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Abstract

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 According to surveillance system records and historical documents, cholera epidemics have led to thousands of deaths throughout the country in past centuries.

Aims: The aim of this study was an overview of cholera disease during the last 5 decades (1965–2014) and the epidemiological features of the most recent large-scale outbreaks.

Methods: In this descriptive study, cholera incidence data provided by the National Surveillance Database were extracted and significant fluctuating trends for 1965–2014 were tested using the Cochran–Armitage test. To identify the factors most associated with cholera incidence in the outbreaks, adjusted odds ratios were computed by ordinal logistic regression.

Results: Analysis of data has shown a tremendous decrease in incidence trends, from 19.7/100 000 to 0.01/100 000 over the 9 cholera epidemics that occurred at 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. The virulence of the pathogen and the case fatality rates have not changed during the last 3 epidemics.

Conclusion: The burden of cholera in terms of case load has dramatically reduced during 1965–2014. Furthermore, the epidemiological feature of cholera with regard to transmission route, domicile, 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, outbreaks, epidemics, Iran

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Introduction

Cholera is a severe and acute diarrhoeal disease. The etiologic agent, Vibrio cholera, was identified by Robert Koch in 1883 (1). The association of the disease with drinking water supplies contaminated with sewage was discovered during an 1854 cholera outbreak in London (2). If dehydration and electrolyte imbalance are properly compensated for, the prognosis of the disease will be favourable in most patients, otherwise it results in potentially high mortality rates (3,4). Environmental investigation of the pathogen and its interaction with susceptible hosts as well as other organisms makes the dynamics of cholera extremely complex (5). According to a 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, witness the 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 enormous 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 still considered an endemic disease in the Islamic Republic of Iran. 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 lives 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 sociodemographic characteristics and their relationship with variations in transmission routes through the past 3 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 is divided into 31 provinces. At the time of this study, urban inhabitants made 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. 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 travellers arriving inro the country from neighbouring endemic countries to the east and west (based on WHO reports) 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 of any confirmed case of cholera based on laboratory certification via the district health centre.

All confirmed cases are cross-checked by stool culture and serotyping in national reference laboratories. As part of the National Cholera Surveillance System, the sensitivity of V. cholerae to antimicrobials should be assessed annually. Furthermore, a round of active case investigation is conducted by health staff 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 comprise demographic characteristics, domicile, nationality, date of onset of signs and symptoms, date of diagnosis, date of entry to the Islamic Republic of Iran, questions about type and frequency of meals during the 5 days prior to diagnosis, and history of travelling outside the region.

Data source, statistical procedures

In this descriptive study, cholera incidence data provided by the National Surveillance Database during the last 5 decades (1965–2014), and coverage data on accessibility to safe drinking water based on the WHO definition of sanitation (14) in the Center for Communicable Disease Control were extracted for 1965–2014. The national census data for 6 periods over 1965–2011 were used to estimate incidence rates and consequential trends. For analysis of linear trend of cholera incidence rates, the Cochran–Armitage test for trend using Winpepi software was employed. Any unexpected increase/departure from a linear trend based on the Cochran–Armitage test in number of cases of cholera incidents over this period was considered an outbreak. Data on the past 3 outbreaks were disaggregated by province. To realize the most important determinants of cholera incidence in the outbreaks, adjusted odds ratios were computed by ordinal logistic regression using STATA, version 11. This method takes into account the effect of exposure(s) over the 3 levels of an ordered outcome (outbreaks in 1998, 2005 and 2011), and yields an OR summarizing effect(s) across given exposure levels. P-value ≤ 0.05 was considered significant.

Results

Analysis of cholera incidence during 1965–2014 revealed a tremendous decrease in incidence trends from 19.7/100 000 in 1965 to 0.01/100 000 in 2014 (P = 0.0001), with 9 epidemics having occurred at 5–6 year intervals (Figure 1). The highest incidence was in 1970 at 66.7/100 000 population.

Figure 2 shows the frequency of cholera cases by province in the last 3 epidemics in the country: 21 provinces reported at least one outbreak during the period 1998–2014, and in the north and central plateau regions, 5 provinces experienced the last 3 outbreaks.

Figure 3 indicates coverage rate of accessibility to safe drinking water and sanitation in the past 4 decades. The number of households with access to safe drinking water and sanitation

has increased dramatically, however the gradient of the slope for increasing accessibility to sanitation is dissimilar: and at least 20% of inhabitants in the south-east regions did not have access to sanitation by 2011.

