A retrospective analysis of oral cholera vaccine use, disease severity and deaths during an outbreak in South Sudan

Cavin Epie Bekolo,a Joris Adriaan Frank van Loenhout,b Jose Manuel Rodriguez-Llanes,b John Rumunu,c Otim Patrick Ramadan,a & Debarati Guha-Sapirb

Objective To determine whether pre-emptive oral cholera vaccination reduces disease severity and mortality in people who develop cholera disease during an outbreak.

Methods The study involved a retrospective analysis of demographic and clinical data from 41 cholera treatment facilities in South Sudan on patients who developed cholera disease between 23 April and 20 July 2014 during a large outbreak, a few months after a pre-emptive oral vaccination campaign. Patients who developed severe dehydration were regarded as having a severe cholera infection. Vaccinated and unvaccinated patients were compared and multivariate logistic regression analysis was used to identify factors associated with developing severe disease or death.

Findings In total, 4115 cholera patients were treated at the 41 facilities: 1946 (47.3%) had severe disease and 62 (1.5%) deaths occurred. Multivariate analysis showed that patients who received two doses of oral cholera vaccine were 4.5-fold less likely to develop severe disease than unvaccinated patients (adjusted odds ratio, aOR: 0.22; 95% confidence interval, CI: 0.11–0.44). Moreover, those with severe cholera were significantly more likely to die than those without (aOR: 4.76; 95% CI: 2.33–9.77).

Conclusion Pre-emptive vaccination with two doses of oral cholera vaccine was associated with a significant reduction in the likelihood of developing severe cholera disease during an outbreak in South Sudan. Moreover, severe disease was the strongest predictor of death. Two doses of oral cholera vaccine should be used in emergencies to reduce the disease burden.

Introduction

Cholera is an extremely virulent diarrhoeal disease that affects both children and adults and can kill within hours if left untreated. Although the disease was largely eliminated from industrialized countries over a century ago by water and sewage treatment, it remains a major cause of morbidity and mortality in many areas of Africa and Asia. Every year, there are an estimated 3 to 5 million cases and 100 000 to 120 000 deaths due to cholera.1 Areas where minimum requirements for clean water and sanitation have not been met, such as peri-urban slums and camps for internally displaced people or refugees, are most at risk.2,3 Although the attack rate of cholera is high, fewer than 25% of those infected become ill.4 Among people who develop symptoms, 80% have mild or moderate disease, whereas around 20% develop acute watery diarrhoea with severe dehydration. As many as 80% can be treated successfully through prompt administration of oral rehydration salts and, with good or adequate fluid replacement (oral or intravenous), mortality is reduced to about 1%.5

The causative agent of cholera, Vibrio cholerae, is autochthonous to aquatic environments and cannot be eradicated. However, hydroclimatology-based prediction and prevention is an achievable goal. Access to clean water and adequate sanitation remain the mainstays of preventing both endemic cholera and cholera outbreaks, and health education can promote the adoption of appropriate hygiene practices.6 Cholera vaccination is increasingly being used as a safe and effective additional tool to supplement existing priority cholera control measures under the right conditions.7,8 In emergencies, vaccines provide immediate, short-term protection while interventions to improve access to safe water and sanitation are put into place. Infectious disease can occur in previously vaccinated individuals: primary breakthrough infections are due to vaccine failure, whereas secondary breakthroughs are due to waning protective immunity. In such cases, the disease is usually milder than in the unvaccinated.7

Two oral cholera vaccines have been prequalified by the World Health Organization (WHO): Dukoral® and Shanchol®.9,10 Dukoral® provides 85–90% protection for 6 months in all age groups, whereas Shanchol® ensures 65% protection for at least 5 years in individuals older than 1 year, both following two doses given at an appropriate interval. There is growing evidence that the vaccine also provides herd protection by interrupting disease transmission. A high level of immunization could, therefore, provide even greater protection to populations at risk.10 In total, more than 1.6 million doses of WHO prequalified oral cholera vaccine have been deployed in mass vaccination campaigns since 1997.7 In 2012, following the adoption of resolution WHA 64.15 by the 64th World Health Assembly in 2011,1 a WHO technical working group recommended that global cholera management should be boosted by creating a stockpile of 2 million doses of oral cholera vaccine for use in emergencies. This stockpile would help ensure that countries have rapid access to vaccine for cholera control.

