

"CHOLERA"

"The [death] toll due to cholera in Haiti has reached 4672, since the 1st case was detected in October 2010, an official report said." ProMED-mail 4.4.2011

A look at Cholera and the Role of Infectious Disease Medicine in Disaster Relief.

JAN 12TH, 2010 EARTHQUAKE: HAITI

- + 250,000 people dead
- + 300,000 injured
- + >1.3 million homeless

- + 2002: Haiti ranked 147th out of 147 countries surveyed in the Water Poverty Index.
- + 27% of the country basic sewerage
- + 70% of Haitian households either rudimentary or no toilets

Responding to Cholera in Post-Earthquake Haiti David A. Walton, M.D., M.P.H., and Louise C. Ivers, M.D., M.P.H. N Engl J Med 2011; 364:3-5

- + October 20th 60 cases of acute, watery diarrhea L'Hôpital de Saint Nicolas,
- + Stool -> national laboratory in Port-au-Prince
- + Within 48 hours, L'Hôpital de SN received >1500 additional patients with acute diarrhea.
- + Rapid spread along river route
- + Worsened after Hurricane in Nov

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WHO standard case definition of cholera:

- + Area with no known cholera
 - a patient aged five years or more develops severe dehydration or dies from acute watery diarrhea
- + Epidemic cholera area
 - a patient aged five years or more develops acute watery diarrhea, with or without vomiting

http://www.who.int/cholera/publications/cholera_vaccines_emergencies_2005.pdf

SOURCE OF OUTBREAK??

- + South East Asia
- Human activity
- + Vibrio cholerae O1, serotype Ogawa, biotype El Tor
 - increased virulence
 - enhanced ability to survive in the environment and in a human host
 - increased antibiotic resistance

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+ One week trip to Haiti in Dec 2011 – Jan 2012

- + 6 Night duties 7pm -> 8am
- + In-patient and admission care of cholera patients
- + Care of Pediatric tent!







CHOLERA: INTRODUCTION

According to the WHO:

- + ~3 5 million cholera cases / year
- + 100,000 120,000 deaths / year
- + ~80% of cases successfully treated with oral rehydration salts
- + Effective control measures require:
 - prevention
 - preparedness
 - response
- + Safe water and sanitation are critical
- "Oral cholera vaccines are considered an additional means to control cholera, but should not replace conventional control measures"

HISTORY OF CHOLERA

- + 1st cholera pandemic 1817 spread outside the Indian subcontinent -> along trade routes -> west as far as southern Russia
- + 2nd pandemic 1826 -> major European cities by early 1830s
- + 1831- UK: establishment of local Boards of Health and a "Cholera Gazette"
- + John Snow 1854
- + Three more pandemics, continuing up to 1925, involved Africa, Australia, Europe, and all the Americas
- + New York cholera epidemic first Board of Health in the USA 1866
- + 1st notifiable disease in USA
- + The causative agent, *Vibrio cholerae*, was not identified until 1884 in Kolkata during the fifth pandemic

7TH PANDEMIC

- + Current pandemic worldwide
- + Began Indonesia
- + Biotype of *V cholerae* serogroup O1 El Tor. (1905 -Indonesian pilgrims travelling to Mecca – quarantine station in village of El Tor, Egypt)
- + 1937 Indonesia
- + 1964 India
- + 1970 Africa, S Europe
- + 1991 S America
- + In 1992, a new non-O1 serogroup of *V cholerae*, designated O139 Bengal cholera outbreaks in India and Bangladesh.

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VIBRIO CHOLERAE - MICROBIOLIGY

- + Gram negative rod
- + Identified on biochemical tests
 - oxidase positive
- + >200 Serogroups based on O antigen
 - only 01 and 0139 cause pandemics
- + Other serogroups may cause diarrheal disease, wound infection or sepsis especially in patients with liver disease & in immunocompromised patients
- + Rapid ID by microscopy darting organisms
 - movement inhibited by antisera
- + Growth on TCBS (thiosulfate-citrate-bile salts-sucrose) yellow colonies raised centre

