Cholera in pregnancy

Iza Ciglenecki, Médecins Sans Frontières

GTFCC Case management meeting, 2018

MEDECINS SANS FRONTIERES

Cholera treatment center, Sierra Leone

Cholera treatment center, 400 beds
Cap Haitian, Haiti 2010

CHOLERA, AND ITS RELATION TO PREGNANCY AND CHILD-BIRTH.

By Carl Proegler, M.D., Aurora, Ill.

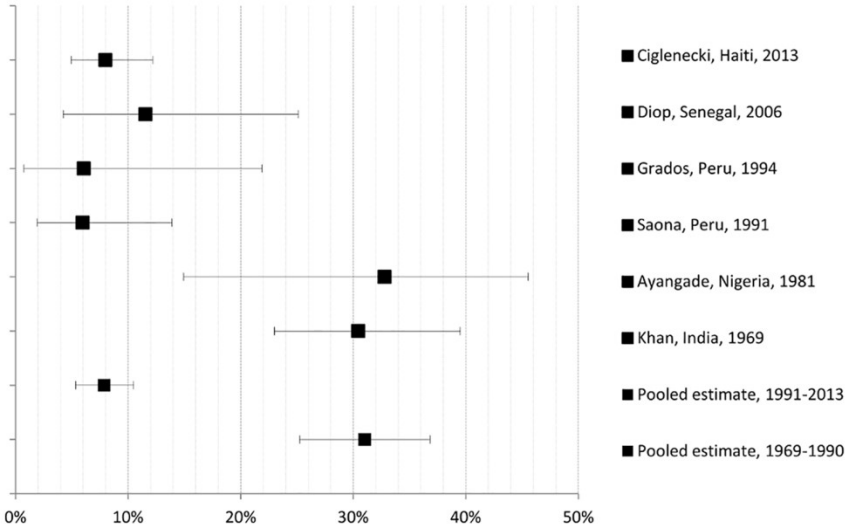
As we may expect the approach of cholera again, it will not be without interest to a good many physicians, who have not had occasion, perhaps, to study that fatal disease, for me to endeavor to give some of my experience. It was during an epidemic (collapse). There is nothing abnormal in these deaths compared with cases of non-complicated cholera. Cramps which can be noticed with other non-complicated cases occurred rather frequently with pregnant women, but were probably due to uræmia.

We have seen that pregnancy does not modify the causation of cholera; let us now see how much pregnancy and child-birth will be influenced by cholera.

Proegler C (1871). Cholera, and its relation to pregnancy and child-birth. Boston Med Surg J 85: 200–202.

Effect of cholera on pregnancy: fœtal deaths

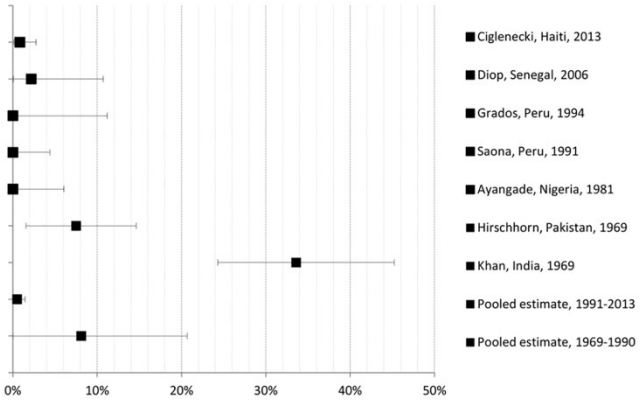
Fetal death rate with maternal cholera: study and pooled estimates per 100 pregnancies with 95% CI



