

# Single-dose oral ciprofloxacin prophylaxis as a meningococcal meningitis outbreak response: results of a cluster-randomized trial

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## INTRODUCTION

- A novel strain of NmC emerged in 2013, causing large epidemics in Niger and Nigeria in 2015 and 2017
- Reactive vaccination, often with polysaccharide vaccines, is a core part of outbreak response in the meningitis belt, but supplies against NmC are low (2.4M doses for 2018)
- Antibiotic prophylaxis of contacts of cases is standard in high-resource settings, but not recommended in the meningitis belt
  - Lack of evidence and concerns about operational feasibility
- Given emergence of NmC and limited supply of vaccine, a WHO expert panel recommended formal testing of antibiotic prophylaxis in the meningitis belt

## OBJECTIVES

- 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.
- Document the effect of the intervention on community-level prevalence of faecal carriage of ciprofloxacin-resistant bacteria.



## METHODS

- 3 arm cluster-randomized trial (1:1:1 randomization)
  - **Arm 1:** Standard care
  - **Arm 2:** Ciprofloxacin to household contacts of suspect cases within 24 hours of case notification
  - **Arm 3:** Mass distributions of ciprofloxacin to entire village of origin of suspect case within 72 hours of first case notification from a village
- Directly-observed, single-dose oral ciprofloxacin administered on an age-based scale (oral suspension and tablets)
- All villages in Health Areas crossing epidemic threshold eligible
- Surveillance:
  - Facility-based surveillance by dedicated nurse
  - Standard WHO definitions and MOH protocol for sample flow to national reference lab for PCR
  - Exhaustive census of each included village
- Statistical analysis: cluster-level t-test of log-transformed attack rates, Poisson regression to adjust for age structure of village, timing of inclusion during epidemic, timing of first rains and timing of reactive vaccination campaign
- Antibiotic resistance sub-study: 200 individuals in standard care arm and 200 in village-wide prophylaxis arm provided stool samples at Days 0,7 and 28. Swabbed on selective media and presence of Cipro-R and ESBL bacteria confirmed.
- **Funding:** Médecins Sans Frontières
- **Trial registration:** clinicaltrials.gov NCT02724046
- **Ethical review:** CCNE of Niger and MSF-ERB
- **Full protocol:** Coldiron et al., *Trials* 2017;18:294

## RESULTS

**Table 1:** Baseline description of included villages

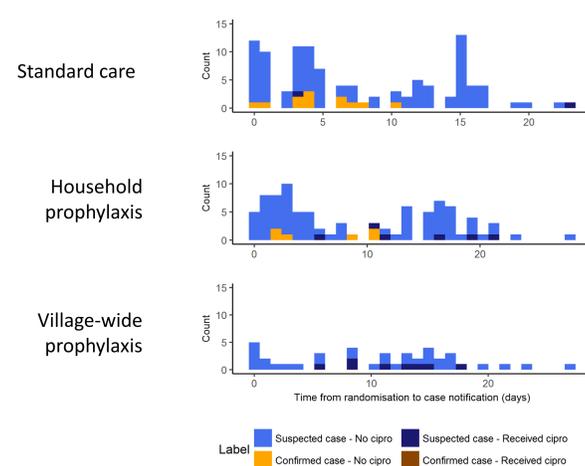
	Standard care	Household cipro	Village-wide cipro
Number of villages	18	17	15
Total population	26 162	23 621	22 177
Age of cases, mean±SD	18±13	17±15	18±17
Female population (%)	58	55	54
Proportion <30y (%)	78	77	76
Days between inclusion and reactive vaccination, mean±SD	11.1±7.8	10.8±9.5	12.2±8.8
Days between inclusion and first rains, mean±SD	7.2±7.1	6.4±8.1	7.1±6.5

**Table 2:** Attack rates and attack rate ratios by study intervention

	Standard care	Household cipro	Village-wide cipro
Number of cases	113	91	43
Attack rate (95%CI), cases/100K	432 (255-738)	386 (219-679)	194 (103-364)
Crude ARR vs standard care	Ref	0.89 (0.44-1.82) p=0.75	0.44 (0.18-1.12) p=0.08
Adjusted ARR vs standard care	Ref	0.88 (0.51-1.51) p=0.64	0.43 (0.22-0.86) p=0.02

- Laboratory confirmation: 52 samples sent from 247 post-randomization cases (21 NmC, 31 negative)
  - **Standard care:** 16 NmC from 28 tested
  - **Household ppx:** 5 NmC from 16 tested
  - **Village-wide ppx:** 0 NmC from 8 tested

**Figure 1:** Time from randomization to case notification



**Table 2:** Prevalence of faecal carriage of ciprofloxacin-resistant bacteria

	Standard care	Village-wide cipro
Day 0	95%	95%
Day 7	93%	97%
Day 28	95%	99% (p=0.12)

## DISCUSSION AND CONCLUSION

- Village-wide prophylaxis with single-dose oral ciprofloxacin reduces overall attack rates.
- The strategy is promising (low-cost, quick to implement, no need for injection or cold chain) but needs further research.
- Levels of carriage of ciprofloxacin-resistant bacteria should be evaluated in other contexts, does not preclude its use for meningitis prophylaxis.