Modelling the use of ciprofloxacin for epidemic response in the African meningitis belt

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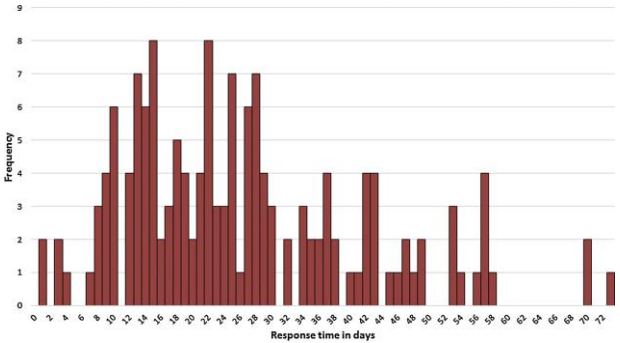
Outbreak response in the meningitis belt

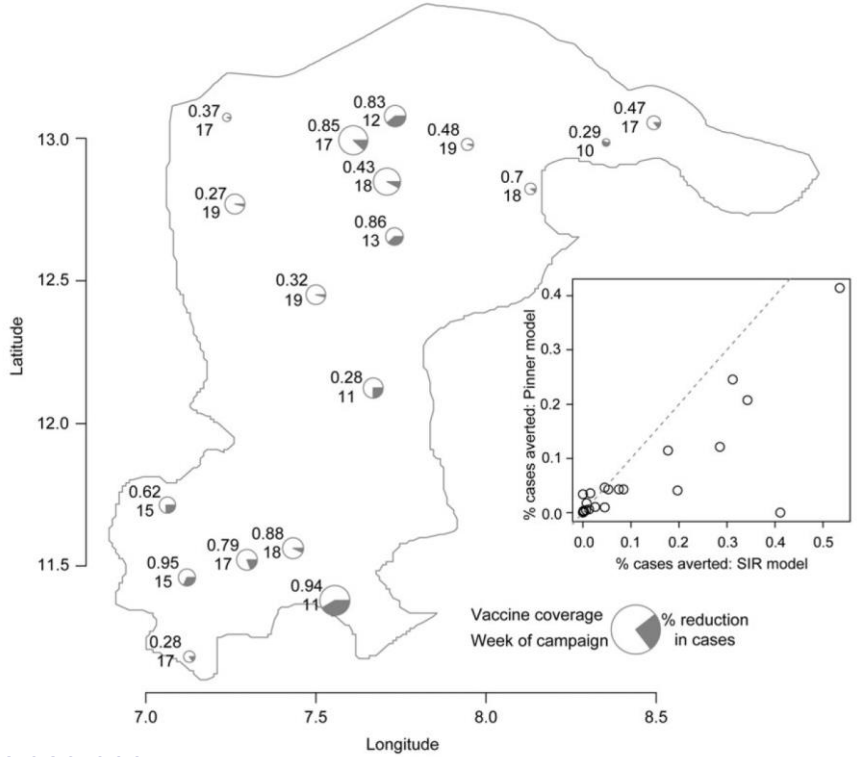
- Enhanced surveillance
- Case management
- Reactive vaccination
  - Often late – limited impact
  - More cases averted if vaccination faster *
  - Limited supply (2.4M doses of serogroup C-containing vaccine for 2020 season)



Days from crossing the epidemic threshold to vaccine implementation among 151 vaccine requests to the International Coordination Group (ICG) between 2006 and 2013.

