Use of antibiotics for cholera chemoprevention

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GTFCC Case management meeting, 2018

GLOBAL TASK FORCE ON
CHOLERA CONTROL

Technical Note
Use of antibiotics for the treatment and control of cholera
May 2018

6. Mass chemoprophylaxis is not recommended. There is currently insufficient evidence to evaluate the effectiveness of selective chemoprophylaxis (household contacts, enclosed communities). It is recommended that any use should be within the context of a prospective study specifically designed to measure effectiveness of antibiotic prophylaxis and development of antibiotic resistance in household contacts (i.e., sharing a meal) of a suspect cholera patient, as well as any impact of such strategy on outbreak evolution.

Outline of presentation

- Key questions:
  - Rationale for household prophylaxis – household contacts at higher risk?
  - Rationale for antibiotic use?
  - What is the effectiveness?
  - What is the impact on the epidemic?
  - Risk of antimicrobial resistance
  - Feasibility during outbreak control interventions

- Example: Single-dose oral ciprofloxacin prophylaxis in response to a meningococcal meningitis epidemic in the African meningitis belt: a three-arm cluster-randomized trial

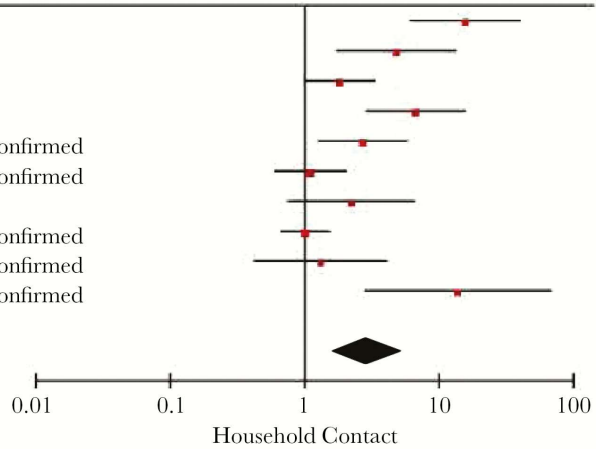
- Prevention of cholera infection among contacts of case: a cluster-randomized trial of Azithromycine

Rationale: risk for household contacts

Forest plot of studies included in meta-analysis: association of presence of household contact with cholera with symptomatic cholera

Study or Subgroup	log[Odds Ratio]	SE	Cases Total	Controls Total	Weight	Odds Ratio IV, Random, 95% CI	Out come
Kone-Coulibaly 2010	2.7498	0.4872	140	140	9.8%	15.64 [6.02, 40.64]	Clinical
Rosewell 2011	1.5686	0.5238	43	43	9.4%	4.80 [1.72, 13.40]	Clinical
Mahamud 2012	0.5933	0.313	93	93	11.5%	1.81 [.98, 3.34]	Clinical
Cummings 2012	1.8976	0.4368	99	99	10.3%	6.67 [2.83, 15.70]	Clinical
Grandesso (Carrefour study) 2014	0.9933	0.393	90	180	10.7%	2.70 [1.25, 5.83]	Culture-confirmed
Grandesso (Gonaives study) 2014	0.0953	0.3178	90	180	11.5%	1.10 [.59, 2.05]	Culture-confirmed
Nguyen 2014	0.7975	0.5559	49	98	9.1%	2.22 [.75, 6.60]	Clinical
Moradi 2016	0.01	0.2163	229	458	12.3%	1.01 [.66, 1.54]	Culture-confirmed
Matias 2017	0.27	0.5821	33	117	8.8%	1.31 [.42, 4.10]	Culture-confirmed
Nguyen 2017	2.6189	0.8164	60	240	6.7%	13.72 [2.77, 67.97]	Culture-confirmed
Total (95% CI)			**926**	**1648**	**100.0%**	**2.91 [1.62, 5.25]**	