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CLASSIFICATION PATHOGENIC STRAINS OF V. CHOLERAE

Serogroup 01

Serogroup 0139

India / Bangledesh

Oct 1992

Biotype Classical

1st 6 Pandemics

Biotype El Tor

7th Pandemic

Serogroup 01 can also be divided into 3 serotypes: Ogawa, Inaba and Hikojima according to somatic antigens

- + 01 and O139 serotypes have different ribotypes
- + Molecular studies show only certain clonal ribotyps responsible for outbreaks

EPIDEMIOLOGY

- + Water/Food Bourne
- + Reservoir in shellfish and plankton
- + Seasonality of infection

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- + Rice-water stools contain 10¹¹ to 10¹² *V. cholerae* organisms per liter.
- + 50% of household contacts of a patient who is the index case in Bangladesh develop diarrhea about 2 days after the index case occurs

Antibiotics for Both Moderate and Severe Cholera, Eric J. Nelson, M.D., Ph.D., Danielle S. Nelson, M.D., M.P.H., Mohammed A. Salam, M.B., B.S., and David A. Sack, M.D. N Engl J Med 2011; 364:5-7

FACTORS AFFECTING INFECTION

- + Ratio of cases to infections ranges from 1:3 to 1:100*
- + Local intestinal immunity
 - from previous natural exposure or vaccination
- + Size of inoculum ingested
- + Gastric-acid barrier
- + Patient's blood group
 - blood group O higher risk
- + A high infectious dose (10⁸ bacteria)->severe cholera in healthy volunteers
- + Lower dose (10⁵) with antacids

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*Ratio of infected symptomatic : asymptomatic varied classical cholera ~ 50:50, El Tor ~ 1:20-100

Infectious dose differs by vehicle – higher if water, lower dose if food

Mandell, Principles and Practices of Infectious Disease

PATHOGENESIS

- + Pass through stomach
- + Colonization of upper intestine
 - by fimbriae
 - virulence gene tcpA codes for toxin coregulated pilus extending from the cell wall-> attach to receptors on the mucosa
 - bacterium's motility -> penetrate mucous
- + Multiply
 - Concentrations of vibrios on the mucosal surface rapidly increase to 10⁷ or 10⁸ cells / g.
- + Effectively deliver toxin to mucosal surface

VIRULENCE FACTORS

- + ctx genetic element
 - genome of a lysogenic bacteriophage designated ctx
 - carries the genes encoding cholera toxin
- + vibrio pathogenicity island (VPI)
 - + carries genes for the pilus colonisation factor TCP.
 - + facilitates microcolony formation via pilus-mediated bacterial interactions and perhaps direct attachment to the intestinal brush border
- + horizontal gene transfer may lead to the development of new epidemic strains.
- + Multiple virulence genes regulated by environmental conditions

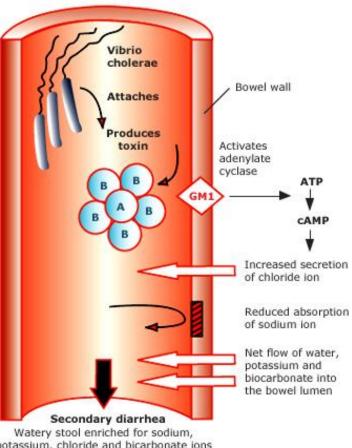
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TOXIN

- ➤ Virulence genes ctxA, ctxB -> cholera toxin subunits A & B

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- ➤ B subunits bind the holotoxin to the GM1 ganglioside receptors in the small-intestinal mucosa
- > A subunit -> cell -> Activates adenylate cyclase
- Increase c-AMP
 - > chloride secretion in the crypt cells
 - inhibition of neutral sodium chloride absorption in the villus cells
- Massive outpouring of fluid -> the small intestine
- Volume secreted > normal absorptive capacity of bowel
 - > PROFUSE WATERY DIARRHEA

Pathophysiology of vibrio cholerae infection



potassium, chloride and bicarbonate ions

Schematic representations of the mechanisms involved in diarrhea production by Vibrio cholerae.