- 1991-2013: 7.9%, 95% CI 5.3–10.4
- 1969–1990: 31.0%, 95% CI 25.2–36.6

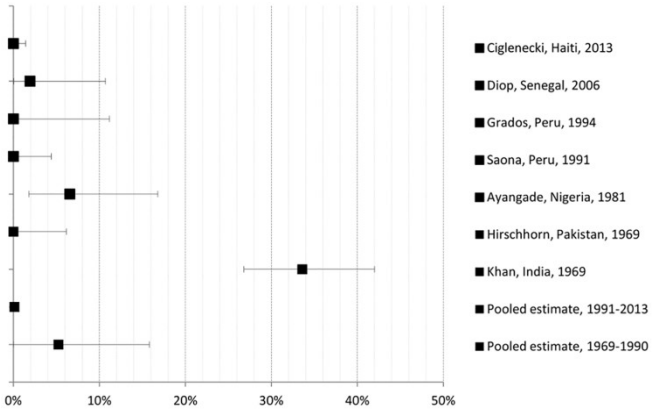
Tran TN et al. Plos One 2015

Effect of cholera on pregnancy: neonatal and maternal mortality



Neonatal death rate : study and pooled estimates per 100 pregnancies with 95% CI

- No evidence of increased risk



Maternal death rate with maternal cholera: study and pooled estimates per 100 pregnancies with 95% CI

- No evidence of increased risk

Tran TN et al. Plos One 2015

Background: Why?

- Not due to cholera toxin itself
- Probable haemodynamic and metabolic cause
  - Maternal dehydration and hypovolemia – foetal hypovolemia and hypoxia
  - Maternal acidosis – foetal acidosis
- + difficult assessment of dehydration in pregnancy (physiological hypervolemia)

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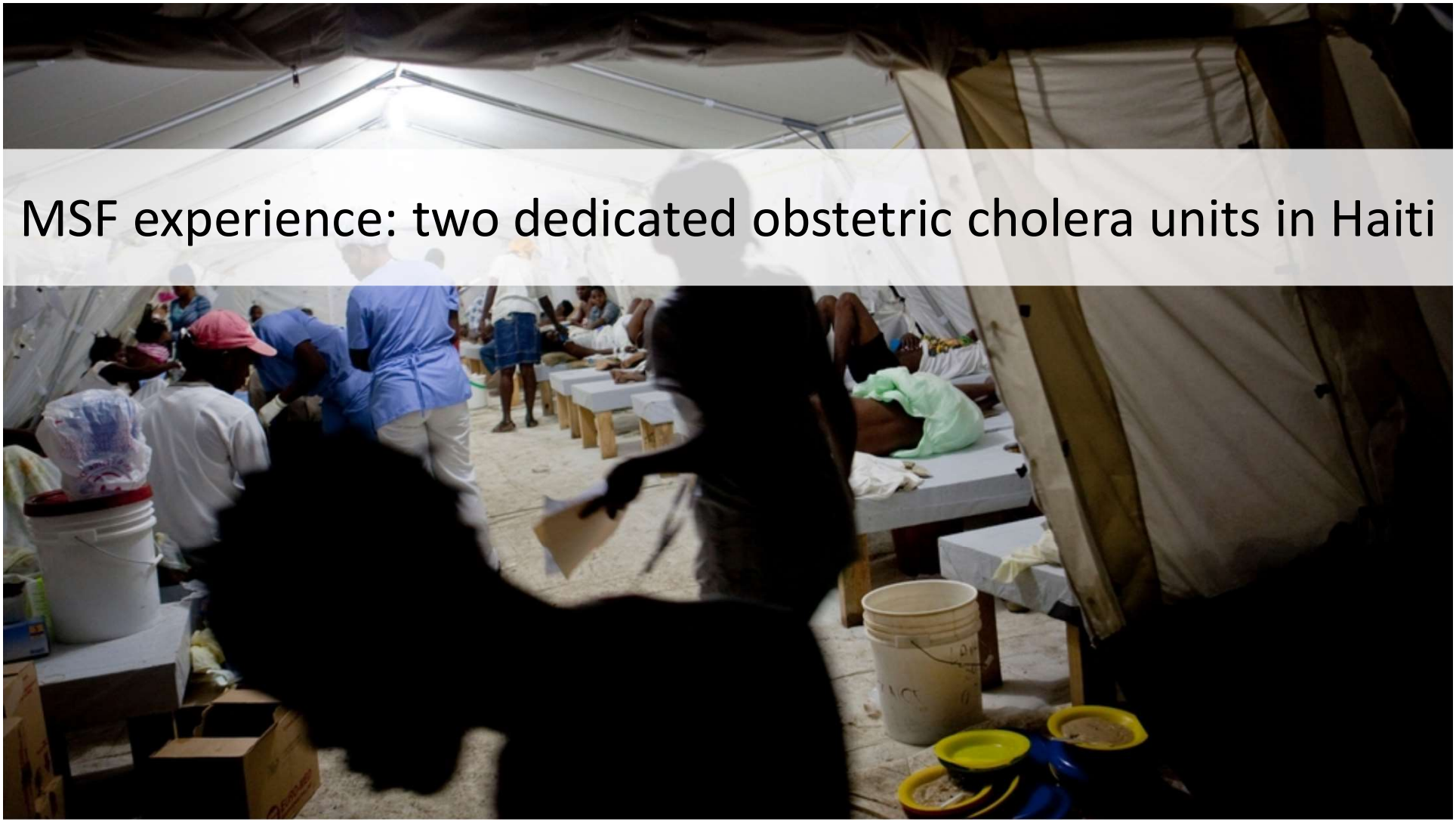
MSF experience: two dedicated obstetric cholera units in Haiti