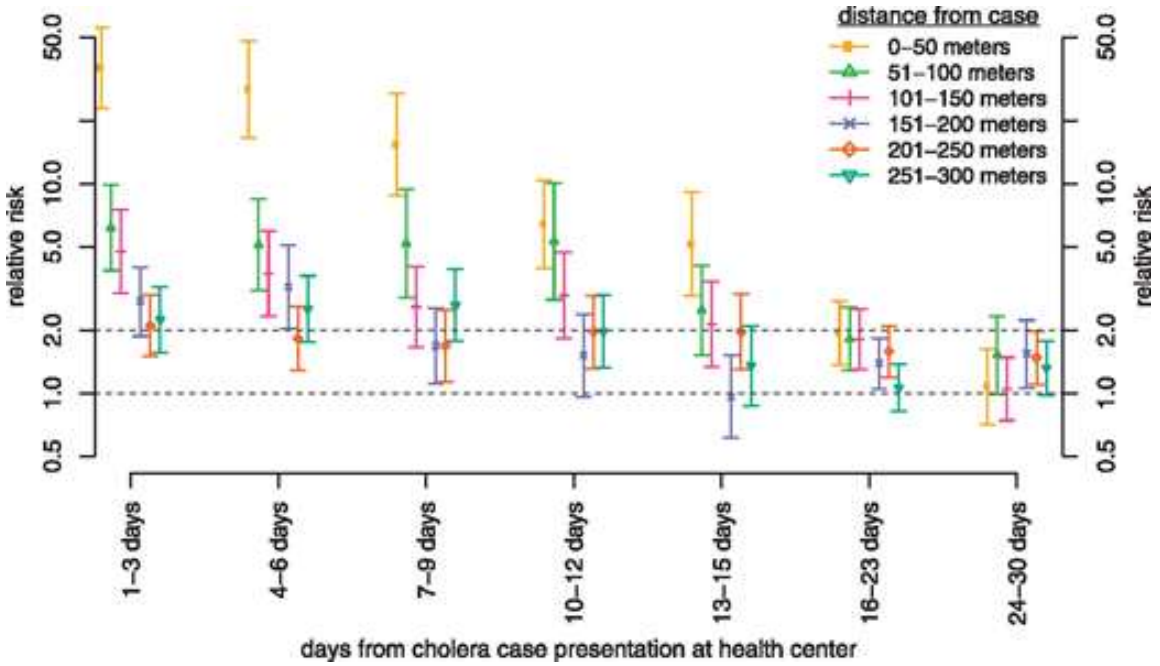
Heterogeneity: $Tau^2 = 0.69$; $Chi^2 = 48.54$, $df = 9$ ($P < .00001$); $I^2 = 81\%$
Test for overall effect: $Z = 3.55$ ($P = .0004$)



Richterman et al. Individual and Household Risk Factors for Symptomatic Cholera Infection: A Systematic Review and Meta-analysis. JID 2018

Rationale: clustering of cholera cases in time and space

Relative risk for cholera among case cohorts compared with control cohorts at different spatio-temporal scales

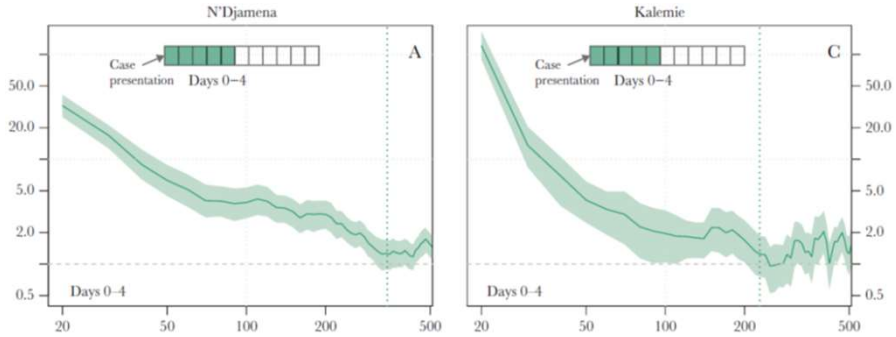


Living within 50 m of the index case: RR 36 (95% CI: 23–56) within 3 days of the index case presenting to the hospital