Modified from Butterton, JR, Calderwood, SB. Vibrio cholerae O1. In: Infections of the Gastrointestinal Tract, Blaser, MJ, Smith, PD, Ravdin, LI, et al (Eds), Raven Press, New York, 1995, p. 649. http://www.lww.com



- Loss of blood volume -> hypotension and shock
- + Loss of Bicarbonate and Potassium -> metabolic acidosis and hypokalemia
- + Highly infectious stools
 - Contamination of food and water
 - Environmental seeding

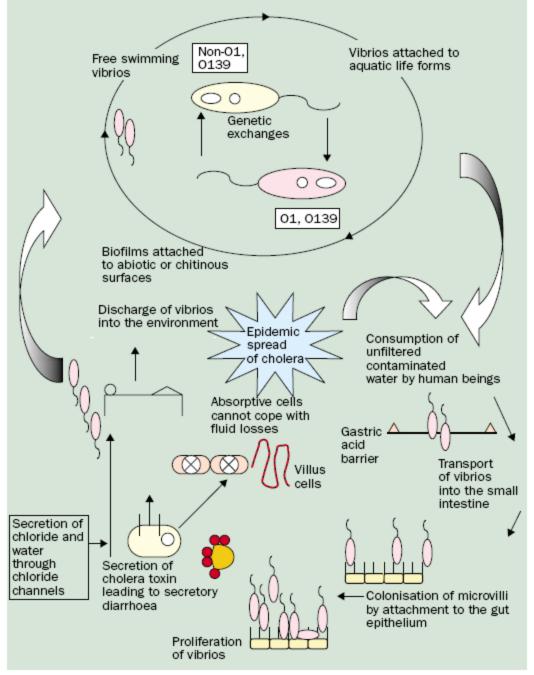


Figure 4: Life cycle of V cholerae involves both environmental and human segments, which sometimes intersect

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CLINICAL PRESENTATION

http://bcove.me/tpzkcp1n



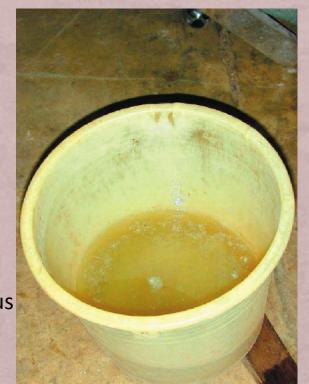
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CLINICAL PRESENTATION

- + Incubation 18 hours to 5 days
- + May be asymptomatic / mild diarrhea
- + Painless severe watery diarrhea (500-1000 ml/hr)
- + Vomiting
- + Cholera "sicca" abdominal distension and ileus
- + Signs of dehydration
- + < 5% have fever

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EXPECTED LABORATORY FINDINGS & COMPLICATIONS

- + Increased packed cell volume and protein
- + Prerenal azotemia
- + Metabolic acidosis with high anion gap (lactate), normal/low potassium, normal/low sodium
- + High calcium / magnesium
- + High white cell count in severe disease
- + Acute renal failure
- + Hypoglycemia / seizures / fever / altered mental status more common in children
- + Electrolyte imbalance Hypokalemia
- + Fetal loss ~ 50%

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TREATMENT

- Assess dehydration
- + Rapidly rehydrate -intravenous Ringer's solution /ORS
- + Monitor stool output
- + Monitor hydration
- Monitor severity of purging
- + Maintain hydration
- + Oral antibiotic (eg, doxycycline) to dehydrated patients as soon as vomiting stops
- + Provide food as soon as patient is able to eat

WHO guidelines for assessment of dehydration

	Predicted degree of dehydration						
Clinical feature	None (<5 percent)	Some dehydration (5-10 percent)	Severe dehydration (>10 percent)				
General appearance	Well, alert	Restless, irritable	Lethargic or unconscious				
Eyes	Normal	Sunken	Sunken				
Thirst	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly or unable to drink				
Skin pinch	Goes back quickly	Goes back slowly	Goes back very slowly				
Estimated fluid deficit	<50 mL/kg	50-100 mL/kg	>100 mL/kg				

Data from: World Health Organization. The treatment of diarrhea: A manual for physicians and other senior health workers, 4th revision. WHO/FCH/CAH/05.1. World Health Organization, Geneva 2005. (Available at http://whqlibdoc.who.int/publications/2005/9241593180.pdf).