Cholera: Haiti

- Population: 10M
- Cholera since 2010: >800’000 reported cases & >9700 deaths
- In 2018: still hundreds cases/week…

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Specialized cholera treatment unit in Leogane

- Within general hospital, easy access to obstetric and neonatal care
- All pregnant women with cholera admitted
- Adapted protocol:

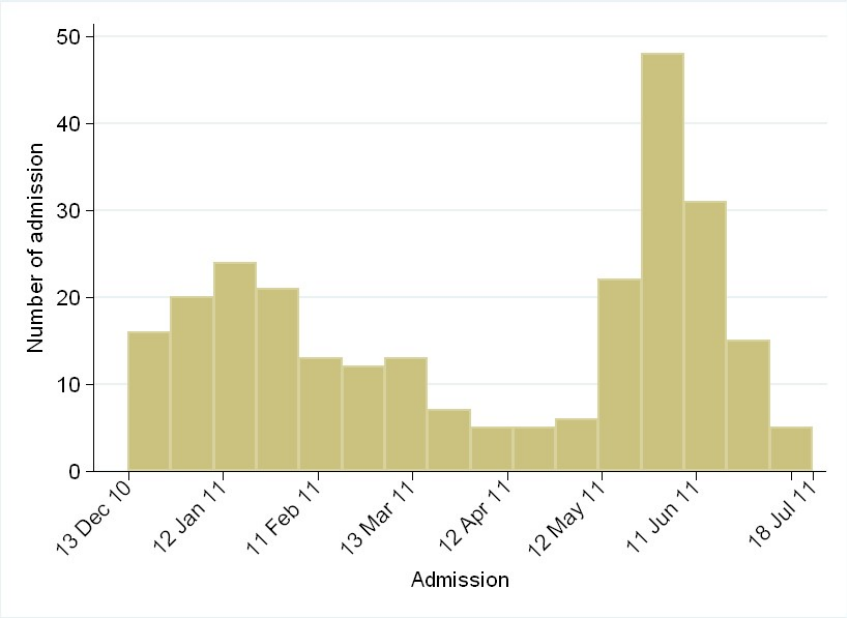
Clinical protocol Leogane

- Plan A:
  - maintenance fluids only (2 l of IV Ringer lactate per day)
  - ORS: 250 ml/loose stool (or RL if vomiting)
- Plan B:
  - RL: 75 ml/kg in first 4 hours, then maintenance
  - ORS: same as A
- Plan C:
  - RL: same as WHO standard, then maintenance
  - ORS: same as A

- Hypoglycemia
  - Dextrose, 50 ml of 50% bolus for all
  - Dextrose, 50 ml of 50% in each liter of RL if no ORS
- Antibiotic
  - Erythromycin for all
- Monitoring:
  - BP, pulse
  - Glucose
  - Foetus: doppler
- Birth:
  - Vulva wash with 0.05% chlorine solution, rinse with water
  - Wash newborn with 0.05% chlorine solution

