REVIEW ARTICLE

Epidemiology, Determinants and Dynamics of Cholera in Pakistan: Gaps and Prospects for Future Research

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ABSTRACT

Cholera is one of the notifiable endemic diseases in Pakistan, but the reporting of cholera cases is still unsatisfactory. Most of the diagnosed cases are never reported to the relevant authorities. In the year 1993 - 2005, the country did not report any single case of cholera to the WHO. The objectives of this review were to understand the epidemiology and to identify the possible determinants of cholera infection in Pakistan. Medscape, Medline, PakMedinet and PubMed, was searched, using key words, epidemiology and determinants of cholera infection in Pakistan during 1995 - 2010. Morbidity and mortality due to cholera infection during 1995 - 2010, without any language restriction. Out of 27 articles published between 1995 - 2010, 17 articles were included in the review. *Vibrio cholerae* O139 identified as a major cause of infection in older age group, while O1 biotype of cholera as a predominant cause of cholera among young individuals. Mainly reported determinants of cholera in Pakistan include poor sanitation and hygiene practices, increased population density in urban areas, leading to rapid and unplanned urbanization of the major cities and climate change due to increased environmental pollution in Pakistan are plausible factors for endemicity of cholera in Pakistan. Cholera reporting as a notifiable disease to the relevant departments and timely action can prevent the risk of outbreaks. There is a need to identify specific behavioral and environmental determinants responsible for outbreaks and epidemics of cholera in Pakistan which can help to design appropriate preventive and control interventions.

Key Words: *Epidemiology. Determinants. Cholera. Pakistan.*

INTRODUCTION

Cholera is a preventable and treatable communicable infectious disease still remains a significant threat to public health particularly in developing countries of Asia and Africa.[1] Started from Asian subcontinent thousands years ago, cholera was repeatedly responsible for causing dreaded pandemics in history.[2,3] Over the past few years, the burden of cholera has increased steadily by 24% from 2004 to 2008 compared with the period from 2000 to 2004 and the burden is expected to continue to rise with outbreaks affecting several continents.[4] Poor climatic conditions and natural disasters like earthquacks and floods are the possible contributing factors.[2-4]

Cholera is a key indicator of social development and the risk is highest in areas where basic infrastructure is not available, as well as in the camps for internally displaced population or refugees, where even minimum requirements of clean water and sanitation are not met. Despite of these facts, cholera is substantially underreported communicable disease and till 2012, 93 - 98% of total cases worldwide were reported from Africa.[5,6] Many cases remained unaccounted as many countries in South Asia like Bangladesh and Thailand are not reporting their cholera cases.[7]

Globally it is estimated that 3 - 5 million cases and 100,000 - 120,000 deaths are attributable to cholera every year, which are much higher than the 178000 - 589000 cases reported annually to WHO over the past 5 years.[8] Limited capabilities of surveillance system, lack of systematic studies, fear of trade and travel sanctions among the government and healthcare professionals and differences in reporting procedures are few identified causes which complicate disease burden estimate.[9,10]

Pakistan is a developing country, currently facing the double burden of disease with infectious diseases contributing to 26% of the total disease burden.[11] The priority infectious diseases in Pakistan include acute respiratory infections which accounts for 51%, malaria 16%, viral hepatitis 7.5% and diarrhea / dysentery 23% of the overall burden of disease.[12] Cholera is an endemic disease in Pakistan and has never been considered a significant cause of diarrhea before 1988.[13] Recent outbreaks of cholera are attributed to poor environment / sanitation condition and consumption of contaminated water and food due to natural calamities which has displaced thousands of population.[14,15] Cholera is a notifiable disease in Pakistan, however, this passive healthcare facility based surveillance system is criticized by experts due to poor data quality, poor skill development of staff, lack of ownership, motivation and