The cholera vaccine stockpile was first used in 2014 in South Sudan, which peacefully seceded from Sudan in 2011 after 50 years of conflict. The country has a low level of physical, industrialized country over a century ago by water and sewage treatment, it remains a major cause of morbidity and mortality in many areas of Africa and Asia. Every year, there are an estimated 3 to 5 million cases and 100 000 to 120 000 deaths due to cholera.1 Areas where minimum requirements for clean water and sanitation have not been met, such as peri-urban slums and camps for internally displaced people or refugees, are most at risk.2,3 Although the attack rate of cholera is high, fewer than 25% of those infected become ill.4 Among people who develop symptoms, 80% have mild or moderate disease, whereas around 20% develop acute watery diarrhoea with severe dehydration. As many as 80% can be treated successfully through prompt administration of oral rehydration salts and, with good or adequate fluid replacement (oral or intravenous), mortality is reduced to about 1%.5

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The cholera vaccine stockpile was first used in 2014 in South Sudan, which peacefully seceded from Sudan in 2011 after 50 years of conflict. The country has a low level of physical,
Results

In total, 4115 cholera patients were treated at the 41 cholera treatment facilities between 23 April and 20 July 2014. The results of cholera rapid diagnostic tests were available for 258 patients, of which 101 (39.1%) were positive. In addition, V. cholerae culture results were available for 31 patients, of which 22 (71.0%) were positive. However, only a few positive tests are necessary to confirm a cholera outbreak. Of the 4115 affected, 1907 (46.3%) were women and 900 (21.9%) were children younger than 5 years (Table 1). The median age of the patients was 20 years (IQR: 5–32). Eight patients (0.2%) had received one dose of oral cholera vaccine and 75 (1.8%) had received the recommended two doses.

The first case was a 28-year-old man who had received a single dose of oral cholera vaccine and who attended a Médecins Sans Frontières clinic at a camp for internally displaced people in Juba County. Almost 90% of the 4115 patients were observed in two of the nine study counties: 2077 patients (50.5%) in Juba County and 1614 (39.2%) in Torit County (Table 1). The attack rate could not be determined because not all cases were identified. Local health facilities treated 3142 patients (76.4%) – the others were treated in facilities run by Médecins Sans Frontières. The epidemic curve (Fig. 1) depicts the number of cases reported daily between the start of the outbreak in the 17th week of 2014 and the 29th week. The epidemic propagated in two distinct waves: the first wave occurred before the
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25th week and the second, after the 25th week. Most cases, namely 2380 (57.8%), occurred in the second wave. The mean time from disease onset to presentation at a health facility was 0.4 days, although 206 patients (5.0%) sought care more than 1 day after onset.

Of the 4115 cholera patients, 1946 (47.3%) were severe (Table 1). Three of the eight patients (37.5%) who had received one vaccine dose were severe, as were 12 of 74 (16.2%) who had received two doses. After controlling for confounding, multivariate analysis showed that the odds of developing severe disease was around 4.5-fold lower in patients who had received two vaccine doses than in unvaccinated patients (aOR: 0.22; 95% CI: 0.11–0.44; Table 2). Other factors independently linked to lower odds of severe disease included: (i) presentation in the second wave of the epidemic (aOR: 0.43; 95% CI: 0.36–0.53); and (ii) the absence of multiple symptoms (aOR: 0.13; 95% CI: 0.10–0.15). Factors independently associated with higher odds of severe cholera were: (i) presentation more than 1 day after disease onset (aOR: 2.33; 95% CI: 1.53–3.55); (ii) rice-water stools (aOR: 3.25; 95% CI: 2.66–3.96); and (iii) vomiting (aOR: 6.38; 95% CI: 4.28–9.52).

Of the 4115 patients with cholera disease, 62 (1.5%) died (Table 1). None of the eight patients who received one vaccine dose died. The main risk factor for death was severe disease, which was associated with nearly a fivefold increase in odds compared with mild or moderate disease (aOR: 4.76; 95% CI: 2.33–9.77; Table 3). The odds of death was also raised in patients aged 50 years or more compared with younger adults (aOR: 3.42; 95% CI: 1.65–7.08). In contrast, hospitalization was associated with a significantly lower odds of death (aOR: 0.08; 95% CI: 0.03–0.19).