Physical findings of volume depletion in infants and children

Finding	Mild (3-5 percent)	Moderate (6-9 percent)	Severe (≥10 percent)
Pulse	Full, normal rate	Rapid	Rapid and weak OR absent
Systolic pressure	Normal	Normal to low	Low
Respirations	Normal	Deep, rate may be increased	Deep, tachypnea OR decreased to absent
Buccal mucosa	Tacky or slightly dry	Dry	Parched
Anterior fontanelle	Normal	Sunken	Markedly sunken
Eyes	Normal	Sunken	Markedly sunken
Skin turgor	Normal	Reduced	Tenting
Skin	Normal	Cool	Cool, mottled, acrocyanosis
Urine output	Normal or mildly reduced	Markedly reduced	Anuria
Systemic signs	Increased thirst	Listlessness, irritability	Grunting, lethargy, coma

Composition of oral rehydration solutions (ORS) and commonly used beverages

	Carbohydrate		mEq/L	Osmolarity		
	(g/L)	Sodium	Potassium	Base (HCO3-)	(mOSM/kg H2O)	
Oral rehydration solutions						
CeraLyte®	40	70	20	10	235	
Enfalyte®	30	50	25	30	200	
Pedialyte®	25	45	20	30	250	
Rehydralyte®	25	75	20	30	310	
WHO (1975)	20	90	30	30	310	
WHO (2002)	13.5	75	20	30	245	
Commonly Used	Beverages (not app	ropriate f	or repletion t	therapy)		
Apple juice	100-150	3	20	0	700	
Chicken broth	0	250	5	0	450	
Colas	100-150	2	0.1	13	550	
Gatorade®	45	20	3	3	330	
Ginger Ale	90	3.5	0.1	3.6	565	
Tea	0	0	0	0	5	

Composition (mEq/L) of common solutions used for rehydration

Route	Solution	Na+	K+	Cl-	нсоз-	Citrate	Ca++	Glucose/carbohydrate
Intravenous	Normal saline	154	-	154	-	-	-	-
	Ringer's Lactate	130	4	111	28	-	3	-
	Ringer's Lactate + 5 percent dextrose	130	4	109	28	-	3	278
	Cholera saline ("Dhaka solution")	133	13	98	48	-	-	140
Oral	Standard ORS	90	20	80	-	10	-	111
	Hypo-osmolar ORS	75	20	65	-	10	-	75
	ReSoMal* (Reduced Osmolarity ORS for Malnourished Children)	45	40	76	-	7	-	125

ORS is reviewed in detail separately. (See "Oral rehydration therapy").

ORS: oral rehydration solution(s).

* Also contains Mg 6 mmol/L, Zn 300 umol/L, Cu 45 umol/L.

Data from: World Health Organization. The treatment of diarrhea: A manual for physicians and other senior health workers -4th revision. World Health Organization, Geneva 2005. Available at:

http://whqlibdoc.who.int/publications/2005/9241593180.pdf.

Fluid	Sodium (mmol/L)	Chloride (mmol/L)	Potassium (mmol/L)	Bicarbonate (mmol/L)	Carbohydrate (g/L)	Osmolality (mmol/L)
Cholera stool						
Adults	130	100	20	44		
Children	100	90	33	30		
ors						
Glucose (WHO)	75	65	20	10*	13.5†	245
Rice	75	65	20	10*	30-50‡	About 180
Intravenous fluids						
Lactate Ringer's	130	109	4	28§		271
Dhaka solution	133	154	13	48		292
Normal saline	154	154	0	o¨		308

^{*}Trisodium citrate (10 mmol/L) is generally used rather than bicarbonate. †Glucose 13·5 g/L (75 mmol/L). ‡30–50 g rice contains about 30 mmol/L glucose depending on degree of hydrolysis. §Base is lactate. ||Base is acetate.

Table 2: Composition of cholera stools and electrolyte rehydration solutions used to replace stool losses

THE PRINCIPLES OF REHYDRATION THERAPY

- + Rapid replacement of fluid deficits
- + Correction of the metabolic acidosis
- + Correction of potassium deficiency
- + Replacement of continuing fluid losses
- + "Because of the acidosis, the serum potassium concentration may be normal or even high, so the potassium deficiency may not be apparent. As the acidosis is corrected, the serum potassium concentration will fall to dangerously low values unless additional potassium is provided."

