

«Ενιαία υγεία και λοιμώξεις στη Λεκάνη της Μεσογείου/Οστικό Έλλειμμα και Λοίμωξη»

ACUTE DIARRHEAL SYNDROMES

CHOLERA

(Vibrio cholerae Infection)

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Σύγκρουση Συμφερόντων Conflict of Interest Statement

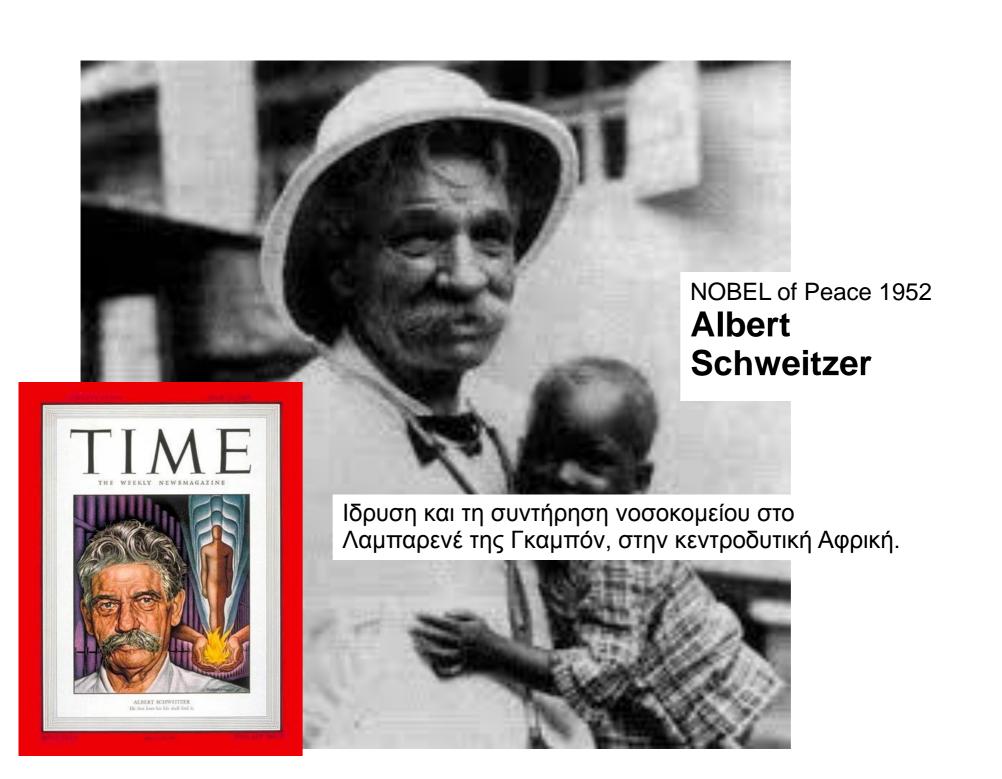
ΚΥΡΙΟΣ ΕΡΕΥΝΗΤΗΣ ΣΕ:

- -Διεθνή Μελέτη του National Institute of Allergy and Infectious Diseases (NIAID)
- -Ομαδική Κλινική Μελέτη του Ελληνικού Ινστιτούτου Σήψης
- -Ομαδική Κλινική Μελέτη της Ελλην Εταιρείας Χημειοθεραπείας
- -Τιμητικές αμοιβές για συμμετοχές σε Εκπαιδευτικές εκδηλώσεις και συμμετοχή σε εκπαιδευτικά συνέδρια από Φαρμακευτικές Εταιρείες Pfizer, Astellas, Angelini, MSD

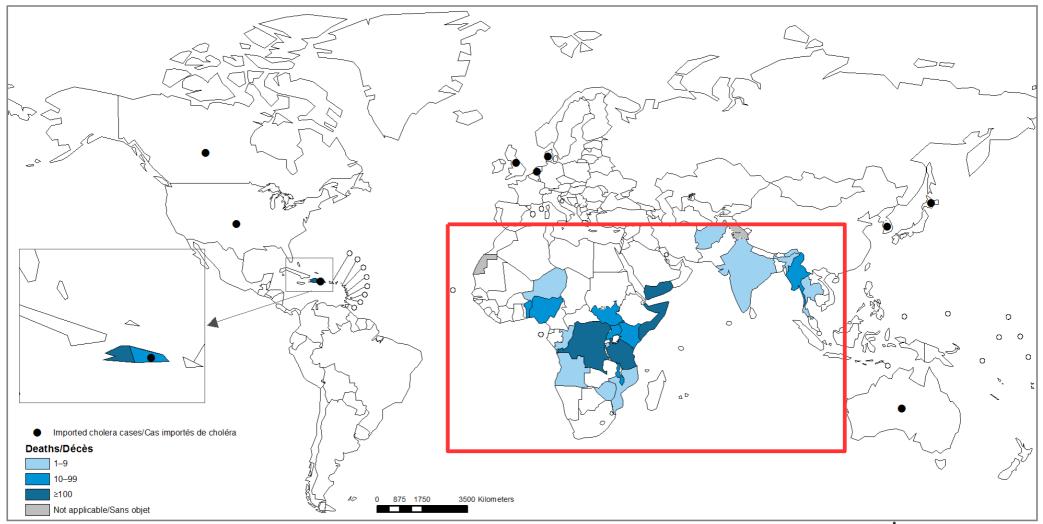
Τμήμα Επιδημιολογικής Επιτήρησης και Παρέμβασης ΧΟΛΕΡΑ (ICD-10 A00)

- → Η χολέρα είναι μια οξεία διαρροϊκή νόσος που οφείλεται στην προσβολή του εντέρου από την εντεροτοξίνη που παράγει το βακτήριο Vibrio cholerae
- → Σύμφωνα με τον Π.Ο.Υ. μόνο τα στελέχη του Vibrio cholerae των οροομάδων Ο1 και Ο139 που παράγουν τοξίνη προκαλούν σοβαρή νόσο που χαρακτηρίζεται ως «χολέρα» και επιδημίες
- → Κάθε οροομάδα έχει 2 βιότυπους τον Κλασικό & τον El-Tor
- → Κάθε βιότυπος έχει 3 οροτύπους Inaba, Ogawa & Hikojima
- → Οι **υπόλοιπες οροομάδες του βακτηρίου τοξινογόνοι ή μη** μπορούν να προκαλέσουν ήπιο διαρροϊκό σύνδρομο και δεν προκαλούν επιδημίες