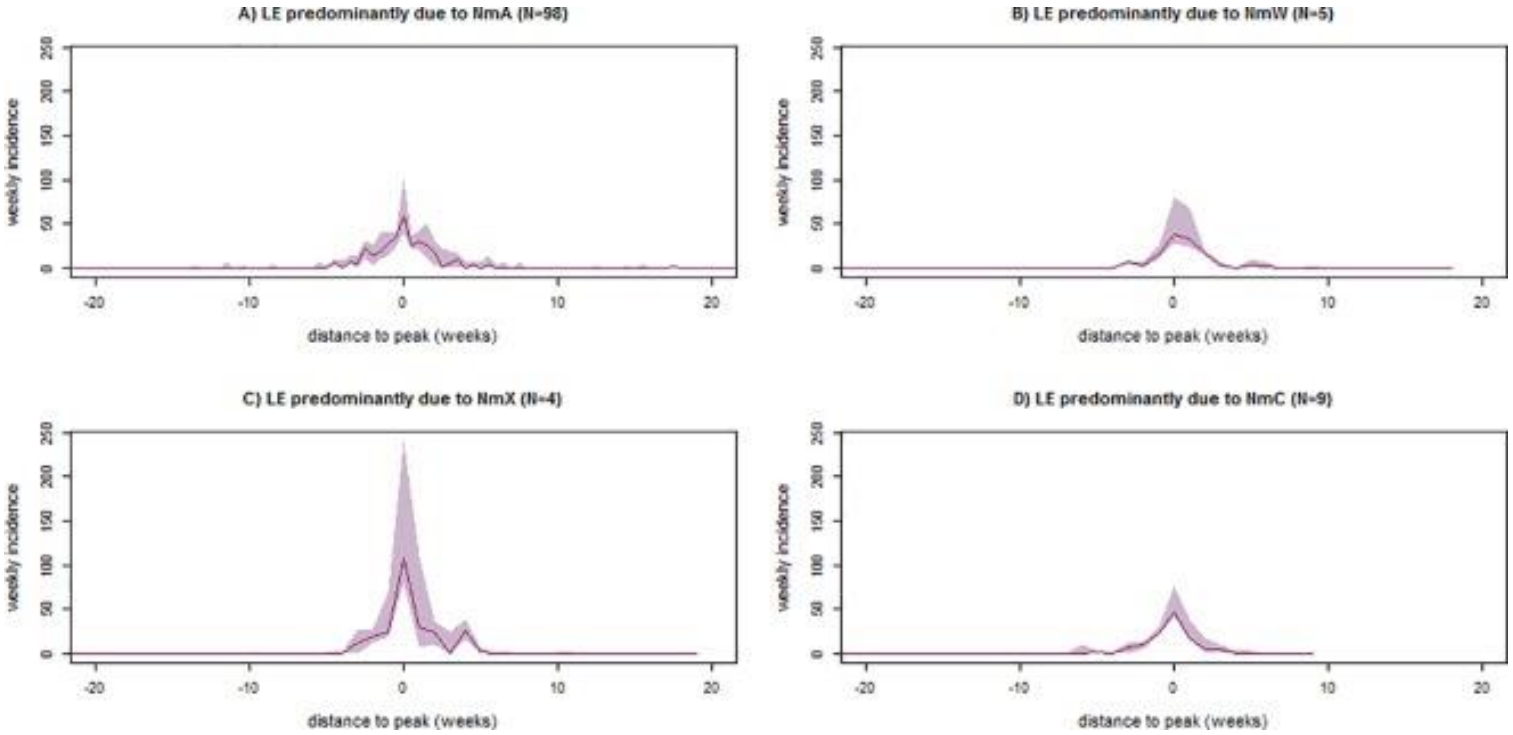
*Trotter et al. *Vaccine* 2015;33:6212–6217

Proportion of cases averted, Katsina, Nigeria, 2009



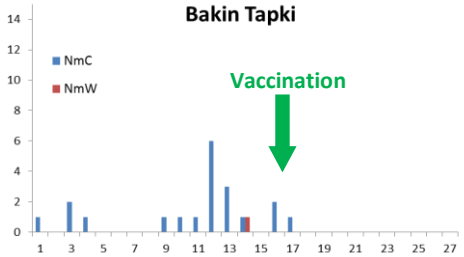
Ferrari et al. *Int. Health* 2014;6:282-290

