BIOSTATISTICS

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DEPARTMENT OF STATISTICS

An Extensive Study on the Epidemic

Cholera

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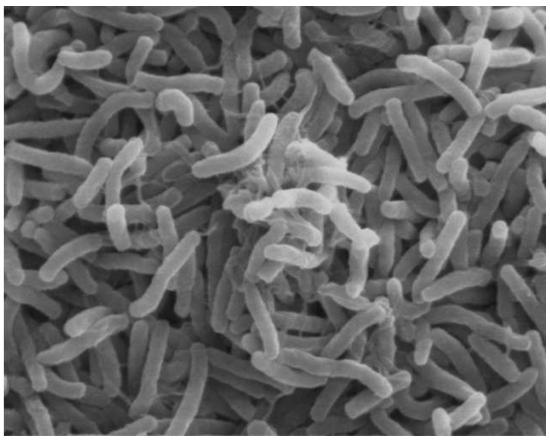
INTRODUCTION

Cholera is an acute, diarrheal illness caused by infection of the intestine with the toxigenic bacterium Vibrio cholerae serogroup O1 or O139. The bacteria typically live in waters that are somewhat salty and warm, such as estuaries and waters along coastal areas. There are hundreds of strains or "serogroups" of the cholera bacteria: V. cholerae serogroups O1 and O139 are the only two strains of the bacteria known to cause outbreaks and epidemics. These strains produce the cholera toxin that cause cells lining the intestines to release increased amounts of water, leading to diarrhea and rapid loss of fluids and electrolytes (salts). A single diarrhea episode can cause a one-million-fold increase of bacterial numbers in the environment, according to the National Institute of Allergy and Infectious Diseases. Cholera is caused by ingestion of food or water contaminated with the bacterium Vibrio cholerae and remains to be a global threat to public health and an indicator of inequity and lack of social development. According to the World Health Organization, 1.3 million to 4 million cases, and 21 000 to 143 000 deaths occur worldwide due to cholera each year. The sickness is especially common in areas where there is a lot of excrement. Poor sanitation, overcrowding, war, and famine are the most common causes of the disease. Parts of Africa, South Asia, and Latin America are common destinations for the same. Despite all the major advances in research, the condition still remains a challenge to the modern medical world. Although the disease may be asymptomatic or mild, severe cholera can cause dehydration and death within hours of onset.



Scanning electron microscope image of Vibrio cholerae bacteria

SYMPTOMS OF CHOLERA

Cholera symptoms can appear as soon as a few hours after infection or up to five days later. The infection is often mild or without symptoms, but can sometimes be severe and life-threatening. About one in every 20 persons infected has severe watery diarrhoea and vomiting, which can quickly dehydrate them. Despite the fact that many infected people have few or no symptoms, they can still help transmit the infection.

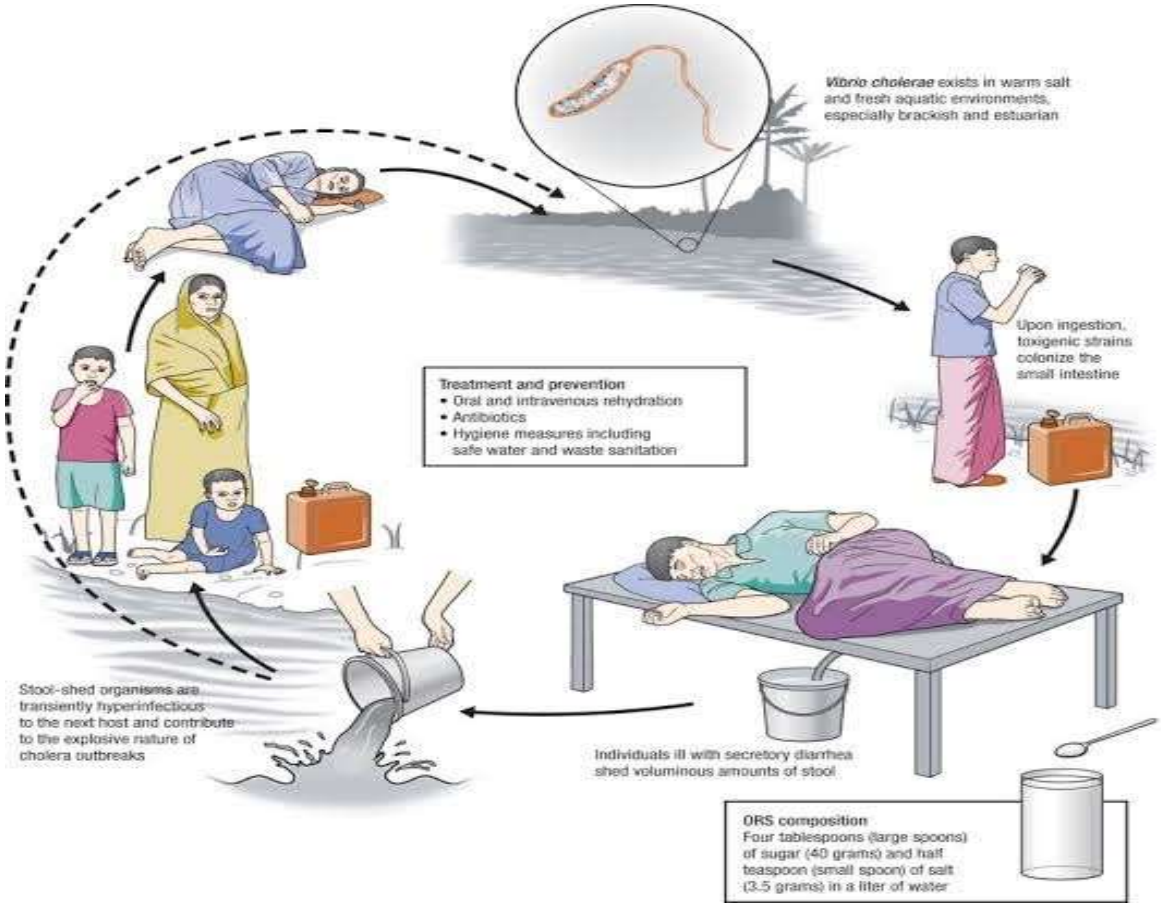
The following are signs and symptoms:

- profuse watery diarrhea, sometimes described as "rice-water stools"
- vomiting
- thirst
- leg cramps
- restlessness or irritability

Health care providers often look for signs of dehydration when examining a patient with profuse watery diarrhea. These include:

- rapid heart rate
- loss of skin elasticity
- dry mucous membranes
- low blood pressure

People with severe cholera can develop severe dehydration, which can lead to kidney failure. If left untreated, severe dehydration can lead to shock, coma, and death within hours.



Cholera Transmission Cycle

TRANSMISSION OF CHOLERA

A person can get cholera by drinking water or eating food contaminated with cholera bacteria. In an epidemic, the source of the contamination is usually the feces of an infected person that contaminates water or food. The disease can spread rapidly in areas with inadequate treatment of sewage and drinking water. The infection is not likely to spread directly from one person to another; therefore, casual contact with an infected person is not a risk factor for becoming ill. Typical at-risk areas include peri-urban slums, and camps for internally displaced persons or refugees, where minimum requirements of clean water and sanitation are not met. The consequences of a humanitarian crisis – such as disruption of water and sanitation systems, or the displacement of populations to inadequate and overcrowded camps – can increase the risk of cholera transmission, should the bacteria be present or introduced.

TREATMENT AND PREVENTION FOR CHOLERA

Cholera can be prevented with vaccination. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) both have specific recommendations for who should receive this vaccine. One may safeguard himself and his family by drinking only boiling, chemically disinfected, or bottled water.

For the following purposes, make sure to use bottled, boiled, or chemically disinfected water.

- Taking a drink
- Creating ice
- Taking care of your teeth
- Taking a shower and washing your face and hands
- Dishes and utensils that one uses to consume or prepare food
- Fruit and vegetable washing

Boil the water for one minute (or three minutes at higher elevations) to disinfect it, or filter it and apply a commercial chemical disinfectant. Raw meals, such as the following, should also be avoided:

- Fruits and vegetables that have not been peeled
- Milk and milk products that have not been pasteurized
- Meat or shellfish that is raw or undercooked
- Fish taken from tropical reefs that could be poisoned

Cholera is very treatable, but because dehydration can occur quickly, it's critical to get care as soon as possible. The mainstay of cholera treatment is hydration. Treatment will consist of oral or intravenous treatments to restore lost fluids, depending on the severity of the diarrhoea.

ORIGINS OF CHOLERA

It's unknown when cholera initially became a problem for people. Isolated cases of cholera-like illnesses are described in early manuscripts from India (by Sushruta Samhita in the 5th century B.C.) and Greece (by Hippocrates in the 4th century B.C. and Aretaeus of Cappadocia in the 1st century A.D.). One of the first thorough accounts of a cholera epidemic comes from Gaspar Correa, a Portuguese historian and author of Legendary India, who documented an outbreak of the disease in the Ganges Delta in Bangladesh and India in the spring of 1543. The sickness was dubbed "moryxy" by the locals, and it was said to kill patients within 8 hours of onset of symptoms, with a fatality rate so high that villagers struggled to bury all of the dead. Throughout the next few centuries, Portuguese, Dutch, French, and British observers reported several cases of cholera along India's west coast.

