(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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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.

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Short duration of direct-acting antivirals for acute HCV infection

I read with interest the report on the HepNet Acute HCV IV study.[1] Katja Deterding and colleagues[1] reported that a short duration of direct-acting antiviral agents, a ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks, achieved a sustained virological response 12 weeks after the end of treatment in 100% of patients (n=20) with acute hepatitis C virus (HCV) genotype 1 monoinfection. However, only two patients in the study had high baseline viral loads (>1 000 000 IU/mL) and most patients (n=15) had baseline viral loads lower than 100 000 IU/mL.[1] Universal recommendation of short-duration treatment for acute HCV infection in patients with high baseline viral loads remains difficult.

Previous studies have shown that 6-week sofosbuvir-based regimens are suboptimal for patients with acute HCV infection with or without HIV co-infection, especially among those with high baseline HCV viral loads. Martinello and colleagues[2] observed that, with 6 weeks of sofosbuvir plus ribavirin for acute HCV infection, none of eight patients with baseline HCV RNA greater than 1 000 000 IU/mL achieved a sustained virological response 12 weeks after the end of treatment, compared with 55% (six of 11) of those with baseline HCV RNA 1 000 000 $\log_{10}$ IU/mL or lower (p=0·018). After exclusion of patients with reinfection during the follow-up period, occurrence of virological failure was found to be significantly higher among patients with baseline HCV RNA greater than 1 000 000 IU/mL than among those with baseline HCV RNA 1 000 000 $\log_{10}$ IU/mL or lower (100% [eight of eight] vs 33% [three of nine], p=0·009).[2] Nine of the 12 patients who had virological failure had relapsed.[2] Rockstroh and colleagues[3] reported similar results with 6 weeks of ledipasvir-sofosbuvir for treatment of acute HCV infection in patients with HIV co-infection. Treatment failure rate was higher in patients with a baseline viral load 800 000 IU/mL or higher (33% [four of 12]; three relapses and one reinfection) than in those with a baseline viral load lower than 800 000 IU/mL (14% [two of 14]; both patients achieved a sustained virological response 4 weeks after the end of treatment but were lost to follow-up).[3] The three patients who relapsed had baseline viral loads greater than 6·96 $\log_{10}$ IU/mL.[3]

The effect of high baseline HCV RNA viral loads on treatment efficacy, in terms of increased relapse rate, with a short duration of antiviral therapy was also noticed among patients with chronic HCV infection treated with both interferon-based[4] and interferon-free[5] direct-acting antiviral regimens. In the C-SWIFT study,[5] which assessed the efficacy of 6 weeks of grazoprevir/elbasvir plus sofosbuvir in patients with non-cirrhotic HCV genotype 1 infection, the sustained virological response rate 12 weeks after the end of treatment was 69% (nine of 13) in patients with baseline HCV RNA greater than 2 000 000 IU/mL, and 100% (17 of 17) in those with baseline HCV RNA 2 000 000 IU/mL or lower.

Further large-scale studies are therefore needed to establish the effectiveness of 6-week direct-acting antiviral regimens for treatment of HCV infection in patients with high viral loads.

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