Countries reporting cholera deaths and imported cases in 2016 Pays ayant déclaré des décès dus au choléra et des cas importés en 2016



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Data Source: Control of Epidemic Diseases Unit World Health Organization

Map Production: Information Evidence and Research (IER) World Health Organization



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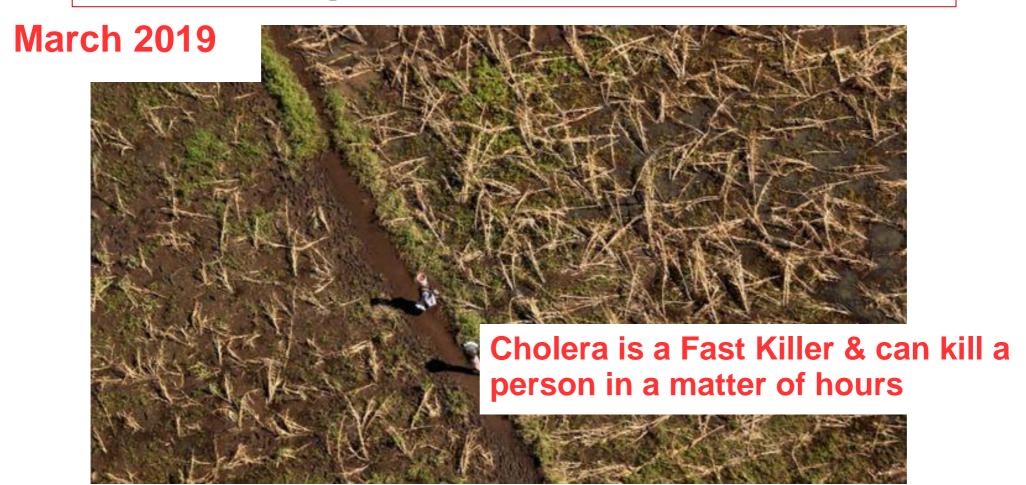
Cholera 101: Why This Ancient Disease Is Making Headlines In 2019

April 2, 2019 · 10:25 AM ET



The figure at left is the personification of cholera, facing resistance from a group of women. This 19th century engraving is from Barcelona.

Cyclone Idai: First cholera death in Mozambique as cases double



Cyclone Idai, which hit on 14 March 2019, caused massive flooding and killed more than 700 people across southern Africa.

More than 500 cases of cholera have since been reported in Beira with cases of the disease almost doubling in Mozambique





- A major public health problem
- Affects primarily developing world populations
- No proper access to adequate water and sanitation resources



- → Η μέση δηλούμενη επίπτωση στις χώρες της Ευρωπαϊκής Ένωσης 2009, ήταν <0,01 κρούσματα ανά 100.000 πληθυσμού
- → Στην Ελλάδα, η τελευταία επιδημία χολέρας καταγράφηκε το 1912-1913 (Βαλκανικοί πόλεμοι)
- → Η χολέρα ανήκει στα νοσήματα άμεσης δήλωσης του συστήματος υποχρεωτικής δήλωσης νοσημάτων του ΕΟΔΥ (ΚΕΕΛΠΝΟ)

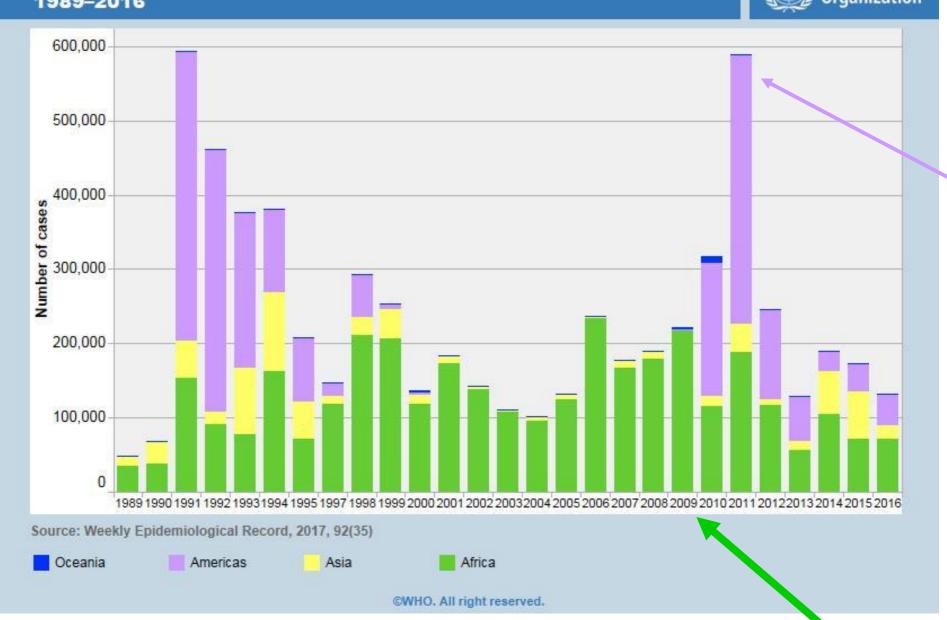


Cholera is under-reported

- 2.9 million cases
- 95,000 deaths are suspected to actually occur each year

Cholera cases reported to WHO by year and by continent 1989–2016





Cholera cases reported WHO worldwide

In 2016:

- 132121 cholera cases
- 2420 deaths
- Outbreaks continued to affect several countries
- 54% of cases were reported from Africa
- 13% from Asia
- 32% from Hispaniola





Epidemiology In 2017:

Cholera continues to hit communities already made vulnerable by tragedies such as conflicts and famines



- Yemen currently faces the world's largest cholera outbreak, with over 700,000 suspected cases and more than 2,000 deaths reported since April
- Somalia: Over 800 people have died of cholera since the beginning of the year, and over 500 in the DRC
- Haiti has now reported nearly 1 million cases and 10,000 deaths since the beginning of the 2010 outbreak



Yemen cholera outbreak accelerates to 10,000+ cases per week: WHO

On May 22, the number of cases began a dramatic trend upward.