Discussion

We found that pre-emptive vaccination with two doses of oral cholera vaccine was associated with a 4.5-fold reduction in the likelihood of developing severe cholera during an outbreak in South Sudan compared with no vaccination. We were unable to determine whether a single dose was protective against severe disease because few vaccinated cholera patients had received only one dose. There is thus still a need to investigate whether a single dose may offer...
cost-effective protection. As the current recommendation for effective disease prevention is two doses of oral cholera vaccine, it is likely that two doses are required to reduce disease severity in vaccinees who develop clinical disease. Consequently, vulnerable communities should be persuaded to accept and adhere to multiple vaccination campaigns. Our study findings suggest that mass cholera vaccination could be useful in emergency settings or with displaced populations where cholera outbreaks are a likely occurrence. More studies to understand the cost-effectiveness of these interventions are needed.

Our findings contrast with those of an Indian study which failed to show that oral cholera vaccine mitigated against severe disease though there was some evidence of protection against clinical disease. Although the results from this and our study – whether oral cholera vaccine can reduce disease severity – are inconsistent, the beneficial effect of vaccines on the severity of other infectious diseases has been extensively described. Milder disease in vaccinees has been reported with the rotavirus vaccine against rotavirus diarrhoeal disease, the pertussis vaccine, the varicella vaccine and the bacille Calmette–Guérin vaccine against tuberculosis.

We found that the burden of severe disease was greatest in the first half of the outbreak. Consequently, control measures must be put in place as soon as possible during an outbreak; the prepositioning of vaccine stocks in areas prone to epidemics would help. In our study, patients who attended treatment centres more than 24 hours after disease onset were at a greater risk of severe cholera. Raising awareness, case-finding, tracing contacts and setting up treatment facilities close to affected populations would reduce the delay in seeking care. Patients who presented with vomiting or rice-water stools were more likely to suffer severe illness. The presence of rice-water stools may suggest a high bacterial load and should be monitored closely. Patients with vomiting should be admitted for rehydration with intravenous fluids since oral treatment may be ineffective.

Almost half the patients in our study presented with severe illness, perhaps because milder cases were less likely to attend the health facilities from which we obtained our data.

The case fatality rate in our study was 1.5%, which is high given that the benchmark for optimal care is below 1%. However, subsequent reports from South Sudan gave a rate of 2.26% in October 2014. In recent years, the highest case fatality rate in the country was 2.9% in 2006. Between 2007 and 2013, the case fatality rate ranged from 0.07% to 1.8%. More recently, the 2015 outbreak had a case fatality rate of 2.6%. Overall, rates in South Sudan are similar to those reported in Africa as a whole, which average 2%, and to those observed during earlier conflicts in the same region. We were unable to analyse the direct effect of the oral cholera vaccine on death due to cholera because there was only one death among vaccinees who developed the disease. However, since death in cholera results from severe volume depletion and since, in our study, severe dehydration (i.e. severe disease) was the greatest risk factor for death, it is reasonable to conclude that the oral cholera vaccine reduced the number of deaths not only by preventing
clinical disease but also by protecting the vaccinated against severe disease. Cholera is distinctive among diarrhoeal diseases in that mortality is high among patients of all ages in the absence of treatment, though a case fatality rate under 1% can be achieved even in make-shift treatment centres.\textsuperscript{31–33} We found that patients aged 50 years and more are particularly vulnerable in a humanitarian crisis, as are children younger than 5 years and pregnant women. Today, as a consequence of the Sphere Project, which advocates minimum standards for a humanitarian response,\textsuperscript{3} humanitarian relief has improved and outcomes after cholera outbreaks are no longer so far below optimal. Any delay in providing adequate rehydration therapy can result in rapid dehydration, even in patients initially classified as having mild disease. In our study, 11 patients with mild or moderate cholera died. Our data identified hospitalization as strongly associated with an increased chance of survival. Although not all cholera patients must be hospitalized, hospitalization may be an option for all patients in a conflict setting where movement is restricted by insecurity, as occurred in South Sudan.

Our study had several limitations. The overall picture of the cholera outbreak was incomplete because our data did not cover cases in the community, the outcomes of cases still being treated in facilities during data collection or cases that occurred after data collection. Moreover, missing observations may have been subject to recall bias and there was no comparison group. As a result, the case fatality rate may have been underestimated. Neither the attack rate nor the risk of acquiring cholera could be calculated because an adequate denominator was lacking. Moreover, the study lacked the power to determine whether the oral cholera vaccine had an effect on mortality. The observational design meant that it was possible to demonstrate only an association between vaccination and cholera severity and not a causal relationship. However, the strength of the association, the temporal sequence between vaccination and the cholera outbreak, the biological plausibility of the action of the vaccine and the consistency of our findings with current knowledge all suggest that the oral cholera vaccine reduced the burden of cholera during the outbreak. Our assessment of the degree of dehydration was based on indicators that may have been open to subjective interpretation. Nevertheless, patients were diagnosed by trained medical personnel in clinical facilities. In the absence of vaccination cards, information about vaccination status was obtained from the patients themselves, which increased the risk of reporting bias. However, efforts were made to verify vaccination status with family members.