THE FIRST CHOLERA PANDEMIC

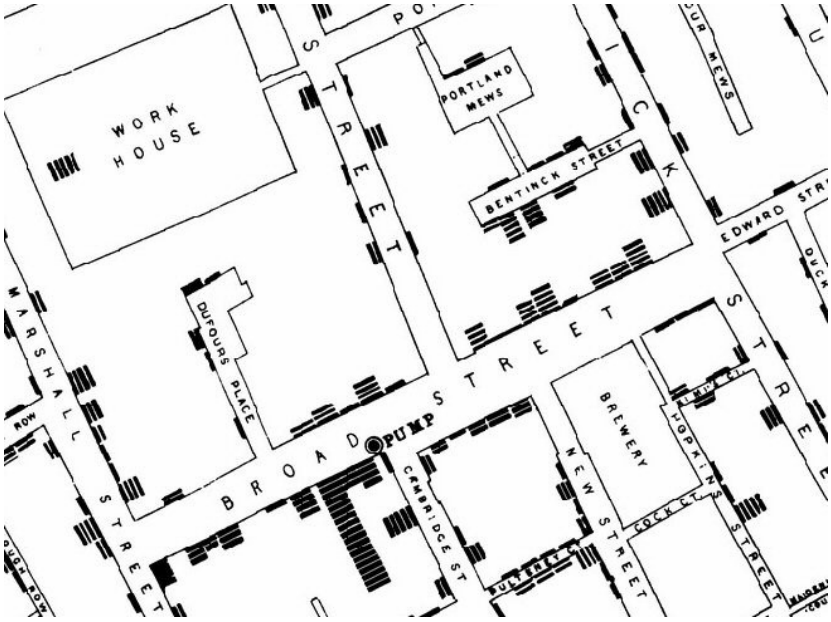
Though cholera has been around for many centuries, the disease came to prominence in the 19th century, when a lethal outbreak occurred in India. Seven cholera pandemics have occurred in the past 200 years, Additionally, there have been many documented cholera outbreaks, such as a 1991–1994 outbreak in South America and, more recently, the 2016–2021 Yemen cholera outbreak. With an outbreak in Jessore, India, in1817, the Ganges Delta saw the first cholera pandemic, which was caused by infected rice. By moving along trade routes established by Europeans, the disease swiftly spread over most of India, modern-day Myanmar, and modern-day Sri Lanka. Cholera had spread to Thailand, Indonesia, and the Philippines by1820, killing 100,000 people on the island of Java alone. By way of diseased persons on ships, the disease spread from Thailand and Indonesia to China in 1820 and Japan in 1822. It was also disseminated outside of Asia. Cholera was introduced to the Persian Gulf by British troops travelling from India to Oman in 1821. The epidemic gradually spread through Europe, reaching modern-day Turkey, Syria, and Southern Russia. The epidemic ended six years after it began, most likely as a result of a harsh winter in1823–1824, which destroyed bacteria in water sources.

CHOLERA INFECTS EUROPE AND THE AMERICA

Around 1829, the second cholera epidemic broke out. The second epidemic, like the first, is assumed to have started in India and spread over commercial and military lines to Eastern and Central Asia, as well as the Middle East. Cholera had reached Moscow by the autumn of 1830. During the winter, the disease's spread slowed, but it started up again in the spring of1831, reaching Finland and Poland. After that, it made its way to Hungary and Germany. The epidemic then spread throughout Europe, reaching the United Kingdom for the first time in late 1831 and early 1832 via the ports of Sunderland and London. Cholera had also found its way to the Americas by 1832. In June of that year, the plague claimed 1,000 lives in Quebec, spreading fast along the St. Lawrence River and its tributaries. Cholera was smuggled into the United States at the same time, and cases were reported in New York and Philadelphia. It would spread across the country over the next few years. In1833, it made its way to Latin America, including Mexico and Cuba. For nearly two decades, the pandemic would die out and resurface across many countries before finally dying out in 1851.

HOW SCIENTISTS STUDIED CHOLERA

There would be four further cholera pandemics between 1852 and 1923. The third pandemic, which lasted from 1852 to1859, was the deadliest. It wreaked havoc on Asia, Europe, North America, and Africa, killing 23,000 people in the United Kingdom alone in1854, the worst year for cholera. In that year, British physician John Snow, who is regarded as one of the inventors of modern epidemiology, meticulously recorded cholera cases in London's Soho neighborhood, allowing him to pinpoint the disease's source: contaminated water from a public well pump. He persuaded officials to remove the pump handle, resulting in an immediate reduction in the number of cholera cases in the area.



Detail of the 1854 John Snow map with the location of the Broad Street pump.

The fourth and fifth cholera pandemics, which occurred from 1863 to 1875 and 1881 to1896, respectively, were less severe than earlier pandemics in terms of overall severity, but they did have their share of lethal outbreaks. For example, cholera claimed the lives of 190,000 people in Hungary during 1872 and 1873. In the 1892 cholera outbreak, Hamburg lost roughly a quarter of its population. The pioneer of modern bacteriology, German microbiologist Robert Koch, examined cholera in Egypt and Calcutta in 1883. He devised a method for growing and describing V. cholerae, as well as demonstrating that the presence of the bacteria in the intestine caused cholera.

Although this knowledge was not well known, Italian researcher Filippo Pacini had identified the cholera bacteria in1854, designating it chlorogenic vibrios (and was likely unbeknownst to Koch). Because of improved water supply and quarantine precautions, the United Kingdom and the United States were relatively safe throughout the fifth pandemic. Because of developments in public health and sanitation, the sixth cholera pandemic (1899–1923) mainly spared Western Europe and North America. However, India, Russia, the Middle East, and northern Africa were nevertheless hit hard by the epidemic. Cholera incidences had decreased over much of the world by1923, with the exception of India, where it killed over half a million people in both 1918 and 1919.

ANALYSIS

1) TEST OF INDEPENDENCE BETWEEN THE DEATHS OCCURRED DUE TO CHOLERA AND THE COUNTRY

H_0: The no. of deaths occurred due to Cholera is independent on the country (ethnicity)

H_1: The no. of death occurred due to Cholera is dependent of the country (ethnicity)

Level of Significance: $\alpha = 5\%$

Test Statistic: $\frac{\sum(Oi-Ei)^2}{E_i} \sim \chi^2_{(r-1)(c-1),\alpha}$

where, r: Number of rows

c: Number of columns

O_i: Observed Values

E_i: Expected Values

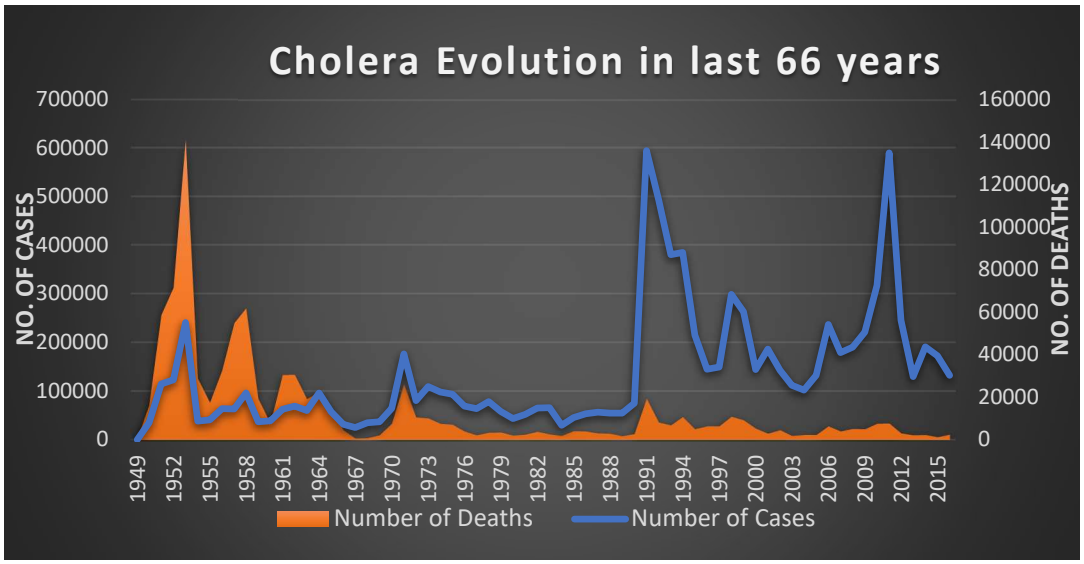
R Code:

```
> test <- matrix(c(509438,853812,137429,157218,30600,364345,22457,499150,21479,288738,
+                  12725,215323,10859,300344,10394,28453,9920,181116,9411,786383),
+                2, 10, dimnames = list(c("Death", "Survived"),
+                                       c("India", "Bangladesh", "Indonesia", "Congo", "Nigeria",
+                                         "Tanzania", "Somalia", "Myanmar", "Angola", "Haiti")))
> test
         India Bangladesh Indonesia  Congo Nigeria Tanzania Somalia Myanmar Angola  Haiti
Death   509438     137429     30600  22457   21479    12725   10859   10394   9920   9411
Survived 853812     157218    364345 499150  288738   215323  300344   28453 181116 786383
> test_of_ind <- chisq.test(test)
> test_of_ind

        Pearson's Chi-squared test

data:  test
X-squared = 896491, df = 9, p-value < 2.2e-16
```

Conclusion:

Clearly, since p-value is far less than our level of significance, we reject the null Hypothesis and conclude that **the number of deaths that occurred due to Cholera in the top 10 (worse affected) countries in the world is dependent on the country (ethnicity).**