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inadequate trainings.[16] WHO defined alert of cholera as one suspected case of cholera, whereas outbreak is a confirmed case, or a cluster of three or more suspected cases in a single locality. These outbreaks are distributed as sporadic at wide geographical locations.[17] In 2005, Disease Early Warning System (DEWS) was introduced in Pakistan by WHO, to undertake a prompt investigation and mitigation of alerts and outbreaks of priority diseases through establishment of active surveillance in earthquack affected districts as well as all over Pakistan. Between 2005 - 09, around 261 alerts and 46 outbreaks of acute watery diarrhea/suspected cholera were responded by DEWS team all over Pakistan.[17] A total of 4,610 cases of suspected cholera were reported by Ministry of health (MOH) Pakistan in 2006.[12] In 2010, after flood, this condition got even worse, Ministry of Health reported 99 confirmed *Vibrio cholerae* O1 cases in the country.[18]

Despite of steady rise in the incidence of outbreaks of cholera in Pakistan, a thorough understanding of the epidemiology of the disease aiding its persistence is still lacking. A detailed review is needed for dissemination of the existing knowledge and to enhance the understanding of the current situation of cholera in Pakistan. It is necessary to determine the epidemiology of cholera infection in Pakistan and the determinants that have been explored by existing researches done at local level leading to outbreaks in Pakistan and gaps in existing literature which will provide a basis for future research and help policy makers, program directors and health professionals to identify and design potential interventions for cholera control in Pakistan.

The objective of this review were to determine the epidemiology and determinants of cholera in Pakistan from existing researches and identify the gaps therein.

METHODOLOGY

The literature search was carried out by using the database of Medscape, Medline, PakMedinet and PubMed, without any language restriction with MeSH words as cholera in Pakistan, Determinants of cholera infection in Pakistan and Epidemiology of cholera in Pakistan. The relevant articles were obtained for review after examining all titles and abstracts (if available) from each of the searches. Bibliographies of those articles were examined for additional references. No restrictions were put on study design, location, or language of publication.

Only published literature was used to maintain quality and transparency. The selection criteria used to include studies in the review were those discussing the epidemiology and determinants of cholera infection in Pakistan 2010 and those discussing the morbidity and mortality due to cholera infection, from 1995 - 2010. Thirty-six articles/reports were retrieved that were published between 1961 - 2010 discussing the epidemiology, molecular structure of organism, determinants of cholera and sensitivity of organism to anti-microbial in Pakistan. Twenty seven articles were published in indexed and 9 in non-indexed peer reviewed journals. Out of 27 articles published from 1995 - 2010, 17 articles were directly related to epidemiology and determinants of cholera infection in Pakistan.

RESULTS

Out of 17 articles reviewed, 9 articles were published in indexed and 8 were in non-indexed peer reviewed journals. There was only one community based case-control research study. Out of 17 research studies on cholera, 10 were descriptive retrospective reviews of records of patients admitted, 5 were cross-sectional, one was review and another one was case series.

The determinants of cholera infection in Pakistan are shown in Table I as agent, host and environment factors explored in Pakistan. Two articles were published in indexed and non-indexed journal from 1995 - 2000 followed by 8 articles published in 2001 to 2005 and 7 articles published from 2005 to 2010. Most of the researches done in Pakistan were focused on agent factors i.e. *Vibrio cholerae* changing serotype and biotype patterns in Pakistan and its sensitivity to an antimicrobial. Behavioral and environmental determinants leading to outbreaks and epidemics have been underexplored except for the association of contaminated water consumption and toilet other than flush latrines in only one study.

DISCUSSION

Seventeen studies were found exploring the epidemiology and determinants of cholera in Pakistan suitable for review. About half of them were published in non-index peer reviewed journals in Pakistan lacking adequate quality and mostly were hospital based retrospective review of records of patients admitted in certain period of time ignoring the behavioral, social and environmental factors contributing to cholera infection. However, all these studies provide trend of changing in the type (serotype and biotype) of cholera organism.

Epidemiology of cholera in Pakistan: Cholera is endemic in Pakistan, but has never been considered, a significant cause of diarrhea before 1971. Endemic country of cholera is defined by World Health Organization as the one which had reported cholera cases in at least three of the five most recent years. No systemic study has been conducted that identifies the true incidence and the prevalence of cholera in Pakistan. However, in 2011 World Health Organization calculated total annual and age-specific incidence of cholera

from Diseases of the Most Impoverished (DOMI) cholera surveillance programs in Kolkata-India, Jakarta-Indonesia, and Beira-Mozambique. Kolkata's incidence rates were applied to countries of the Eastern Mediterranean Region (EMR) in WHO mortality stratum D (EMR-D), which includes Pakistan, Somalia and other countries with a large cholera burden.[19] Total annual incidence was estimated to be 1.64/1000, highest amongst infants 7.16/1000, followed by 7.01/1000 in 1 - 4 years, 2.19/1000 in 5 - 14 years, 0.93/1000 > 14 years.[19]