Water born Infection

Transmission

- Cholera transmission is closely linked to inadequate access to clean water and sanitation facilities.
- 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 been 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.
- People who are <u>more likely to be exposed</u> to cholera include:
 - healthcare personnel
 - cholera response workers
 - travelers in an area of active cholera transmission (who cannot or do not always follow safe food and water precautions and personal hygiene measures)
- Uninfected dead bodies have never been reported as the source of epidemics



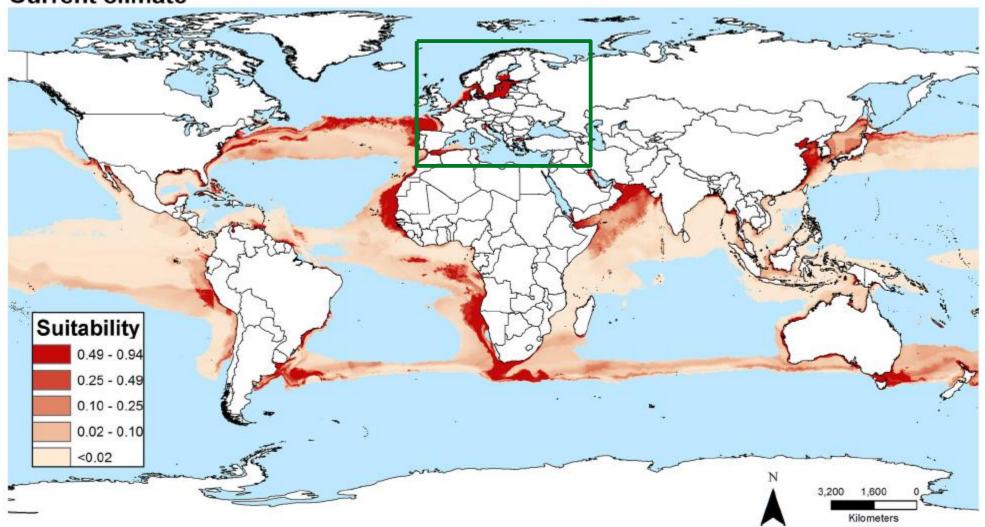
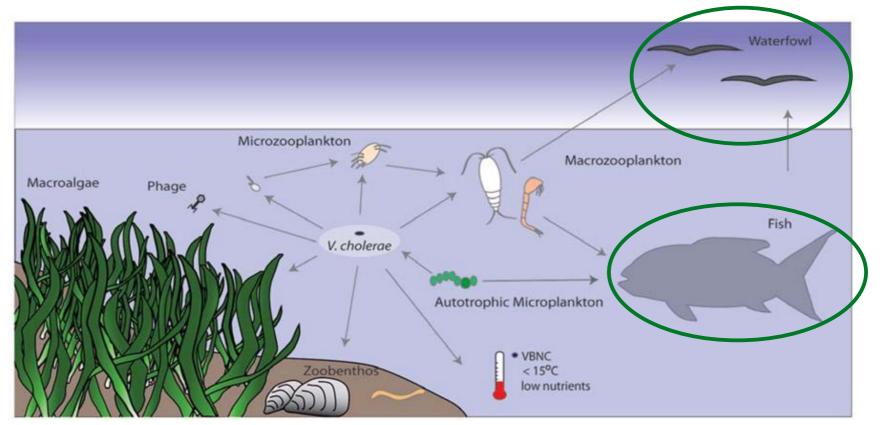


Fig. 4. Global map of Vibrio cholerae suitability in seawaters.

Model generated under the current climate scenario.



Vibrio cholerae interactions with other organisms and the environment:

V. cholerae is part of the bacterioplankton in aquatic environments.

It is under predation **pressure by protozoa and bacteriophage** and is thus incorporated into the microbial loop. Low temperature and nutrient conditions can trigger the VBNC state (*viable but nonculturable* (VBNC) bacteria refers to bacteria that are in a state of very low metabolic activity and do not divide, but are alive and have the ability to become culturable once resuscitated).

V. cholerae can also attach to autotrophic organisms such as **phytoplankton or macroalgae**, which can provide a carbon source. Attachment to chitinous **zooplankton and gelatinous egg masses** (e.g., chironomids) provide nutrients and also facilitate HGT (Horizontal gene transfer).

Fish and birds feed on plankton or mussels that might harbor V.cholerae and can potentially spread the bacterium across long distances.