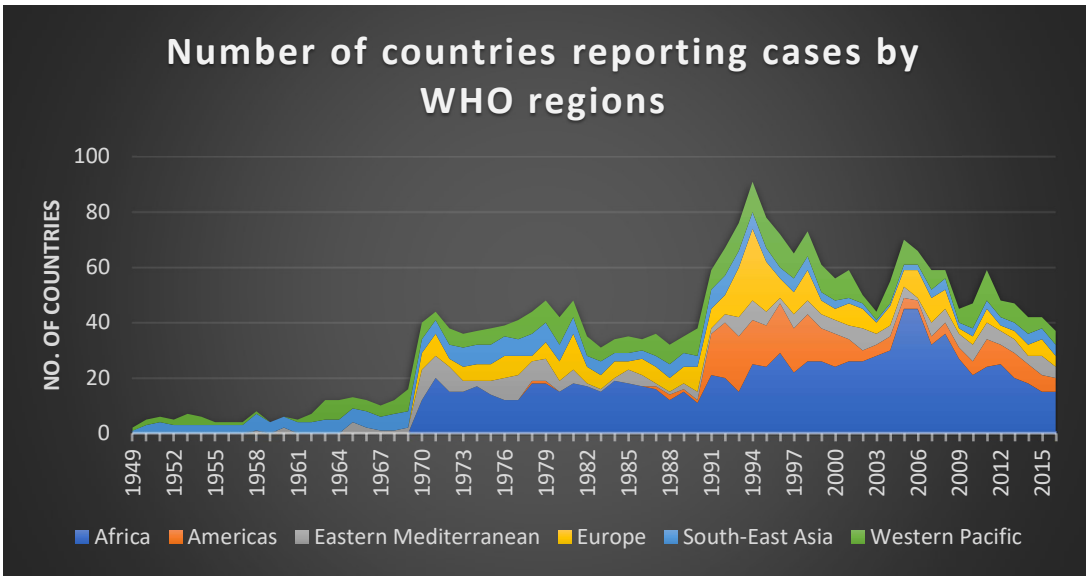
2) HOW HAS THE DISEASE BEEN SPREADING GLOBALLY OVER TIME?



With this graph, we can say that:

- There are 4-crisis (peaks) in the last 70 years, in the 1950s, 1970s, 1990s, 2010s
- The last two peaks had about 400,000 more cases than the first two.
- Since 1990, we observe that a new plateau has been defined, with every year having at least 100,000 cases.
- Until 1960, the number of deaths followed closely the number of cases, that is, the death rate at that time was very high when compared to nowadays. With the ease of getting a cholera vaccine and the economic improvement in several countries, the number of deaths has been decreasing since then.

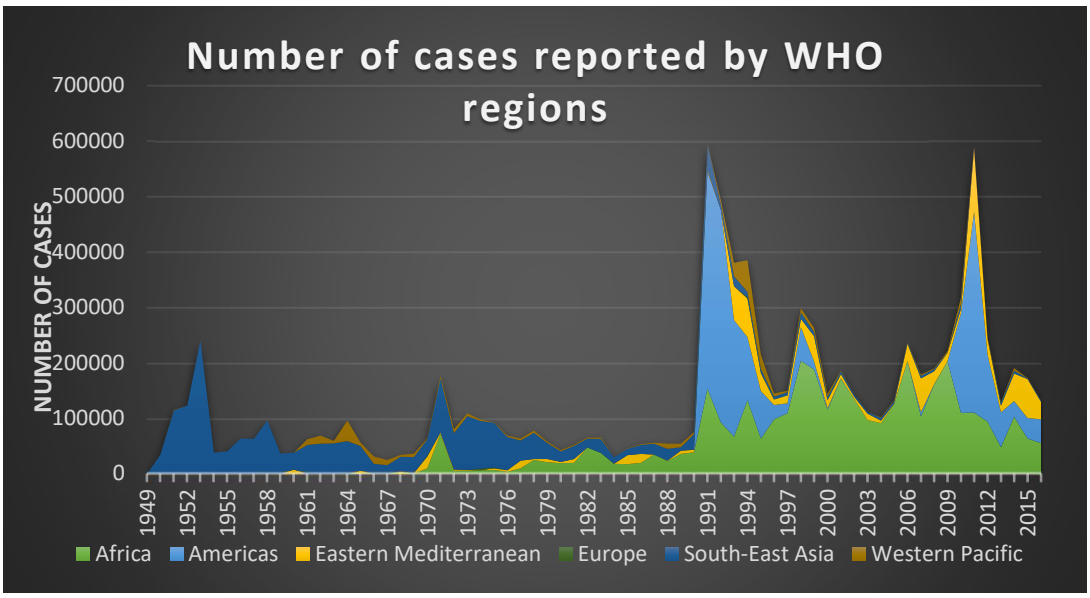
3) HOW MANY COUNTRIES REPORTED CHOLERA CASES EVERY YEAR?



Regarding the number of countries reporting cholera data:

- Around 1970, the number of countries reporting cases to WHO increased from about 20 to 40.
- In the 90s, American and European countries report more causes causing a peak of over 80 countries probably in 1994.
- As we can see, cholera is consistently being reported in a number of African countries.

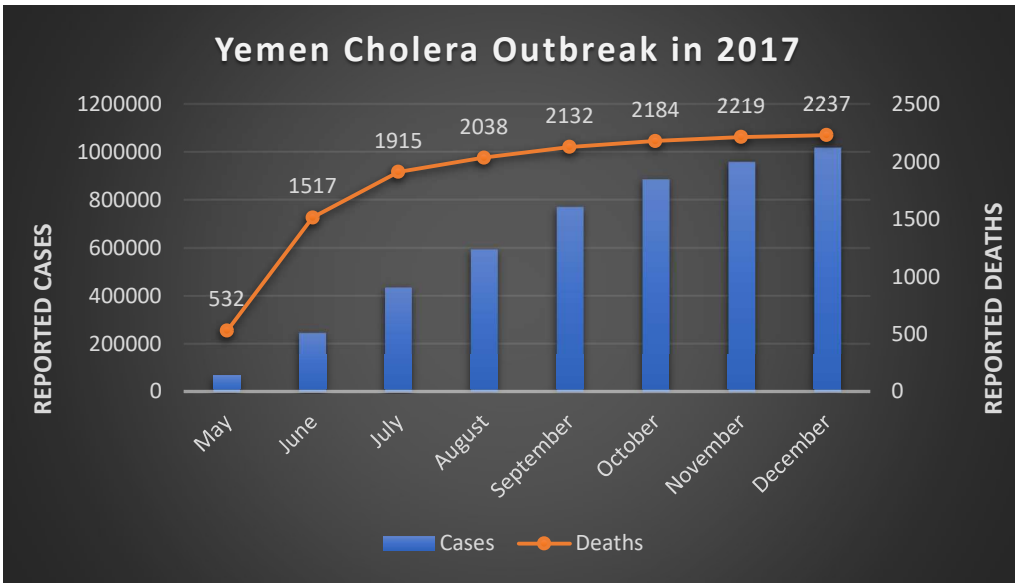
4) WHICH REGIONS ARE AFFECTED THE MOST BY CHOLERA?



- Notice that until mid 70s, south-east Asia was the region that had the highest number of cases. According to the data we have, the mid 50s crisis, for instance, had a strong participation of the countries from south-east Asia and western Pacific.
- South-east Asian countries, together with African countries, had a big impact on the 70s peak.
- In the last two outbreaks, American countries were responsible for the huge increase in the number of cases. African countries has been responsible for new plateau in the number of cases since 90s.
- Since 2010, eastern mediterranean countries have been demonstrating an increase in cases.

5) RISE OF CASES FOR THE MONTHS OF MAY – DECEMBER IN THE YEAR 2017 IN YEMEN

The graph below shows the cumulative number of cases and deaths from cholera in Yemen over the course of 8 months in the year 2017.



- Yemen recently faced a Cholera outbreak in 2017
- In December 2017, the World Health Organization reported the number of suspected cholera cases in Yemen had surpassed **one million.**
- The graph shows that the cases increased consistently from May to December. But the difference between No. of Deaths were mostly insignificant after August 2017.

