Effect of breastfeeding on immunogenicity of oral live-attenuated human rotavirus vaccine: a randomized trial in HIV-uninfected infants in Soweto, South Africa

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Objective To investigate the effect of abstention from breastfeeding, for an hour before and after each vaccination, on the immune responses of infants to two doses of rotavirus vaccine.

Methods In Soweto, South Africa, mother–infant pairs who were uninfected with human immunodeficiency virus (HIV) were enrolled as they presented for the "6-week" immunizations of the infants. Each infant was randomly assigned to Group 1 – in which breastfeeding was deferred for at least 1 h before and after each dose of rotavirus vaccine – or Group 2 – in which unrestricted breastfeeding was encouraged. Enzyme-linked immunosorbent assays were used to evaluate the titres of rotavirus-specific IgA in samples of serum collected from each infant immediately before each vaccine dose and 1 month after the second dose. Among the infants, a fourfold or greater increase in titres of rotavirus-specific IgA following vaccination was considered indicative of seroconversion.

Findings The evaluable infants in Group 1 ($n = 98$) were similar to those in Group 2 ($n = 106$) in their baseline demographic characteristics and their pre-vaccination titres of anti-rotavirus IgA. After the second vaccine doses, geometric mean titres of anti-rotavirus IgA in the sera of Group-1 infants were similar to those in the sera of Group-2 infants ($P = 0.685$) and the frequency of seroconversion in the Group-1 infants was similar to that in the Group-2 infants ($P = 0.485$).

Conclusion Among HIV-uninfected South African infants, abstention from breastfeeding for at least 1 h before and after each vaccination dose had no significant effect on the infants' immune response to a rotavirus vaccine.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Rotavirus is the leading cause of severe gastroenteritis in young children.[1] It was estimated that 453 000 of the deaths – or 37% of all of the diarrhoea-related deaths – that occurred globally in 2008 were attributable to rotavirus infection.[1] In South Africa in 2009, diarrhoea was the leading cause of death among children younger than 5 years and accounted for 18% of the deaths in this age group.[2] In a review of relevant published studies, the median rate of rotavirus detection reported among children hospitalized for diarrhoea in South Africa was found to be 24% (range: 13–55%).[3,4]

Two live oral vaccines against rotavirus – Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq® (Merck Vaccines, Whitehouse Station, United States of America) – have been licensed for international use. Both are being introduced into national immunization programmes, in accordance with World Health Organization recommendations.[5] Clinical trials have demonstrated that the two vaccines are highly effective against severe rotavirus gastroenteritis in middle- and high-income countries in Europe and Latin America.[6,7] However, the vaccines appear to show relatively lower efficacy and immunogenicity in some low- to middle-income countries in Africa and Asia.[8–11] In an African study, two or three doses of Rotarix® were found to reduce the incidence of severe rotavirus gastroenteritis during the first year of life by 77% in South Africa and 49% in Malawi.[8] RotaTeq® was found to have vaccine efficacies – again measured against severe rotavirus disease in the first year of life – of 64% in a multicentre trial in Ghana, Kenya and Mali[9] and of 51% in a separate study based in Bangladesh and Viet Nam.[10] Other live oral vaccines, such as those against polio and cholera and earlier potential rotavirus vaccines, have also shown relatively lower efficacies when tested in low-income countries.[12]

There are several possible reasons why rotavirus vaccines might show relatively lower efficacies in low- and middle-income countries in Africa and Asia. These include interference from high levels of rotavirus-specific antibodies that infants may acquire – either transplacentally or via breastfeeding – from their mothers; the co-administration of oral polio vaccine; micronutrient deficiency; enteric co-infections and other concurrent diseases, such as infection with human immunodeficiency virus (HIV).[11] In trials of earlier vaccine candidates for the control of rotavirus infection, seroconversion was sometimes found to be less common among breastfed infants than among non-breastfed infants who had been given the same number of doses of the vaccine.[13–15] Although there appears to be no evidence to indicate that, during the first year of life, Rotarix® or RotaTeq® shows lower efficacy among breastfed infants than among infants given only formula milk, there has been no detailed attempt to explore this possibility.[16,17] Titres of anti-rotavirus IgA in sera of infants and levels of lactoferrin and rotavirus-specific neutralizing activity in the breast milk of mothers have been shown to vary by setting. For example, breast milk samples from Indian and South African women with low socioeconomic status tend to have

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higher titres of anti-rotavirus IgA and neutralizing activity than those collected from women in the United States.[18–20] Such differences may partially explain why current rotavirus vaccines have relatively poor efficacy in low-income settings. Among infants, the efficacies of both Rotarix® and RotaTeq® appear to be positively correlated with serum titres of rotavirus-specific IgA.[20]

The main objectives of the present study were to determine the titres of rotavirus-specific IgA in infant serum, maternal serum and maternal breast milk in a cohort of HIV-uninfected South African mother–infant pairs, and to investigate the effect of abstention from breastfeeding at the time of vaccination on the immunogenicity of the Rotarix® vaccine.