Debes et al. Cholera cases cluster in time and space in Matlab, Bangladesh: implications for targeted preventive interventions. Int J Epid 2016

Rationale: clustering of cholera cases in time and space

Relative risk of next cholera case being within specific distance to another case within days 0-4

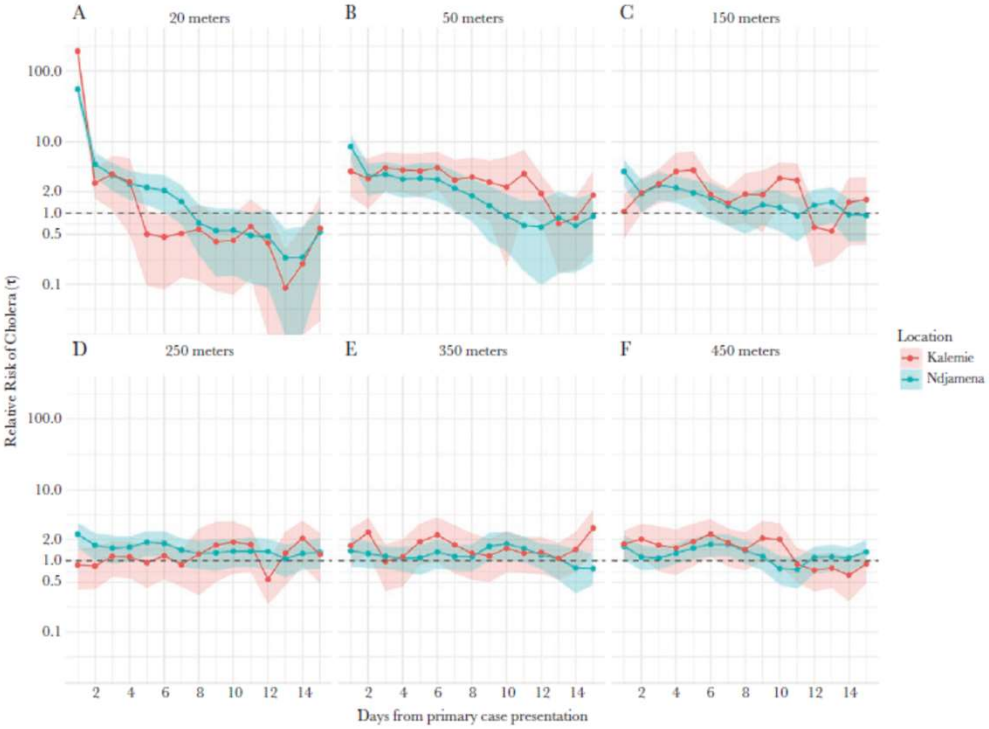


Within 40 m:

Ndjamena: RR 32.4 (95% 25-41)

Kalemie: RR 121 (95% CI 90-165)

Relative risk of next cholera case occuring at different distances from primary case



Azman et al. Micro-hotspots of risk in urban cholera epidemics. JID 2018

Rationale for use of antibioitics for cholera

- Duration of diarrhea: median duration shorten for -36.77 hours (95% CI -43.51 to -30.03)
  - Mean duration in control group: 29-127 hours
- Stool volume reduction: 50% (ROM 0.5, 95% CI 0.45 to 0.56)
  - Volume in control group: 13.5 liters in adults, 368 ml/kg in children
- Amount of rehydration fluids required reduced by 40% (ROM 0.60, 95% CI 0.53 to 0.68)
  - Volume required in control group: 14 liters in adults, 374 ml/kg in children
- Fecal excretion of vibrios: median duration shorten for -2.74 days, 95% CI -3.07 to - 2.40)
  - Mean duration in control group: 2.97-6 days