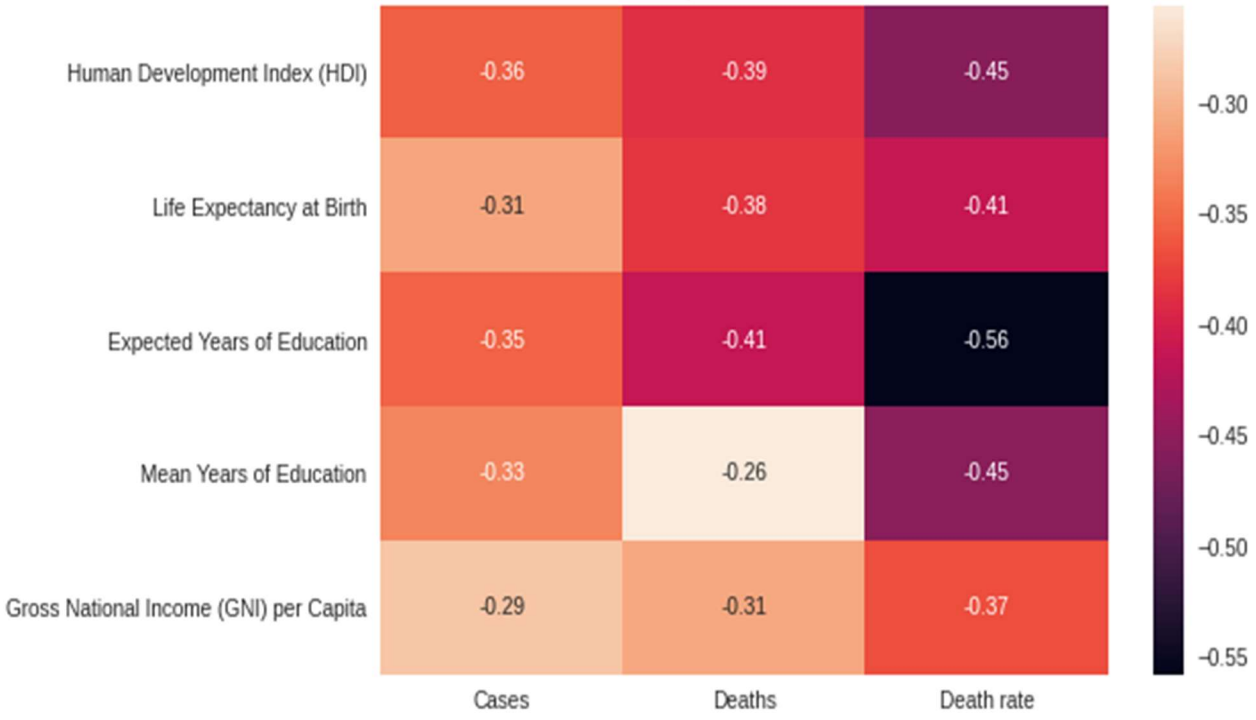
6) CORRELATION BETWEEN HUMAN DEVELOPMENT INDICES AND REPORTED CHOLERA METRICS

The Human Development Index is a statistic composite index of life expectancy, education, and per capita income indicators, which are used to rank countries into four tiers of human development.

The HDI is calculated as the geometric mean (equally-weighted) of life expectancy, education, and Gross National Income (GNI) per capita, as follows:

$$HDI = (I_{Health} * I_{Education} * I_{Income})^{1/3}$$

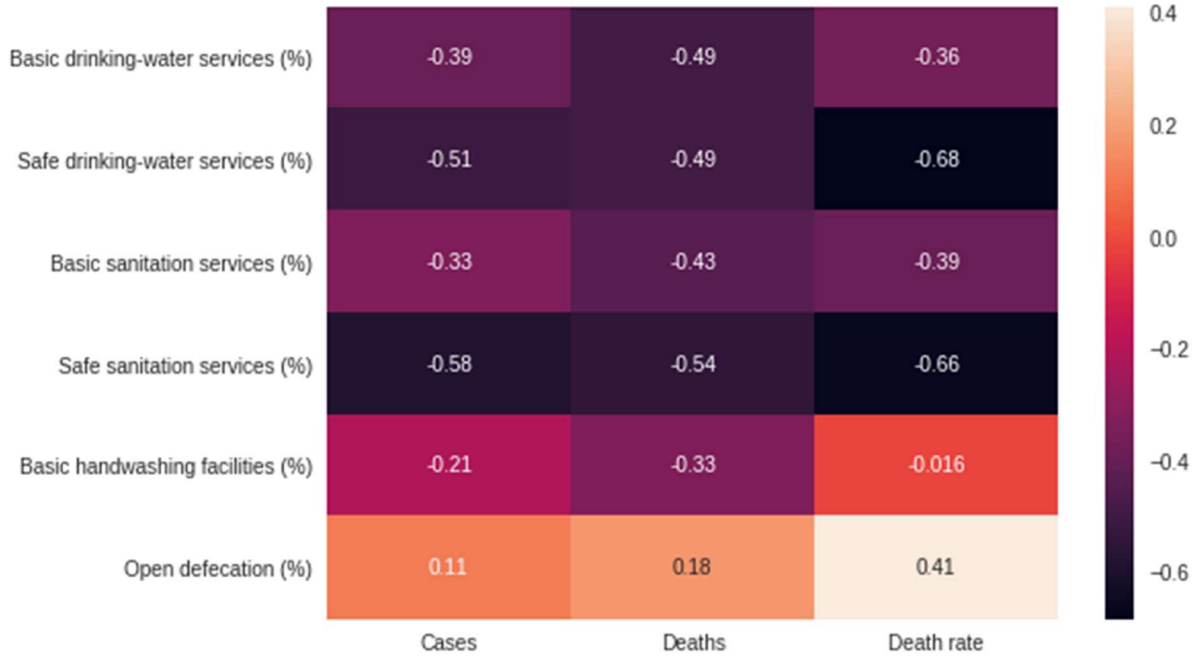
The education dimension is the arithmetic mean of the two education indices (mean years of schooling and expected years of schooling).



- We can see low negative correlations between the metrics.
- The lowest correlation is between death rate and expected years of education.
- In other words, it means that countries with higher death rates have lower expected years of education.

7) CORRELATION BETWEEN PUBLIC HEALTH INDICES AND REPORTED CHOLERA METRICS.

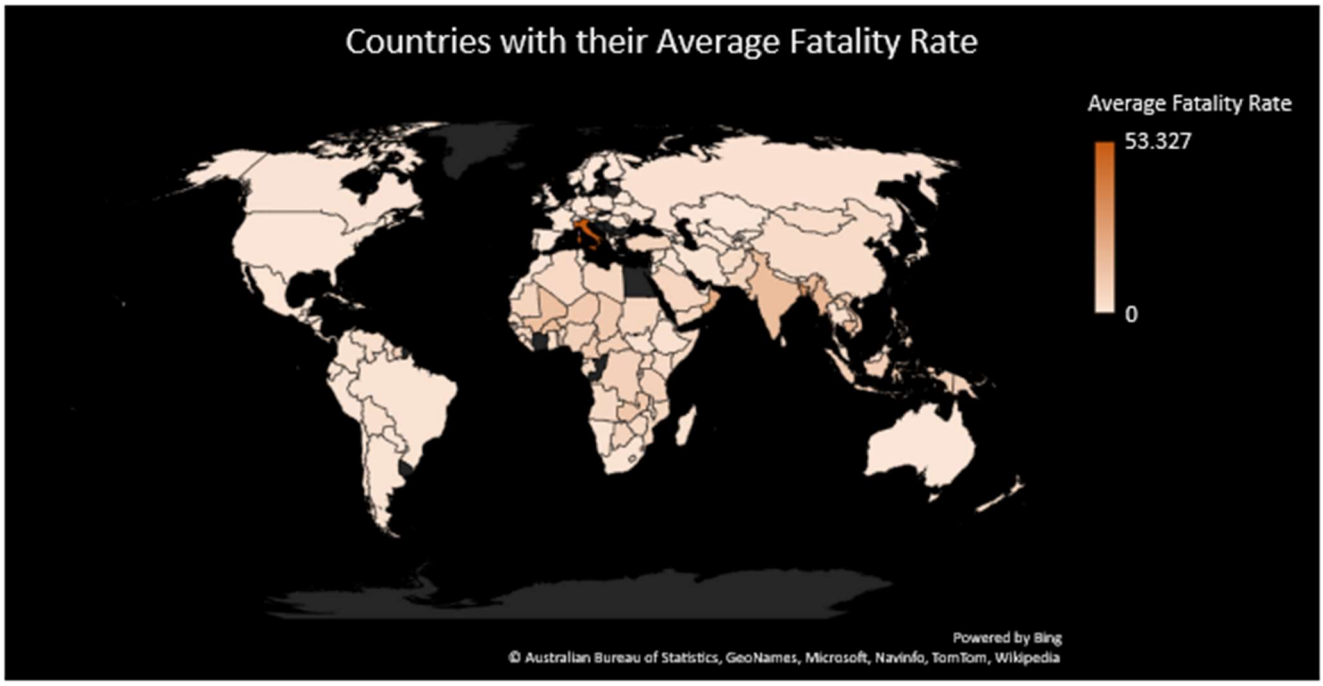
Health Index is a composite score incorporating 23 indicators covering key aspects of health sector performance. In this case, we are selecting 6 of these indicators which we believe might have an effect on Cases, Deaths and Death Rate of Cholera. In simple terms, Public Health Index is the percentage of population having access to a particular facility. For e.g., Safe drinking-water services.



- First, the percentages of population with access to safe sanitation and water-drinking services are the variables with the lowest negative correlations with the death-rate. In other words, countries where these metrics are low have a high death rate. As we already know, public water sanitation is a key strategy to prevent new cases and this chart shows why.
- Surprisingly, easy access to basic handwashing facilities isn't much correlated with cholera incidence.
- It's worth noticing that there is a considerable positive correlation between the percentage of population practicing open defecation and death rates. That is, countries with high percentages of open defecation usually have higher cholera death rates.