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Patient Name/Nom:Date/ Date:Age:kg:							
Admission: LR	bolus: 30mL/kg		Physical Exam/Examen Physique Alert/Lethargic/Unresponsive				
Hour/Heure	Intake/	C	output/ Expulsio	n	Reveillé/Lethargique/Pas de réponse		
	Réhydratation				Lung Sounds: Clear or Crackling Tones de Poumons: Claires ou Grinçants		
	IV and Oral (mL)	Vomit/	Diarrhea/ <i>Diarrhé</i>	Urine/ <i>Urine</i>	↑ Respiratory Rate		
		Vomi			↑ Taux de Respiration		
EIRST 4 HR PLAN	/ Premiere 4h <i>Plan d</i>	'évaluation -	MD Orders/Les	ordinances d	e Docteur: Sinutes or/ou 60 minutes (circle		
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<i>r</i>	0.0.0	2	*	\	Bullion (Soup as tol		
AM/8	M#96R 30	70			Doctor Josephan		

	Intake/		Output/ Expulsion	on	Physical Exam/Examen Physique Alert/Lethargic/Unresponsive Reveillé/Lethargique/Pas de réponse					
Hour/Heure	Réhydratation IV and Oral (mL)	Vomit/ <i>Vomi</i>	Diarrhea/ Diarrhé	Urine/ Urine	Lung Sounds: Clear or Crackling Tones de Poumons: Claires ou Grinçants ↑ Respiratory Rate ↑ Taux de Respiration					
Reassess 6 hr Plan <i>/Plan de Reévaluation</i> — Doctors Orders/ <i>Les ordinances de Docteur</i> :										
Adjusted IV Rate: LR 260 mL/hr (60 gtt/min) xh Potassium: Peds/L'enfants: Potassium 1 mEq/kg PO BID Adult/Adulte: Potassium 60 mEq PO BID or if vomiting change IV fluids to / S'il vomi, le changez pour: LR with/avec KCl 10mmol/LmL/hr (gtt/min) xh										
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ROLE OF ANTIBIOTICS

- + Effective (depending on S/T):
 - Doxycycline
 - Ciprofloxacin
 - Azithromycin
- + Epidemic strain in Haiti:
 - Susceptible to tetracycline and azithromycin
 - Resistant to nalidixic acid, sulfisoxazole, and trimethoprim sulfamethoxazole

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USEFULLNESS OF ANTIBIOTICS

With antibiotics

- + Decreased purging rate by ~50%
- + Shorter illness by ~ 50%,
- + Shorter excretion of Vibrio cholerae in the stool to 1 or 2 days
- + Quicker recovery
- Less nursing care required
- Discharge home earlier

Without effective antibiotics

+ Excrete *V. cholerae* for 5 or more days

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- + WHO only recommends antibiotics in severe cholera (>10% dehydration)
- + Antibiotics for moderate cases (see prev. slide)
- + Antibiotic prophylaxis of contacts
 - not recommended
- + Timing of antibiotic
 - after vomiting stops

N Engl J Med 2011; 364:5-7

- + Zinc replacement especially in children
 - 30mg/day -> 12% decrease in duration and 11% decrease in stool volume

Mandell, Principles and Practices of Infectious Disease

ANTIBIOTIC RESISTANCE

- + *V cholerae O1* conjugative-plasmid mediated multiply antibiotic-resistant (including to tetracycline) (MARV)
 - Spatial and temporal fluctuatoins in drug resistance depending on antibiotic selection pressure
 - Conjugative plasmids
 - Conjugative transposons
 - Integrons (group of gene expression elements incorporate open reading frames (gene cassettes) - convert them to functional genes
- + V cholerae 0139
 - Novel conjugative, self-transmissible, chromosomally integrating SXT element
 - Conferred resistance to sulphamethoxazole, trimethoprim, chloramphenicol, and low levels of streptomycin
- + gyrA and parC, efflux -quinolone resistance