As cholera is amongst notifiable disease a number of cases of cholera and deaths are reported to World Health Organization by the Ministry of Health, Pakistan and published in Weekly Epidemiological Record. Highest number of cholera cases and deaths were reported in 1971 (1185 cholera cases and 43 deaths), 1993 (12092 cases and 206 deaths) and in 2011 (527 cases and 219 deaths). Cholera is distinctive among diarrheal diseases in that mortality is high among patients of all ages. Data reported showed that case fatality rate of cholera varies from 3.63 - 41.56 during 1970 - 2012 (Figure 1).[19,20]

Cholera is a seasonal disease occurring mostly during rainy seasons. However, studies conducted in Pakistan showed seasonality of *Vibrio (v.) cholerae* infection is not a critical issue as infections have been reported in both rainy and dry seasons. A retrospective descriptive analysis was done of the stool samples submitted for bacterial culture from January 1997 to December 2001. A total of 16379 stool samples collected, detection rate of *Vibrio cholerae* 01 Ogawa was high in summer followed by spring. Isolations peaked between June and August. Overlapping epidemics occurred in 1993 and 1994 of serogroup O1 (May to August), and serogroup O139 (August to October).[21]

There is paucity of data on the spatial distribution of cholera outbreaks in Pakistan. Available studies and reports published shows that outbreaks of cholera are sporadic and distributed over a wide geographical locations. A study was conducted in 2010 based on the genomic analysis of all *V. cholerae*, to identify the population dynamics and transmission of *V. cholerae* in Pakistan after 2010 floods. Findings of the study suggest that all isolates formed 2 new sub-clades (PSC-1 and

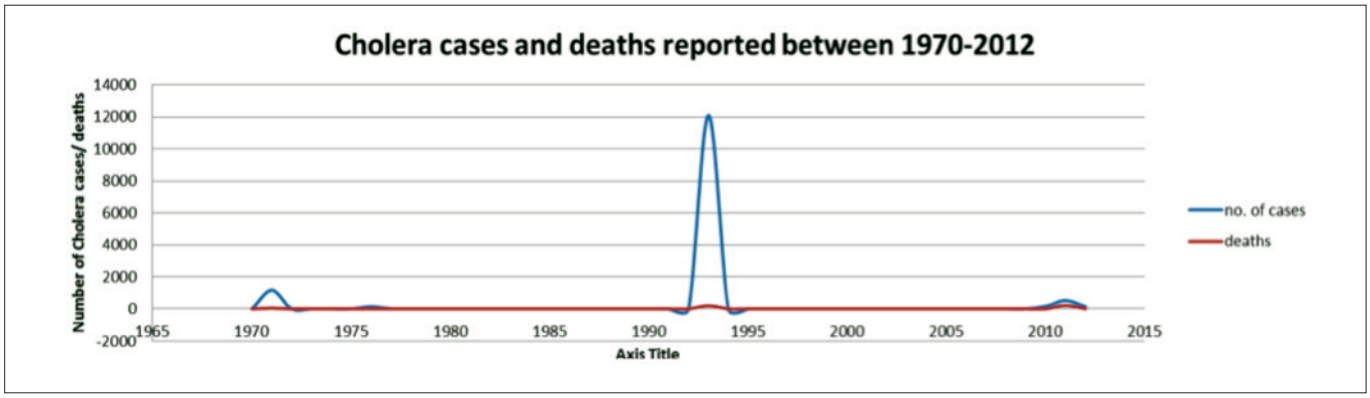

Figure 1: Number of cholera cases and deaths reported to World Health Organization between 1970 to 2012, data taken from official WHO cholera database.[41]

Table I: Epidemiology and determinants of cholera infection in Pakistan from published research articles from 1995 - 2010.

