. Even though women, younger age groups and inhabitants in urban areas were more vulnerable to cholera disease in recent epidemics, the case fatality rate of pathogens has not differed during the last three epidemics. However, the epidemiological features of cholera have changed considerably, as follows.

The first most important change in cholera epidemiologic feature in the Islamic Republic of Iran is related to the transmission route. In low- and middle-income countries and in non-sanitary
environments without access to potable water, the main route of cholera transmission is waterborne. However, in two recent epidemics in 2005 and 2011, the pathogen was isolated from sewage, raw vegetables and human samples simultaneously (15–17). Moreover, laboratory findings with genotyping and molecular techniques have showed clonal dissemination of a single V. cholera strain throughout the Islamic Republic of Iran in 2005 (18).

In addition to raw vegetables, having a meal outside the home was associated with cholera occurrence in a meta-analysis study in 2005 (19). In this way, the annual incidence rate of typhoid fever as water-food borne disease, having common transmission mechanism (oral–faecal) with cholera was dramatically reduced from 133.4 to 0.52 per 100 000 population in the country from 1965 to 2011 (20).

The second change is related to place of inhabitants by domicile. This change in the cholera transmission mechanism in recent years is likely due to a significant expansion of urban populations following huge migrations from villages seeking better job opportunities to marginal areas of cities, where no facilities were planned (13). Furthermore, increasing accessibility of safe drinking water in rural areas along with improvement in socio-economic conditions in general may explain the decreasing slope of incidents trends in rural areas. However, similar to other middle-income countries, there is an increasing trend of having meals, especially fast food with salad, outside of the home in urban areas and this plays a significant role in occurrence of diseases with oral–faecal transmission routes in recent years in compared with rural areas (17,19).

The third change is age distribution of cholera disease. Comparison of age groups in cholera epidemics in 2005 and 2011 showed that older age groups were less affected than in 1998. A study on the effect of age on cholera morbidity in the Islamic Republic of Iran has indicated that partially acquired immunity in endemic areas acts as an important determinant of epidemics with 5–6 year intervals. Younger age groups with insufficient prior immunity against the cholera pathogen might be the result in recent epidemics (21).

The fourth change is the main challenge of controlling of cholera in the country in related to illegal migration from neighbouring countries. Even though the role of foreign immigrants during the three studied epidemics was not prominent, the number of cholera cases imported from outside Iranian borders is overrepresented between interval years of epidemics. Accordingly, among 256 total confirmed cholera cases in the country during 2013, more than 211 (83%) cases were imported from Afghanistan (22,23). The results of an evaluation of cholera outbreak in the south-east region of the Islamic Republic of Iran during 2010–2013 showed 63.3% of all cases were imported from Afghanistan (24).
The fifth notifiable change of cholera epidemiology is related to cholera mortality. There is no significant difference in cholera mortality and case fatality rate was around 1% throughout the three epidemics. There have been fewer cases of death in recent epidemics, mainly due to more recent better case management and access to treatment services (25).

The main challenge in cholera disease control in the next decade will depend on prevalence of antimicrobial resistance. According to the latest report of V. cholera sensitivity to antimicrobials and its susceptibility testing on the 60 V. cholera serotype, Inaba showed all isolates were resistant to nalidixic acid, tetracyclin, and trimethoprim sulfamethoxazole with intermediate resistance to erythromycin, while they were sensitive to ciprofloxacin, cefixime and ampicillin (22). Furthermore, while all isolates were sensitive to tetracyclin, ciprofloxacin, and erythromycin in 2005 (15), in 2013 they were resistant to tetracyclin with intermediate resistance to erythromycin (22). The results of a study in 2005 in Tehran on antibiotic sensitivity testing of V. cholera showed that 86%, 84%, 84%, and 82% of the isolates were resistant to streptomycin, chloramphenicol, co-trimoxazole, and tetracycline, respectively. All of the isolates were susceptible to three antimicrobial agents including ciprofloxacin, cefixime, and ampicillin (18). In 2011, another study in the Islamic Republic of Iran revealed that all of the isolates were susceptible to three antimicrobial agents including ciprofloxacin, cefixime, and ampicillin, and the highest rate of resistance was seen to nalidixic acid (96.7 %) and co-trimoxazole (91.8 %) (26).

Limitations

This is the first study in the Islamic Republic of Iran to use longitudinal data and describe the incidence trends of cholera disease over five decades (1965–2014). Moreover, epidemiologic feature and control of cholera disease based on related factors was investigated for the last three epidemics in this study. While under-ascertainment of cholera cases due to mild or no symptom of infections (90–95%) is common, under-reporting and variations for case definitions and methods of case finding in communicable disease surveillance system in the country during 50 years should be indicated as main limitation of our study (27,28). However, in case of cholera, under-ascertainment and under-reporting issues were improved following intensified sensitivity of the communicable diseases surveillance system, so that it has become an urgent notifiable disease for at least three decades (29,30). Even though cholera outbreaks were analyzed by logistic regression method in our study, to consider time series analysis of the fluctuations of cholera incidence after adjustment for trend, periodicity, and seasonality may be useful.

Conclusion
Burden of cholera disease in terms of case load has been reduced dramatically in the past five decades. Further, the epidemiological feature of cholera with regard to transmission route, place of inhabitant, age, immigration, mortality and antimicrobial resistance has changed considerably in recent epidemics. While the number of epidemic regions has diminished, some areas are still susceptible for cholera outbreak over the country. Besides continuing and strengthening of the National Cholera Surveillance System that focuses on changes in cholera epidemiologic features, well-designed control measures by community health authorities are recommended.

Acknowledgments

The authors would like to thank the kind collaboration of all staff in the Center for Communicable Diseases Control (Tehran), provincial and district health centres and laboratory technicians throughout the country for data collection.

Funding: None.

Competing interests: None declared.

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