Methods

Participants and specimen collection

We conducted a prospective, randomized, longitudinal cohort study of consenting, healthy, HIV-uninfected mother–infant pairs. The mothers and infants were enrolled – between 2 December 2009 and 9 April 2010 – as they presented for their "6-week" routine immunization visits at Diepkloof Primary Health Clinic, Soweto, South Africa. Follow-up continued until August 2010. Infants were considered for enrolment if they were aged 5 to 8 weeks, were being breastfed, had received no vaccines except oral polio vaccine and bacille Calmette–Guérin (BCG) at birth and had mothers who had been found seronegative for HIV after week 24 of gestation. Infants with known underlying immunosuppressive conditions and infants showing failure to thrive – that is, infants who fell below the third centile for weight-for-age or had dropped more than two weight-for-age centiles since birth – were excluded. Enrolled infants were randomized into two groups, known simply as Group 1 and Group 2. Mothers of Group 1 infants were instructed not to breastfeed their infants for at least 1 h before and after administration of each dose of rotavirus vaccine. Unrestricted breastfeeding was encouraged among the mothers of Group 2 infants. Breastfeeding of the enrolled infants was monitored at the study clinic as the mother–infant pairs presented for vaccination. The laboratory personnel who tested sera and breast-milk samples were blind to the group allocation.

All vaccines were provided according to the standard schedule of the expanded programme on immunization in South Africa. According to this schedule, each South African infant should be given trivalent oral polio vaccine (OPV-Merieux; Sanofi Pasteur, Lyon, France) at 6 weeks of age, a combination diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus and *Haemophilus influenzae* type b conjugate vaccine (Pentaxim; Sanofi Pasteur) and a hepatitis B vaccine (Heberbiovac HB; Heber Biotec, Havana, Cuba) at 6, 10 and 14 weeks, and rotavirus vaccine (Rotarix®) and a heptavalent pneumococcal conjugate vaccine (Prevenar; Wyeth, Madison, USA) at 6 and 14 weeks.

Serum samples were collected from the infants immediately before the first and second doses of Rotarix® and 1 month after the second dose. Samples of serum and breast milk were collected from the mothers shortly before their infants received each dose of Rotarix®. All of the sera and breast-milk samples were given code numbers to hide the identities of their donors. The samples were kept frozen at −70 °C until they were shipped – on solid carbon dioxide – to the Division of Viral Diseases of the United States Centers for Disease Control and Prevention, in Atlanta, United States, where they were investigated. Titres of anti-rotavirus IgA in all of the sera and breast milk samples, titres of anti-rotavirus IgG in the sera collected from the infants before the first dose of Rotarix®, and levels of rotavirus-specific neutralizing antibodies in the breast-milk samples were evaluated.

The protocol was reviewed and approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (M090824). Written informed consent was obtained from a parent of each enrolled infant. The trial was registered on the South African National Clinical Trial Register (DOH-27–0511–2991).

Specimen testing

Titres of rotavirus-specific IgA were determined in enzyme-linked immunosorbent assays.[18] For these assays, microplate wells were coated with rabbit hyperimmune serum to rhesus rotavirus and incubated either with diluted Rotarix® strain or 5% (v/v) skim milk in phosphate-buffered saline (PBS). After washing, breast milk diluted 1:5–1:5120 in diluent buffer – PBS supplemented with 1% (v/v) skim milk and 0.5% (v/v) of a 10% solution of polyoxyethylene ether W1 – or serum diluted 1:20–1:10 240 in the same buffer – was added to each well, followed by biotin-conjugated goat anti-human IgA antibodies (KPL, Gaithersburg, USA). After incubation and washing, Extravidin (Sigma-Aldrich, St Louis, USA) was added to the wells and incubated, and then the reactions were developed with 3,3′,5,5′-tetramethylbenzidine (Sigma-Aldrich) and stopped with 1 M HCl. The optical density of the contents of each well was determined, at 450 nm, in a plate reader (MRX Revelation; Dynex Technologies, Chantilly, USA).

Anti-rotavirus IgA titres were calculated as the reciprocals of the highest dilutions that gave mean optical densities that were greater than the cut-off value. The cut-off value was set three standard deviations above the mean optical density for the negative-control wells. Rotavirus-specific IgG was tested and analysed in the same manner as IgA except that biotin-conjugated goat anti-human IgG antibodies (KPL) were used and 0.5% (v/v) normal rabbit serum was added to the biotin-conjugate solution.

The level of rotavirus-specific neutralizing activity in each breast-milk sample was evaluated in a microneutralization assay.[18] For this, a twofold serial dilution of each breast-milk sample was prepared and 50 µl of each dilution were mixed with an equal volume of trypsin-activated Rotarix® vaccine virus in the well of a microtitre plate – to yield a concentration of 4000 focus-forming units per well – and incubated at 37 °C for 1 h. The contents of each well were then placed on a PBS-washed monolayer of MA104 cells that had been grown in a 96-well plate. After another incubation at 37 °C for 1 h, the plate was washed with PBS and 100 µl of Iscove's modified Dulbecco's medium (Invitrogen, Carlsbad, USA) containing 5 µg trypsin per ml were added to each well. After incubation at 37 °C for 20 hours, 15 µl of 37% (w/v) formaldehyde were added to each well and left at 4 °C for 30 minutes. Rotavirus antigen in the MA104 cells was detected by incubating plates with a rabbit anti-rhesus-rotavirus hyperimmune serum, then anti-rabbit IgG labelled with horseradish peroxidase, and finally with 3,3′,5,5′-tetramethyl-

benzidine. The neutralizing titre in a breast milk sample was determined as the reciprocal of the highest dilution that showed a reduction in the absorbance value – relative to that in the virus-only controls – of more than 70%.