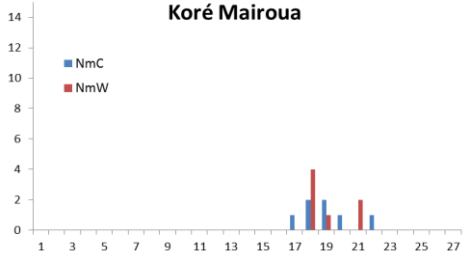
At a local level, very short epidemics

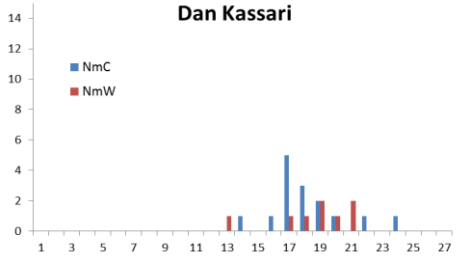


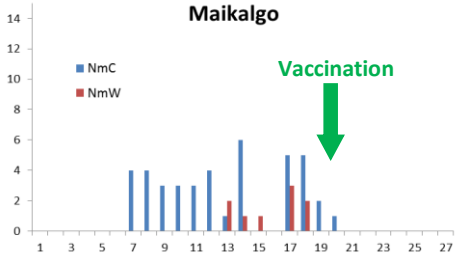
Maïnassara et al., PLoS One. 2016;11(9)e0163110

