Long-term effectiveness of one and two doses of a killed, bivalent, whole-cell oral cholera vaccine in Haiti: an extended case-control study

Molly F Franke, Ralph Ternier, J Gregory Jerome, Wilfredo R Matias, Jason B Harris, Louise C Ivers

Summary

Background No study of long-term protection following killed oral cholera vaccination has been done outside of the historically cholera-endemic areas of south Asia, or has examined protection after a single-dose vaccination regimen. To address this, we examined the duration of protection of the standard two-dose regimen and an incomplete regimen of one dose up to 4 years after vaccination in Haiti.

Methods In the setting of two-dose vaccination campaigns with a killed, bivalent, whole-cell oral cholera vaccination, we did a case-control study from October, 2012 through November, 2016. Eligible participants were required to be resident in the vaccine catchment area (Artibonite Department or Central Department) where they were recruited at the start of the study; and be eligible for the vaccination campaign (ie, aged ≥12 months, not pregnant, and living in the region at the time of the vaccine campaign). Patients with cholera had a positive stool culture and were recruited from cholera treatment centres. Community controls were matched to people with cholera by age group, time, and neighbourhood. We did adjusted matched regression analyses to calculate vaccine effectiveness and examine heterogeneity in effectiveness over time. The primary outcome was the effectiveness of one and two oral cholera doses as compared with zero doses from 2 months to 48 months after vaccination, measured by self reporting.

Findings Among 178 people assigned to the case group and 706 people assigned to the control group, we found no evidence that two-dose effectiveness decreased during follow-up. In adjusted analyses, the average cumulative 4 year effectiveness for two doses was 76% (95% CI 59–86). In contrast, single-dose effectiveness decreased over time in a log-linear fashion, with a predicted vaccine effectiveness of 79% at the end of 12 months (95% CI 43–93), which declined to zero before the end of the second year.

Interpretation In a setting of epidemic and newly endemic cholera in Haiti, single-dose vaccination with killed, bivalent, whole-cell oral cholera vaccination provided short-term protection; however, vaccination with two doses was required for long-term protection, which lasted up to 4 years after vaccination. These results add to the evidence in support of the use of killed, bivalent, whole-cell oral cholera vaccination as part of comprehensive cholera control plans.

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Introduction

Understanding the effectiveness and duration of protection afforded by oral cholera vaccines is needed to develop effective vaccination programmes. One meta-analysis of killed oral cholera vaccines showed an average protective efficacy of 58% and average protective effectiveness of 73%.1 Although efficacy studies suggest a decline in protection 2 years after oral vaccination1, few studies have reported long-term two dose-effectiveness, and no long-term prospective study of effectiveness has been done outside of Asia, where cholera has been endemic for centuries. The absence of studies of the duration of oral cholera vaccines protection outside the historically cholera-endemic areas of south Asia necessitates evaluating these effects in other populations where conditions of previous and ongoing exposure to *Vibrio cholerae* might differ.

Cholera was introduced to Haiti in 2010, and since then has become endemic. Use of killed, bivalent, whole-cell oral cholera vaccines (Shantha Biotechnics, Hyderabad, India) were first implemented as part of a comprehensive response to cholera in selected high cholera-incidence communities in rural and urban Haiti in April, 2012.2,3 It was in this context that we initially did a case-control study to evaluate the effectiveness of killed, bivalent, whole-cell oral cholera vaccines in the rural campaign catchment area up to 2 years after vaccination.4,5 Killed, bivalent, whole-cell cholera vaccines were subsequently deployed in vaccination campaigns in other communities in Haiti with a high cholera-incidence.