The incidence rate of cholera in the country has fallen since the 1998 outbreak, primarily in the provinces in the northern and south-eastern parts of the country: Figure 4 shows the distribution by province over the last 3 outbreaks. While inaccessibility of safe drinking water was prominent in the 1998 outbreak, consumption of raw vegetables that were cultivated using sewage was the main route for cholera transmission in the northern region in 2005 and 2011. The main route for disease transmission in the south-eastern region in 2011 was the consumption of unsafe drinking water.

Cholera transmission season in the Islamic Republic of Iran begins in July and extends to December (Table 1). Comparison of the most recent epidemic (2011) against the previous 2 (1998 and 2005) shows that the incidence decreased from July to December, and in 2005 and 2011 this reduction in incidence occurred earlier (July–October) compared with 1998. Generally, the number of cholera cases decreased in the older age groups in the last 2 epidemics (2005, 2011) compared with 1998. Comparison of urban and rural populations showed the likelihood of cholera had decreased in rural areas to 37%, and urban populations were more likely to be affected in the past 2 epidemics compared with 1998. Iranians made up the majority of cholera patients in all 3 epidemics. There was no change in the hospitalization rates in all 3 epidemics, and in accordance with this, the cholera case fatality rates did not change either. Although there has been a switching pattern between Inaba and Ogawa as the dominant serotypes during the last 3 epidemics, Ogawa was isolated more often in the most recent epidemic.

Discussion

Cholera incidence distribution during previous epidemics has been characteristically different over time. While the burden in terms of case load has been reduced in recent years and the number of epidemic regions has diminished, 5 provinces have been susceptible in all 3 epidemics. Evidence on the transmission mechanism in the past 3 epidemics has revealed different routes within and between affected regions: 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. Women, younger age groups and inhabitants in urban areas were more vulnerable to cholera disease in recent epidemics, nevertheless, the case fatality rate has not differed over the last 3 epidemics. However, the epidemiological features of the disease have changed considerably.

The most important change seen in the epidemiological features of cholera in the Islamic Republic of Iran is 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 was water. However, in 2 recent epidemics (2005, 2011), the pathogen was isolated from sewage, raw vegetables and human samples simultaneously (15–17). Moreover, laboratory findings with genotyping and molecular techniques showed clonal dissemination of a single strain of V. cholerae throughout the country in 2005 (18).

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

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

The third change is age distribution of the disease. Comparison of age groups the epidemics of 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 outcome in recent epidemics (21).

The fourth change is the main challenge of controlling of cholera in the country in relation to illegal migration from neighbouring countries. Even though the role of foreign immigrants during the 3 epidemics we studied was not prominent, the number of cholera cases imported from outside Iranian borders is overrepresented in the interval years between epidemics. Accordingly, among 256 total confirmed cholera cases in the country during 2013, 211 (83%) were imported from Afghanistan (22,23). An evaluation of cholera outbreaks in the south-east

region during 2010–2013 showed 63.3% of all cases were imported from Afghanistan (24).

The fifth notable change in cholera epidemiology is in mortality. There was no significant difference in mortality: the case fatality rate was around 1% throughout the 3 epidemics. There have been fewer deaths in recent epidemics, mainly due to recent improvements in case management and access to treatment services (25).

The main challenge for cholera disease control in the next decade will depend on the prevalence of antimicrobial resistance. According to the latest report on V. cholerae sensitivity to antimicrobials and its susceptibility testing on the 60 samples of V. cholerae 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). In 2005, a study in Tehran 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 3 antimicrobial agents, including ciprofloxacin, cefixime and ampicillin (18). In 2011, another Iranian study revealed that all of the isolates were susceptible to 3 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).

This is the first study in the Islamic Republic of Iran to use longitudinal data and describe the incidence trends of cholera disease over 5 decades (1965–2014), however there were some limitations in the study. Epidemiologic features and control of cholera disease based on related factors were investigated for the last 3 epidemics. While under-ascertainment of cholera cases due to mild or no symptoms of infections (90–95%) is common, under-reporting and variations in case definitions and methods of case finding in the communicable disease surveillance system in the country over 50 years should be indicated as the main limitation (27,28). However, in the case of cholera, under-ascertainment and under-reporting issues improved following intensified sensitivity of the communicable diseases surveillance system: it has been an urgent notifiable disease for at least 3 decades (29,30). Even though we analysed cholera outbreaks using logistic regression, it may be useful to consider time series analysis of the fluctuations of cholera incidence after adjustment for trend, periodicity and seasonality.