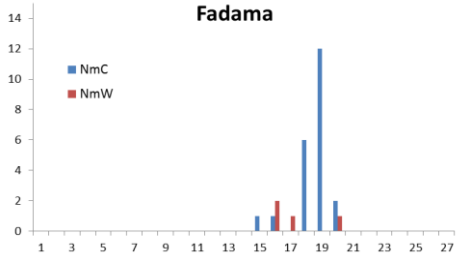
Doutchi, Niger, 2015

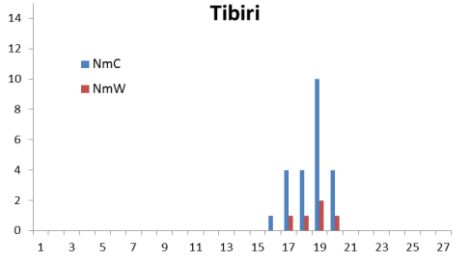




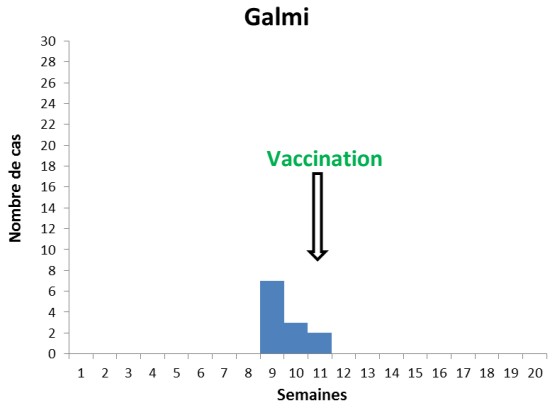


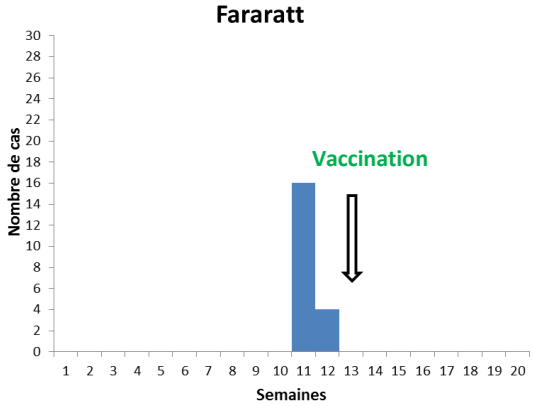


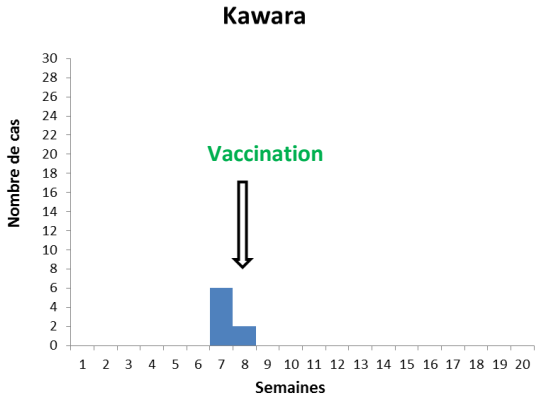


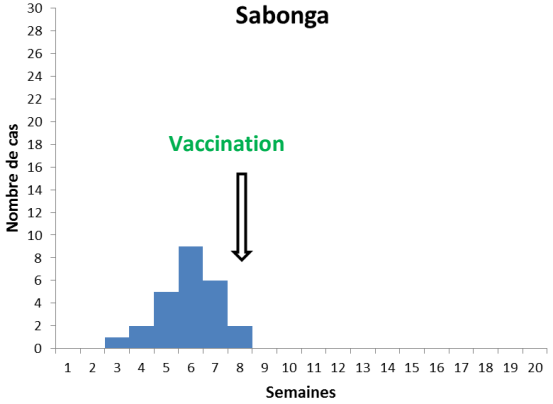


Tahoua, Niger, 2016

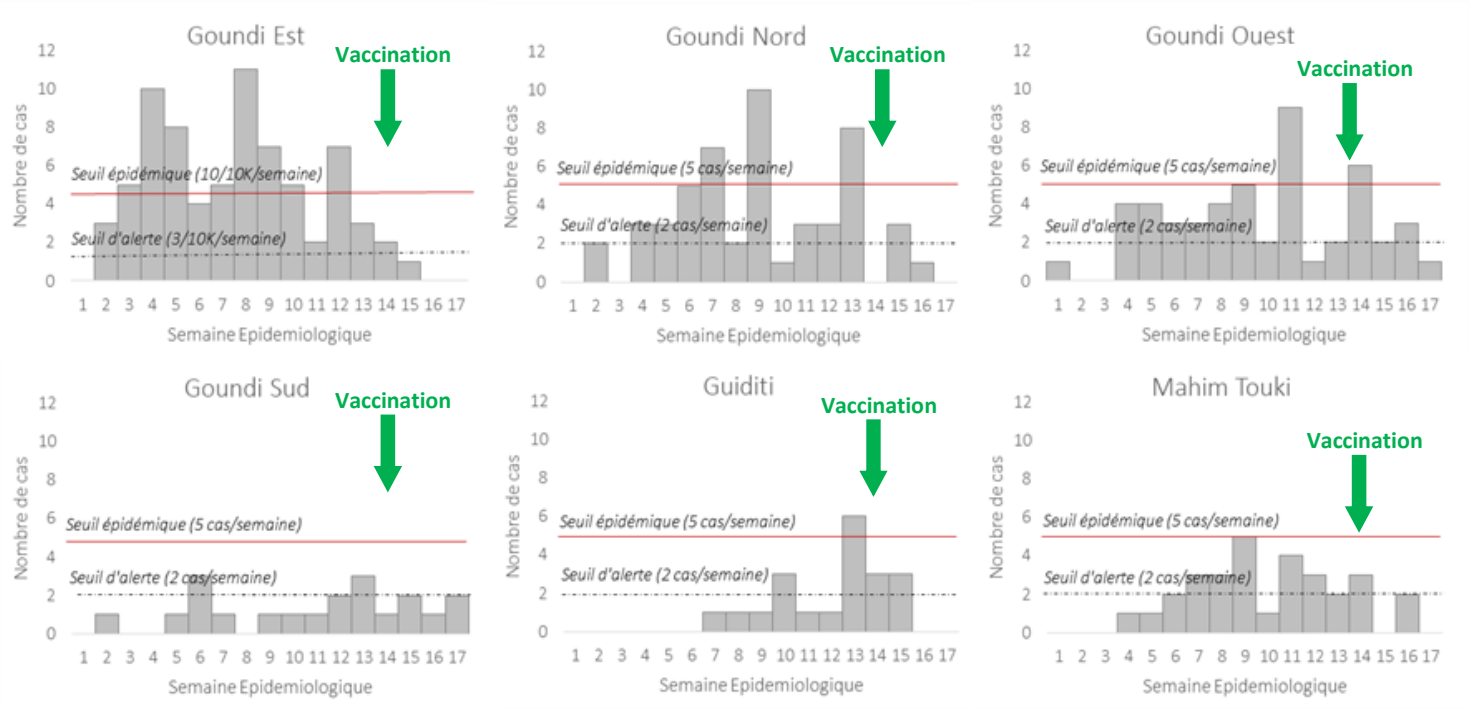








Goundi, Chad, 2019



Antibiotic prophylaxis for meningitis

- High-income countries: recommended for close contacts of cases
  - Rifampicin x2 days (oral)
  - Ciprofloxacin x1 dose (oral)
  - Ceftriaxone x1 dose (injectable)

- Meningitis belt: not recommended during epidemics
  - No evidence; concerns about logistics / resources