8) COMPARING THE AVERAGE FATALITY RATE IN THE NATIONS USING A HEAT MAP

WHO Regions	Countries	Average Fatality Rate
Europe	Italy	53.327
South-East Asia	Bangladesh	27.30295455
Eastern Mediterranean	Oman	22.2225
South-East Asia	Myanmar	17.53288889
Western Pacific	Cambodia	16.7
Africa	Burkina Faso	15.69318182
South-East Asia	India	15.14859375
Africa	Mali	14.18291667
Eastern Mediterranean	Djibouti	12.722
Europe	Czechia	12.5

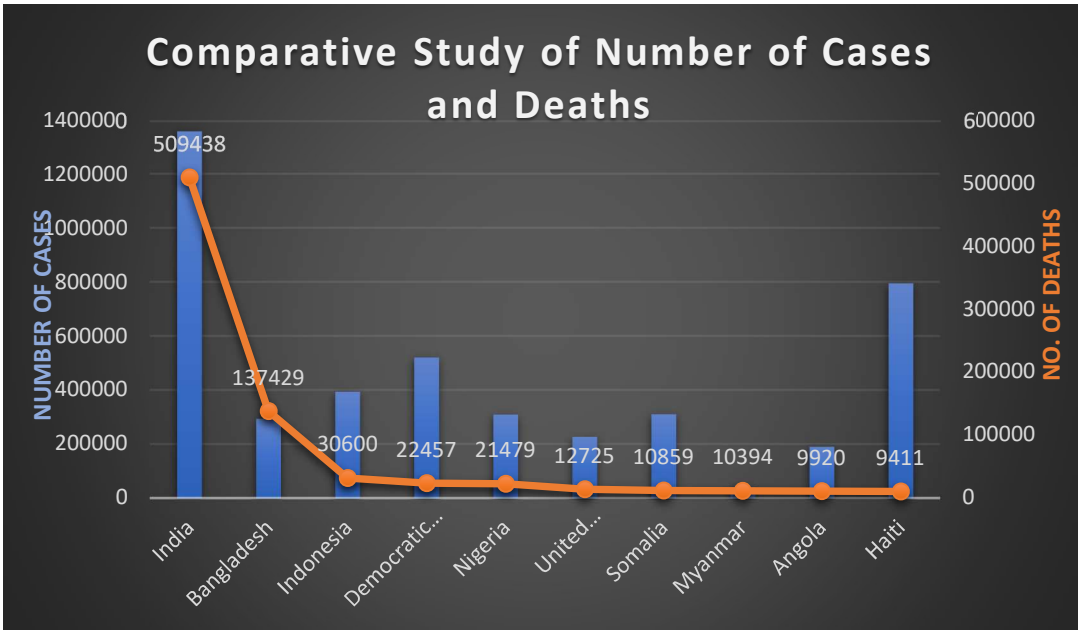


- Italy has the highest Average Fatality Rate among all the countries followed by Bangladesh and Oman
- From the heat map, it is clearly seen that African nations have a higher fatality rate, followed by the Northern portions of South America and Southern Asia.
- One clear indication that can be identified here is these nations are in developing or underdeveloped stages- with densely populated areas.
- Since the waterbodies present are much more polluted here as compared to the developed nations- the chances of Cholera spread and fatality is much more in these parts of the world.

9) COMPARATIVE STUDY BETWEEN THE COUNTRIES CONSIDERING THE NUMBER OF CONFIRMED CASES AND THE NUMBER OF DEATHS.

Countries	Cases	Deaths
India	1363250	509438
Bangladesh	294647	137429
Indonesia	394945	30600
Democratic Republic of the Congo	521607	22457
Nigeria	310217	21479
United Republic of Tanzania	228048	12725
Somalia	311203	10859
Myanmar	38847	10394
Angola	191036	9920
Haiti	795794	9411

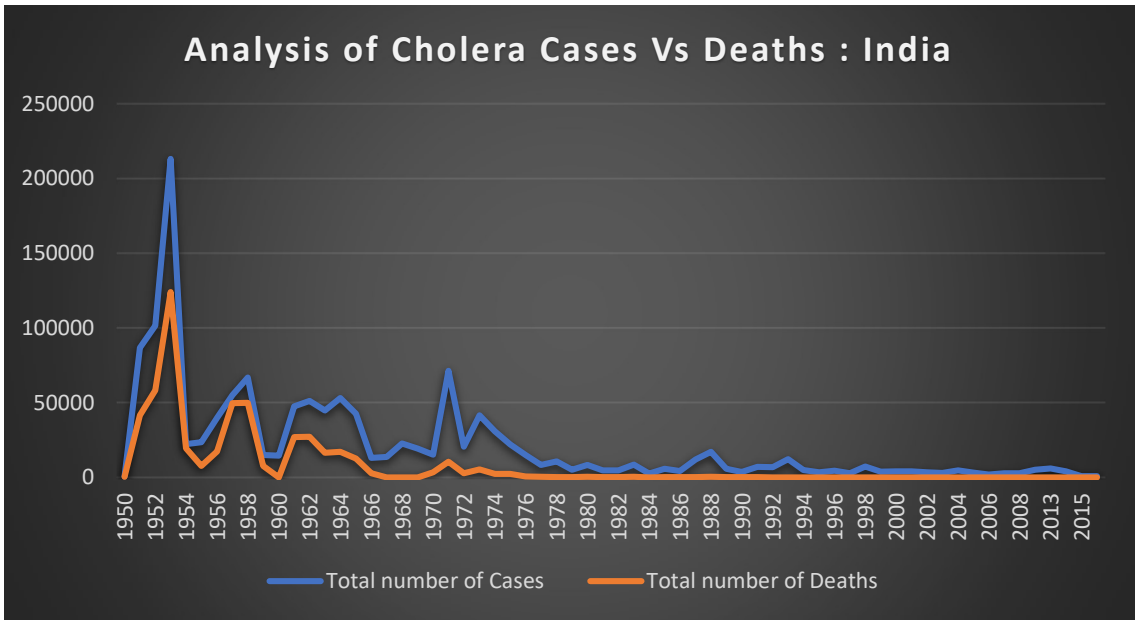
We analyzed the top 10 worst affected countries with respect to the highest number of Deaths. It shows the No. of Cases on the primary y-axis and No. of Deaths on the secondary y-axis between the years 1949 to 2016. The X-axis here has the countries.



- The above graph shows that India had the highest number of reported cases. India also has the highest number of deaths i.e., 65.76% of the total Reported Deaths that occurred among these 10 countries.
- Haiti has the 2nd highest number of cases but its death rate is lowest among the above-mentioned countries. Whereas Bangladesh stands 7th in terms of number of cases but it has the 2nd highest number of deaths.

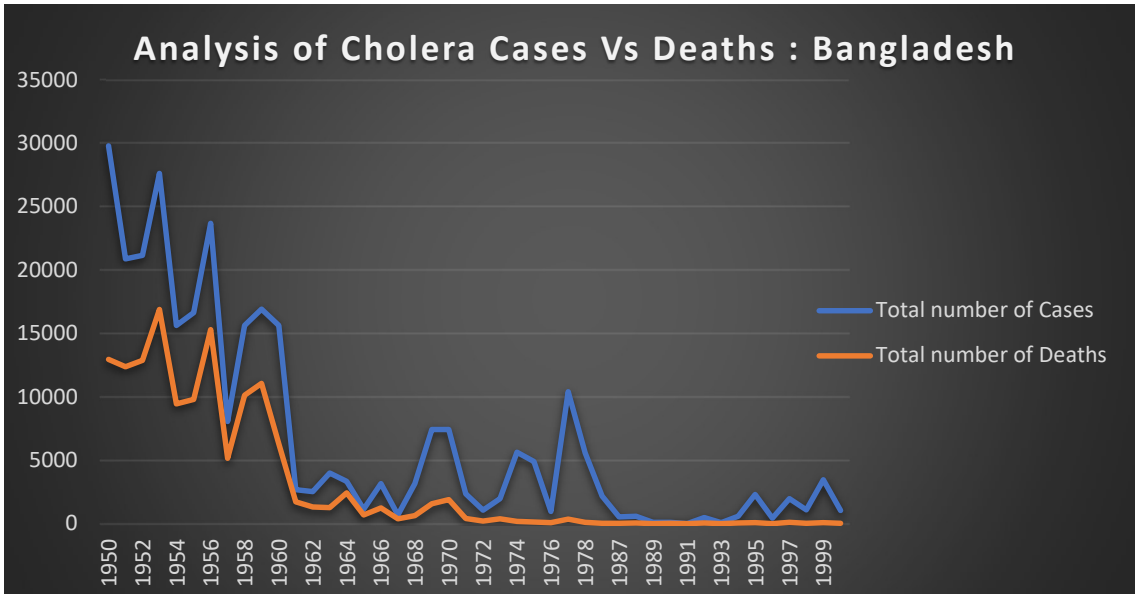
We will now be summarizing the overall data for 3 nations- One which has the highest cases in all time data, one with the second highest number of deaths in all time data and the last having the highest counts in the past 10 years i.e., from 2006 to 2016