Conclusion

The burden of cholera disease in terms of case load has been reduced dramatically in the past 5 decades. Further, the epidemiological features of cholera in regard to transmission route,

location, age, immigration, mortality and antimicrobial resistance have changed considerably in recent epidemics. While the number of epidemic regions has diminished, some areas throughout the country are still susceptible to outbreaks. Besides maintaining and strengthening the National Cholera Surveillance System, which focuses on changes in the epidemiologic features of cholera, well-designed control measures by community health authorities are recommended.

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Competing interests: None declared.

Épidémiologie du choléra en République islamique d’Iran (1965-2014)

Résumé

Contexte : Le choléra est endémique en République islamique d’Iran. D’après les registres du système de surveillance et les documents publiés, les épidémies de choléra ont causé des milliers de décès à travers le pays au cours des siècles passés.

Objectifs : L’objectif de la présente étude était d’établir une vue d’ensemble de l’épidémiologie du choléra au cours des cinq dernières décennies (1965-2014) et des caractéristiques épidémiologiques des dernières grandes flambées épidémiques.

Méthodes : Dans cette étude descriptive, les données sur l’incidence du choléra fournies par la base de données nationale de surveillance ont été extraites et les tendances fluctuantes significatives pour 1965-2014 ont été évaluées au moyen du test de Cochran-Armitage. Pour identifier les facteurs les plus associés à l’incidence du choléra au cours des flambées épidémiques, des odds ratios ajustés ont été calculés par régression logistique ordinale.

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Résultats : L’analyse des données a révélé une diminution considérable dans les tendances d’incidence de la maladie. En effet, l’incidence du choléra est passée de 19,7 pour 100 000 à 0,01 pour 100 000 au cours des neuf épidémies de choléra qui se sont produites à cinq ou six ans d’intervalle entre 1965 et 2014. Les groupes d’âge les plus jeunes (15-44 ans) et les habitants des zones urbaines ont été plus vulnérables au choléra lors des épidémies récentes. La virulence de l’agent pathogène et le taux de létalité n’ont pas changé au cours des trois dernières épidémies.

Conclusions : En termes de nombre de cas, le fardeau du choléra a diminué de manière manière considérable au cours de la période comprise entre 1965 et 2014. En outre, les caractéristiques épidémiologiques du choléra en ce qui concerne les voies de transmission, le domicile, l’âge, l’immigration, la mortalité et la résistance aux antimicrobiens ont notablement évolué au cours des dernières épidémies. Bien que le nombre de régions touchées par ces épidémies ait diminué, certaines zones sont toujours vulnérables aux flambées de choléra.

وبائيات الكوليرا في جمهورية إيران الإسلامية، 1965-2014

حسين معصومي اصل، غودارز كوليفرهود، محمد مهدي جويا

الخلاصة

: تتوطن الكوليرا في جمهورية إيران الإسلامية . ووَفقاً لسجلات نظام الترصدالخلفية
والمستندات السابقة، فقد تسببت الكوليرا في آلاف الوفيات في جميع أنحاء إيران على
مدار القرون الماضية .

: يتمثل الهدف من هذه الدراسة في استعراض مرض الكوليرا على مدار العقود الخمسةالأهداف
الماضية (1965-2014) والخصائص الوبائية لآخر الفاشيات التي حدثت على نطاق واسع .

: في هذه الدراسة الوصفية، استُخرجت البيانات عن معدلات الإصابة بالكوليراطرق البحث
من قاعدة البيانات الوطنية لترصَّد الأمراض، كما فُحصت الاتجاهات المتذبذبة بصورة
كبيرة في الفترة من 1965-2014 باستخدام اختبار كوكران - أرميتاج . وحُسبت نسب الأرجحية
باستخدام الانحدار اللوجستي التتابعي لتحديد العوامل الأكثر ارتباطاً بحدوث الإصابة
بالكوليرا أثناء الفاشيات .

: أظهر تحليل البيانات انخفاضاً هائلاً في الاتجاهات السائدة في الإصابة، حيثالنتائ ج

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[illegible] 100000 [illegible] 0.01 [illegible] 100000 [illegible] 19.7 [illegible] .1965-2014 [illegible] 5-6 [illegible] (44- 15) [illegible] .[illegible] .[illegible]

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