Cochraine review. Antimicrobial drugs for treating cholera (2014)

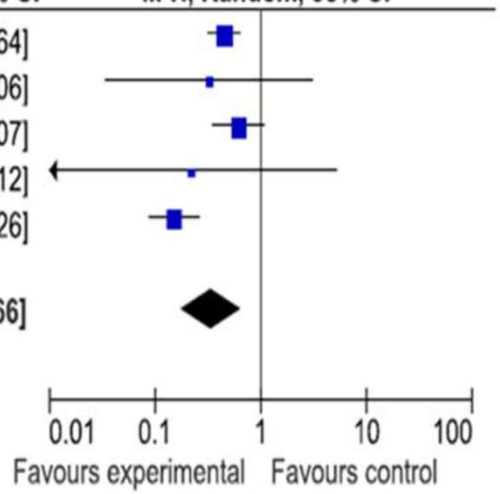
Efficacy of chemoprophylaxis: culture positive cholera

Culture positive cholera, 1414 participants;
RR 0.34 (95% CI 0.18 to 0.66)

	Chemoprophylaxis		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Deb 1976	42	221	47	112	32.2%	0.45 [0.32, 0.64]	
Echevarria 1995	1	107	3	104	6.9%	0.32 [0.03, 3.06]	
Gupta 78	17	137	28	139	28.3%	0.62 [0.35, 1.07]	
Joint 71	0	23	1	15	3.9%	0.22 [0.01, 5.12]	
McCormack 68	17	413	39	143	28.7%	0.15 [0.09, 0.26]	
Total (95% CI)		**901**		**513**	**100.0%**	**0.34 [0.18, 0.66]**	
Total events	77		118				

Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 15.41$, df = 4 (P = 0.004); $I^2 = 74\%$

Test for overall effect: Z = 3.19 (P = 0.001)



Reveiz et al. Chemoprophylaxis in Contacts of Patients with Cholera: Systematic Review and Meta-Analysis. Plos One 2011.

Efficacy of chemoprophylaxis: hospitalisation

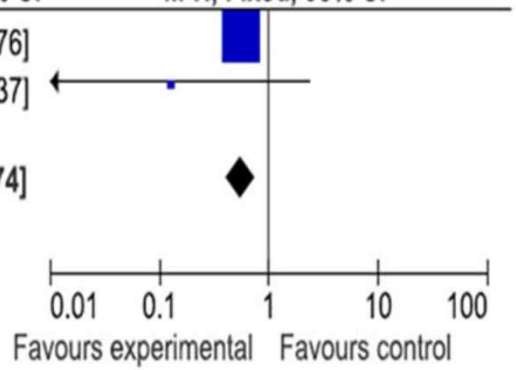
Hospitalisation, 2826 participants;

RR 0.55 (95% CI 0.41 to 0.75)

	Chemoprophylaxis		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Khan 82	81	1817	74	930	96.3%	0.56 [0.41, 0.76]	
Lapeyssonie 71	0	42	3	37	3.7%	0.13 [0.01, 2.37]	
Total (95% CI)		**1859**		**967**	**100.0%**	**0.54 [0.40, 0.74]**	
Total events	81		77				

Heterogeneity: $Chi^2 = 0.99$, $df = 1$ ($P = 0.32$); $I^2 = 0\%$

Test for overall effect: $Z = 3.94$ ($P < 0.0001$)



Reveiz et al. Chemoprophylaxis in Contacts of Patients with Cholera: Systematic Review and Meta-Analysis. Plos One 2011.