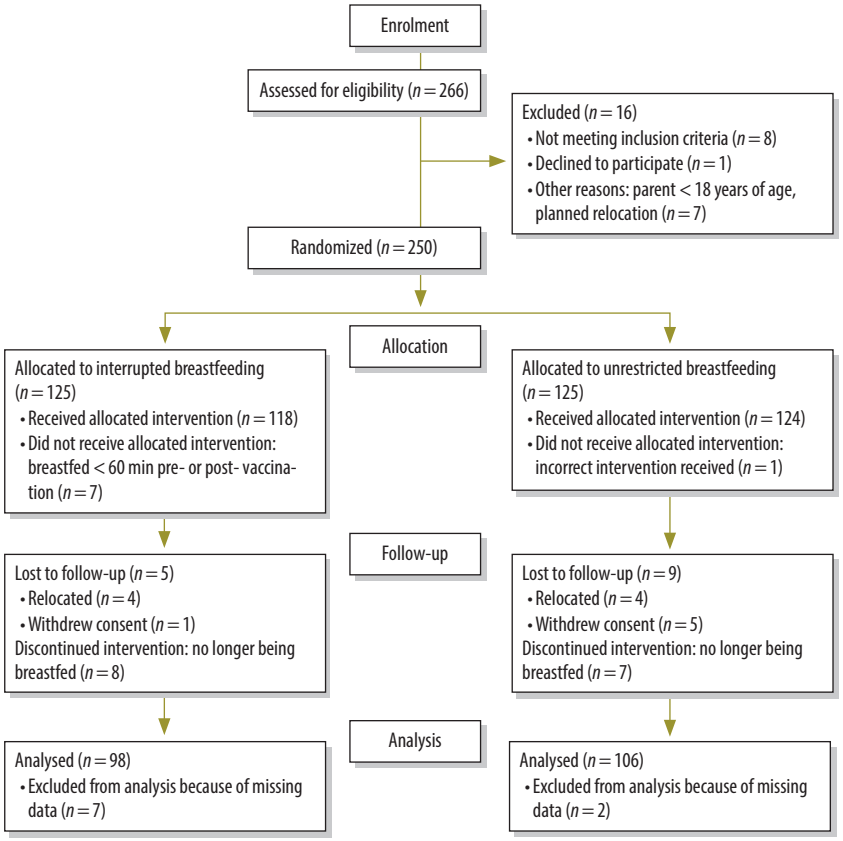
Sample size

The study was powered to detect at least a 20% higher frequency of seroconversion among the Group 1 infants than among the Group 2 infants. It was assumed that about 55% of the Group-2 infants would seroconvert in terms of their anti-rotavirus IgA, since 57% of infants given two doses of the vaccine had previously shown such seroconversion in a trial of the efficacy of Rotarix® in South Africa.[8] After setting a 5% significance level and 80% power and allowing for 20% loss to follow-up, our aim was to enrol at least 123 infants into each of the two study groups.

Statistical analysis

For the allocation of infants to each study group, a randomization list was generated using the SAS software package (SAS Institute, Cary, USA). Data analysis was performed using version 12.1 of the STATA package (StataCorp. LP, College Station, USA). A *P*-value of 0.05 or lower was considered statistically significant. Titres were log-transformed to give a better approximation to a normal distribution. Geometric mean titres were calculated. Continuous variables were compared using two-sample Student's *t*-tests – if the data were normally distributed – or Wilcoxon rank-sum tests. Temporal changes in the log-transformed titres within a single study group were investigated in *t*-tests for matched pairs. Categorical variables were compared using χ^2 tests. For the calculation of geometric mean titres, titres of anti-rotavirus IgA in serum that fell below 20 and titres of anti-rotavirus IgA in breast milk that fell below 5 were each assigned a value of 1. Even the data for infants who had pre-vaccination titres of anti-rotavirus IgA in serum that exceeded 20 were included in the final analyses. Seroconversion was defined as a fourfold or greater increase in anti-rotavirus IgA titre compared with the titre recorded before the first dose of Rotarix®.