Microbiology

Class: Gamma Proteobacteria

Order: Vibrionales

Family: Vibrionaceae

Genus: Vibrio

Species: V. cholerae

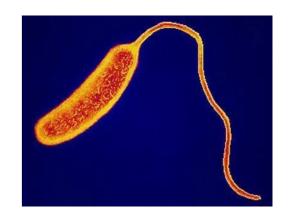
V. parahaemolyticus

Diarrhea

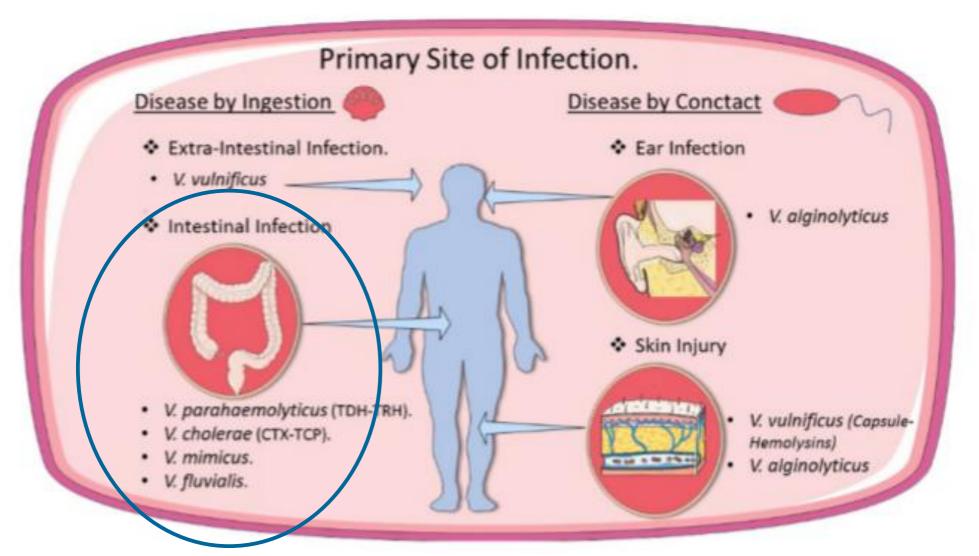
V. fluvialis

V. mimicus

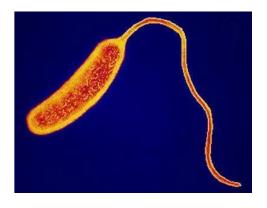
V. vulnificus



Vibrio spp



Microbiology

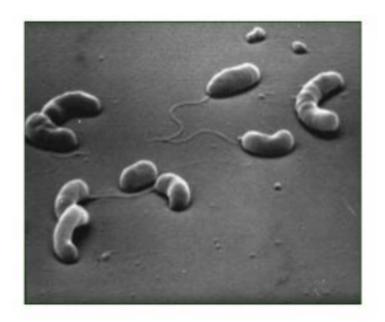


- Many serogroups of Vibrio cholerae
- Only two O1 and O139 cause outbreaks
- V. cholerae O:1 has caused all recent outbreaks
- V. cholerae O:139 first identified in Bangladesh in 1992 – caused outbreaks in the past. It has never been identified outside Asia.
- There is no difference in the illness caused by the two serogroups.

Microbiology

Vibrio cholerae Morphology

- Gram negative
- rigid, curved rods that are actively motile
- Comma shaped
- Sheathed, polar flagellum
- About 1.5*0.2-0.4μm in size



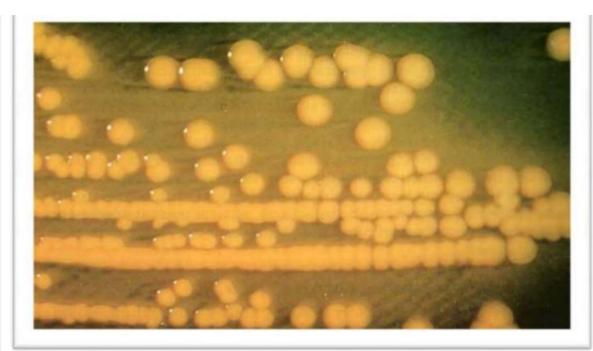


Figure IV-1. Overnight colonies of *V. cholerae* on TCBS because of the fermentation of sucrose. They are characterislightly flattened.



Vibrio cholerae growing on thiosulphate citrate bile salt sucrose (TCBS) agar plates

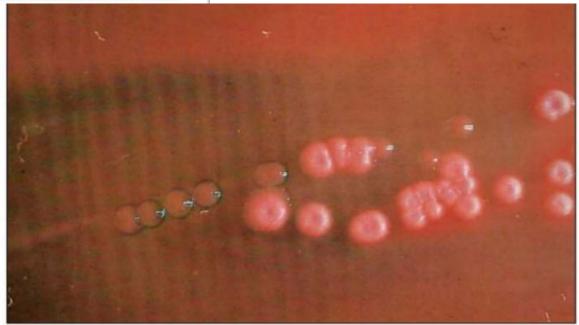


Figure IV-3. Overnight growth of *V. cholerae* on MacConkey agar appears as small (1- to 3 mm), translucent, colorless-to-light pink (lactose-negative) colonies.

Diagnosis

✓ Confirmed by Culture or PCR

A suspected case with Vibrio cholerae O1 or O139 confirmed by culture or PCR

In countries where cholera is not present or has been eliminated, the *Vibrio cholerae* O1 or O139 strain is demonstrated to be toxigenic

√ Rapid Tests

In areas with limited or no laboratory testing, the **Crystal® VC dipstick rapid test** can provide an early warning to public health officials that an outbreak of cholera is occurring *Sensitivity and specificity of this test is not optimal*. Recommended, **always be confirmed using traditional culture-based** methods suitable for the isolation and identification of V. cholerae

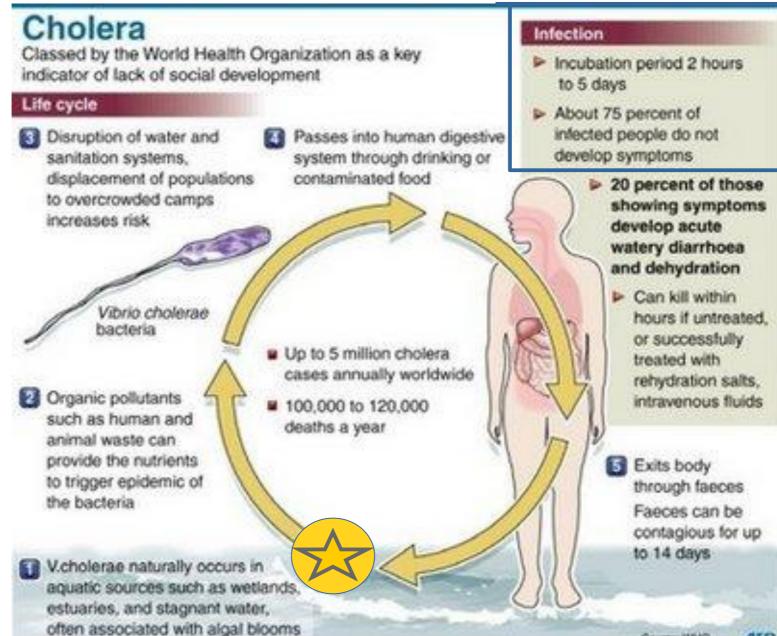
Table 1
Minimum inhibitory concentration (MIC) values of antibiotics for outbreak causing V. cholerae O1 biotype El Tor serotype Ogawa isolates in Kolkata, India.