VACCINATION

- + "Dukoral" WHO prequalified
 - consists of killed V cholerae organisms along with the cholera B subunit
 - stimulates both antibacterial and antitoxic immunity
 - Give in 150ml of safe water
 - two doses 1–6 weeks apart
 - recommended for use in refugee settings at risk of cholera
- + Licensed >60 countries
- + Short-term protection 85–90% against V. cholerae O1
 - all age groups
 - 4–6 months following immunization.
- + "Shanchol" pending WHO prequalification
 - longer-term protection against V. cholerae O1 and O139 in children under five years of age.
 - doesn't contain B subunit of toxin
- + Both vaccines are administered in two doses given between seven days and six weeks apart.

http://www.who.int/mediacentre/factsheets/fs107/en/index.html

CONTROL

- + Safe water supply
- + Sanitation
- + Food safety
- + Health education / Media
 - importance of purifying water and seafood
 - washing hands after defecation and before food preparation
 - recognition of the signs of cholera
 - locations of treatment

DEAD BODIES

- + Individuals handling human remains risks:
 - Hepatitis B and C.
 - HIV.
 - Tuberculosis.
 - Diarrheal disease.
- + Graveyards 30m from groundwater sources for drinking water
- + Bottom of grave -1.5m above the water table with a 0.7m unsaturated zone. Surface water from graveyards must not enter inhabited areas.
- + Universal precautions for blood and body fluids
- + Correct use and disposal of gloves
- + Use of body bags
- + Hand washing with soap after handling bodies and before eating
- + Disinfection of vehicles and equipment
- + Bodies do not need to be disinfected before disposal (except in case of cholera, shigellosis, or hemorrhagic fever)
- + Vaccinate workers against hepatitis B"

World Health Organization: http://www.who.int/hac/techguidance/ems/flood_cds/en/index1.html
http://www.paho.org/english/dd/ped/DeadBodiesFieldManual.pdf
CDC: http://www.cdc.gov/ncidod/eid/13/1/1-T.htm

BAD NEWS

+ The onset of the rainy season is leading to a new upsurge in Cholera cases in Haiti

INTERNATIONAL DISASTER RELIEF

In 2010:

- + 373 natural disasters
- + ~300,000 deaths
- + ~207 million affected
- + Cost ~US\$110 billion in economic losses

Ten critical emergency relief measures

- 1. Rapidly assess the health status of the affected population
- 2. Establish disease surveillance and a health information system
- 3. Immunize all children aged 6 months to 5 years against measles and provide vitamin A to those with malnutrition
- 4. Institute diarrhea control programmes
- 5. Provide elementary sanitation and clean water
- 6. Provide adequate shelters, clothes, and blankets
- 7. Ensure at least 1900 kcal of food per person per day
- 8. Establish curative services with standard treatment protocols based on essential drug lists that provide basic coverage to entire community
- 9. Organize human resources to ensure one community health expert per 1000 population
- 10. Coordinate activities of local authorities, national agencies, international agencies, and non-governmental organizations

EK Noji. ABC of Conflict and Disaster. Public Health in the aftermath of disasters. BMJ 2005;330:1379–81 What accounts for 60-95% of the mortality among internally displaced persons?

60 – 95% OF MORTALITY AMONG DISPLACED PERSONS:

- 1. Malnutrition
- 2. Diarrheal diseases
- 3. Malaria
- 4. Measles
- 5. Acute respiratory infections

EK Noji. ABC of Conflict and Disaster. Public Health in the aftermath of disasters. *BMJ* 2005;330:1379–81

FACTORS INFLUENCING DISEASE TRANSMISSION AFTER DISASTERS

- + Pre-existing disease
 - E.g. cholera, measles, typhus
- + Immunization rates
- + Concentration of population
- + Damage to utilities, contamination of water or food
- + Increased disease transmission by vectors
 - E.g. breeding sites
- + Personal hygiene,
- + Interruption of control programmes

FACTORS CONTRIBUTING TO INCREASED RISK OF INFECTION IN DISASTERS

- + Destruction of water sanitation facilities
 - if present
- + Destruction of sewage systems
- + Displacement of populations
- + Disruption of local healthcare facilities

ROLE OF INFECTIOUS DISEASE SPECIALISTS

- + Acute patient care
- + Prevention
- + Control
- + Research
- + ...

+ "...disaster preparedness and prevention programmes remain in the domain of assumptions instead of evidence"