Fig. 1. **Flowchart of mother–infant pair enrolment and follow-up in study of the effect of breastfeeding on the immunogenicity of rotavirus vaccine, South Africa, 2009–2010**



Results

In total, 250 infants were enrolled at a median age of 6.1 weeks. At enrolment, each of these infants received a first dose of Rotarix®, oral polio vaccine and other, scheduled, childhood vaccines. Although 125 infants were allocated to each study group, only 98 (78%) of those allocated to Group 1 and 106 (85%) of those allocated to Group 2 were fully adherent to the study protocol and included in the final analysis (Fig. 1). No significant differences were observed – in infant age at enrolment, sex or birth weight or baseline titres of anti-rotavirus IgA and IgG in the infants and their mothers – between the "evaluable" infants who were included in the final analysis and the other enrolled infants (data not shown).

In terms of sex, birth weight and age at vaccination, the evaluable infants in Group 1 were similar to those in Group 2 (Table 1). The second Rotarix® dose was administered at a median of 9.1 weeks (range: 5.4–16.9) after the first dose and subsequent immunogenicity was measured a median of 4.5 weeks (range: 3.9–8.3) later. The timing of these events was similar in the two study groups. When measured before the first vaccine dose, the geometric mean titres of anti-rotavirus IgG and IgA in infant sera and anti-rotavirus IgA in maternal sera and breast milk samples and the geometric mean neutralizing titres in breast milk were also similar in the two study groups (Table 1).

There were no significant between-group differences in the geometric mean titres of anti-rotavirus IgA in infant sera measured after the first ($P = 0.612$) or second doses ($P = 0.685$) of Rotarix® (Table 1). However, in both the Group 1 infants and the Group 2 infants, such mean titres were higher after both the first dose of Rotarix® (53.4 and 46.0, respectively) and the second (137.7 and 122.7, respectively) than the titres recorded before the first dose (14.2 and 14.6, respectively). These within-group temporal changes were all statistically significant ($P < 0.001$).

Compared with the values recorded at baseline, the maternal sera and breast milk samples collected after the infants had received their first dose of Rotarix® also showed significantly higher geometric mean titres – of anti-rotavirus

Table 1. **Comparison of mother–infant pairs assigned to two arms of a study on the effect of breastfeeding on the immunogenicity of rotavirus vaccine, South Africa, 2009–2010**

Infants/mothers	Group[a]		*P*
	1	2	
Infants			
No. evaluated in full	98	106	–
Males, no. (%)	55 (56.1)	57 (53.8)	0.736
Mean birth weight, kg (SD)	3.0 (0.5)	3.1 (0.5)	0.641
Median age, weeks (range)			
On enrolment	6.3 (5.7–7.7)	6.1 (5.9–7.3)	0.200
When investigated after first vaccine dose	15.7 (11.6–23.4)	15.3 (13.9–19.9)	0.418
When investigated after second vaccine dose	20.6 (17.4–27.4)	20.1 (18.0–24.1)	0.408
Serum anti-rotavirus IgG, GMT (95% CI)			
On enrolment[b]	1508.6 (1194.8–1904.9)	1524.7 (1220.4–1904.9)	0.948
Serum anti-rotavirus IgA, GMT (95% CI)			
On enrolment	14.2 (9.8–20.6)	14.6 (10.0–21.5)	0.910
After first dose of vaccine[c]	53.4 (36.7–77.7)	46.0 (29.7–71.3)	0.612
After second dose of vaccine	137.7 (90.2–210.2)	122.7 (84.6–177.9)	0.685
Mothers			
Serum anti-rotavirus IgA, GMT (95% CI)			
On enrolment[d]	26.2 (15.6–44.0)	27.4 (16.5–45.5)	0.908
After infant received first dose of vaccine[e]	164.0 (103.8–259.1)	186.8 (125.4–278.1)	0.670
Breast-milk anti-rotavirus IgA, GMT (95% CI)			
On enrolment[e]	39.3 (28.5–51.6)	42.4 (32.2–55.7)	0.624
After infant received first dose of vaccine[e]	52.2 (39.3–69.2)	56.4 (41.4–76.8)	0.715
Breast-milk neutralizing activity, GMT (95% CI)			
On enrolment	8.8 (6.0–13.0)	8.3 (6.0–11.5)	0.813
After infant received first dose of vaccine[f]	19.1 (12.9–28.3)	21.5 (14.9–31.1)	0.662

CI, confidence interval; GMT, geometric mean titre; SD, standard deviation.
[a] Each infant was randomly assigned to either Group 1 – in which there was an abstention from breastfeeding for at least 1 h before and after each dose of rotavirus vaccine – or Group 2 – in which unrestricted breastfeeding was encouraged.
[b] No data available for four infants (one in Group 1).
[c] No data available for 21 infants (11 in Group 1).
[d] No data available for one mother of an infant in Group 1.
[e] No data available for one mother of an infant in Group 2.
[f] No data available for two mothers (one of an infant in Group 1).