A. The Country with the highest number of Cases and Deaths of all time- India



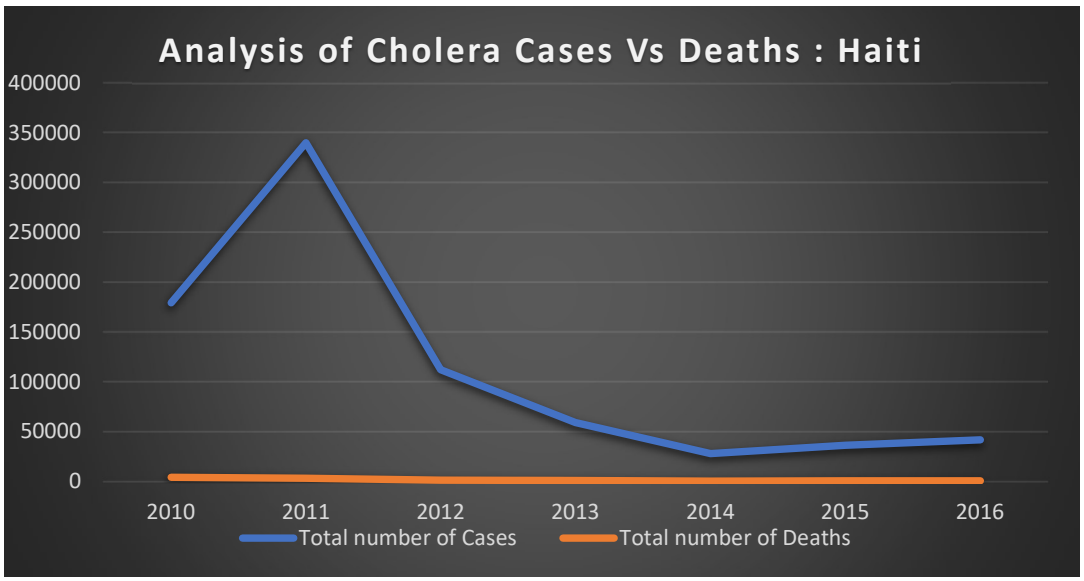
- The Year 1953 has seen the maximum number of Cholera Cases i.e., **213225**
- The Year 1953 also has seen the maximum number of deaths due to Cholera i.e., **124227**
- India, although had an extremely tough phase handling Cholera in the 1950s and a slightly controlled phase of Cholera in 1960-70, has been able to control the disease in the recent years.
- The number of reported cases and deaths have been low in the recent times.

B. Country with the second highest number of Deaths of all time data- Bangladesh



- The Year 1950 has seen the maximum number of Cholera Cases: **29809**
- The Year 1953 has seen the maximum number of deaths due to Cholera: **16904**
- The data of Bangladesh shows the high extent of risk for Cholera in 1950-70s period.
- Although the number of cases and deaths were significantly decreasing with time- we are unsure about the metrics in the last 20 years due to unavailability of the Data

C. The Country with the highest number of Cases between 2006 to 2016- Haiti



- The Data available for Haiti is only from the Span 2010-2016. Thereby Comparative analysis with a country like India was not feasible.
- But the pattern here has seen a different layout. The number of Cases has been on the rise between 2010-2011, and has dropped for the next 3 years.
- There has been a slight increase from 2014 and is on the increasing direction. Due to less amount of Data, this cannot be further forecasted.
- The death rate although has been very controlled throughout.

PREVENTIVE MEASURES TAKEN BY VARIOUS COUNTRIES TO STOP THE SPREAD OF PANDEMIC:

Although cholera may be life-threatening, prevention of the disease is normally straightforward if proper sanitation practices are followed. In developed countries, due to nearly universal advanced water treatment and sanitation practices present there, cholera is rare. For example, the last major outbreak of cholera in the United States occurred in 1910–1911. Cholera is mainly a risk in developing countries in those areas where access to WASH (water, sanitation and hygiene) infrastructure is still inadequate.

The following are the preventive measures taken by some countries to combat the spread of pandemic:

- Improving access to safe water, sanitation, and hygiene supplies
- Establishing a national surveillance system for accurate and timely identification of cholera cases
- Conducting environmental health assessments, such as testing of the water supply, in various communities throughout the country
- Carrying out site inspections at hospitals and clinics to assess their capacity to deliver health care
- In Bangladesh, the "sari filter" is a simple and cost-effective appropriate technology method for reducing the contamination of drinking water. This practice was found to decrease rates of cholera by nearly half. Zinc supplementation reduced the duration and severity of diarrhea in children with cholera when given with antibiotics and rehydration therapy as needed. It reduced the length of disease by eight hours and the amount of diarrhea stool by 10%.
- Rural drinking water has been included by the Government of India in rural infrastructure development plan called “Bharat Nirman”, which aims at providing adequate safe drinking water of good quality to all so far uncovered habitations. In 2014, the Prime Minister of India launched the “Swachh Bharat

Abhiyan", a program to create awareness about sanitation by eradicating open defecation, preventing water contamination, and improving public health. "Prevention and Control of Water Pollution Act" was enacted to restore and maintain water bodies in India in 1974. The 'Central Pollution Control Board' has established a network of monitoring stations on rivers across the country and initiated monitoring of water quality in 1977–78 under the Global Environmental Monitoring System (GEMS).

CHOLERA PANDEMIC MODEL (SIRB MODEL)

Cholera is a living testimony of poor sanitary conditions. Cholera spreads in areas with poor sanitation and through contaminated water, and the ideal solution is to improve infrastructure to provide clean water and effective sanitation -- an approach that has been successful since the 19th century. Cholera transmission depends on excretion of bacterium *"Vibrio cholera"* by infected persons and on ingestion of 'vibrios' in contaminated food or water. *Vibrio Cholerae* bacteria live in, and are transmitted by contact with contaminated water or food. Environmental and climatic conditions, such as water and temperature have direct impact on the abundance and/or toxicity of *Vibrio cholera.*

Administration of vaccine, a staple of preventive medicine, is one of the few potentially life-saving and implementable solutions. Decisions regarding whether and how to pursue mass vaccination during epidemic cholera present logistical and policy challenges. Mathematical models of disease transmission aim to provide guidance in making such decisions. Models can estimate key parameters such as R0 (the basic reproductive number, referring to the number of infectious cases caused by an average infectious person in an otherwise entirely susceptible population), and the impact of control strategies.

The disease transmission model aims to estimate the dynamics of cholera transmission and the impact of possible interventions, with a goal of providing guidance to policy-makers in deciding among alternative courses of action, including vaccination, provision of clean water, and antibiotics. This model was explicitly designed for simplicity and qualitative analysis (rather than for quantitative prediction).

SIRB Model:

The SIRB model is a simple model in which the total population (N) is divided into 3 components (N = S+I+R):

- S is the number of susceptible, who are not infected but could become infected.
- I is the number of infective. These individuals have the disease and can transmit it to the susceptible.
- R is the number of recovered individuals. They may have a natural immunity, or they may have recovered from the disease and are immune from getting it again, or they may have the disease but are incapable of transmitting it (e.g. because they may have been placed in isolation).

In this model, B represents the concentration of *Vibrio-cholerae* in the water reservoir used by this population.

PARAMETERS OF THE MODEL:

- λ is called as the force of infection which is the per capita rate of infection experienced by susceptible individuals. It is defined as $\lambda = \frac{\beta B}{(B+\kappa)}$
- β is the "Contact Rate" between the susceptible population with contaminated water.
- κ is the concentration of *Vibrio-cholerae in the water reservoir* that will make 50% of the susceptible population ill.
- ξ is the rate at which infectious people contribute *Vibrio-cholerae* to the water reservoir.

- δ is the rate of removal of infectious *Vibrio-cholerae* from the water reservoir.
- γ is the recovery rate of infected people. (also; 1/ γ = *duration of infectiousness)*

ASSUMPTIONS:

Few assumptions have also been considered. They are:

- This is an abstract concept that in the context of this model must be related to the amount of reservoir water consumed, but is not expressed in units that include volume and has no upper or lower bounds.
- Recovered persons can continue to shed vibrios for 1-2 weeks, with a very small fraction shedding for longer.
- The ratio of asymptomatic to symptomatic infections is constant throughout an epidemic, and that dose determines the likelihood of infection but not the likelihood of being symptomatic.

EQUATIONS:

1. **For the Susceptibles**

$$\frac{dS}{dt} = -\lambda S$$

where, S: Number of Suscpetibles
λ: Force of infection

Here rate of change of suscpetibles decreases with the time as susceptibles becomes infectives due to the interactions between the susceptible individual and *Vibrio-cholerae* with a concentration in the environment κ, the transmission rate β and the concentration of *Vibrio-cholerae* in the water reservoir used by this population, which is the force of infection λ.

2. **For Infectives,**

$$\frac{dI}{dt} = \lambda S - \gamma I$$

where, S: Number of Susceptibles
λ: Force of infection
I: Number of Infectives
γ: Recovery rate of infected people

Here rate of change of infective increases due to the interactions between the susceptible individual and *Vibrio-cholerae* with a concentration in the environment κ, the transmission rate β and the concentration of *Vibrio-cholerae* in the water reservoir used by this population, which is the force of infection λ. Infected individuals are reduced due to the recovered rate γ.

3. **For Recovered,**

$$\frac{dR}{dt} = \gamma I$$

where, R: Number of Recovered individuals
I: Number of Infectives
γ: Recovery rate of infected people

Here, rate of change of recovered individual increases due to recovery rate from infected individuals as γ

4. **For concentration of *Vibrio-cholerae* in the water reservoir**

$$\frac{dB}{dt} = \xi I - \delta B$$

Where, ξ: rate at which infectious people contribute Vibrio-cholerae to the water reservoir.
I: Number of Infectives
δ: Rate of removal of infectious *Vibrio-cholerae* from the water reservoir.
B: Concentration of *Vibrio-cholerae* in the water reservoir

Here, rate of change of concentration of *Vibrio-cholerae* in the water reservoir increases due to the increase in rate of contribution of Vibrio-cholerae to the water reservoir by the infectious individuals and the number of infected individuals. The decrease in concentration is due to the increase in removal rate of infectious *Vibrio-cholerae* from the water reservoir.