Strains	MICs of antibiotics (μ g/mL)								
	Am	C	Tm	T	Er	Nx	Cp	Ak	Cfx
Resistant isolates	75-200	-	75-200	75-100	64-128	32-64	10	-	-
Sensitive isolates	2-4	2-8	-	4	2	4-8	0.66	2-4	2-8

Am = ampicillin, Ak = amikacin, C = chloramphenicol, Cfx = cefotaxime, Cp = ciprofloxacin, Er = erythromycin, Nx = nalidixic acid, Tm = trimethoprim, T = tetracycline.



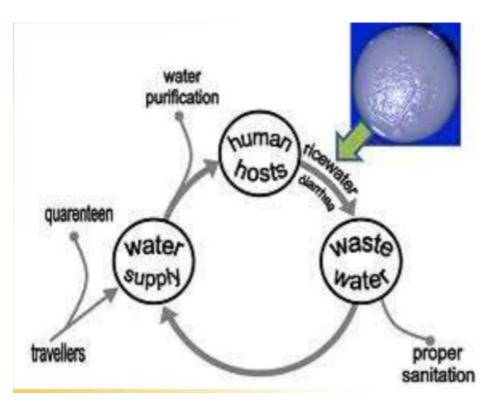
Life Cycle

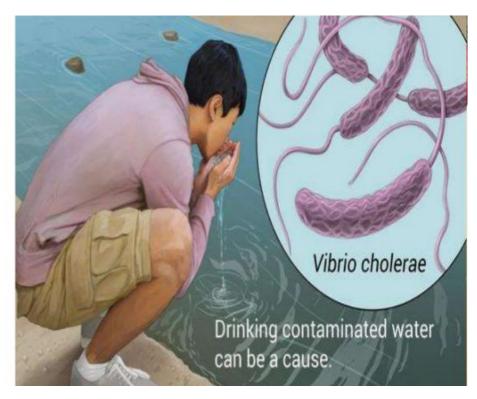


Source: WHO

AFP

Life Cycle

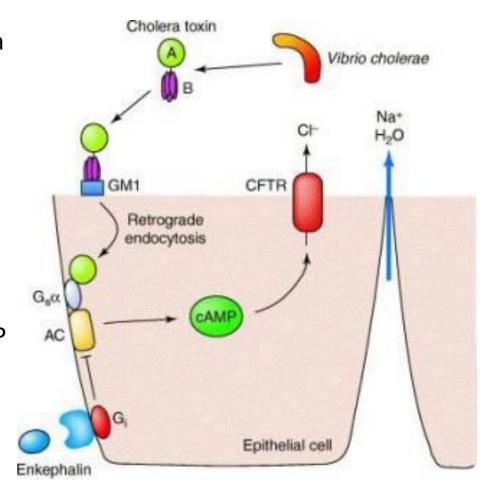




Incubation periods: 1-5 days

Pathophysiology - Biochemistry

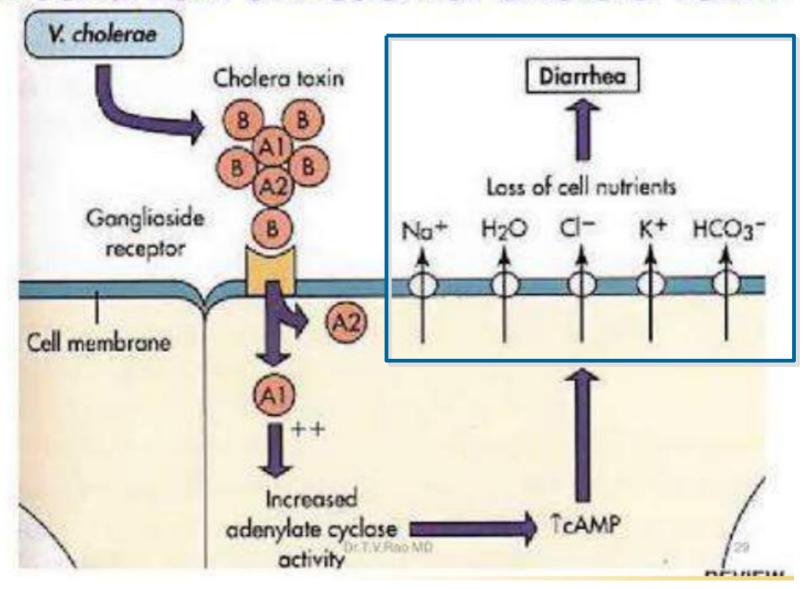
- O1 and O139 cholera bacteria strains secrete a toxin that contains Cholera Toxin Subunit B (CTB)
- CTB binds to Ganglioside GM1 on the cell membranes of enterocytes and the toxin is internalized
- The A1 domain of the toxin's A subunit is cleaved and travels to the cytosol
- A1 binds and activates Gsa, locking it in its GTP form
- The GTP form of Gsa stimulates adenylate cyclase (AC), which produces cyclic AMP (cAMP)



^{1.} Ganglioside GM1. (2018). U.S. National Library of Medicine.