    - Trial encouraged after emergence of Serogroup C epidemics in Africa in 2015
  - Recommended for contacts of cases during non-epidemic periods (but not implemented)

Trial design

3-arm, open-label, cluster-randomized trial to assess the impact of prophylaxis with single-dose oral ciprofloxacin on the overall meningitis attack rate during an epidemic.

Arm 1: no prophylaxis

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

Coldiron et al. *Trials* 2017;18:294

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

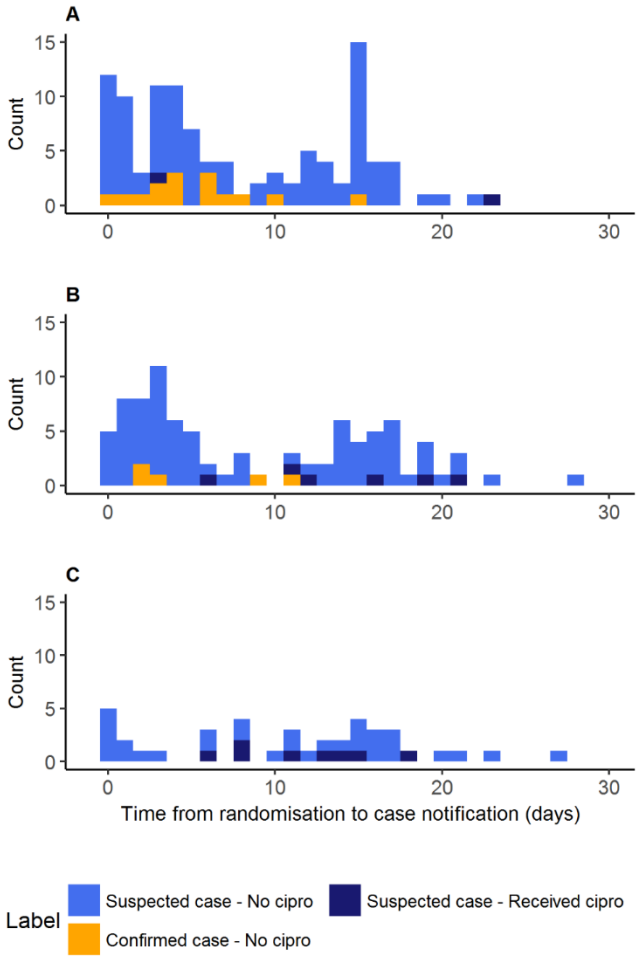
* Adjusted for whether village was included after the first day of rainfall