In this case-control study, we expand the analysis of our previously described case-control study of oral cholera vaccines effectiveness in Haiti to evaluate the duration of...
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Evidence before the study
A systematic review of PubMed and meta-analysis published in October, 2017 reviewed randomised controlled trials and observational studies that reported estimates of direct protection against medically-attended cholera conferred by killed oral cholera vaccines (bivalent whole-cell vaccine and or whole-cell vaccine with B-subunit). They included seven trials and six observational studies (in South Asia, African countries, and Peru) and found that vaccination with two doses of killed oral cholera vaccines offered moderate to high protection against medically attended cholera for the first 3 years after vaccination. There was some evidence to suggest protection beyond 3 years. With regard to single-dose protection, few studies had this as a primary endpoint, but those that did found statistically significant protection over the short-term (eg, up to 1 year after vaccination, protection was 69% effectiveness [95% CI 35–85] from two observational studies and 40% efficacy from one trial [95% CI 11–60]). There were no studies with single-dose protection as a primary endpoint with follow-up of more than 6 months after vaccination and all data on single-dose protection were from populations with regularly occurring cholera transmission. To supplement this review, we searched PubMed using the search terms “cholera” and “vaccine” and (“efficacy” or “effectiveness” or “protect”) and without language restriction for articles published from July 9, 2016, to Nov 21, 2017 and identified 36 articles, none of which reported direct protection of vaccination with a single dose of killed oral cholera vaccines or long-term protection with two-dose vaccination, disaggregated over time.

Added value of this study
This study fills three crucial knowledge gaps related to the long-term effectiveness of vaccination with killed, bivalent, whole-cell oral cholera vaccines. First, this is the first study, to our knowledge, to report the field effectiveness of two doses of killed, bivalent, whole-cell oral cholera vaccines up to 4 years after vaccination. We found consistent protection with two killed, bivalent, whole-cell oral cholera vaccines doses, which remained unchanged throughout the 4 years of follow-up (cumulative, adjusted 4 year effectiveness was 76%). Second, we provide the first evidence of long-term protection with two doses of killed, bivalent, whole-cell oral cholera vaccines outside of South Asia, where cholera is historically endemic. The three existing studies of long-term protection of killed oral cholera vaccines were done in India and Bangladesh, where cholera has been endemic for centuries. We did this study in Haiti, where cholera is newly endemic and where ongoing exposure to cholera might differ from places with historically endemic cholera. Third, we provide the first estimates of the duration of protection with a single dose of killed, bivalent, whole-cell oral cholera vaccines. We found a high prevalence of protection during the first year, which declined to zero by the end of the second year after vaccination. These data are crucial for understanding the optimal use of oral cholera vaccines in the context of comprehensive cholera control and prevention.

Implications of all the available evidence
Evidence suggests that although single-dose killed, bivalent, whole-cell oral cholera vaccines campaigns are useful in the short term, two-doses are required for long-term protection. These results add to the evidence in support of the use of killed, bivalent, whole-cell oral cholera vaccines as part of comprehensive cholera control plans and of investment in continued support of a global stockpile of killed, bivalent, whole-cell oral cholera vaccines.

Methods

Study design
The catchment area for the present study corresponded to those of two vaccination campaigns. The first campaign targeted two rural communities (Bocozel and Grand Saline) in the Artibonite Department and took place from April 15 to June 19, 2012, and the second campaign took place in Mirebalais in the Central Department from Aug 25 to Sept 19, 2014. Each campaign aimed to deliver two oral doses of the vaccine 14 days apart. Details on study design, setting, and participant recruitment have been previously described. Participant recruitment began in October, 2012 in the Artibonite Department and November, 2014 in the Central department and occurred continuously through November, 2016. Because the vaccination campaign in the Artibonite Department occurred more than 2 years before the campaign in the Central Department, participants from the Artibonite Department contributed the majority of information regarding effectiveness beyond 24 months.

Eligible participants were required to meet two conditions: residency in the vaccine catchment area where they were recruited at the start of the study and eligibility for the vaccination campaign (ie, aged ≥12 months, not pregnant, and living in the region at the time of the vaccine campaign).

Patients with acute watery diarrhoea—defined as three or more watery, non-bloody stools in a 24 h period with an onset of 3 days or fewer before presentation—were recruited from cholera treatment facilities in the study catchment area. Participants with a stool sample that was culture positive for V cholerae O1 were assigned to the cholera group. Only one person per household was enrolled in the study.

For each person with cholera, four community-based people were recruited from their residences and assigned to the control group. People in the community control
**Procedures**

Stool samples were collected in sterile containers, and transported in Cary–Blair media to the Haitian National Public Health Laboratory in Port-au-Prince or the Enteric Diseases Laboratory in Saint Marc for subsequent culture on thiosulphate–citrate–bile salts–sucrose agar. Identification of *V cholerae* serogroup O1 at the serotype level was done using a standard slide agglutination method. PCR was not routinely available in Haiti for cholera diagnosis during the study period.