Effectiveness of chemoprophylaxis

- Nairobi, Kenya, 2015 (>3000 cases reported)
- Doxycicline prophlyaxis to household contacts recommended, but not universally distributed
- Retrospective cohort study among households with at least one reported cholera case

- Included in the study: 391 household contacts with doxycycline; 468 without

- aRR against developing diarrhea: 0.32 (05% CI 0.13 – 0.71)
- aRR against hospitalisation: 0.54 (95% CI 0.17 – 1.52)
- aRR against requiring i.v. rehydration: 0.28 (95% CI 0.01 – 1.88)

Grandesso et al, Epicentre. Unpublished data

Large-scale targeted chemoprophylaxis: feasibility and «impact»

- Duala, Cameroon, 2004 (5,020 patients Jan – Aug 2004)
- Doxycicline prophlyaxis to household contacts recommended
- Contact: same roof, table, food, water point, latrine

- Proportion of household contacts among cases:
  - 30% in January,
  - 0.2% at the end
- No change in *V. cholerae* sensitivity

Table 1. Distribution of antibiotics during the 2004 cholera outbreak in Douala.

	Antibiotiques			
Nombre de bénéficiaires (N)	**Doxycycline orale (cp)**	**Amoxicilline orale (cp)**	**Amoxicilline sirop**	**Total**
Malades	4 572	423	18	5 013
Contacts intrahospitaliers	15 484	118	26	15 628
Contacts communautaires	145 895	12 625	3 205	161 725
TOTAL bénéficiaires	**165 951**	**13 166**	**3 249**	**182 366**
Ratio Contacts/malade				*35,37*

Guevart et al. Large-scale selective antibiotic prophylaxis during 2004 cholera outbreak in Duala, Cameroon. Santé 2007

Guevart et al. Antibiotic susceptibility of Vibrio cholerae 01: evolution after prolonged curative and preventive use during the 2004 cholera epidemics in Douala (Cameroon)]. Med Mal Infect 2006

Targeted chemoprophylaxis: prisons

- Duala, Cameroon, 2004 (5,020 patients Jan – Aug 2004)
- New Bell central prison – housing around 3000 prisoners in deplorable conditions
- Feb 2004: 5 suspected cases reported
  - Single 300-mg dose of doxycycline administered > 3000 prisoners and staff
  - No cases for 4 months
  - June 2004: 2 new suspected cases, followed by mass chemoprophylaxis

Guevart et al. Mass antibiotic prophylaxis against cholera in the New Bell central prison in Douala during the 2004 epidemic. Santé 2006

Antibiotic resistance: azythromicine MDA for trachoma

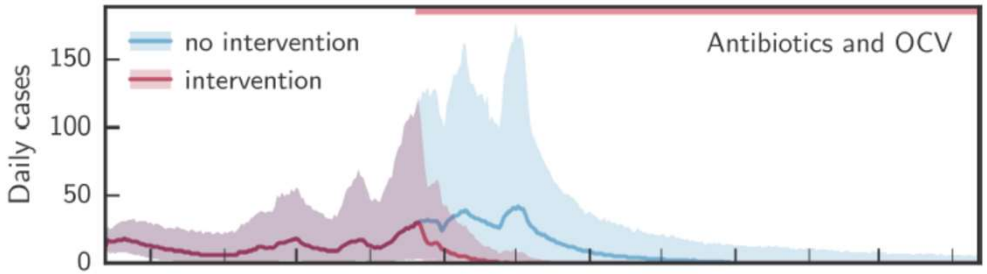
- Increased resistance of nasopharyngeal *Streptococcus pneumoniae:*
  - Ethiopia RCT: azithromycin resistance in treated group from 3.6% at baseline to 46.9% at month 12; control group 9.2% at month 12 *Skalet et al, Plos Med 2010*
  - Tanzania communities with and without azyhtro MDA: at 6 months, the percentage of AZM-resistant isolates significantly higher in the MDA group (81.9% vs 46.9%, P < .001) *Colet et al, CID 2013*
- Macrolide resistance of nasopharyngeal *Streptococcus pneumoniae* decreases after antibiotic pressure is removed:
  - Ethiopia: 12 and 24 months after the last treatment, resistance decreased from 76.8% to 30.6% and 20.8% *Haug et al, CID 2010*
- Increased carriage of macrolide-resistant fecal E. coli, decrease over time:
  - Tanzania: 21% at baseline, 61% month 1, 42% month 3 and 31% month 6 *Siedman et al, Int J Epid 2014*

Antibiotic resistance

- Mass administration ≠ targeted prophylaxis for household members
- Azytromicine: treatment of STIs

Feasibility

- Cameroon example
- Rapid response teams
- Package interventions – wash + antibiotics + OCV around index case



Azman et al. Case- area targeted interventions in response to cholera outbreaks. Plos Med 2018.

