Vaccination against cholera in Juba

Stanislas Rebaudet, Jean Gaudart, Renaud Piarroux

promoted, at least partly, by fluoroquinolone resistance itself. But why community transmission of fluoroquinolone-susceptible strains should be more efficient is unclear, particularly since most fluoroquinolone use in our study was in the community. Additionally, if fluoroquinolone resistance itself confers hospital adaptation, reduction of its use would be expected to reduce hospital adaptation; this is not considered in the model.

The second assumption is competition between fluoroquinolone-resistant and fluoroquinolone-susceptible *C difficile* (ie, infection by one precludes infection by the other). This is required for the incidence of susceptible strains to remain unchanged despite hospital infection control interventions. However, as acknowledged by van Kleef and colleagues, this assumption is a simplification; rates of *C difficile* infection with multiple genotypes are about 7%.[2] Third, the model's parameters produce implausibly high *C difficile* prevalence (>20% in the hospital, and 10% in the community), contradicting empirical observations (typically ≤10% in the hospital and about 4% in the community).[3] Both assumptions exaggerate competition in the model.

Fourth, the model assumes that bacteria are transmitted in hospitals exclusively via health-care workers. Although patient-to-patient transmission is modelled in the community, it is not modelled within hospitals and no contribution from the environment or other reservoirs is allowed. This substantially amplifies the effect of any health-care worker intervention.

Fifth, the model considers only asymptomatic colonisation, which is never treated, so the mean 200-day carriage duration of resistant bacteria, regardless of location, might be reasonable. However, for reasons that are unclear, susceptible bacteria are assumed to be lost 3·3 times faster than resistant bacteria in hospitals, but at the same rate in the community. Infections are not directly modelled, despite symptoms of *C difficile* infection being a key determinant of transmission (in contrast with those of MRSA).[4] Instead, the model assumes one in ten colonisations result in symptomatic infections; these would be treated, and most fluoroquinolone-susceptible and fluoroquinolone-resistant isolates are equally susceptible to first-line therapy for *C difficile* infection (metronidazole or vancomycin), giving no advantage to either.

The authors raise an intriguing question that merits careful consideration across a range of health-care-associated infections. We would welcome the opportunity to work with them to explore the performance of their model under realistic assumptions for *C difficile*, particularly to explore why stewardship interventions could achieve *C difficile* control despite previous multifactorial hospital infection control measures not doing so,[5] and why reductions in *C difficile* infection have not occurred in the USA and Canada, despite similar hospital infection control interventions but without fluoroquinolone restriction.

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1 Dingle KE, Didelot X, Quan TP, et al. Effects of control interventions on *Clostridium difficile* infection in England: an observational study. *Lancet Infect Dis* 2017; **17:** 411–21.
2 Eyre DW, Walker AS, Griffiths D, et al. *Clostridium difficile* mixed infection and reinfection. *J Clin Microbiol* 2012; **50:** 142–44.
3 Loo VG, Bourgault A-M, Poirier L, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med* 2011; **365:** 1693–703.
4 Mawer DP, Eyre DW, Griffiths D, et al. Contribution to *Clostridium difficile* transmission of symptomatic patients with toxigenic strains who are fecal toxin negative. *Clin Infect Dis* 2017; published online Feb 3. DOI:10.1093/cid/cix079.
5 Valiquette L, Cossette B, Garant M-P, Diab H, Pepin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis* 2007; **45** (suppl 2)**:** S112–21.

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In an interesting Personal View, Lucy Parker and colleagues[1] reported the difficulties regarding implementation of a reactive oral cholera vaccination (OCV) campaign during the 2015 cholera epidemic in Juba, South Sudan.[1] They support the choice to address the global shortage of vaccines by providing just one dose to twice the number of people. However, the epidemic curve provided by Parker and colleagues suggests that the South Sudan epidemic was not hugely affected by this campaign. Indeed, the basic reproductive number (R_0), which we calculated as previously described[2] using data extracted from this curve with the Plot Digitizer tool and R software, using the R0 package, was not reduced after the campaign was finally launched on July 31, 2015; the R_0 was already less than 1 between the first peak on June 28 and the start of the OCV campaign (0·94 [95% CI 0·92–0·95]), only 0·72 (0·66–0·78) between the second peak on July 19 and the start of OCV, and still 0·92

(0·90–0·94) from the start of OCV until the last confirmed case on Sept 12, 2015.