To collect data for sociodemographic characteristics, cholera risk factors, and self-reported vaccination, study workers interviewed cholera cases at the cholera treatment facility. Within 2 weeks of enrolment, study workers visited patients in their homes to collect additional information on household water storage receptacles and to request vaccination cards for verification, if applicable. Community controls were recruited from and interviewed at their homes. For children and other participants who were unable to respond to interview questions, guardians or a family member proxy responded. Study workers described a study worker abstracted clinical data from the medical charts of cholera cases.

**Assessment of vaccination**

Oral cholera vaccination was assessed by self-report during the face-to-face interview. Study workers described the vaccine to study participants in terms of its function, timing of delivery, and mode of administration to differentiate it from other vaccines. If the participant reported receiving the oral cholera vaccines, they were asked how many doses they received. We attempted to verify self-reported vaccination by asking individuals who reported receipt of at least one dose of the vaccine to produce their oral cholera vaccination card during the home visit; only 35% of individuals who reported vaccination were able to produce a vaccination card. This result is probably due to the long time (up to 4 years for some participants) since the vaccination campaigns. Additionally, from 2012 to 2014, digital vaccine registers were reviewed in addition to vaccination cards to confirm vaccination status. From 2014 onwards, the campaigns led by the Ministry of Health used paper registries that were not amenable to review by hand. Because self-reported vaccine prevalence more closely approximated known population vaccine coverage estimates, we used this as our primary exposure assessment. We conducted sensitivity analyses in which we (1) considered only verified vaccination status as recorded by cards or registries and (2) prioritised verified information over self-report, but used self-reported information if the patient was unable to produce a vaccination card. The latter approach also has been used in other oral cholera vaccines effectiveness case control studies.

**Statistical analysis**

Because there was a delay between the vaccination campaign and study initiation in each catchment area, we did not have data for vaccine effectiveness during the first 2 months following vaccination. Enrollment in the case control study started 2 months following vaccination. The primary outcome was therefore the effectiveness of one and two oral cholera vaccine doses as compared with zero doses from 2 months to 48 months after vaccination. We used indicator variables to model the number of vaccine doses received (one or two) relative to the reference group of no vaccination. We examined whether vaccine effectiveness changed over time by creating interaction terms for the number of doses received and time between vaccination campaign and cholera diagnosis. Time between vaccination campaign and cholera diagnosis was calculated as the time from the date of vaccination to the date of admission to the cholera treatment centre or interview (if the admission date was missing). The date of each participant’s vaccination was established on the basis of the midpoint of the vaccination campaign dates for each department (May 17, 2012 for Artibonite Department and Sept 6, 2014 for the Central Department) and the location of each participant’s residence. We modelled time since vaccination (up to 48 months after vaccination) as a linear variable and as a natural cubic spline with three equally spaced knots. We compared models with the linear form to those with a spline using the Akaike information criterion. We used Cochran's Q test to test for homogeneity in vaccine effectiveness estimates across the two study sites.

We calculated odds ratios, 95% CIs, and p values using conditional logistic regression, which accounted for matching factors. In multivariable analyses, we additionally adjusted for the following cholera risk factors, identified a priori, that were found to be associated with cholera (at p<0.20) in univariable
Figure 1: Overview of enrolment of cholera cases and community controls

CTC=Cholera treatment centre. HSN=Hospital St Nicholas. RHEMA=J Peter Gruits Medical Center.

- 13,021 individual cases seen by CTC
  - 5,257 HSN
  - 1,399 RHEMA
  - 641 Drouin
  - 3,793 Mirabalais
  - 1,931 Lacolline

11,694 did not meet clinical, residence, or age criteria on initial screening

- 1,527 individuals with diarrhoea invited to participate
  - 1,103 excluded based on factors at detailed screening
    - 27 declined to participate
    - 1,076 ineligible
    - 59 currently live outside of catchment area
    - 82 lived outside catchment area during the campaign
    - 29 were pregnant during the campaign
    - 251 were <1 year old during the campaign
    - 86 received antibiotics before specimen collection
    - 321 did not provide a specimen
    - 316 had bloody or chronic diarrhoea
    - 132 reason unknown

- 414 cases of acute non-bloody diarrhoea treated at a participating centre, met eligibility criteria, and enrolled