^{2.} Lauer, S., et al (2002). Analysis of Cholera Toxin–Ganglioside Interactions by Flow Cytometry. Biochemistry. 41(6): 1742-1751

Mechanism of Action of Cholera Toxin



Mechanism → **Symptoms**

- cAMP binds to a transmembrane protein called Cystic Fibrosis
 Transmembrane Regulator, which releases chloride ions into the extracellular space
- Efflux of chloride ions triggers efflux of sodium and water as well, as cell tries to restore a balance in charge
- O Efflux of abnormal amounts of water and ions from the intestine induces watery diarrhea (which causes dehydration and a decrease in blood volume), cramps (due to electrolyte imbalance), hypovolemic shock (due to decreased blood volume), and vomiting in the infected individual



Signs & Symptoms

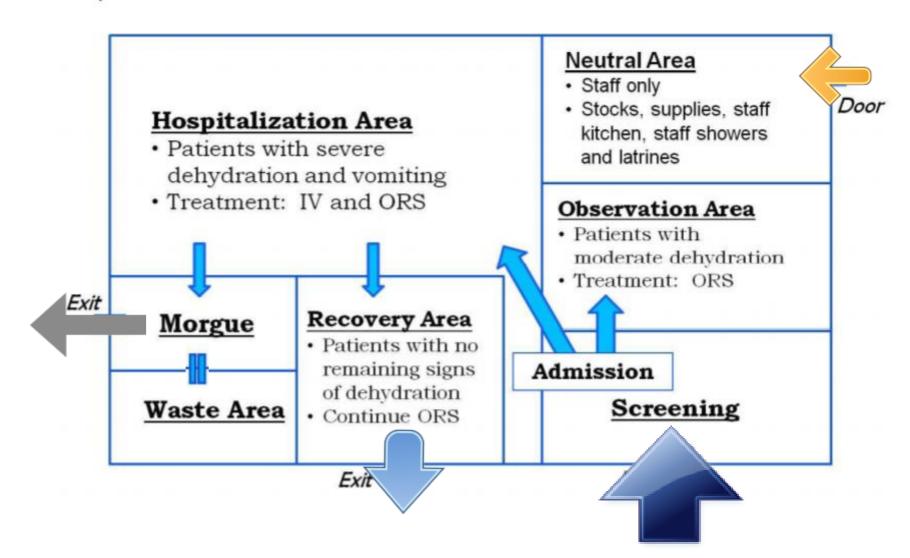
Symptoms: Watery diarrhoea, vomiting, thirst, dehydration, muscle cramps

Complications: Muscular pain, renal failure, pulmonary edema, cardiac arrhythrnias



Cholera Treatment Centers should be:

- 1. Where patients can easily access the facility
- Located away from water sources and functioning facilities (e.g. schools, markets, dispensaries)
- 3. Separated from other patient wards, if located within an existing healthcare facility
- 4. Easy to clean



Steps in the management of suspected cholera:

- Step 1. Assess for dehydration.
- Step 2. Rehydrate the patient, and monitor frequently. Then reassess hydration status.
- Step 3. Maintain hydration: replace ongoing fluid losses until diarrhoea stops.
- Step 4. Give an oral antibiotic to the patient with severe dehydration.
- Step 5. Feed the patient.

Cholera



Cholera Treatment

- Oral Rehydration Therapy (ORT)
- Timely administration of oral rehydration salts can reduce the fatality rate to less than 1%
- For severe dehydration and hypovolemic shock, **intravenous fluids** (ex. Ringer's lactate) and **electrolytes** are required
 - Zinc Treatment
 - Recommended for use in cases of pediatric diarrhea
 - Helps reduce the duration of diarrhea and volume of stool
 - Reduces cAMP concentration

STEP 1

Table 1: Assessment and classification of cholera patients for dehydration

Degree of Dehydration	No dehydration	Some Dehydration	Severe dehydration	
 Look at: General condition 	Well, alert	Restless, Irritable Fluid loss less than 10% of body weight	Lethargic or Unconscious / floppy Fluid loss more than 10% of body weight. Pulse: barely detectable.	
b. Eyes	Normal	Sunken	Very sunken and dry	
c. Tears	Present	Absent	Absent	
d. Mouth and tongue	Moist	Dry	Very dry	
e. Thirst	Not thirsty, drinks normally	Thirsty, drinks Eagerly	Drinks poorly or not able to drink	
2. Feel	Skin pinch Goes back quickly	Goes back slowly (within 2 seconds) Care must be taken for the elderly persons	• • •	
3. Decide	No sign of dehydration: (<5 percent) Plan A	The patient has two or more signs including at least one bold sign (5-10 percent) Plan B		
4. Treatment	ORS plus health Education, counseling and rehabilitation observe for 4 hours then discharge on ORS, recommended antibiotics and zinc for children under 5 years	recommended antibiotic and zinc for children under 5 years, vigorous monitoring at CTU.	Antibiotics, and zinc for children under 5 years and ORS as soon as able	



Minimal to No Dehydration – Plan A Treatment

ORS amounts to prevent dehydration (WHO recommendation)

Age	Amount of ORS after each loose stool	ORS quantity needed
Less than 24 months	50 to 100 ml	Enough for 500 ml/day (1 sachet)*
2 to 10 years	100 to 200 ml	Enough for 1000 ml/day (1 sachet)*
Over 10 years	as much as wanted	Enough for 2000 ml/day (2 sachets)*

^(*) ORS bags are usually for 1 litre. In some countries, ORS bags are conditioned for less than 1 litre.



Moderate dehydration – Plan B Treatment

ORS administration in the <u>first 4 hours</u> (generally 75ml x weight (kg))

- If unable to take oral, use NG tube
- Vomiting often ceases within 2-3 hours after dehydration has improved.
- If pt. is thirsty, administer more ORS
- Observe pt. to ensure required amount of ORS is administered
- If <u>after 4 hours</u>, pt. has signs of dehydration, use Plan C
- Monitor urine output

STEP 2

Rehydration protocol for Plan B

Age	<5months	6—11 Months	12- 23months	2-4 yrs	5-14 yrs	15+ years
Weight	<5kg	5-7kg	8-10kg	11- 15kg	16-29kg	30+
ORS ml	200-400	400- 600	600-800	800- 1200	1200-2200	2200- 4000
Zinc tablet 20 mg (tab)	1/2 tab for 10 days	1 tab for 10 days	1 tab for 10 days	1 tab for 10 days	Not recommended	
IΦET : Solvazinc tab eff 125mg Wilzin cap 50mg		Recommended for under- five children only				

M Imran Qadir et al. Zinc: Role in the management of diarrhea and cholera World J Clin Cases 2013 July 16; 1(4): 140-142