LIMITATIONS:

- Fitting a model to an aggregate epidemic curve will generate a single R0, but this R0 may suggest a level of vaccination that would be protective in some constituent communities but not others.
- The practice of fitting epidemic models to cumulative incidence curves rather than incidence curves can obscure these features, while also violating statistical assumptions of independence between fitted data points.
- As long as we know the size of the water reservoir and the amount of water consumed per day from that reservoir, we can estimate the infection rate. While we agree that it is plausible in theory, it is very difficult in practice to estimate the size of the reservoir, as they are not even well defined. People may obtain their drinking water from multiple sources.

VACCINES AND THEIR CLINICAL TRIALS

INTRODUCTION

Cholera continues to be a serious global public health problem in most impoverished nations with poor infrastructure, clean water, sanitation, and hygiene. Each year, an estimated 1.3–4.0 million cases of cholera and 21,000–143,000 cholera-related fatalities occur globally. The exact number of cholera cases worldwide is estimated to be significantly greater than what is reported. V. cholerae is a gram-negative, comma-shaped bacteria that causes cholera. Only serogroups O1 and O139 produce pandemic illness among the more than 200 serogroups. Since its discovery in 1992, O139 has been isolated only a few times. The O1 group is further separated into biotypes known as classical and El Tor, each of which produces cholera enterotoxin.

Based on the structure of the lipopolysaccharide membrane, each biotype has two different serotypes: Inaba and Ogawa. Hikojima, a third serotype, is rarely isolated. V. cholerae colonises the proximal small intestine and generates an enterotoxin that causes copious diarrhoea with water and electrolytes to cause illness. With one-third of the world's population at danger of cholera, we can expect enormous, rapidly diffused, and long-term cholera epidemics like those seen recently in Yemen and Haiti. The provision of drinkable water, sanitation, and hygiene are all important in preventing cholera epidemics like this (WASH). This method has been used for many years. However, it will be several years before everyone in the world has access to WASH. Study data has revealed that licensed and WHO prequalified cholera vaccinations are valuable instruments for cholera prevention while striving toward universal WASH.

The following are the 4 major vaccines that were developed with the intentions of preventing the spread of Cholera –

❖ INJECTABLE VACCINES

Several injectable whole-cell cholera vaccines were developed between 1894 and 1960. Injected cholera vaccines are rarely used today, although they may have some benefit. It is valuable to summarize the evidence for effectiveness of injected cholera vaccines for comparison with newer oral vaccines.
Vaccination against cholera was first tested in the nineteenth century and may play a role in controlling epidemics. Injected (parenteral) whole cell vaccines were used in the 1960s and 1970s, but they went out of favour as their efficacy was thought to be low and short-lived, and associated with a high rate of adverse effects.

Sixteen trials, involving over one million adults, children and infants, fulfilled the inclusion criteria. Twenty-four comparisons were reported on vaccine efficacy (cholera cases and/or deaths) and 11 comparisons considered adverse effects (nine reported on both). Compared to placebo, vaccines had a reduced risk of death from cholera (RR 0.49, 95% CI 0.25 to 0.93; 837,442 participants) and a reduced risk of contracting cholera at 12 months (RR 0.52, 95% CI 0.42 to 0.65, random-effects model; 1,512,573 participants). This translates to an efficacy of 48%, 95% confidence interval 35% to 58%. Significant protection lasted for two years, even after only a single dose, and for three years with an annual booster. Children over five years and adults were protected for up to three years, while children under five years were protected for up to a year. Injected cholera vaccines were associated with more systemic and local adverse effects compared to placebo, but these were not severe or life-threatening.

Injected cholera vaccines appear to be safe and relatively more effective than usually realized. Protection against cholera persists for up to two years following a single dose of vaccine, and for three years with an annual booster. However, they have been superseded by oral vaccines.

❖ DUKORAL

Dukoral is used to prevent sickness caused by Vibrio cholerae serogroup O1 in adults and children as young as 2 years old who will be traveling to endemic or epidemic locations. The use of Dukoral should be based on official recommendations, which take into account the variety of epidemiology and the risk of developing disease in various geographic areas and travel conditions. Dukoral should not be used in place of basic safety precautions. In the event of diarrhoea, rehydration measures should be implemented.

The vaccination is meant to be taken orally. The suspension should be combined with the buffer (sodium hydrogen carbonate) solution before eating. The sodium hydrogen carbonate is delivered in the form of effervescent grains that should be dissolved in a glass of cool water (approx. 150 ml). It is possible to utilize chlorinated water. After that, the suspension must be combined with the buffer solution and consumed within two hours. One hour before and one hour after vaccination, food and drink should be avoided. Oral administration of other pharmaceutical drugs should be avoided for 1 hour before and after Dukoral administration. Children aged 2 to 6 years old: drain out half of the buffer solution and mix the remaining portion (approximately 75 ml) with the full contents of the vial.

FERTILITY, PREGNANCY AND LACTATION

There are no animal studies on reproductive toxicity. Although no specific clinical studies have been undertaken to address this issue, the vaccination may be delivered during pregnancy and to breast-feeding women after thorough benefit/risk assessment. 196 pregnant women in Zanzibar received at least one dose of Dukoral during a mass vaccination campaign. There was no statistically significant evidence that Dukoral exposure during pregnancy had a negative effect.

Three randomized double-blind placebo-controlled clinical trials were done in Bangladesh (endemic zone) and Peru to investigate efficacy against cholera (non-endemic region).

- For the first 6 months of follow-up in the Bangladesh field trial, Dukoral's preventive effectiveness in the entire population was 85% (95% CI: 56, 95, per-protocol analysis). Vaccine protection lasted 6 months in children and 2 years in adults, depending on their age. In adults, an exploratory investigation found that two vaccine doses were as effective as three doses.
- The short-term protective efficacy against cholera after two vaccine doses was 85% in the second experiment, which was done in Peru and enrolled military recruits (95% CI: 36, 97, per-protocol analysis).
- The third study, a Peruvian field trial, failed to show any protection against cholera within the first year. The protective efficacy during the second year after a booster dose 10-12 months after primary immunization was 60.5% (95% CI: 28,79).

During two mass-vaccination efforts in Mozambique (December 2003–January 2004) and Zanzibar (February 2009–May 2010), the efficiency of the vaccine against cholera was assessed.

- For the first 5 months of follow-up, the protective efficacy of 2 doses of Dukoral was 84% (95% CI: 43, 95, per-protocol analysis; p=0.005) in a case-control study done during a mass vaccination campaign in Mozambique.
- Protective effectiveness after two doses of Dukoral was 79% (95% CI: 47, 92) for a 15-month follow-up period in a longitudinal cohort study done during the mass vaccination campaign in Zanzibar. In the examined scenario, it was discovered that Dukoral provided significant indirect (herd) protection in addition to direct protection.

Following repeated booster vaccinations, the protective efficacy of Dukoral against cholera has not been evaluated.

UNDESIRABLE EFFECTS

Dukoral's safety was tested in clinical studies for cholera and enterotoxigenic Escherichia coli (ETEC) producing heat-labile enterotoxin in both endemic and non-endemic nations, involving both adults and children as young as two years old (LT).

During the clinical studies, almost 94,000 doses of Dukoral were given out. In terms of mode of monitoring, symptom description, and follow-up time, the evaluation of safety differed amongst trials. Passive surveillance was used to assess adverse events in the majority of trials. The most often reported side effects, such as abdominal pain, diarrhoea, loose stools, nausea, and vomiting, were observed at equal rates in both the vaccine and placebo groups.

Frequency classification: Very common (1/10,000 to 1/1,000); common (1/100 to 1/10); uncommon (1/1,000 to 1/100); rare (1/10,000 to 1/1,000); very rare (1/10,000); not known (cannot be estimated from the available data).

- **SHANCHOL**

Shanchol Oral Vaccine is an inactivated vaccine (made from a dead bacteria) which has been WHO prequalified since September 2011, licensed in India, Bangladesh and 16 other countries in Asia, Africa and Latin America. It helps develop immunity by forming antibodies, which are proteins that protect against infection caused by cholera bacteria. It can be given to anyone above the age of 1 year orally. Two doses are given at an interval of at least two weeks. The protective effect begins within 7-10 days of completion of the vaccination schedule. This vaccine is a powder that is mixed with water before you take it. This vaccine should be taken on an empty stomach, at least 1 hour before or 1 hour after eating.

CLUSTER-RANDOMIZED PLACEBO-CONTROLLED EFFICACY TRIAL IN KOLKATA, INDIA:

- The primary objective of the study was to evaluate the protection conferred to the vaccines by a two-dose regimen of the modified oral whole cell cholera vaccine in cholera-endemic areas. Two doses of the vaccine/placebo at an interval of 14 days was offered to consenting residents who were at least a year old and were not pregnant. The study was performed in three administrative wards of Kolkata Municipal Corporation (wards 29, 30 and 33). Initially, surveillance was performed in nine community clinics established for the trial and in two hospitals serving the study population.
- There were 3933 clusters and 107,774 eligible individuals of which, there were 69,329 one-dose recipients and 66,900 two-dose recipients. The primary analysis included 1721 clusters with 31,932 two-dose vaccine recipients and 1757 clusters with 34,968 two-dose placebo recipients. The cumulative five-year protective efficacy (PE) of this vaccine for eligible subjects against cholera was 65% (one-sided 95% CI lower bound = 54%, $p < 0.001$). Stratified by age, protective efficacy for subjects 1.0 to 4.9, 5.0 to 14.9, and ≥15 years old was 42% ($p = 0.01$), 68% ($p < 0.01$) and 74% ($p < 0.01$), respectively.
- The shorter length of protection observed among younger children may be due to a number of host factors that inhibit or interrupt the development of mucosal immune memory responses to the vaccine or vaccine components.