- 240 diarrhoea cases
  - 223 culture positive for *Vibrio cholerae*
  - 19 no culture result

- 184 culture positive for *V. cholerae* (cholera case)
  - 6 patients did not meet the criteria

- 178 presented within 4 years of vaccination, reported the number of oral cholera doses received and had >1 control who reported the number of oral cholera doses received
  - 74 cases from the Artibonite Department
  - 104 cases from the Central Department

Matched to 706 community controls by residence, enrolment date, and age group

- 12 patients did not meet the criteria
  - 11 patients had diarrhoea
  - 1 patient did not provide a specimen

Ethical considerations

Written informed consent was obtained for all participants, or from a health-care proxy if the participant was unable to consent. Consent from a parent or guardian was obtained for children younger than 18 years of age, and assent was sought from children aged 7–17 years. The study protocol was approved by Partners Human Research Committee and the Haiti National Bioethics Committee.

Role of the funding source

The study funders had no role in the design of the study; collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.
Results
178 people assigned to the case group and 706 people assigned to the control group were included for analysis (figure 1). 21 of the 177 cases (12%) occurred in children less than 5 years of age. We excluded four people assigned to the cases of cholera group occurring beyond 48 months of follow-up and four participants (two cases of cholera and two controls) for whom we had no information on self-reported number of vaccine doses received (figure 1). Table 1 shows vaccination frequency in cholera cases and controls, stratified by case time from vaccination to cholera diagnosis. 32 cases (18%) occurred more than 2 years after vaccination, with the majority of these (n=23, 72%) occurring in the fourth year, and only nine (28%) cases occurring in the third year after vaccination. Relevant data for sociodemographic characteristics and cholera risk factors for this cohort have been previously reported and are therefore not repeated here.14

Two-dose vaccine effectiveness estimates across the 4 year follow-up period were 70% (95% CI 54–80) for unadjusted data and 76% (59–86) for adjusted data (p<0·0001 for both; table 2). Using Akaike information criterion, we concluded that neither the model with a natural cubic spline (predicted vaccine effectiveness estimates by month shown in appendix), nor the model with a linear interaction fit the data better than the model assuming a constant vaccine effectiveness across the 4 years of follow-up (p value for interaction when time since vaccination was modelled as a linear variable=0·57). The Akaike information criterions for the different models are compared in the appendix. We concluded that two-dose effectiveness did not vary importantly throughout the 4 year follow-up period and that any observed variability was due to chance. The interaction term between two-dose vaccination and time since vaccination was therefore excluded from the final model.

25 cases (14%) and 76 controls (11%) received a single vaccine dose (table 1). Adjusted single-dose effectiveness estimates decreased log-linearly with each month since vaccination ($p_{interaction}=0·0004$; model estimates in appendix), and modelling time since vaccination using a natural cubic spline did not improve model fit relative to the linear form (appendix). We observed high vaccine effectiveness ranging from 96% to 79% during the first year after vaccination, which eventually declined to 0 after month 20, though the lower 95% confidence bound first dropped below 0 after month 16 (figure 2).

The distribution of the cases according to time since vaccination are shown (table 3). Only two (10%) of these 21 cases in children aged less than 5 years of age received a single dose, whereas 13 (62%) received two doses. Unadjusted one-dose vaccine effectiveness was 10% in this group (95% CI −468 to 86), and two-dose vaccine effectiveness was 32% (95% CI −117 to 79). When we restricted analyses to the first 2 years of follow-up, unadjusted one dose was 67% (95% CI −250 to 97) and unadjusted two dose effectiveness was 48% (95% CI −75 to 85). None of these estimates was significant. When we examined vaccine effectiveness in children who were younger than 5 years of age at the time of vaccination (vs at the time of cholera), there were no notable changes (appendix).