Patient's characteristics

264 women admitted Dec 2010 - July 2011



Ciglenecki et al, Plos NTD 2012

	Number (%)	Mean (SD)	Median (min - max)
Age		26.8 (6.2)	26 (16-43)
>20	25 (10%)		
20--35	199 (76%)		
>35	37 (14%)		
Trimester (week)		23.8 (8.8)	23 (5-40)
First	38 (14%)		
Second	134 (51%)		
Third	90 (34%)		
Delay to treatment		1.3 (1.5)	1 (0-8)
<=24 hours	93 (35%)		
> 24 hours	162 (62%)		
Rehydration plan at admission			
A	136 (52%)		
B	110 (42%)		
C	16 (6%)		
Vomiting (Nb)		5.5 (11.4)	1 (0-86)
No	100 (38%)		
1-10	104 (40%)		
>10	38 (14%)		
Stools (Nb)		56.3 (57.7)	35 (0-311)
0-30	102 (39%)		
>30	142 (54%)		
Length of stay (days)		3.0 (2.0)	3 (0-10)
<2	59 (22%)		
2-4	128 (49%)		
>5	53 (20%)		

Outcomes

- No maternal deaths
- 227 (86%) discharged with preserved pregnancy
- 15 deliveries – live babies (6%)
  - 5 admitted to ICU
  - 2 neonatal deaths
- 21 foetal deaths (8%)
  - 11 (53%) before admission

Ciglenecki et al, Plos NTD 2012

Risk factors for fœtal death, Leogane

	Positive outcome N = 242	Foetal death N = 21	RR (95% CI)	RR adjusted (95% CI)
Age				
>20	21 (9%)	4 (19%)	1	
20--35	184 (76%)	15 (71%)	0.56 (0.26-1.23)	
>35	35 (14%)	2 (10%)	0.45 (0.14-1.43)	
Trimester				
First	35 (14%)	3 (14%)	1	
Second	124 (51%)	10 (48%)	0.94 (0.27-3.26)	
Third	82 (34%)	8 (38%)	1.12 (0.31-4.02)	
Delay to treatment				
<=24 hours	84 (35%)	9 (43%)	1	
> 24 hours	151 (62%)	11 (52%)	0.70 (0.30-1.63)	
Dehydration at admission				
None	132 (55%)	4 (19%)	1	1
Moderate	99 (41%)	11 (52%)	3.4 (1.11-10.38)	2.76 (0.77-9.98)
Severe	10 (4%)	6 (29%)	12.75 (4.012-40.44)	9.44 (2.5-35.28)
Vomiting (Nb)				
No	98 (41%)	2 (10%)	1	1
1-10	94 (39%)	10 (47%)	4.81 (1.08-21.40)	3.16 (0.70-14.26)
>10	31 (13%)	7 (33%)	9.21 (2.00-42.38)	5.05 (1.07-23.83)

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Specialized cholera treatment unit in Port au Prince

3 groups:

- Sep 2011 – April 201: pregnant women treated within general CTC
- April 2012 – June 2013: specialized unit
- June 2013 – Dec 2014: adapted treatment protocol introduced:
  - More agressive rehydration (systematic i.v.)
  - Systematic antibiotic (azytromicine)
  - Close fœtal monitoring (doppler)

Schillberg et al, EID 2016

Clinical protocol Port au Prince

- Plan A:
  - RL: 1000ml over 5 h + ORS: 500–750ml per h
- Plan B:
  - RL: 1000ml over 2.5 h + ORS: 750–1000ml per h
- Plan C
  - RL: 1000ml over 15 min, repeat if pulse remains weak, then 1000ml over 45 min, then 1000ml over 2.5 h, then 1000ml over 5 h (4L over 8.5 hr)
  - ORS: 250ml over 15 min
- Azithromycin 1g single dose
- D/W 50% 20ml in 1000ml RL over 2 h for hypokalemia
- APE: 20–60mg furosemide depending on edema, repeat after 6h if required then reduce to 20mg each morning until edema stabilized
- Fetal HR monitoring every 15-60 minutes (depending on presence and stage of labor)
- Dexamethasone for pregnancy weeks 24-36
- Birth:
  - Vulva wash with 0.05% chlorine solution, rinse with water
  - Wash newborn with 0.05% chlorine solution
  - Keep amniotic sac intact as long as possible
  - Avoid the presence of any stool in the environment at time of birth.