| Table 2. Factors associated with severe cholera, South Sudan outbreak, 2014 |
|---------------------------------|-----------------|-----------------|-----------------|
| **Risk factor**                | **No. of all cholera cases\(^b\)** | **No. of severe cholera cases (%)\(^b\)** | **Risk of severe cholera** |
|                                 | **Univariate analysis** | **Multivariate analysis** | **OR (95% CI)** | **aOR (95% CI)** |
| **Oral cholera vaccine doses, no.** |                             |                             |                |                   |
| 0                               | 3939 (48.9)           | 1926                       | 0.20 (0.11–0.38) | 0.22 (0.11–0.44)  |
| 2                               | 74 (16.2)             | 12                        | Reference       | Reference         |
| **Phase of cholera epidemic**   |                             |                             |                |                   |
| First wave (weeks 17–24 of 2014) | 1733 (71.5)           | 1239                       | Reference       | Reference         |
| Second wave (weeks 25–30 of 2014)| 2295 (30.8)           | 707                        | 0.18 (0.15–0.20) | 0.43 (0.36–0.53)  |
| **Delay before presentation, days** |                             |                             |                |                   |
| ≤ 1                             | 3808 (47.3)           | 1801                       | Reference       | Reference         |
| > 1                             | 203 (65.5)            | 133                        | 2.12 (1.57–2.85) | 2.33 (1.53–3.55)  |
| **Nature of diarrhoea**         |                             |                             |                |                   |
| Clear-water stools               | 1900 (22.0)           | 418                        | Reference       | Reference         |
| Rice-water stools                | 2030 (74.3)           | 1508                       | 10.24 (8.84–11.87) | 3.25 (2.66–3.96)  |
| **Vomiting**                    |                             |                             |                |                   |
| No                              | 340 (10.0)            | 34                         | Reference       | Reference         |
| Yes                             | 3588 (52.9)           | 1898                       | 10.12 (7.06–14.51) | 6.38 (4.28–9.52)  |
| **Multiple symptoms\(^c\)**    |                             |                             |                |                   |
| Yes                             | 2328 (72.9)           | 1697                       | Reference       | Reference         |
| No                              | 1442 (12.9)           | 186                        | 0.06 (0.05–0.07) | 0.13 (0.10–0.15)  |

\(aOR\): adjusted odds ratio; \(CI\): confidence interval; \(OR\): odds ratio.
\(\textsuperscript{a}\): All cholera cases reported at 41 treatment facilities in three states for whom relevant data were available.
\(\textsuperscript{b}\): Percentage of all cholera cases.
\(\textsuperscript{c}\): Multiple symptoms included abdominal, leg or arm cramps, body weakness and headache.

| Table 3. Factors associated with death due to cholera, South Sudan outbreak, 2014 |
|---------------------------------|-----------------|-----------------|-----------------|
| **Risk factor**                | **No. of all cholera cases\(^a\)** | **No. of deaths (%)\(^a\)** | **Risk of death** |
|                                 | **Univariate analysis** | **Multivariate analysis** | **OR (95% CI)** | **aOR (95% CI)** |
| **Age, years**                 |                             |                             |                |                   |
| < 5                            | 700 (2.0)                | 14                         | 1.44 (0.77–2.71) | 1.17 (0.85–3.40)  |
| 5–49                           | 2428 (1.4)              | 34                         | Reference       | Reference         |
| ≥ 50                           | 245 (4.9)               | 12                         | 3.55 (1.81–6.95) | 3.42 (1.65–7.08)  |
| **Cholera severity**           |                             |                             |                |                   |
| Mild or moderate                | 1571 (0.7)              | 11                         | Reference       | Reference         |
| Severe                         | 1720 (2.5)              | 43                         | 3.62 (1.86–7.04) | 4.76 (2.33–9.77)  |
| **Hospitalization**            |                             |                             |                |                   |
| No                             | 87 (1.2)                | 11                         | Reference       | Reference         |
| Yes                            | 3188 (1.6)             | 51                         | 0.11 (0.06–0.22) | 0.08 (0.03–0.19)  |

