Outbreak

Cholera outbreak in the Republic of Congo, the Democratic Republic of Congo, and cholera worldwide

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Abstract

Cholera is an acute intestinal disease caused by infection of the *Vibrio cholerae* bacterium. Often manifested as a constant diarrhoeal disease, cholera is associated with significant mortality as well as economic loss due to the strain on health care. Cholera often affects nations with lower economic status. The recent outbreak of cholera in the Republic of Congo and the Democratic Republic of Congo has affected thousands of people. Here we review the past cholera epidemiology, molecular mechanisms of the bacterium, and the political and environmental aspects that affect the treatment and eradication of this disease.

Key words: cholera; Congo; diarrhoeal; multiple-drug resistant bacterium

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Introduction

Cholera, an acute diarrhoeal disease, is often associated with low-income nations where it can cause significant mortality and economic loss during outbreaks and even be endemic to a certain region. Severe dehydration and electrolyte imbalance may occur due to constant diarrhoea and lead to death in 50% of cases when it is left untreated [1]. *Vibrio cholerae* (*V. cholerae*), the bacterium which is the etiologic agent of cholera, is transmitted through fecal-contaminated water and food [2]. Cholera is considered endemic to a region when the bacterium inhabits the native environment and outbreaks are independent of imported cases [3]. Cholera may become endemic to a region through various routes which are dependent on the local environmental conditions. Commonly, the collapse of water sanitization and water routing infrastructure is the main cause of cholera outbreaks [4]. Recently, multiple-drug-resistant *V. cholerae* species have been reported [3,5]. Furthermore, the interaction between this waterborne bacterium, the human host, and the environment needs significant consideration when building strategies for cholera management and eradication [2]. The World Health Organization (WHO) requires all cholera cases to be reported to the organization. Importantly, due to the overburden of many health-care systems, frequently cholera cases go underreported [6].

2011 outbreak of cholera in the Republic of Congo and the Democratic Republic of Congo

Cholera outbreaks are currently being reported in the Democratic Republic of Congo and the Republic of Congo, specifically in locations in proximity to the Congo River [7,8]. The outbreak originally was identified in March 2011 and has increased in severity since. On 4 July 2011, Medecins Sans Frontiers reported the expansion of the cholera outbreak, which now includes three additional provinces; the outbreak originally began in the city of Kisangani [8]. The WHO has reported 3,896 cases with 265 associated deaths attributed to this cholera outbreak as of 20 July 2011 [7].

Global cholera outbreaks

Cholera in continental Africa

Cholera is endemic in many countries in the southern portion of continental Africa and outbreaks have been reported in countries such as Zimbabwe, Guinea-Bissau, Angola, Tanzania and Goma [4,9-11].

Recently in 2008-2009 it was reported that Zimbabwe experienced the most devastating cholera

outbreak of recorded history in continental Africa, with a fatality rate of 22-48% [4]. Before this outbreak, cholera outbreaks had become increasingly more severe and in turn more difficult to control since the early 1990s in Zimbabwe. Prior to 2008, outbreaks had occurred only in communities that bordered countries with endemic cholera, suggesting that Zimbabwe's past outbreaks had originated outside the country [4]. A change was seen in the occurrence of cholera cases during the 2008-2009 outbreak when cholera was reported in urban areas distant from border communities. These aspects have identified the outbreak as distinct from the past cholera outbreaks of the area. Importantly, cholera is now imported from Zimbabwe to neighbouring countries such as South Africa, Mozambique, Botswana and Zambia [4]. Both Ogawa and Inaba serotypes of *V. cholerae* have been isolated from this outbreak.

Cholera in the Caribbean

In October 2010 a significant outbreak of cholera occurred in the Island of Haiti. The identified bacterium was *V. cholerae* 01 serotype Ogawa, which had never been seen in Haiti prior to the 2010 outbreak [1]. Farmer and colleagues reported that Haiti has been affected by over 270,000 cases of cholera with over 4,700 related deaths [1]. Since this outbreak, cholera has been reportedly exported to other areas of the Caribbean as well as distant countries such as Canada, the United States, and the Dominican Republic [1,12].

Cholera in Asia

V. cholerae 01 Ogawa of the El Tor biotype was reported to be the most prevalent serotype of *cholerae* bacterium in India in 2010 where *V. cholerae* 0139 previously dominated [3,5]. In India before 2003, Ogawa was prevalent but in 2004 the Inaba strain increased over the Ogawa levels until 2009 [5]. Importantly, cholera-related deaths have significantly increased by 24% in the past five years. Furthermore, the actual burden of cholera in this region is estimated to be 3 to 5 million cases per year with approximately 100,000 deaths or more [3]. Cholera outbreaks commonly occur in India.