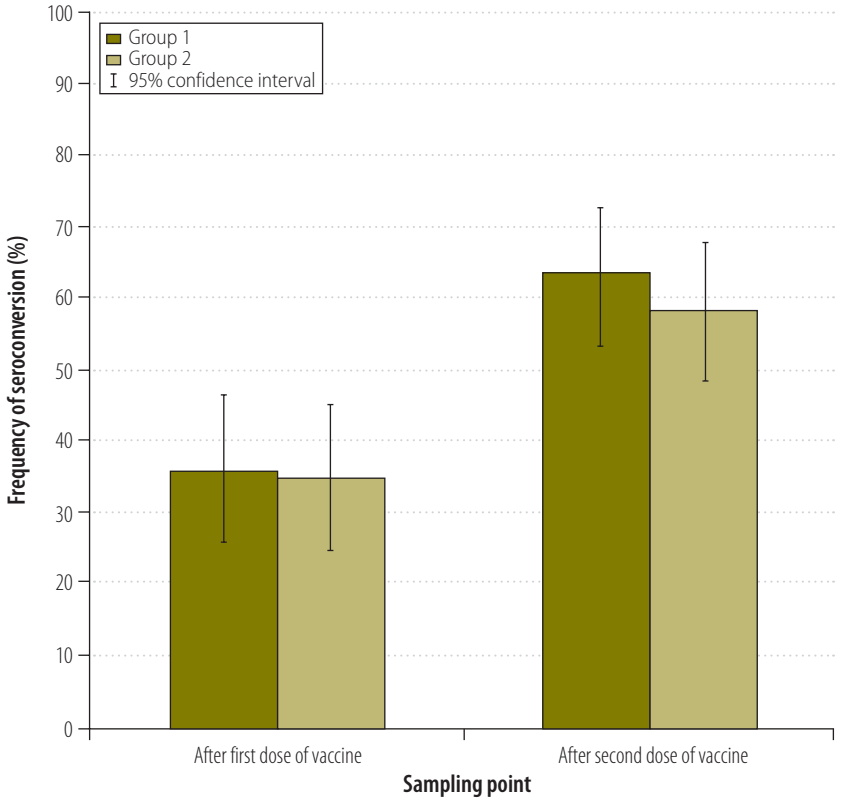
IgA, neutralizing activity or both – in both Group 1 and Group 2 (Table 1). At each time point that we investigated, the distribution of titres among Group 1 infants was similar to that seen in Group 2 (data not shown). There were also no significant between-group differences in the frequency of seroconversion after either one dose ($P = 0.859$) or two doses ($P = 0.485$) of Rotarix® (Fig. 2). The frequency of seroconversion in the whole study cohort was 35% (95% confidence interval, CI: 28–42) after one dose of Rotarix® and 61% (95% CI: 54–68) after two doses.

Discussion

There has been much speculation about the reasons for the relatively low efficacy and immunogenicity of rotavirus vaccines in low- and middle-income countries in Africa and Asia. One hypothesis is that rotavirus-specific antibodies and other neutralizing factors present in breast milk may diminish a breastfed infant's immune responses to a rotavirus vaccine – by lowering the effective titre of vaccine delivered to the infant's gut. This hypothesis was supported by the results of two recent in vitro studies in which levels of lactoferrin, anti-rotavirus IgA and neutralizing activity in breast milk samples from mothers who were breastfeeding their infants were evaluated. Breast milk with low titres of rotavirus-specific neutralizing activity did not seem to affect the vaccine virus but milk with high titres could neutralize the vaccine virus, even when diluted.[18,19] These observations indicated that a short abstention from breastfeeding at the time of each vaccination could potentially improve the immunogenicity of a rotavirus vaccine. However, the results of the present study indicate that abstaining from breastfeeding for at least an hour before and after each of two doses of Rotarix® had no significant effect on the frequency of seroconversion among the vaccinated infants or the titres of anti-rotavirus IgA in the sera of the same infants.

The results of earlier, related in vivo studies – in which the effects of breast milk on immunogenicity and seroconversion after the administration of candidate vaccines against rotavirus were investigated – were equivocal.[21–23] Although each of two meta-analyses led to the conclusion that breastfeeding did significantly reduce the immune response to a single dose of rhesus rotavirus vaccine, the data analysed came from studies that differed markedly in terms of the number of vaccine doses,

Fig. 2. **Frequency of seroconversion in infants assigned to two arms of a study on the effect of breastfeeding on the immunogenicity of rotavirus vaccine, South Africa, 2009–2010**



Note: Each enrolled infant was randomly assigned to either Group 1 – in which there was an abstention from breastfeeding for at least 1 h before and after each dose of rotavirus vaccine – or Group 2 – in which unrestricted breastfeeding was encouraged. The bars indicate the median frequencies of seroconversion observed after one and two doses of rotavirus vaccine.

the antibody assays and the criteria for seroconversion and breastfeeding that were used.[13,14] It appears that the effect of breast milk interference on the immunogenicity of rotavirus vaccines can be overcome by administering more than one dose of vaccine.[15]

Our results are consistent with those of a study on the effects of breastfeeding on antibody response to oral polio vaccine in infants. In this polio study, the frequency of post-vaccination seroconversion among infants on unrestricted breastfeeds was found to be similar to that seen among infants abstaining from breastfeeding for a period of time.[24]