Year of publication	No. of articles published	Agent	Host	Environment
1995-2000	2	1989-1992: Major serotype responsible was Ogawa 01 1993-94: Reappearance of non-01 (O139) 1990-98: Ogawa biotype El Tor predominant 1999: Emergence of classical Ogawa 01 serotype	All ages and both gender are at risk of getting disease. Non-01 involved mostly adults, youngest child infected with cholera was 7 days old. Mean age for child affected with El Tor was 31+/-34 months.	Environmental factors of cholera infection were not explored in this period in Pakistan.
2001-2005	8	2000-2001: Predominant serotype non-01 (O139). However, classical Ogawa also exist in this period. 2002-2004: El Tor biotype of Ogawa responsible for outbreaks and epidemics of cholera in this period.	Mean age for non 01 infection was 40 years while for 01 it was 23 years. Both gender at risk. Poverty and low education were also important host factor determinants. Severity of infection and fever along with symptoms of diarrhea common with non 01.	No primary research done in Pakistan to explore environmental aspect of cholera infection.
2006-2010	7	2004-2005: upsurge in the isolation of *Vibrio cholerae* Inaba. 2008: predominant serotype 01 biotype El Tor.	Involvement of both children and adults with younger age affected with Ogawa 01 and older age in non-01 infection.	Environmental factors such as water contamination with *V. cholerae,* use of toilet other than flush system associated with increased infection.

PSC-2). Geographically, PSC-1 isolates originated from the coast, whereas PSC-2 isolates originated from inland areas flooded by the Indus River.[22]

Determinants of cholera: *Vibrio cholerae*, a curved Gram-negative bacillus comprises of both pathogenic and nonpathogenic strains. It has two biotypes - classical and El Tor - that include three serotypes (Inaba, Ogawa and, rarely, Hikojima). *V. cholerae* O139 was first identified in Bangladesh in 1992 and is currently present in various areas in South Asia.[17] In Pakistan, *V. cholerae* O139 first appeared in 1993 and disappeared in 1994 associated with deadly outbreaks and increase in hospital admission rates.[23,24] O139 re-emerged in 2000 and remained a major cause of infection till 2001 although, it possesses the same virulence factors as O1, the clinical symptoms it produces were more severe than O1 in Pakistani population. There are four studies done in Pakistan that explore the clinical consequences of O139 infection. It was identified that O139 affect older individuals (mean age 40 years) and is responsible for producing more severe clinical manifestations leading to acute renal failure, dehydration and shock within few hours along with high grade fever that is not usual with O1 infection.[25-29]

O1 biotype of cholera that remained a significant and predominant cause of cholera infection in Pakistan throughout the years usually involved young individuals (mean age adults: 23 years and 31 - 34 months in children). Ogawa and Inaba are the main infectious serotypes with Inaba peaking between years 2004 - 2005.[30] Clinical manifestations and signs/ symptoms of Inaba infection are not different from Ogawa serotype.[31] Irrespective of the type causing infection, the morbidity and mortality was higher amongst individuals having deranged immune status or having concurrent infection with other pathogens. This changing trend of most prevalent organism in Pakistan is more or less similar to the pattern in other countries of south Asia (India and Bangladesh).[31,32] The reason behind this changing epidemiology of organism is not known yet but change in the environmental factors, new mutations in the structures of organism and re-emergence of different serotype might be possible causes.

Emergence of drug resistance organism also remained an issue over the years and has been studied well in Pakistan. Quinolones are the only group of agents to which organism is 100% sensitive throughout many years. The sensitivity patterns of Tetracyclines, Co-trimoxazol, Chloramphenicol and Ampicillin never remained constant.[33,34] This is due to new mutations in the existing structure of organism or change in biotype or serotype of *V. cholerae*.