Worryingly, several multiple-antibiotic-resistant strains of *V. cholera* have been documented and the El Tor *cholerae* serotypes from India have immigrated to other parts of Asia and into Africa [3,5]. Das and colleagues have recently reported the emergence of multiple-drug-resistant *V. cholerae* 01 species in India where the first examples were noted in 2007 [5]. It was found that various *V. cholerae* 01 isolates were commonly resistant to nalidixic acid, furazolione and cotrimoxazole but susceptible to gentamicin and tetracycline throughout the observation period [5]. Furthermore, multiple-antibiotic-resistant *V. cholera* isolates have been identified in Bangladesh as well [13]. The emergence of multiple-antibiotic-resistant species can occur by spontaneous gene mutation within a single organism or by horizontal gene transfer when two species inhabit the same host at the same time [5].

Molecular mechanisms of cholera

The diarrhoeal illness of cholera is caused by a rod-shaped, Gram-negative bacterium, *V. cholerae* [1]. The diarrhoeal illness is a result of secretion of the cholera toxin by the bacterium. Cholera toxin is an 86 kDa ADPribosylating exotoxin that is highly immunogenic. It has been suggested the production of the cholera toxin functions to aid the bacterium to overcome the innate mucosal barrier in the gut and allow bacterial colonization and survival [14]. Specifically, once *V. cholerae* is present in the gut, stimulation by gut components leads to downregulation of gene sets involved in aquatic environmental adaptation while upregulating genes for toxin production. Cholera toxin has been shown to bind GM1 ganglioside [15,16], an ubiquitous cell membrane component of lipid rafts [14]. After binding, the toxin is sequestered into the endoplasmic reticulum by route of the Golgi apparatus, eventually ending up in the cytosol [17]. This leads to increased cyclic AMP (cAMP) levels Via G proteins, and ADP ribosylation leads to profoundly increased levels of cyclic (cAMP), subsequently affecting the cystic fibrosis transmembrane conductance regulator (CFTR) protein of the gut. Loss in regulation of this ion transporter results in increased Cl^- ion secretion that clinically manifests as electrolyte imbalance and fluid expulsion or diarrhoea [14].

Essentially, serological categorization of the various strains of *V. cholerae* are based on the lipopolysaccharide O side chain found on the bacterium outer membrane, of which there are over 200 different types [11,18]. Specifically, *V. cholerae* of the serogroup O1 or O139 are the strains commonly responsible for the devastating cholera outbreaks. Furthermore, the O1 serogroup is classified into two biotypes, classical and El Tor, and El Tor is also broken down into Ogawa and Inaba types. Each of the biotypes causes a distinct clinical

phenotype and work through distinct biochemical mechanisms.

Cholera Management

Treatments

Various strategies for treating cholera are employed depending on the severity of the disease [1] and the World Health Organization has created cholera management guidelines [19]. Rehydration (by oral or intravenous route) and/or antibiotic treatments are the major therapies. Importantly, rehydration alone is 80% effective in patients suffering from mild cholera, although rehydration in combination with antibiotic therapy is preferred for those with moderate and severe cholera disease [1]. In India, antibiotics and rehydration techniques are commonly employed to treat people suffering from cholera. Shanachol (Shantha Biotechnics Ltd, Hydrabad AP, India) is an inexpensive bivalent inactivated whole-cell oral cholera vaccine (OCV) that has recently been approved for use in India. Furthermore, Shanachol is related to ORC-Vax and is thought to be a reasonable treatment for endemic cholera [3].

Obstacles and tactics for cholera

It has been found that cholera is significantly underreported in India, which can possibly be expanded further to other regions of the world [3]. The main reason for this situation is the limitations of disease surveillance. As well as monitoring disease outbreaks and tracking individual cholera infections and mortalities, it is also imperative to have vigilant testing for antibiotic resistance as several multiple-drug-resistant *V. cholerae* species have been identified [5].

Inadequate and poorly monitored water treatment and supply systems are often responsible for cholera outbreaks. For example, the transfer of water supply responsibility from independent city councils to the Zimbabwe National Water Authority has been suggested as a precipitating factor in the major outbreak of cholera in Zimbabwe [4]. Water supply-and-demand infrastructure issues can cause local people to use self-maintained shallow wells that can easily become contaminated with bacterium that cause cholera. As well, in India, poor water sanitation and open drains allowing easy contamination of *V. cholerae* to water supplies have been identified as issues perpetuating the cholera struggles [5]. Furthermore, access to adequate sanitized water also played a significant role in the 2010 cholera outbreak in Haiti, where even prior to the 2009 earthquake only 12% of Haitians received treated water [1]. Following the earthquake, water treatment further declined, creating a habitable environment for the bacterium.

Nicely reviewed by Sedas in a JIDC article, environmental factors have significant influence on the outbreak potential and pathogenesis of *V. cholerae* as well as other pathogens [2]. It is obvious that the fecal-oral transmission route relies heavily on the ecology of the native water supply. Furthermore, the seasonal water cycles have been shown to affect the emergence and re-emergence of *V. cholerae* and the health of local populations [2].

Conclusions

Cholera is a devastating disease that affects hundreds of thousands of people per year. Over 200,000 cases were reported to the WHO in 2009 but case estimates exceed 500,000 [6]. It is clear that management of this disease requires consideration of many aspects including molecular biology, the environment, local governmental water treatment programs, and improved international case reporting.

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