The mothers of both groups of infants enrolled in the present study showed higher titres of anti-rotavirus IgA and rotavirus-specific neutralizing activity after their infants had received one dose of Rotarix® than before this dose. These increases may partly reflect the mothers' natural infection with rotavirus during the peak rotavirus season in South Africa, which generally runs from April to September each year.[4] However, the majority (71%) of the maternal samples collected after the corresponding infants had received one dose of Rotarix® were collected after the rotavirus season of 2009 and before the onset of the rotavirus season of 2010. No attempt was made to check the mothers of the enrolled infants for the signs or symptoms of rotavirus disease. An alternative explanation for the increasing immunogenicity of the mothers to the Rotarix® vaccine strain is that maternal antibodies were boosted by the vaccination of the infants of these women. The conferring of immunity to people in close contact with vaccinated children has been observed in studies on oral polio vaccine[25] and may also occur with rotavirus vaccine. The horizontal transmission of a human rotavirus vaccine strain – from vaccinated children to their unvaccinated twins – was demonstrated in a placebo-controlled study of twins who lived in close contact with each other in the Dominican Republic.[26]

The overall frequency of seroconversion observed in the present study following the second dose of Rotarix® – 61% – is reassuring, bearing in mind that the rotavirus vaccination schedule currently followed in South Africa, of doses at 6 and 14 weeks of age, has not yet been studied in clinical trials. This frequency of seroconversion is similar to the values observed in the South African trial of the clinical efficacy of Rotarix®, which were 57.1% (95% CI: 44.7–68.9) after two doses and 66.7% (95% CI: 54.0–77.8) after three doses.[8] However, comparisons between the efficacy trial and the present study must be made with caution since different assays to assess immunogenicity were used in the two investigations. In the efficacy trial, a commercial enzyme-linked immunosorbent assay with a cut-off point for seroconversion of 20 "units" per ml was used, whereas we used another immunosorbent assay and defined seroconversion as a fourfold or greater increase in an infant's titres of anti-rotavirus IgA. The dosing schedule used in the two investigations also differed: the two-dose group in the efficacy trial received Rotarix® at 6 and 10 weeks of age, while in the present study the same vaccine was given at approximately 6 and 14 weeks of age. The identification of a correlate of protection after rotavirus vaccination has proven difficult, mainly because of differences between the relevant studies in terms of vaccine type, dose schedule, regional pre-immunization titres, laboratory assays and the impact of natural exposure. However, serum titres of anti-rotavirus IgA have been identified as one important predictor of protection.[20]

There were some limitations to our study. The second dose of Rotarix® could only be given to some of the infants one month later than scheduled because the vaccine stocks became exhausted between April and May of 2010. This meant that not all infants received two doses before the onset of the rotavirus season in 2010. Towards the end of our study, therefore, there may have been natural rotavirus in circulation and this could have affected the titres of the antibodies that we investigated, in both the infants and the mothers. However, the level of natural exposure to rotavirus would have been similar in the two study groups and not likely to have affected our conclusions.

We only assessed whether abstention from breastfeeding for about 1 h before and after each vaccination had an effect on immunogenicity. Although it remains possible that a more prolonged abstention may have had a greater impact, leaving an infant unfed for more than 2 h may not be programmatically possible or acceptable. Although the mothers of Group 2 infants were encouraged to breastfeed their infants soon after the vaccines were given, the length of each first feed after the vaccination was not recorded. As suckling is often used as a comfort, a full feed may not have been given at this time. The interaction between vaccine and breast milk in the Group 2 infants may therefore have been less than the maximum possible.

The present study was designed to detect a 20% difference in the frequency of seroconversion between the two groups of infants. A larger sample size may have allowed detection of a significant difference of smaller magnitude. However, policy-makers are unlikely to promote changes in national breastfeeding habits if such changes only lead to small increases in the immunogenicity of rotavirus vaccines given to infants.

Abstention from breast-feeding for 1 h before and after vaccination does not appear to have any significant effect on the immune response to Rotarix® in a low- to middle-income African setting. The reason or reasons that oral rotavirus vaccines appear to have relatively low efficacy in low-income settings – which may include enteric co-infections and concurrent medical conditions – require further investigation. The potential for boosting the efficacy of such vaccines – for example, by zinc supplementation or the co-administration or probiotics – and other approaches to rotavirus vaccination – such as vaccines derived from neonatal strains or parenteral vaccines – should also be investigated. ■

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ملخص

أثر الرضاعة الطبيعية على قابلية اكتساب المناعة للقاح الفيروس العجلي البشري الموهن الحي الفموي: تجربة عشوائية على الرضع غير المصابين بعدوى فيروس العوز المناعي البشري في سويتو، بجنوب أفريقيا

الغرض تحري أثر الامتناع عن الرضاعة الطبيعية لمدة ساعة، قبل كل تطعيم وبعده، على استجابات الرضع المناعية لجرعتي لقاح الفيروس العجلي.