Single-dose oral ciprofloxacin prophylaxis in response to a meningococcal meningitis epidemic in the African meningitis belt: a three-arm cluster-randomized trial

Coldiron et al, Plos Med 2018

Outbreak response in the meningitis belt

- Reactive vaccination often late
  - As a result, impact is mitigated[1]
  - More cases averted if vaccination happens faster[2]
  - Limited vaccine supply (2.4M doses for 2018 season)
- Shortage of Men C vaccines after re-emergence of serogroup C epidemics in Africa in 2015
- Antibiotic prophylaxis for contacts of cases not recommended during epidemics
  - No evidence; also concerns about logistics / resources
  - Trial recommended by WHO panel after emergence of Serogroup C epidemics in Africa in 2015

[1]M.J. Ferrari et al. *Int. Health* 2014;6:282-290

[2]C.L. Trotter et al. *Vaccine* 2015;33:6212–6217

Objective and interventions:

Study design:

3-arm, open-label, cluster-randomized trial

Primary objective:

To assess the impact of prophylaxis with single-dose oral ciprofloxacin (to household contacts and to entire villages) on the overall meningitis attack rate during an epidemic.

- Arm 1: standard care
- Arm 2: ciprofloxacin to household contacts
  - Given by nurse at home <24h of case notification
- Arm 3: ciprofloxacin to entire village
  - Village-wide distribution of ciprofloxacin <72h after declaration of first case from a village

- Directly-observed, age-based dosing of ciprofloxacin, including children and pregnant women

Randomization and surveillance

- Study Launch: 2 Health Areas of a Health District cross epidemic threshold in same week
- Villages randomized after first case notified from that village
  - Household ppx arm: only one distribution per household
  - Village-wide ppx arm: only one distribution per village
- Dedicated surveillance nurse in each Health Area in study
  - WHO case definitions of suspect and confirmed meningitis used
  - Standard MOH procedures and sample flow from periphery to District Hospital and then national reference laboratory for PCR confirmation
- Door-to-door exhaustive census after inclusion to have accurate denominators

Resistance sub-study methods

- Sample size: 10 villages / 200 individuals in control/village-wide arms
  = 20 individuals randomly selected in each of 20 villages, individual written consent

- Stool collection at days 0, 7 and 28

- Detection of the carriage of enterobacteriae resistant to cipro and/or cefotaxime by plating on selective media
  - Simplification of identification / confirmation methods after 5 villages showing very high prevalence of resistant bacteria