Coldiron et al. *PLoS Medicine* 2018;15(6): e1002593

Standard care

Household prophylaxis

Village-wide prophylaxis



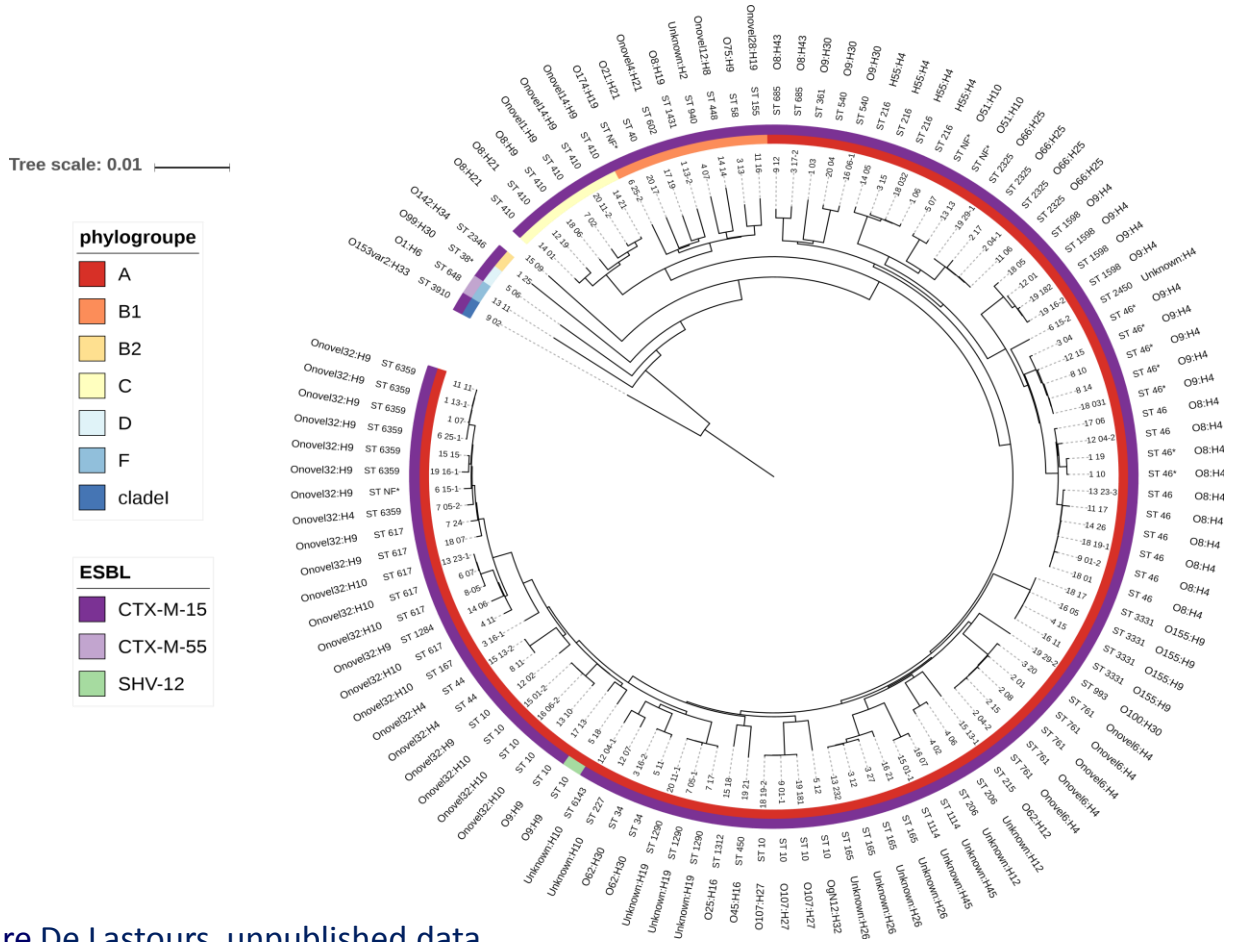
Coldiron et al. *PLoS Medicine* 2018;15(6): e1002593

Resistance sub-study - Results

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

	Standard care	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;15(6): e1002593



Courtesy Victoire De Lastours, unpublished data

Clustering of meningococcal carriage and disease

- MenAfriCar study: 21% of individuals living with a carrier became a carrier
  - Overall acquisition rate 2.4% per month, highest among children
  - But acquisition happens from outside the household too

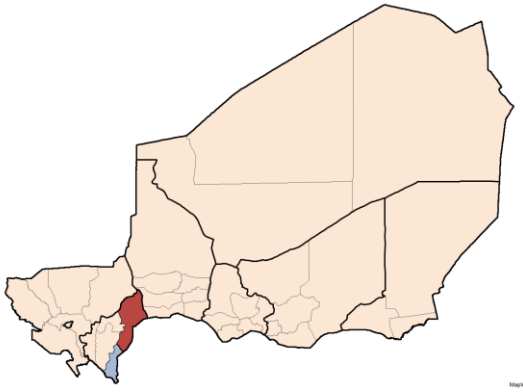
- Niger, Doutchi District, 2015:
  - 346 households affected during epidemic, 13% had more than 1 case
  - Attack rate for subsequent cases in a household >20x the general population