\(aOR\): adjusted odds ratio; \(CI\): confidence interval; \(OR\): odds ratio.
\(\textsuperscript{a}\): All cholera cases reported at 41 treatment facilities in three states for whom relevant data were available.
\(\textsuperscript{b}\): Percentage of all cholera cases.
In conclusion, this study indicates that two pre-emptive doses of oral cholera vaccine can reduce the severity of cholera disease among vaccinees during an outbreak and thereby reduce the disease burden. Importantly, our data were collected during an outbreak and not simply in an endemic setting. It should be recognized that two doses of oral cholera vaccine are probably necessary and that oral cholera vaccine campaigns should include two rounds. Moreover, oral cholera vaccine should be used in emergencies to reduce the disease burden.

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Competing interests: None declared.

Research
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Objective
To determine if the oral cholera vaccine can reduce the severity of cholera disease among vaccinees in an outbreak and thereby reduce the disease burden. Importantly, our data were collected during an outbreak and not simply in an endemic setting. It should be recognized that two doses of oral cholera vaccine are probably necessary and that oral cholera vaccine campaigns should include two rounds. Moreover, oral cholera vaccine should be used in emergencies to reduce the disease burden.

Déterminer si la vaccination orale préventive contre le choléra diminue la gravité de cette maladie et de la mortalité qui lui est associée lors d’une flambée au Soudan du Sud

Objectif
Déterminer si la vaccination orale préventive contre le choléra diminue la gravité de cette maladie et la mortalité qui lui est associée chez les individus qui attrapent le choléra lors d’une flambée.

Analysis of the use of the oral cholera vaccine, the severity of the disease, and the mortality associated with it in South Sudan

Objective
To determine if the oral cholera vaccine can reduce the severity of cholera disease among vaccinees in an outbreak and thereby reduce the disease burden. Importantly, our data were collected during an outbreak and not simply in an endemic setting. It should be recognized that two doses of oral cholera vaccine are probably necessary and that oral cholera vaccine campaigns should include two rounds. Moreover, oral cholera vaccine should be used in emergencies to reduce the disease burden.

Analyse rétrospective de l’utilisation du vaccin oral contre le choléra, de la gravité de cette maladie et de la mortalité qui lui est associée lors d’une flambée au Soudan du Sud

Objectif
Détecter si la vaccination orale préventive contre le choléra diminue la gravité de cette maladie et la mortalité qui lui est associée chez les individus qui attrapent le choléra lors d’une flambée.
Resumen

Un análisis retrospectivo del uso de la vacuna oral contra el cólera, la gravedad de la enfermedad y las muertes durante un brote en Sudán del Sur

Objetivo Determinar si la vacunación oral preventiva contra el cólera reduce la gravedad de la enfermedad y la mortalidad en personas que desarrollan esta enfermedad durante un brote.

Métodos El estudio involucró un análisis retrospectivo de datos demográficos y clínicos de 41 instalaciones de tratamiento del cólera en Sudán del Sur en pacientes que desarrollaron la enfermedad entre el 23 de abril y el 20 de julio de 2014 durante un gran brote, pocos meses después de una campaña de vacunación oral preventiva. Los pacientes que desarrollaron deshidratación grave fueron diagnosticados con el cólera. Se comparó a los pacientes vacunados con los no vacunados y se utilizó un análisis de regresión logística multivariable para identificar los factores relacionados con el desarrollo de la enfermedad grave o la muerte.

Resultados En total, se trató a 4 115 pacientes con cólera en las 41 instalaciones. 1 946 (47,3%) sufrieron de enfermedad grave y se produjeron 62 (1,5%) muertes. El análisis multivariable mostró que los pacientes que recibieron dos dosis de vacuna oral contra el cólera eran 4,5 veces menos propensos a desarrollar la enfermedad grave en comparación con los pacientes sin vacunar (rapport de cotes ajustado, RCa: 0,22; intervalo de confianza, IC, del 95%: 0,11–0,44). Asimismo, los pacientes con cólera grave tenían muchas más posibilidades de morir que los que no lo padecían (ICa: 4,76; IC del 95%: 2,33–9,77).

Conclusion La vacunación preventiva con dos dosis de vacuna oral contra el cólera se relacionó con una importante reducción de las posibilidades de desarrollar la enfermedad grave del cólera durante un brote en Sudán del Sur. Asimismo, la enfermedad grave fue el mayor indicador de muerte. Deberían utilizarse dos dosis de vacuna oral contra el cólera en urgencias para reducir la carga de la enfermedad.
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