- Quality control at IAME laboratory, Inserm, Paris, France

Timeline

20 April: Trial start criteria met in Madarounfa District, Niger

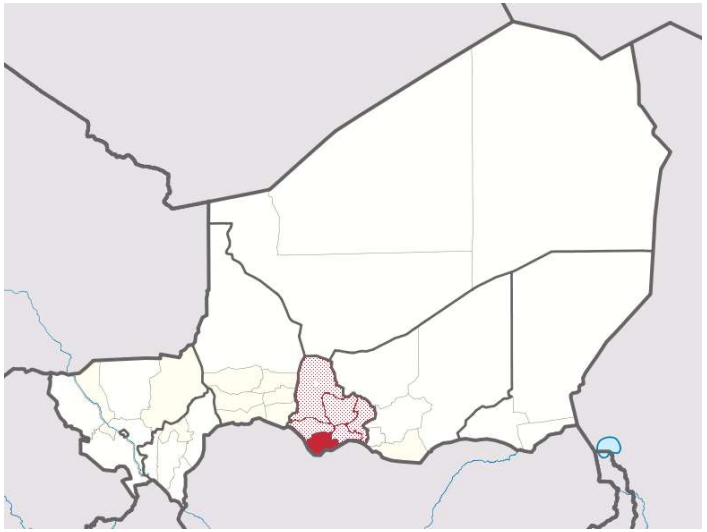
22 April: First villages included

10 May: First rains

12 May: First vaccination began

18 May: Last village included

23 May: Last case notified



Baseline characteristics of villages

	Standard care	Household cipro	Village-wide cipro
Number of villages	17	17	15
Total population	25 510	23 621	22 177
Age of cases, mean±SD	18±13	17±15	18±17
Female population (%)	51	51	51
Proportion <30y (%)	78	77	76
Days between inclusion and reactive vaccination, mean±SD	11.1±7.8	10.8±9.5	12.2±8.8
Days between inclusion and first rains, mean±SD	7.2±7.1	6.4±8.1	7.1±6.5

Coldiron et al. PLOS Medicine, 2018

Primary results

	Standard care	Household ciprofloxacin	Village-wide ciprofloxacin
Post-randomization cases	115	91	42
Attack rate (95%CI), cases/100 000 people	451 (262-776)	386 (225-662) p=0.68	190 (99-364) p=0.03
Adjusted attack rate ratio versus standard care (95% CI)*	Ref	0.94 (0.52-1.73) p=0.85	0.40 (0.19-0.87) p=0.02

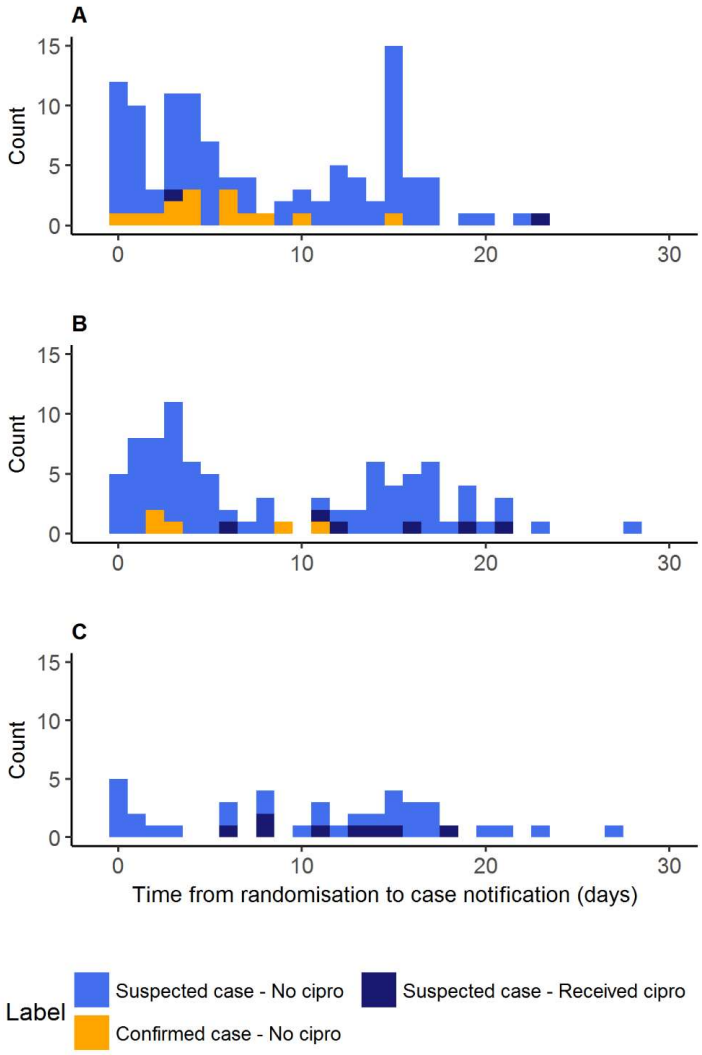
* Adjusted for whether village included after the first day of rainfall