- Hajj pilgrims, 2014:
  - No data on direct disease, baseline carriage among arrivals from meningitis belt low, and reduced at departure post-ciprofloxacin

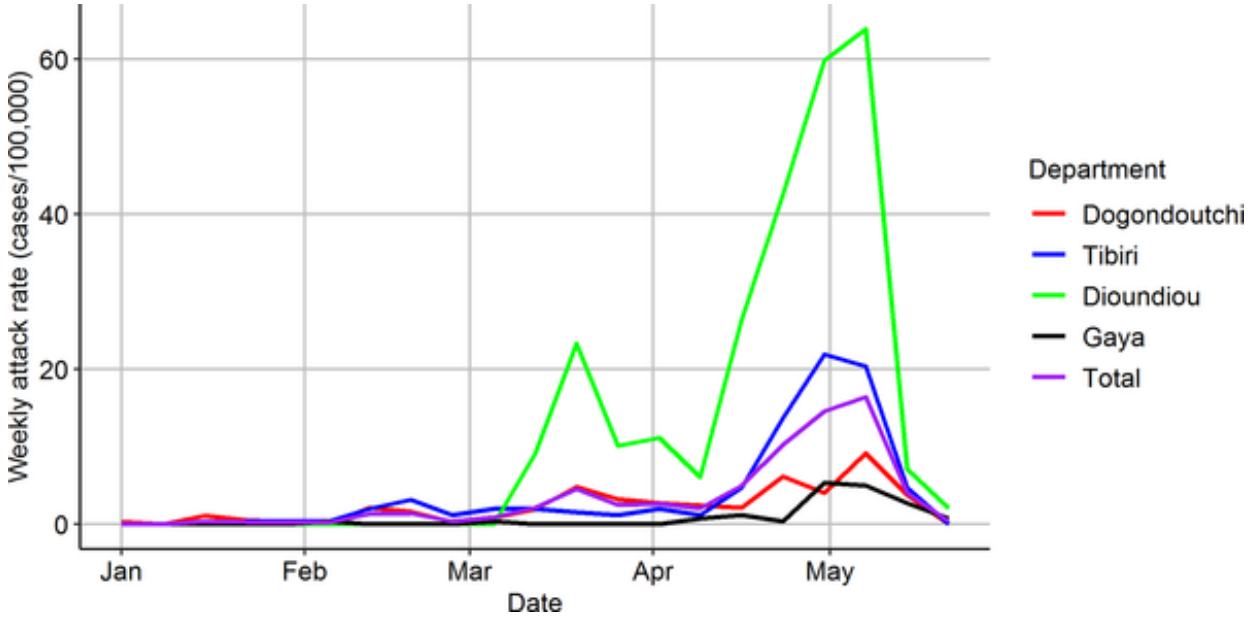
MenAfriCar Consortium. *Lancet GH* 2016;4:e989-95
Coldiron et al. *EID* 2016;22:1827-9
Memish et al. *Vaccine* 2017;35:2473-8

Data sources for modeling study

- 2015 surveillance data from 4 departments
  - Dogondoutchi, Tibiri, Gaya and Dioundiou
  - 752 suspected cases
    - 689 with village name and population
  - 495 cases (66%) had lumbar puncture
    - 291 (59%) confirmed *N. meningitidis* C or W
    - 17 (3%) confirmed *S. pneumoniae*
    - 187 (38%) negative by PCR
- Household survey performed September 2015
  - 348 of 429 cases in Dogondoutchi and Tibiri visited at home to evaluate for sequelae