Severe dehydration – Plan C Treatment - Intravenous fluids



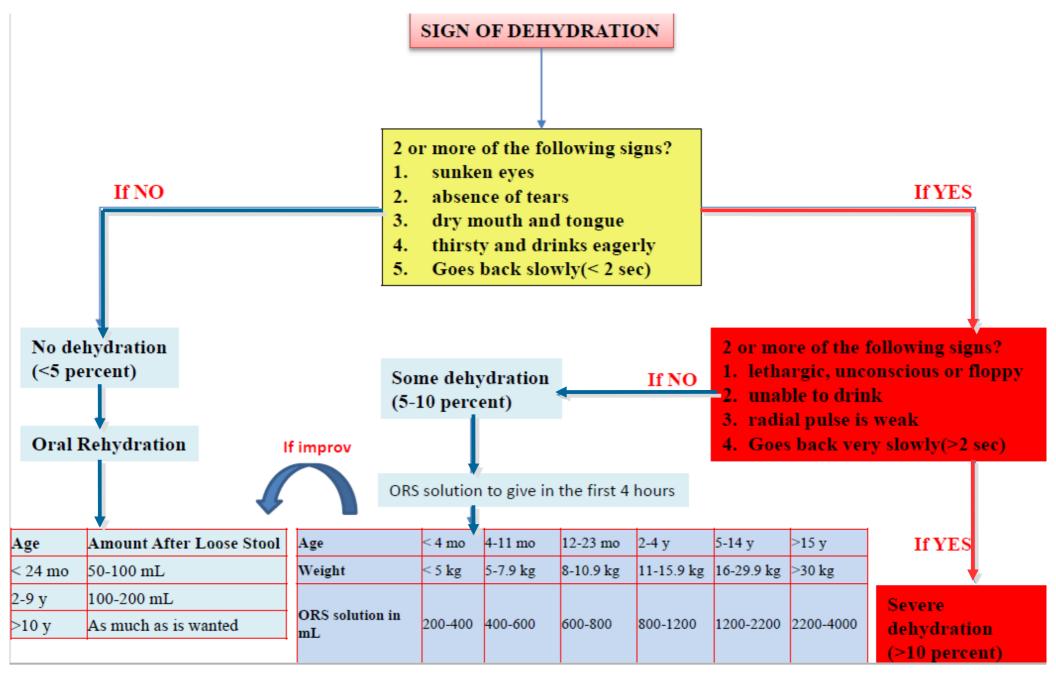


- -Large bore 18 gauge IV needles
- -Can use nasogastric tube if IV cannot be placed (20ml/kg 1st hour)

Source: CDC trainers of trainers presentation



Algorithm of Rehydration



Cholera Treatment

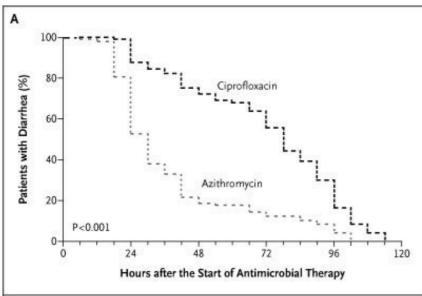
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- Zinc Treatment
 - Recommended for use in cases of pediatric diarrhea
 - Helps reduce the duration of diarrhea and volume of stool
 - Reduces cAMP concentration

Organization 21 for cholera patients with severe dehydration only Pan American Health Organization 22 Organization 22 International Centre for Diarrhoeal Disease Research, Bangladesh 23 Antibiotic treatment Frontieres 24 Antibiotic treatment gingle dose of the dehydration Single dose of the dehydration of the de	Organization	Recommendation	drug choice	choices	Drug choices for special populations
Health Organization 22 for cholera patients with moderate or severe dehydration International Centre for Diarrhoeal Disease Research, Bangladesh 23 Medicins Sans Frontieres 24 for cholera patients with moderate or severed dehydration Antibiotic treatment for severely Antibiotic treatment for cholera patients with some or severe dehydration Antibiotic treatment for cholera patients with some or severe dehydration Antibiotic treatment for severely Azithromycin 1gr* Ciprofloxacin 1gr* Azithromycin 1gr* Azithromycin 1gr* Cotrimoxazole Frythromycin recommended as first-line drugs for pregnant women and children Ciprofloxacin 1gr* Azithromycin 1gr* Cotrimoxazole Frythromycin 1gr* Cotrimoxazole Frythromycin 1gr* Azithromycin 1gr* Azi		for cholera patients with severe	300mg	,	12,5 mg/kr x 4 x 3d
Centre for Diarrhoeal Disease Research, Bangladesh 23 Medicins Sans Frontieres 24 for cholera patients with some or severe dehydration for cholera patients with some or severe dehydration 300mg single dose Azithromycin 1gr* Cotrimoxazole *single dose *single dose Totrimoxazole Azithromycin 1gr* Cotrimoxazole *single dose *single dose *single dose Totrimoxazole Erythromycin Cotrimoxazole	Health	for cholera patients with moderate or	300mg	Azithromycin 1gr*	recommended as first-line drugs for pregnant women and children Ciprofloxacin and doxycycline recommended as second-line drugs for
Frontieres ²⁴ for severely _{300mg} Cotrimoxazole	Centre for Diarrhoeal Disease Research,	for cholera patients with some or severe	300mg	Azithromycin 1gr* Cotrimoxazole	line drug for children and pregnant women 500mg x 4 x 3d
only Furazolidone http://www.cdc.gov/cholera/index.html		for severely dehydrated patients		Cotrimoxazole Chloramphenicol Furazolidone	

Single-Dose Azithromycin for the Treatment of Cholera in Adults



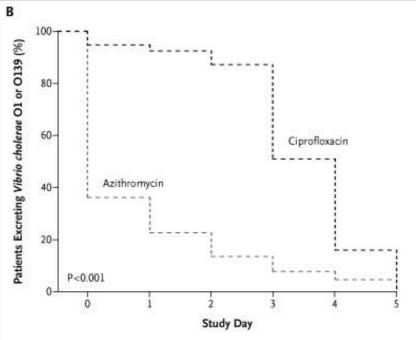


Table 3. Multivariate Logistic-Regression Analysis of Variables Predicting Clinical Failure of Therapy among 195 Patients with Cholera Treated with Azithromycin or Ciprofloxacin.*

Variable Odds Ratio (95% CI) P.