Several complementary factors might explain such a disappointing effect. First, vaccine effectiveness of this one-dose campaign could have been lower than the 87·3% (95% CI 70·2–100) calculated in a case-cohort observational study by the same group of authors.[3] Efficacy of one-dose OCV was estimated to be about 40% (95% CI 11–60) in a double-blind placebo-controlled clinical trial.[4] Using the WHO screening method[5] with provided data, we calculated that 36% of cholera cases were expected to occur in vaccinated individuals in Juba. The observed proportion was only 6%,[3] which suggests biases that the authors could not address despite their efforts to do so. Second, one-dose OCV did not generate any obvious herd immunity, even in the area targeted by mass vaccination, where coverage reached 64%;[3] surprisingly, vaccine effectiveness tended to be much higher there (97%) than in the non-mass-vaccinated area (66% with 19% coverage),[3] and the calculated cholera attack rate among non-vaccinees was two times higher than in the non-mass-vaccinated area (2·5 *vs* 1·3 cases per 10 000 inhabitants).[3] Finally, this late campaign probably provided little additional protection to a population in which adaptations to water sanitation and hygiene (WaSH) behaviour—rather than acquired immunity—were probably already reducing cholera transmission.

This insightful cholera vaccination field report shows that WaSH activities must remain the cornerstone of cholera control and elimination strategies, even if they are difficult to implement. Reactive vaccination campaigns might help, provided they are promptly rolled out and include two doses as originally recommended.

See Online for appendix

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1 Parker LA, Rumunu J, Jamet C, et al. Adapting to the global shortage of cholera vaccines: targeted single dose cholera vaccine in response to an outbreak in South Sudan. *Lancet Infect Dis* 2017; **17:** e123–27.
2 Azman AS, Rumunu J, Abubakar A, et al. Population-level effect of cholera vaccine on displaced populations, South Sudan, 2014. *Emerg Infect Dis* 2016; **22:** 1067–70.
3 Azman AS, Parker LA, Rumunu J, et al. Effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. *Lancet Glob Health* 2016; **4:** e856–63.
4 Qadri F, Wierzba TF, Ali M, et al. Efficacy of a single-dose, inactivated oral cholera vaccine in Bangladesh. *N Engl J Med* 2016; **374:** 1723–32.
5 Orenstein WA, Bernier RH, Dondero TJ, et al. Field evaluation of vaccine efficacy. *Bull World Health Organ* 1985; **63:** 1055–68.

Authors' reply

Stanislas Rebaudet and colleagues argue that the oral cholera vaccination (OCV) campaign in South Sudan that we described in our Personal View[1] had little effect on the epidemic curve, and that low vaccine effectiveness is the likely explanation. We described the challenges with deploying timely reactive campaigns, claiming nothing about their impact. Outbreak response timeliness greatly dictates effect, and given that cases were consistently declining when the campaign in South Sudan started, we agree that it probably did not have a profound influence on the epidemic curve. Rebaudet and colleagues also make several qualitative and quantitative claims, but we were unable to reproduce most of them (appendix).

Using the WHO screening method, they suggest that the high short-term vaccine effectiveness obtained in our case-cohort study[2] was biased. Using the same method, we calculated the expected proportion of patients with cholera who were vaccinated to be 8%, not 36% as they calculated, compared with the 6% observed, suggesting that this rough method provides similar estimates of vaccine effectiveness to the 87% that we observed in our study (appendix).

Rebaudet and colleagues suggest that adaptations to water sanitation and hygiene (WaSH) behaviour probably reduced cholera transmission, but provide no evidence, and we are not aware of any data supporting this statement. We believe that the ultimate solution to cholera control is universal access to (and use of) safe water, sanitation, and hygiene. The WaSH interventions used during this outbreak primarily consisted of distribution of point-of-use water disinfectant and hygiene promotion, which, although justified during an emergency, are very different from making real gains towards universal access.

Rebaudet and colleagues state that reactive OCV campaigns "might help", but only when a two-dose regimen is used. This is not supported by current evidence: immunological data, observational studies, and clinical trials published to date support single-dose protection.[2–4] Estimates of short-term efficacy of one and two doses of OCV in south Asia are similar, suggesting that, at least in the short-term, one dose might provide similar protection to two doses.[3,5]

Single-dose campaigns allow the vaccinated population to double, with fewer doses, which might improve the effect of reactive campaigns through direct and herd protection.[6] Considering the best evidence available, the South Sudan Ministry of Health made the difficult decision to use the small amount of vaccine available in a single-dose campaign to cover more people. Had a second dose been available, it would have been delivered after the epidemic was over.

More vaccines are urgently needed globally, and although universal solutions to cholera are required, locally tailored interventions using all available effective tools are essential to reduce cholera cases and deaths.