Outcomes

- Sep 2011 – Dec 2014: 936 pregnant women admitted
- 3 maternal deaths (0.03%)
- Pregnancy outcome available for 900 women:
  - 141 foetal deaths (15.%)
  - 64 (45%) before admission

Schillberg et al, EID 2016

Table 1. Characteristics of pregnant cholera patients by pregnancy outcome and risk factors, Haiti, 2011–2014*

Characteristic	No. (%) fetal deaths, n = 141	Unadjusted analysis		Adjusted analysis†	
		OR (95% CI)‡	p value§	OR (95% CI)‡	p value§
Age group, y					
<20	30 (21.3)	2.08 (1.30–3.33)	0.01	1.98 (1.21–3.24)	0.02
20–34	96 (68.1)	Referent		Referent	
≥35	15 (10.6)	1.02 (0.57–1.83)		1.00 (0.55–1.84)	
Missing	0				
Time from onset to admission, h					
≤24	59 (41.8)	Referent	0.04	Referent	0.04
>24	82 (58.2)	1.47 (1.02–2.12)		1.49 (1.02–2.17)	
Missing	0				
Trimester of pregnancy					
First	17 (12.1)	Referent	0.02	Referent	0.001
Second	41 (29.1)	1.39 (0.76–2.53)		1.37 (0.74–2.53)	
Third	79 (56.0)	2.08 (1.19–3.64)		2.43 (1.37–4.31)	
Missing	4 (2.8)				
Dehydration level					
None	37 (26.2)	Referent	0.001	Referent	0.02
Moderate	73 (51.8)	1.83 (0.20–2.79)		1.54 (0.99–2.41)	
Severe	31 (22.0)	2.62 (1.55–4.44)		2.17 (1.24–3.81)	
Missing	0				
Vomiting					
Yes	116 (82.3)	2.25 (1.42–3.59)	0.001	2.10 (1.27–3.47)	0.001
No	24 (17.0)	Referent		Referent	
Missing	1 (0.7)				

*Of 900 pregnancies analyzed. OR, odds ratio.
†Adjusted for all list characteristics.
‡From logistic regression model with fetal death as the outcome and list characteristics as exposure.
§From Wald tests of parameters of logistic regression model.

Schillberg et al, EID 2016

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20–34	96 (68.1)	Referent		Referent	
≥35	15 (10.6)	1.02 (0.57–1.83)		1.00 (0.55–1.84)	
Missing	0				
Time from onset to admission, h					
≤24	59 (41.8)	Referent	0.04	Referent	0.04
>24	82 (58.2)	1.47 (1.02–2.12)		1.49 (1.02–2.17)	
Missing	0				
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Third	79 (56.0)	2.08 (1.19–3.64)		2.43 (1.37–4.31)	
Missing	4 (2.8)				
Dehydration level					
None	37 (26.2)	Referent	0.001	Referent	0.02
Moderate	73 (51.8)	1.83 (0.20–2.79)		1.54 (0.99–2.41)	
Severe	31 (22.0)	2.62 (1.55–4.44)		2.17 (1.24–3.81)	
Missing	0				
Vomiting					
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Schillberg et al, EID 2016

Table 2. Characteristics of pregnant cholera patients by pregnancy outcome and treatment group, Haiti, 2011–2014*