Variable	Odds Ratio (95% CI)	P Value
Ciprofloxacin treatment (vs. azithromycin)	10.2 (4.8–21.5)	<0.001
No. of stools before admission†	1.1 (1.0–1.1)	0.02
Stool volume during 4-hr observation period‡	1.1 (1.1–1.2)	0.002

- * Variables that were considered in the model were treatment received, the duration of illness before admission, the number of stools after the onset of illness and before admission, the weight on arrival, the change in weight between arrival and full hydration, the serum creatinine level, and the volume and numbers of stool during the observation period. CI denotes confidence interval.
- † For each additional stool before admission, the risk of clinical failure increased by an odds ratio of 1.1.
- ‡ For each additional milliliter of stool per kilogram of body weight per hour, the risk of clinical failure increased by 1.1.

Vibrio cholerae - Resistance

Many studies emphasize the critical problem of increasing antimicrobial resistance

- → In Bangladesh and elsewhere, has developed **substantial antimicrobial resistance to**:
- -Trimethoprim-sulfamethoxazole
- -Furazolidone
- -Tetracycline
- → Resistance is emerging to:
- -Ciprofloxacin
- -Azithromycin

http://www.cdc.gov/cholera/index.html

^{1.} Khan WA, Bennish Mlet al.. Comparison of single-dose azithromycin for childhood cholera: a randomized, double-blind trial. Lancet. 2002;360:1722-7.

^{2.} Saha D, Bennish Mlet al. . Single-dose azithromycin for the treatment of cholera in adults. N Engl J Med. 2006;354(23):2452-62





Cholera Therapy - What Not To Use

Mass chemoprophylaxis

- Mass administration of antibiotics to the community is NOT recommended in controlling a cholera outbreak as it may worsen the situation through false confidence.
- Nevertheless, chemoprophylaxis may be useful when a cholera outbreak occurs in a closed population, such as a prisons, mental health institutions, child care homes, boarding schools, barracks (police and army), IDP/Refugee camps.

OUTCOMES

More likely to have severe disease from cholera and suffer poor outcomes:

- → Individuals with achlorhydria
- → Blood type O
- → Chronic medical conditions
- Those without ready access to rehydration therapy and medical services

Prevention



Oral Cholera Vaccine Campaign For People 1 Year and Above

In Landslide and Flood Affected Communities

Dates: 1st Dose - 15th - 20thSeptember, 2017

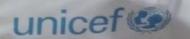
2nd Dose– 5th – 10th October, 2017

Protect yourself and your family from cholera! Take two doses of the vaccine, drink safe water and practice proper hygiene!









Prevention

- Oral Vaccines (offer incomplete protection)
 - Bivalent killed whole-cell vaccine (Sanchol) ASIA
 - contains serotypes of *V. cholerae* O1 and **O139** without the toxin B subunit
 - WC/rBS cholera vaccine (**Dukoral**) ______ Out of ASIA
 - contains serotypes of *V. cholerae* O1 and recombinant cholera τοχιη Β subunit
 - Lyophilized CVD 103-HgR (Vaxchora), a single-dose <u>live oral</u> cholera vaccine, approved by FDA in 2016 ~ (3 mo 80% protection)
- Drink and use safe water (water that is bottled, has been boiled, or has been treated with a chlorine product)
- Wash your hands often
- Cook your food (espesially seafood) well and keep it covered
- Clean up safely

Centers for Disease Control and Prevention (2018). Cholera - Vibrio cholerae Infection

CHOLERA OUTBREAK

ASSESSING THE OUTBREAK RESPONSE AND IMPROVING PREPAREDNESS First steps
managing
outbreak
of acute
iarrhoea

ET AIMS AT GUIDING YOU THROUGH

RY FIRST DAYS OF AN OUTBREAK

emergencies regarding acute diarrhoea exist:

nolera = acute watery diarrhoea

a dysentery = acute bloody diarrhoea

nsmitted by contaminated water, unsafe food, ands and vomit or stools of sick people.

ses of diarrhoea may produce severe illness tient, but will not produce outbreaks which an immediate threat to the community.

Direct Relief

CHOLERA

TREATMENT KIT

This leaflet is designed to

Identify kev issues relevan





A GLOBAL ROADMAP TO 2030

Figure 1: Theory of change of the Global Roadmap

Countries commit to implementation of evidencebased cholera control plans

Partners commit to providing oversight and technical expertise

Donors commit to supporting the global mechanism and/or the country plans

Axis 1 Early detection and response to contain outbreaks

Axis 2 Multi-sectoral interventions in cholera hotspots

Axis 3 Effective coordination at country and global levels

By 2030

- 20 countries eliminate cholera
- · No more catastrophic cholera outbreaks in fragile settings

90%

Reduction in cholera deaths





SUMMARY

- **Description:** Infectious disease caused by ingestion of contaminated food containing bacterium *Vibrio cholerae*
- 2 strains of Vibrio cholerae causes outbreak O1 and O139
- Symptoms (if any) include: vomiting, leg cramps and watery diarrhea

Treatment:

- ✓ Oral Rehydration Therapy is the first-line treatment
- ✓ Doxycycline or tetracycline for adults
- ✓ Azithromycin for children and pregnant women can be used as an adjunctive therapy
- **Prevention:** use **safe water** (boiled or water treated with a chemical disinfectant), cook your food well and eat it hot, wash your hands often, consider vaccination **(Sanchol** and **Dukoral** or **Vaxchora** [USA])
- Ending Cholera—A Global Roadmap to 2030 operationalises the new global strategy for cholera control at the country level and provides a concrete path toward a world in which cholera is no longer a threat to public health