Results were similar for both one dose and two dose analyses when we excluded children younger than 5 years of age (table 2, appendix), when we did multivariable analyses on multiply imputed datasets to account for

Table 1: Enrolment of cases and controls, by time since vaccination campaign

| Time since vaccination campaign | Cases (n=178) | Controls (n=706) | Cases (n=74) | Controls (n=291) | Cases (n=104) | Controls (n=415) |
|--------------------------------|--------------|----------------|--------------|----------------|--------------|----------------|
| 0–12 months from vaccination campaign | 54 | 215 | 11 | 44 | 43 | 171 |
| None | 28 (52%) | 70 (33%) | 3 (27%) | 2 (5%) | 25 (58%) | 68 (40%) |
| One dose | 4 (7%) | 23 (11%) | 1 (9%) | 8 (18%) | 3 (7%) | 15 (9%) |
| Two doses | 22 (41%) | 122 (57%) | 7 (64%) | 34 (77%) | 15 (35%) | 88 (51%) |
| 12–24 months from vaccination campaign | 92 | 367 | 34 | 135 | 58 | 232 |
| None | 44 (48%) | 114 (31%) | 10 (29%) | 18 (13%) | 34 (59%) | 96 (41%) |
| One dose | 15 (16%) | 51 (14%) | 2 (6%) | 11 (8%) | 13 (22%) | 40 (17%) |
| Two doses | 33 (36%) | 202 (55%) | 22 (65%) | 106 (79%) | 11 (19%) | 96 (41%) |
| 24–36 months from vaccination campaign | 9 | 36 | 6 | 24 | 3 | 12 |
| None | 1 (11%) | 17 (47%) | 1 (17%) | 8 (33%) | 0 (0%) | 9 (75%) |
| One dose | 1 (11%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (33%) | 0 (0%) |
| Two doses | 7 (78%) | 19 (53%) | 5 (83%) | 16 (67%) | 2 (67%) | 3 (25%) |
| 36–48 months from vaccination campaign | 23 | 88 | 23 | 88 | 0 | 0 |
| None | 12 (52%) | 13 (15%) | 12 (52%) | 13 (15%) | – | – |
| One dose | 5 (22%) | 2 (2%) | 5 (22%) | 2 (2%) | – | – |
| Two doses | 6 (26%) | 73 (83%) | 6 (26%) | 73 (83%) | – | – |

See Online for appendix
the small amount of missing covariate data (table 2, appendix) and when we varied the presumed vaccination dates (appendix). We found no evidence of heterogeneity of effect across the two study sites (appendix) and model estimates were similar when we restricted data to the first two years of follow-up (appendix). We found no evidence of heterogeneity of effect across the two study sites (appendix) and model estimates were similar when we restricted data to the first two years of follow-up (appendix). Average two dose effectiveness was consistent regardless of whether vaccination was assessed by self-report, verification, or a combination of the two methods (appendix). In contrast, single dose effectiveness was similar to primary analyses when we accepted self-report for individuals who could not produce a vaccination card, but was not significantly different from zero when we considered a participant vaccinated only if it could be verified by card or registry (appendix).

Discussion
We found consistent, lasting protection of 76% with two doses of killed, bivalent, whole-cell oral cholera vaccines up to 4 years after vaccination. These data from Haiti are the first, to our knowledge, from outside of Asia to provide evidence for the long-term effectiveness of two doses of killed, bivalent, whole-cell oral cholera vaccines and support the role of vaccination as part of cholera control efforts. Our findings are consistent with the two-dose long-term vaccine protection of killed, bivalent, whole-cell oral cholera vaccines reported in studies done in India (65% and 69%) and Vietnam (50%). Although the long-term effectiveness estimate was lower in the Vietnam study, nearly a third of cholera cases lacked culture confirmation; if some of these clinically diagnosed cases did not have cholera this would have been expected to attenuate vaccine effectiveness estimates. The two-dose vaccine effectiveness we observed in children under 5 years of age, although not significant, corresponds to the average estimates reported in a recent meta-analysis (30% [95% CI 15–42]) and highlights the need for alternative strategies to reduce cholera incidence in this vulnerable group.