Coldiron et al. PLOS Medicine, 2018

Standard care

Household prophylaxis

Village-wide prophylaxis



Coldiron et al. PLOS Medicine, 2018

Coverage of ciprofloxacin

- In household prophylaxis arm, a total of 1245 people in 87 households were treated (4% of population)

- In village-wide prophylaxis arm, a total of 16792 people were treated (76% of population)
  - Median coverage by village (IQR): 77% (75%-80%)

Coldiron et al. PLOS Medicine, 2018

Resistance sub-study - Results

- Baseline carriage of resistant enterobacteriae was very high
- Trend for increased prevalence of carriage of Cipro-R enterobacteriae after village-wide distribution
  - Non-significant difference in change between D7/D0 and D28/D0 between arms (p=0.12)

	No cipro	Village-wide cipro
Cipro-R (%)		
D0	95	95
D7	93	97
D28	95	99
ESBL (%)		
D0	91	94
D7	87	93
D28	93	93

Coldiron et al. PLOS Medicine, 2018

Conclusions

- Village-wide prophylaxis with single-dose oral ciprofloxacin <72h after meningitis case notification significantly reduced attack rates
  - Could be an attractive new epidemic response strategy (faster, cheaper…)
  - Would have preferred more confirmed cases, but trends are the same

- High level individual level protective effectiveness: 82% (95% CI 67%–90%)

- Very high prevalence of carriage of CiproR and ESBL bacteria at baseline
  - Hopefully not representative of all regions in the meningitis belt
  - Clinical significance of carriage is unknown
  - Need more information about potential impact of strategy on antibiotic resistance (both of meningococcus and gut flora)

Prevention of cholera infection among contacts of case: a cluster-randomized trial of Azithromycine

Luquero et al – Epicentre / MSF

Study objectives

Primary objective:

- Compare the incidence of cholera infection among household members receiving standard care or standard care plus azithromycin prophylaxis.

Secondary objectives:

- Estimate the individual efficacy of oral azithromycin for the prevention of cholera infection.
- Compare the incidence of cholera by sex in the two different intervention arms.
- Compare the incidence of cholera by age in the two different intervention arms.
- To explore factors that related with acceptance of antibiotic prophylaxis among the target population

Sub-study objective:

- Compare the prevalence of enterobacteriaceae resistant to macrolide before and after distributions of azithromycin in communities receiving distributions versus in communities not receiving distributions.

Design and interventions:

Study design:

2-arm, open-label, cluster-randomized trial

Study starting criteria (nb cases/ district)

Randomisation of villages 1 : 1

Based on confirmed cholera case (enriched RDT)

- Arm 1: standard care
- Arm 2: azythromicine to household contacts (> 1 year),
  - Given by nurse at home <24h of case notification
  - Age adjusted dose:

Age	Dose (mg)	Formulation
>12 years	500	1 tablet
5-12 years	250	1 tablet
1-4 years	125	½ tablet (250 mg tablet)

Sample size – not predifined

Reduction in infection rate due to intervention		Average cluster size					
		5	10	15	20	30	40
90%		22	12	10	8	6	6
70%		42	24	18	14	12	10
50%		90	50	38	30	24	22

Resistance sub-study methods

- Sample size: 200 individuals in each arm
- In each village, 20 participants randomly selected
- Stool collection at days 0, 7, 14 and 28
- Detection of the carriage of enterobacteriae resistant to azithromycin/erythromycin by plating on selective media
- Quality control at reference laboratory

Conclusion

- Individual preventive efficacy demonstrated
- Impact on transmission? Who is close contact at most risk?
- Risk of antimicrobial resistance – needs to be verified, but limited if chemoprophylaxis targeted? What to monitor?
- Feasibility due to additional task – combined interventions