الطريقة في سويتو، بجنوب أفريقيا، تم تسجيل أزواج الأمهات والرضع غير المصابين بفيروس العوز المناعي البشري عند الحضور لتلقي تطعيمات الرضع في سن "6 أسابيع". وتم تخصيص كل رضيع على نحو عشوائي للمجموعة 1 – التي تم تأجيل الرضاعة الطبيعية فيها لمدة ساعة واحدة على الأقل قبل أو بعد كل جرعة من لقاح الفيروس العجلي – أو المجموعة 2 – التي تم تشجيع الرضاعة الطبيعية غير المقيدة فيها. وتم استخدام مقايسات الممتز المناعي المرتبط بالإنزيمات لتقييم عيارات الغلوبولين المناعي A الخاص بالفيروس العجلي في عينات مصل الدم التم تم جمعها من كل رضيع قبل كل جرعة من اللقاح مباشرة وبعد الجرعة الثانية بشهر واحد. وتم اعتبار الزيادة بنسبة أربعة أضعاف أو أكثر في عيارات الغلوبولين المناعي A الخاص بالفيروس العجلي بعد التطعيم بين الرضع مؤشراً على انقلاب تفاعلية المصل.

النتائج تشابه الرضع القابلون للتقييم في المجموعة 1 (العدد=98) مع الرضع في المجموعة 2 (العدد=106) في الخصائص الديمغرافية الأساسية وعيارات الغلوبولين المناعي A المضاد للفيروس العجلي السابقة لتطعيمهم. وبعد جرعات اللقاح الثانية، تشابهت عيارات المتوسط الهندسي للغلوبولين المناعي A المضاد للفيروس العجلي في أمصال دم رضع المجموعة 1 مع العيارات في أمصال دم رضع المجموعة 2 (الاحتمال=0.685) وتشابه معدل تواتر انقلاب تفاعلية المصل في رضع المجموعة 1 مع المعدل في رضع المجموعة 2 (الاحتمال = 0.485).

الاستنتاج لم يكن للامتناع عن الرضاعة الطبيعية لمدة ساعة واحدة قبل كل جرعة تطعيم وبعدها، بين الرضع غير المصابين بفيروس العوز المناعي البشر، أثر كبير على استجابة الرضع المناعية للقاح الفيروس العجلي.

摘要

母乳喂养对人轮状病毒口服减毒活疫苗免疫原性的影响：南非索韦托艾滋病病毒未感染婴儿随机试验

目的 调查在每次疫苗接种之前和之后一个小时避免母乳喂养对婴儿对两剂量轮状病毒疫苗的免疫反应的影响。

方法 在南非索韦托，在提出"6周"婴儿免疫接种的母婴对中招募未受艾滋病毒（HIV）感染的母婴对。将每个婴儿随机指定到第1组（该组在每剂轮状病毒之前和之后至少隔开1小时母乳哺育）或者第2组（该组鼓励不受限制的母乳喂养）。使用酶联免疫吸附试验评估在每剂疫苗即将接种时和接种第二剂之后1个月所收集每个婴儿血清样本中的轮状病毒特异性IgA滴度。在这些婴儿当中，如果疫苗接种之后轮状病毒特异性IgA的滴度出现四倍或更多的增加，则表示出现血清转换。

结果 在基线人口特征和疫苗接种前抗轮状病毒IgA滴

度方面，第 1 组（n=98）和第 2 组（n=106）可评估婴儿的结果相似。在第二剂疫苗接种之后，第 1 组婴儿血清抗轮状病毒 IgA 的几何平均滴度与第 2 组婴儿血清中的滴度相似（P=0.685），第 1 组婴儿血清转化率和第 2 组第 2 组婴儿相似（P=0.485）。

结论 在南非未受艾滋病毒感染的婴儿中，在每剂疫苗接种之前和之后一个小时避免母乳喂养对婴儿对轮状病毒疫苗的免疫反应没有显著影响。

Résumé

Effet de l'allaitement sur l'immunogénicité du vaccin oral vivant atténué contre le rotavirus humain: un essai randomisé parmi les nourrissons séronégatifs à Soweto, en Afrique du Sud

Objectif Étudier l'effet de l'abstention d'allaitement, une heure avant et après chaque vaccination, sur les réactions immunitaires des nourrissons à deux doses de vaccin contre le rotavirus.

Méthodes À Soweto, en Afrique du Sud, des couples mère-enfant non infectés par le virus de l'immunodéficience humaine (VIH) ont été inscrits à cette étude, alors qu'ils se présentaient pour les vaccinations des nourrissons de 6 semaines. Chaque enfant a été placé au hasard dans le groupe 1 – au sein duquel l'allaitement était reporté au moins d'une heure avant et après chaque dose de vaccin contre le rotavirus - ou dans le groupe 2 - au sein duquel l'allaitement sans restriction a été encouragé. Des dosages immuno-enzymatiques ont été utilisés pour évaluer les titres d'IgA spécifiques du rotavirus dans des échantillons de sérum prélevés chez chaque enfant immédiatement avant chaque dose de vaccin et un mois après la deuxième dose. Chez les nourrissons, une augmentation par 4 ou plus des titres d'IgA spécifiques du rotavirus après la vaccination a été considérée comme une indication de séroconversion.