Cholera vaccination with the standard two-dose regimen can be challenging, especially in settings of crisis, conflict, or humanitarian emergency. Because of this, the use of a single dose has been proposed as a temporising measure to reduce cholera risk in the short term, leading to an interest in understanding the protective effect of a single dose of oral cholera vaccines. One modelling study suggested that the one-dose approach could avert more cholera cases by generating greater herd immunity relative to what could be achieved by vaccinating fewer
people with two doses; however, these findings were based on scarce short-term single-dose efficacy data. Our estimates of single-dose effectiveness appeared higher or extended, or both, relative to those previously reported; however, confidence intervals around our estimates were wide owing to a relatively small number of individuals who received a single dose (ie, we aimed to give everyone in the campaign two doses). The only single-dose efficacy trial reported 40% (95% CI 11–60) protection over 6 months, whereas a case-cohort analysis reported 87% (70–100) effectiveness within 2 months. We estimated effectiveness at 96% (95% CI 77–99) at 3 months and 93% (69–98) at 6 months. Similarly, although the average of two studies reporting one-dose cumulative effectiveness was 69% (95% CI 35–85) over the course of a year, we found an effectiveness of 79% (43–93) at the end of that year. Importantly, our analysis allowed us to estimate effectiveness at a given point in time, versus providing average estimates over an interval during which effectiveness might be declining; therefore, our estimates are not directly comparable with the averaged estimates.

The benefit of this analytic approach is that it allowed us to examine changes in effectiveness over time. For vaccination with a single, killed, bivalent, whole-cell oral cholera vaccines dose, we found that effectiveness appeared to diminish completely within 2 years; however, confidence intervals included 0% effectiveness after 16 months. Future studies with larger numbers of single-dose recipients will allow more precise estimates of short-term and long-term protection, and additional work is needed to understand the contexts and implementation strategies in which single-dose vaccination is most appropriate and effective.

The limitations of this study include the relatively small number of people vaccinated with a single dose and the relatively small number of cholera cases occurring at 3 years or more after vaccination. These small numbers resulted in wider confidence intervals around single dose effectiveness estimates and could have concealed small declines in two-dose effectiveness over time. Furthermore, we lacked a gold-standard vaccination registry for vaccination assessment. Self-report of the number of vaccine doses received is imperfect as it might be differentially recalled by cases and controls. Relying on vaccination cards for vaccination assessment is also problematic because individuals could misplace their cards. This factor was a common occurrence in the present study: documented vaccine uptake in the Artibonite Department was between 79% and 92% in Bocozel and 63% in Grand Saline; however, only 44% of controls in this region could produce a vaccination card. This could be due to the environmental conditions in which it is difficult to keep paper cards safely stored, or due to a shortage of experience of vaccination cards for adults in the region, or both. This limitation did not appear to affect long-term two dose oral cholera vaccines estimates, which were robust to vaccine assessment method. However, when we calculated one-dose effectiveness using verified vaccination, we were left with only 20% of our initial sample size of participants who reported receiving one dose, and the protective association of a single dose was no longer evident. Although this latter analysis is highly prone to bias, our estimates of the duration of protection associated with a single dose must nonetheless be interpreted with caution.

A third limitation is that we approximated vaccination date on the basis of area of residence at the time of study recruitment and the midpoint date of the vaccination campaign in that catchment area. Given that campaign dates for each catchment area did not span more than 65 days and that results were unchanged in sensitivity analyses using the start and end dates for each campaign, we do not believe this limitation affected our study findings. PCR testing for cholera was not available in Haiti at the time of our study and we relied on stool culture. However, we do not expect the absence of PCR for cholera diagnosis to have affected our results because the consequence of a less sensitive diagnostic would have been the misclassification and subsequent exclusion of cholera cases with a false negative culture result and this is unlikely to be associated with cholera vaccination.

In conclusion, vaccination with two doses of killed, bivalent, whole-cell oral cholera vaccines provided consistent protection against medically attended cholera over 4 years in Haiti, where cholera has recently become endemic. Furthermore, single-dose vaccination offered short-term protection against medically attended cholera. Our findings are generalisable to other settings with epidemic and newly endemic cholera. These results add to the evidence in support of the use of killed, bivalent, whole-cell oral cholera vaccines as part of comprehensive
cholera control plans and add evidence to the investment case for continued support of a global stockpile of killed, bivalent, whole-cell oral cholera vaccines.

Contributors
MFF designed the protocol and analysis, analysed the data, and drafted the first version of the manuscript. LCI conceived of the study, designed the protocol, and contributed to the analysis and interpretation of the data, and the writing of the first version of the manuscript. JBIH contributed to the study design, data interpretation and the writing of the first version of the manuscript. [G], [R], WRM contributed to the study design and data interpretation. All authors critically reviewed the manuscript and approved the final version for publication.

Declaration of interests
We declare no competing interests.

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