

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	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

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

	Standard care	Household cipro	Village-wide cipro
Number of cases	115	91	43
Attack rate (95%CI), cases/100K	451 (262-776)	386 (225-662) p=0.68	190 (99-364) p=0.03
Crude ARR vs standard care	Ref	0.85 (0.42-1.75) p=0.67	0.42 (0.17-1.06) p=0.07
Adjusted ARR vs standard care	Ref	0.94 (0.52-1.73) p=0.85	0.40 (0.19-0.87) p=0.02

- Laboratory confirmation: 52 samples sent from 248 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

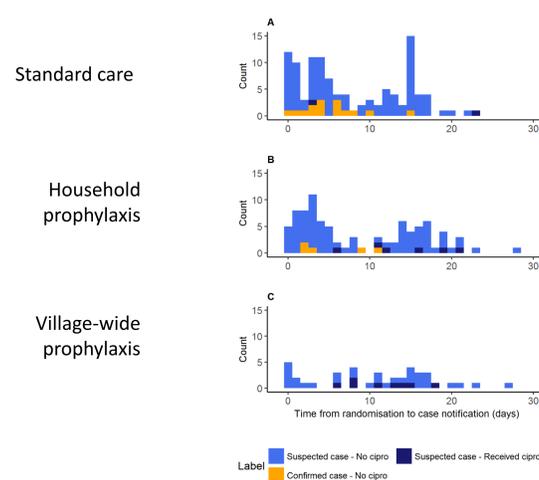


Table 2: Prevalence of faecal carriage of ciprofloxacin-resistant bacteria

	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.