Doutchi District, Niger, 2015



Hitchings et al. *PLoS NTD* 2019;13(3): e0007077

Model parameters

- Surveillance unit: health area, commune, department
- Epidemic threshold: 3, 5 ,7, 10 cases / 100 000 persons / week
- Prophylaxis given to : household, village, villages within 20km
- Delay from trigger case to protection
  - Prophylaxis: 1, 2, 3, 4, 7 days
  - Vaccination: 28 days
- Duration of protection
  - Prophylaxis: 1-4, 7, 14, 21 days
  - Vaccination: 180 days

Hitchings et al. *PLoS NTD* 2019;13(3): e0007077

Clustering in 2015

- 5% of cases had a previous household contact across the entire season (epidemic and non-epidemic periods)
  - No increased risk for household members during an epidemic compared to village population

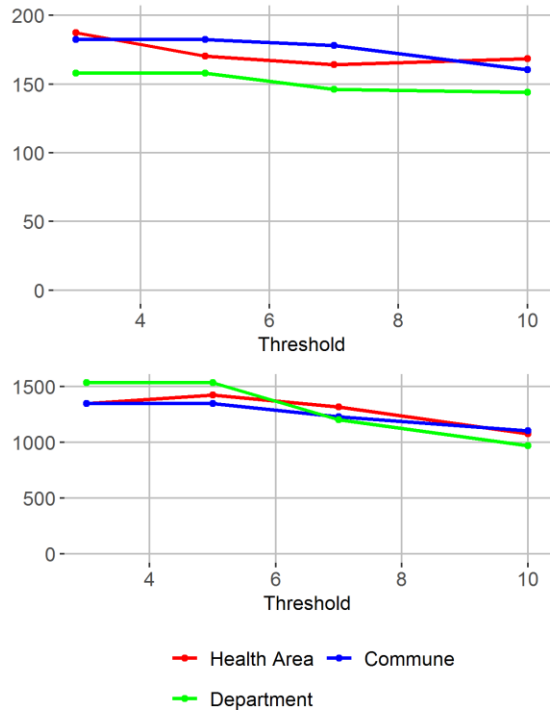
- 62% of cases lived in a village with a previous case

Hitchings et al. *PLoS NTD* 2019;13(3): e0007077

Efficiency of prophylaxis by threshold

Potentially preventable cases

Number needed to treat to prevent one case



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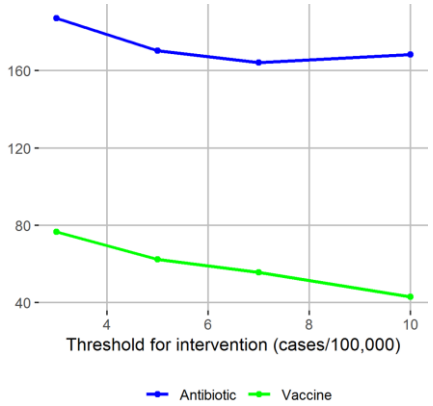
Prophylaxis vs reactive vaccination

Potentially preventable cases



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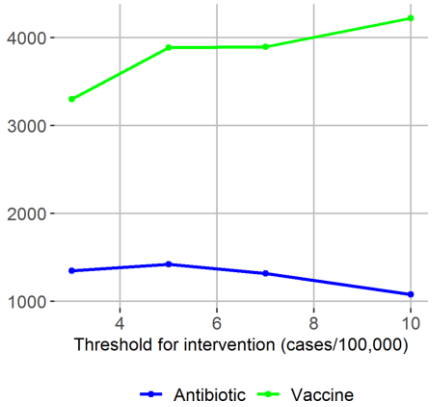

Conclusions

- Village-wide prophylaxis is effective and efficient
  - Significantly cheaper and easier to implement than vaccination
- Speed of intervention allows for greater efficiency compared to reactive vaccination during an epidemic
- Current thresholds appropriate, with emphasis on sub-district level surveillance

Next steps

- Strategic Goal 5 of Defeating Meningitis 2030 Roadmap calls for further research on antibiotic prophylaxis as an epidemic response in African meningitis belt
  - Research protocols approved in Niger and Nigeria if needed
  - Ongoing modeling study using 2015-2017 MenAfriNet databases from Burkina Faso, Niger and Togo

- How much more evidence do we need?


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