A number of host genetic, socio-demographic such as age, gender, nutritional and socio-economic status are known to play crucial role in susceptibility to infection. In Pakistan, although individual level factors like age and gender are commonly studied risk factors information about other socio-demographic factors such as socio-economic and educational status is lacking. In addition, behavioral practices like frequency of hand washing, practices of garbage disposals and maintenance of hygiene and sanitation in and around household has never been studied in Pakistan.[30,33] Sanitation and nutrition are particularly important factors and it has become clear that good sanitation and hygienic practices largely prevent the disease. *Vibrio cholerae* infection is known to be more severe in individuals suffering from malnutrition.[35-38] Moreover, socio-cultural concepts and perceptions about disease and the method of its treatment and prevention are important for many aspects of public health particularly to determine readiness of population to adopt preventive measures such as use of safe drinking water and demand for vaccine as cholera vaccine is available in Pakistan. This can be important findings which help to make appropriate use of existing resources and develop ways to introduce recommendation that community will accept and to formulate policy. A study done in periurban and rural area of Zanzibar showed that community had perceptions that drinking contaminated water, dirty environment and flies were the cause of spread of diseases.[39]

Multitude of environmental factors has influence on the diversity, distribution, incidence, and severity of *cholerae*. These environmental factors can be classified as proximal or distal determinants, proximal environmental determinants including climate change, deforestation, urbanization, road projects, and agricultural practices, that has influence on distal environmental determinants such as fecal contamination of water through affecting population density, water salinity and water flow rate, wind speed and population migration. World is urbanizing at fast pace due to migration of people from rural to urban areas.[40-43] This is either because of better employment opportunities or most probably due to natural disasters affecting villages in Pakistan. Unplanned migration of population has influence on the transmission of infectious diseases by affecting population density creating burden on existing infrastructure of water and sanitation system.[42] Inadequate environmental management due to lack of basic infrastructure and non-availability of water and sanitation system, poor hygiene, contamination of food, unplanned human settlement, especially in urban and peri-urban slums, absence of effective health systems, inadequate health care, poverty and recent natural disasters disrupting water and sanitation systems, or the displacement of populations to inadequate and overcrowded camps are the factors responsible for outbreaks of cholera.[40-43]

Although seasonal variability, inadequate sanitation in and around household, and fecal contamination of water are associated with increased incidence of cholera outbreaks in Pakistan, other environmental factors and their influence on spread and propagation of cholera as an outbreak are not established in Pakistan.[43,44] One study that was conducted in Bangladesh showed increased cholera outbreaks with increased population density.[45] Poor environmental conditions such as lack of sanitation and hygiene, increased population density due to population migration, rapid and unplanned urbanization of the major cities and climate change due to increased environmental pollution in Pakistan are plausible factors for endemicity of cholera in Pakistan. They may also have influence in changing pattern of *V. cholerae* serotype and biotype in Pakistan.

Strengths and limitations: This review is attempted to identify the epidemiology and determinants of cholera, based on review of only published researches/ reports in Pakistan. Although a lot of researches have been done globally to identify the etio-pathogenesis, epidemiology and prevention including vaccine of cholera, quality research is still missing in Pakistan where disease remains a major cause of morbidity and mortality in the form of diarrhea. On the other hand, information and analysis provided in these articles on many points were felt incomplete and patchy; therefore, it was not possible to determine the trend of cholera cases over years and associated risk factors. The reported studies are largely observational and review of hospital record of patients. Only one community based case control study intended to determine the associated factors of cholera such as consumption of contaminated water others are majorly focused on the type of cholera organism isolate from stool of diseased individual. This review is first of its kind that will give trends of cholera infection in Pakistan that could be helpful for students, researchers and policy makers. It also identifies gaps in the available research in Pakistan and also highlights the weakness of published evidence, as most of the studies are hospital based review of patient records that only focused on the serotype and biotype of organism causing the disease, or other proximal environmental determinants. However, environmental determinants at more proximal level and socio-cultural factors that influences and shapes the behavior of individuals, and affects the uptake of preventive measures are not explored.

CONCLUSION

Cholera remains a major cause of morbidity and mortality particularly among susceptible individuals in Pakistan. The paper attempts to take into account of available literature and researches on cholera in Pakistan. Disease is endemic in Pakistan as many other countries of South Asia, Africa, South America and Central America as there is no disease free period from 1995 - 2010 with severe underreporting of cholera cases by the government to World Health Organization. Most of the available studies are of poor quality focused on changing epidemiological pattern of prevalent biotype and serotype of *Vibrio cholerae* over years. An environmental and socio-cultural factors are causally related and help in explaining the outbreaks of cholera in Pakistan but has never been explored. This situation warrants further research that could help in designing potential interventions and formulate policy to reduce burden of cholera in Pakistan.

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