Résultats Les nourrissons évaluables du groupe 1 *(n* = 98) étaient similaires à ceux du groupe 2 *(n* = 106) en ce qui concernaient leurs caractéristiques démographiques de base et leurs titres d'IgA anti-rotavirus avant la vaccination. Après les deuxièmes doses de vaccin, les titres moyens géométriques d'IgA anti-rotavirus du sérum des nourrissons du groupe 1 étaient semblables à ceux du sérum des nourrissons du groupe 2 *(P* = 0,685), et la fréquence de séroconversion des nourrissons du groupe 1 était semblable à celle des nourrissons du groupe 2 *(P* = 0,485).

Conclusion Chez les nourrissons non infectés par le VIH en Afrique du Sud, l'abstention d'allaitement pendant au moins une heure avant et après chaque dose de vaccination n'a eu aucun effet significatif sur la réaction immunitaire des nourrissons à un vaccin contre le rotavirus.

Резюме

Влияние грудного вскармливания на иммуногенность пероральной живой вакцины ослабленного ротавируса человека: рандомизированное исследование среди ВИЧ-неинфицированных младенцев в Соуэто (Южная Африка)

Цель Исследовать эффект воздержания от грудного вскармливания в течение часа до и после каждой вакцинации двумя дозами ротавирусной вакцины на иммунные реакции младенцев.

Методы В исследовании, проводимом в Соуэто (Южная Африка), принимали участие пары мать-ребенок, не зараженные вирусом иммунодефицита человека (ВИЧ) и проходящие «6-недельную» иммунизацию младенцев. Каждый ребенок был случайным образом распределен в одну из групп: группу 1, в которой грудное вскармливание не проводилось, по крайней мере, в течение 1 часа до и после введения каждой дозы ротавирусной вакцины, или группу 2, в которой матерям было предложено неограниченное грудное вскармливание. Для оценки титра антител IgA к ротавирусу в образцах сыворотки использовался иммуноферментный анализ сыворотки, отбираемой у каждого младенца непосредственно перед введением каждой дозы вакцины и через один месяц после введения второй дозы. Увеличение в титрах ротавирусных антител IgA в четыре и более раз после вакцинации считалось показателем сероконверсии у младенцев.

Результаты Дети в группе 1 (*n* = 98) были похожи на детей в группе 2 (*n* = 106) по своим базовым демографическим характеристикам и титрам антиротавирусных антител класса IgA, полученным в ходе предварительной вакцинации. После введения второй дозы вакцины средние геометрические величины титров анти-ротавирусных IgA в сыворотке детей из группы 1 были аналогичны данным величинам у детей из группы 2 (*P* = 0,685), а частота сероконверсии среди детей в группе 1 была такой же, как и у детей в группе 2 (*P* = 0,485).

Вывод Среди ВИЧ-неинфицированных южноафриканских младенцев воздержание от грудного вскармливания, по крайней мере, в течение 1 часа до и после каждой дозы вакцины не оказало существенного влияния на иммунный ответ младенцев на вакцину против ротавируса.

Resumen

Efecto de la lactancia materna en la inmunogenicidad de la vacuna oral contra el rotavirus humano vivo atenuado: un estudio aleatorizado en lactantes infectados por el VIH en Soweto, Sudáfrica

Objetivo Investigar el efecto de la abstención de la lactancia materna, una hora antes y después de cada vacuna, en las respuestas inmunes de los lactantes a dos dosis de la vacuna contra el rotavirus.

Métodos En Soweto, Sudáfrica, se inscribieron parejas de madres-bebés que no estaban infectados por el virus de la inmunodeficiencia humana (VIH), ya que se sometieron a las inmunizaciones de «seis semanas» de los lactantes. Se asignó al azar a cada niño al Grupo 1 – en el cual se aplazó la lactancia materna al menos 1 hora antes y después de cada dosis de la vacuna contra el rotavirus – o al Grupo 2 – en el cual se fomentó la lactancia sin restricciones. Se utilizaron ensayos de inmunoadsorción enzimática para evaluar los títulos de IgA específica de rotavirus en muestras de suero recogidas de cada lactante inmediatamente antes de cada dosis de vacuna y 1 mes después de la segunda dosis. Entre los lactantes, un incremento cuádruple o mayor en

los títulos de IgA específica de rotavirus tras la vacunación se consideró indicativo de seroconversión.

Resultados Las características demográficas de base y los títulos de vacunación previa de la IgA antirrotavirus de los lactantes evaluables del Grupo 1 ($n = 98$) fueron similares a los del Grupo 2 ($n = 106$). Tras la segunda dosis de la vacuna, los títulos de la media geométrica de la IgA antirrotavirus en los sueros de los lactantes del Grupo-1 eran similares a los de los sueros de los lactantes del Grupo-2 ($P = 0,685$) y la frecuencia de la seroconversión en los lactantes del Grupo-1 fue similar a la de los lactantes del Grupo-2 ($P = 0,485$).

Conclusión Entre los lactantes sudafricanos infectados por el VIH, la abstención a la lactancia materna durante al menos 1 hora antes y después de cada dosis de la vacuna no tuvo efectos importantes en la respuesta inmune de los lactantes a la vacuna contra el rotavirus.

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