Characteristic	No. (%) postadmission fetal deaths, n = 77	Unadjusted analysis		Adjusted analysis†	
		OR (95%)‡	p value§	OR (95% CI)†	p value§
Treatment group					
1	12 (15.6)	1.19 (0.58–2.44)	0.85	1.39 (0.66–2.91)	0.68
2	38 (49.4)	1.13 (0.67–1.90)		1.15 (0.67–1.96)	
3	27 (35.1)	Referent		Referent	
Age group, y					
<20	14 (18.2)	1.73 (0.92–3.24)	0.23	1.63 (0.85–3.12)	0.33
20–34	54 (70.1)	Referent		Referent	
≥35	9 (11.7)	1.09 (0.52–2.28)		1.07 (0.50–2.27)	
Missing	0				
Time from onset to admission, h					
≤24	37 (48.1)	Referent	0.57	Referent	0.57
>24	40 (51.9)	1.15 (0.72–1.83)		1.15 (0.71–1.86)	
Missing	0				
Trimester of pregnancy					
First	10 (13.0)	Referent	0.23	Referent	0.06
Second	25 (32.5)	1.44 (0.67–3.08)		1.50 (0.69–3.24)	
Third	41 (53.2)	1.84 (0.90–3.76)		2.28 (1.09–4.76)	
Missing	1 (1.3)				
Dehydration level					
None	20 (26.0)	Referent	0.03	Referent	0.09
Moderate	45 (58.4)	2.08 (1.20–3.61)		1.89 (1.07–3.33)	
Severe	12 (15.6)	1.88 (0.89–3.98)		1.56 (0.71–3.41)	
Missing	0				
Vomiting					
Yes	63 (81.8)	2.10 (1.15–3.82)	0.02	2.05 (1.08–3.90)	0.03
No	14 (18.2)	Referent		Referent	
Missing	0				

*Of 836 women with a viable fetus at admission. OR, odds ratio.
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Schillberg et al, EID 2016

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2	38 (49.4)	1.13 (0.67–1.90)		1.15 (0.67–1.96)	
3	27 (35.1)	Referent		Referent	
Age group, y					
<20	14 (18.2)	1.73 (0.92–3.24)	0.23	1.63 (0.85–3.12)	0.33
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≥35	9 (11.7)	1.09 (0.52–2.28)		1.07 (0.50–2.27)	
Missing	0				
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≤24	37 (48.1)	Referent	0.57	Referent	0.57
>24	40 (51.9)	1.15 (0.72–1.83)		1.15 (0.71–1.86)	
Missing	0				
Trimester of pregnancy					
First	10 (13.0)	Referent	0.23	Referent	0.06
Second	25 (32.5)	1.44 (0.67–3.08)		1.50 (0.69–3.24)	
Dehydration level					
None	20 (26.0)	Referent	0.03	Referent	0.09
Moderate	45 (58.4)	2.08 (1.20–3.61)		1.89 (1.07–3.33)	
Severe	12 (15.6)	1.88 (0.89–3.98)		1.56 (0.71–3.41)	
Missing	0				
Vomiting					
Yes	63 (81.8)	2.10 (1.15–3.82)	0.02	2.05 (1.08–3.90)	0.03
No	14 (18.2)	Referent		Referent	
Missing	0				

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Schillberg et al, EID 2016

Key findings

- 2 biggest cohorts in the literature
- Confirmation of high foetal mortality, and no observed increased risk for mothers
- Half of foetal deaths occurred prior to admission – prevention!
- Confirmation of association of foetal death with severity of dehydration and vomiting

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Conakry Guinea, 2012

May-Dec 2012

- 2808 admissions, 80 pregnant women (2.8%)

- 1 maternal death (1.2%)
- 4 intrauterine fœtal deaths (5%)
- 1 pre-term delivery

Holy Picket, MSF. Donka, Conakry, 2012

Sako et al, Med Santé Trop 2016

Conakry 2012, specialized obstetric unit

July/August – Dec 2012

- CTC within teriary hospital
- Specialized obstetric unit within CTC, with possibility to refer to maternity/neonatal unit for complications
- Protocol: as Leogane
- Additional: electrolite monitoring (late)

Outcomes (total – May-Dec)

- 86 pregnant women
- 1 maternal death (post-delivery (stillbirth))
- 7 live deliveries
- 11 fœtal deaths (12.8%)
  - 8 stillbirths
  - 3 abortions

MSF unpublished data

Draft MSF treatment guideline (2017)

- Correct dehydration in mother
- Prevent negative impact on fœtus by sustaining systolic BP > 90 mmHg
- Clinical evaluation:
  - 2^{nd}-3^{rd} trimester:
    - Left lateral decubitus
    - Measure skin pinch under clavicles
    - Use other standard observations
    - Measure systolic blood pressure and weight (if possible)

Assignment of therapy:

- In 1^{st} trimester, assessment and treatment as standard
- In 2^{nd}-3^{rd} trimester:
  - Severe dehydration **or** SBP < 90 mmHg = Plan C
  - Some dehydration **and** SBP > 90 = Plan B
  - No dehydration **and** SBP > 90 = Plan A

Plan C – or systolic BP > 90 mmHg

- Immediate: Bolus of 30 ml/kg* of RL over 30 minutes (*or assume 60kg weight)
- Repeat the bolus if:
    - the pulse remains weak, or
    - SBP remains ≤ 90, or
    - signs of altered conscience persist
- Once the patient stabilized:
    - Continue with 70 ml/kg of RL over 3 hours
    - at least 250 ml of ORS or RL after each stool

- Clinical Surveillance
    - Standard surveillance + SBP every 30 minutes during the first 4 hours.
    - If the SBP is again ≤ 90 or danger signs reappear, repeat boluses of 30 ml/kg over 30 minutes until the SBP is > 90 and/or danger signs resolve then, resume the previous perfusion of 70 ml/kg.
    - Subsequently, adapt the surveillance of maternal SBP, according to the severity of fluid loss from diarrhea.
- Other**:** antibiotic s.d. in first 4 hours

Plan B

- Treatment
  - Oral rehydration : 75 ml/kg ORS over 4 hours + at least 250 ml of ORS after each stool
  - + single dose antibiotic therapy
  - If difficulty in consuming ORS, IV rehydration (75 ml/kg of RL).
- Surveillance
  - Standard surveillance + SBP every 30 minutes.
  - If the SBP is ≤ 90 or signs of severe dehydration appear, start fluid therapy for severe dehydration.

Plan A

- At least 250 ml of ORS after each stool (under observation for 4-6 hours)
- + single dose antibiotic therapy

Managing obstetric complications

Obstetric evaluation

- After stabilising dehydration
  - Assess gestational age
  - Feotal heart beat
  - History

Normal delivery

- Clean neonate with water and soap
- Breastfeeding: wash with water and soap

Complications

- IUFD – treat dehydration first, refer later
- Abortion – treat dehydration, refer later unless persistent bleeding
- Treatened preterm delivery
- 26-34 weeks: if cervix dilated – refer to maternity for tocolysis, lung maturation etc
- 26-34 weeks – cervix not dilated – contractions will likely stop if cholera treated
- 34 weeks or more – normal delivery

Open questions

- Assessment of dehydration?
- Rehydration protocol
- (Antibiotics)
- Others: glucose, potasium, bicorbonate?

Conclusions

- Cholera is associated with pregnancy loss, at least half of losses occure before admission

- Prevention is key:
  - Vaccine is safe in pregnancy!
  - Other tools? Antibiotic prophylaxis? Etc?

- Special cholera units for pregnant women in big outbreaks or urban settings:
  - adapted follow-up of both cholera and pregnancy status
  - dignity

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Oral cholera vaccine

Guinea, oral cholera vaccination, 2012.

- Limited data on safety in pregnancy
- Pregnant women initially excluded from the vaccination campaigns

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OCV safe in pregnancy!

- Zanzibar Hashim et al, Plos NTD 2012
  - Retrospective, women inadvertedly vaccinated during campaing
- Guinea *Grout et al, Plos NTD 2015*
  - Retrospective cohort post-vacciation
- Bangladesh *Khan et al, Vaccine 2017:*
  - Women inadvertedly vaccinated during RCT
- Malawi *Ali et al, Lancet Inf Dis 2017:*
  - Prospective study following mass vaccination campaign

- No association between OCV and pregnancy loss found

Cholera vaccines: WHO position paper – August 2017

Special populations

Pregnant and lactating women and HIV-infected individuals

These groups should be included in OCV campaigns. Evidence indicates high potential benefit and minimal risks.

Conclusions

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- Prevention is key:
  - Vaccine is safe in pregnancy!
  - Other tools? Antibiotic prophylaxis? Other preventive measures?

- Adapted treatment protocol?

- Special cholera units for pregnant women in big outbreaks or urban settings:
  - adapted follow-up of both cholera and pregnancy status
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Thank you!
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