FEASIBILITY AND ELECTIVENESS TRIAL IN DHAKA, BANGLADESH:

- The aim of this study was to assess overall protection conferred by a two-dose regimen of Shanchol vaccine. All non-pregnant individuals aged one year and older were eligible for this study. There were three groups: vaccination group, vaccination and a behaviour change intervention, or non-intervention.
- During vaccination, eligible participants were requested to receive two doses of the bivalent whole-cell inactivated vaccine Shanchol at an interval of at least 14 days. Two icddr,b hospitals and 10 other hospitals serving the study population were selected for passive surveillance. Vaccine coverage was 65% in the vaccination only group, 66% in the vaccination and behavioural change group.
- During the 14-day post-vaccination follow-up, 95 adverse events were recorded. However, there was no serious adverse event. The study result shows the overall protective efficacy is 37% in the vaccination group and 45% in the vaccination with behavioural change group.
- For severely dehydrating cholera the overall protective efficacy is 53% and 58% in the vaccination only group, and in the vaccination with behavioural change group respectively.

IMMUNOGENICITY STUDY OF OCV, KOLKATA, INDIA:

- Considering the fact that feasibility of vaccinating the community twice, especially in emergency situations, is a challenge, a randomized, placebo-controlled trial was conducted to assess the immune responses following one and two doses of the bivalent, killed, whole-cell, oral cholera vaccine among adults and children in Kolkata, India.
- The study assessed whether receipt of a single dose of OCV is as immunogenic as receipt of two doses among adults and children residing in cholera-endemic areas in Kolkata. It was conducted at the clinical trial unit of the National Institute of Cholera and Enteric Diseases (NICED) in Kolkata from June to September 2007 with adults aged 18–40 years and children aged 1–17 years residing in Kolkata, India. A total of 80 adults and 80 children were enrolled for the study.
- Among vaccinees in both age groups, there were more subjects who "seroconverted", i.e., developed a ≥ 4-fold rise in titers from baseline after a single dose compared to after two doses of the OCV. About 65% of adults and 87% of children seroconverted with vibriocidal antibodies (≥4-fold rise) after the first dose. However the rates of seroconversion after the second dose were 46% of adults and 82% of children. Whether the results of this study indicate that the vaccine may be effective after a single dose will need to be determined through a vaccine-efficacy study.

SINGLE-DOSE OCV STUDY IN DHAKA, BANGLADESH:

- The encouraging results of the immunogenicity study led to the conduct of an individually randomized efficacy study with a single dose of the oral cholera vaccine in urban slums of Mirpur, Dhaka where cholera is highly endemic. A total number of 204,700 non-pregnant residents (58% of the census population) who were one year of age or older were randomly assigned to receive a single dose of oral cholera vaccine or placebo. The frequency of adverse event was similar between two groups.

- The primary outcome was vaccine protective efficacy against culture-confirmed cholera whereas the secondary outcomes included protective efficacy against severely dehydrating culture-confirmed cholera.
- The study shows a single dose of killed oral cholera vaccine provided 40% protection against all cholera at least six months of follow-up in a highly endemic population. Cholera with severe dehydration showed higher protection (65%). Older children (≥5 years of age) or adults who were vaccinated was only evident to be protected.
- Result from 2-year follow-up shows vaccine protective efficacy was 52% and 71% against all cholera episodes and severe cholera episodes respectively in participants aged 5 years to younger than 15 years. Vaccine protective efficacy for participants (≥15 years) was 59% against all cholera episodes and 59% against severe cholera.
- Throughout the period, vaccine protection was sustained in older age groups but the vaccine did not show protection against either all cholera episodes (protective efficacy −13%) or severe cholera episodes (−44%) in participants younger than 5 years.

❖ EUVICHOL

Euvichol vaccine was developed by EuBiologics Co., Ltd with the help of International Vaccine Institute (IVI). Euvichol was accredited by obtaining World Health Organization (WHO) prequalification in 2015 and began to be supplied to all over the world by signing LTA with UNICEF from 2016. Recently, Euvichol-plus, the world's first plastic tube presentation OCV, also received prequalification from WHO.
The vaccine is a liquid formulation of Oral Cholera Vaccine containing O1 and O139 of Vibrio cholerae inactivated by heat or formalin. The vaccine should be administered to anyone above the age of 1 year. Two doses of vaccine should be given at an interval of two weeks. The vaccine is presented as a suspension. Therefore, after shaking the vaccine vial rigorously, 1.5 mL of the vaccine should be squirted into the mouth. Take a sip of water if necessary. The frozen vaccines should not be taken. The vaccine should not be administered parenterally (intramuscularly, subcutaneously or intravenously). The vaccine is only recommended for oral administration.

PHASE I CLINICAL TRIAL IN KOREA:

- The Phase I Study was conducted to determine the Safety and Immunogenicity of Euvichol (Oral Cholera Prevention Vaccine) in Healthy Adult Men. 20 participants were selected for the study. 1vial of 1.5mL was given to them at 2-week intervals twice.
- The proportion of all adverse event and serious adverse event which were occurred during the entire study period was analyzed and casuality between severity and investigational product was presented.

A RANDOMIZED, NON-INFERIORITY TRIAL COMPARING TWO BIVALENT KILLED, WHOLE CELL, ORAL CHOLERA VACCINE (EUVICHOL VS SHANCHOL) IN THE PHILIPPINES:

- The randomized controlled trial was carried out in healthy Filipino adults and children. Two doses of either the current WHO prequalified OCV (Shanchol) or the same composition OCV being considered for WHO prequalification (Euvichol) were administered to participants.
- The pivotal study was conducted in total of 1263 healthy participants (777 adults and 486 children). No serious adverse reactions were elicited in either vaccine groups. Vibriocidal antibody responses to V. cholerae O1 Inaba following administration of two doses of Euvichol were non-inferior to those of Shanchol in adults (82% vs 76%) and children (87% vs 89%). Similar findings were observed for O1 Ogawa in adults (80% vs 74%) and children (91% vs 88%).
- A two dose schedule with Euvichol induces a strong vibriocidal response comparable to those elicited by the currently WHO prequalified OCV, Shanchol. Euvichol will be an oral cholera vaccine suitable for use in lower income countries, where cholera still has a significant economic and public health impact.

PHASE 3 CLINICAL TRIAL IN PHILIPPINES:

- To contribute to the global demand for oral cholera vaccine (OCV), the production of Euvichol® was scaled up with elimination of thimerosal. To demonstrate the equivalence of the variations, a study was carried out in the Philippines.
- Healthy male and female adults and children in Manila were randomized to receive two doses of Euvichol® two weeks apart from either the 100L (Comparator) or the 600L (Test) variation. Primary and secondary immunogenicity endpoints were respectively geometric mean titer (GMT) of vibriocidal antibodies (two weeks post second dose) and seroconversion rate (two weeks after each dose) against O1 Inaba, Ogawa, and O139 serogroups. The GMT of vibriocidal antibodies against O1 Inaba, Ogawa, and O139 two weeks post first dose was also measured. To show the equivalence of two variations of Euvichol®, the ratio of GMT and the difference of seroconversion rate between Test and Comparator vaccines were tested with equivalence margin of [0.5, 2.0] for GMT ratio and of 15% for seroconversion rate, respectively. Safety assessment included solicited reactogenicity within 6 days after each dose and unsolicited and serious adverse events.
- A total of 442 participants were enrolled. For the overall population, equivalence between Test and Comparator was demonstrated for vibriocidal antibody response against O1 Inaba and Ogawa serotypes and O139 serogroup in both modified intention-to-treat (mITT) and per protocol analysis, since the 95% confidence intervals (CI) of GMT to any serotypes were within the lower and upper boundary [0.5, 2.0]. Seroconversion rates after two doses also showed equivalence for O1 Inaba, Ogawa, and O139. The vaccine was safe and well tolerated, similarly between the two groups.
- The study results support the equivalence of the 600L Euvichol® to the 100L formulation in healthy children and adults. The 600L Euvichol® is safe and immunogenic in adults and children.

CONCLUSION

- Clearly, WASH strategies and OCVs can significantly reduce the global cholera burden. Trials and observational studies have shown that two OCV doses offer substantial direct protection for up to five years and can induce herd protection among the unimmunized.
- However, knowledge needs to be developed for current vaccines for their prolonged duration of protection and vaccines need improvements for better immune response in younger children.
- A single dose vaccination regimen would be more cost-effective and easier to deliver. Recent approaches have focused on designing genetically attenuated cholera strains for use in single-dose cholera vaccines.
- Advances in packaging and vaccine temperature control, reduced vaccine costs, the inclusion of pregnant women in vaccine campaigns, and a targeted approach to high incidence endemic areas are further increasing the usefulness of these vaccines for reducing the global cholera burden.
- For rapid access in emergency and equitable distribution of OCV in cholera-endemic low-income countries, a global OCV stockpile was established in 2013 with support from the Global Alliance for Vaccines and Immunization.
- The Global Task Force on Cholera Control (GTFCC) has established a goal to reduce global cholera deaths by 90% and eliminate transmission in 20 countries by 2030, thereby reducing the global burden from cholera until it is “no longer a threat to public health.” This strategy is based on early detection and response to outbreaks, a multisectoral approach to prevent case recurrence in high-risk areas, and mechanisms for local and global coordination.

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