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The distinct impact of maternal antibodies on the immunogenicity of live and recombinant rotavirus vaccines

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ABSTRACT

A high titre of maternal antibodies is one of the possible factors associated with decreased rotavirus vaccine efficacy in low-income countries where rotavirus-associated morbidity and mortality are high. Although some studies show a negative correlation between maternal antibody levels and seroconversion after vaccination, withholding breastfeeding does not improve rotavirus vaccine efficacy. Different types of recombined vaccines were developed as an alternative to produce higher protection in developing areas. In previous studies, we found that recombinantly expressed, truncated VP4* can stimulate high titres of neutralizing antibodies and can confer protection against rotavirus infections and rotavirus-induced diarrhoea. In this study, the impact of maternal antibodies on live and recombinant rotavirus vaccines (VP4*) was evaluated in a mouse model. Dams were infected orally with murine rotavirus 7 days after delivery to mimic a natural rotavirus infection in infants and to evaluate the separate effects of trans-placentally acquired and milk-acquired maternal antibodies, pups were half exchanged. After immunization with live rotavirus, both the neutralizing antibody and IgA antibody responses were inhibited by maternal antibodies, especially by milk antibodies; however, the neutralizing antibody responses after immunization with recombinant VP4* were enhanced. In addition, the *in vitro* incubation of VP4* with immune sera of rotavirus could also enhance the immune responses could also enhance the immune responses. Our finding provides a basis for the development of non-replicating vaccines to address the problem of live attenuated vaccines in low- and middle-income countries.

1. Introduction

Rotavirus is the leading pathogen associated with severe diarrhoea in infants and in children younger than 5 years old. The annual mortality due to rotavirus infection is approximately 146,480 deaths worldwide, and the mortality rate is higher in developing countries in Africa and Asia [1]. Two live attenuated rotavirus vaccines, Rotarix® (GlaxoSmithKline Biologicals) and RotaTeq® (Merck & Co., Inc.) have been licensed worldwide [2] and have been shown to be effective in high-income countries (HIC) [3,4]. However, the protective efficacy of these vaccines was found to be lower than 60% in some low- and middle-income countries (LMIC), where the vaccine was most needed to reduce rotavirus-related morbidity and mortality [5,6].

Many explanations have been proposed to clarify the divergence in the efficacy of rotavirus vaccines in different areas, including maternal antibodies [7-10], co-administration with the oral polio vaccine [11,12], co-infections, chronic diseases [13], malnutrition [14], and histo-blood group antigen type [15]. Among these factors, the impact of maternal antibodies has been the most widely investigated. However, all the results were based on cohort studies, and some of results were even conflicting.

For both Rotarix® and RotaTeq®, it has been found that the sera responses after vaccination were negatively associated with the rotavirus IgG and IgA antibody levels in infants before vaccination [8,9,16]. This is consistent with the finding that the seroconversion rate in infants after vaccination was higher in infants born to mothers with lower levels of rotavirus-specific antibodies in the serum and milk [8,9,16,17]. For another monovalent vaccine, 116E, it was also found that the high titres of transplacental rotavirus-specific IgG antibodies could diminish the immune responses of infants to the vaccine [18]. A study in Zambia also showed that higher

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maternal breast milk IgA titres prior to immunization were associated with a lower frequency of infant seroconversion [7]. It was hypothesized that maternally acquired, rotavirus-specific antibodies may have an inhibitory effect on the infectivity of live attenuated vaccine viruses in the gut and may thereby inhibit the infant's active response to immunization [19]. However, studies in Nicaragua and South Africa have also shown that rotavirus-specific IgA antibodies in breast milk were not correlated with seroconversion after vaccination [8,9]. In addition, the withholding or absence of breastfeeding did not improve the efficiency of the vaccine [20-23].

It was proposed that non-replicating vaccines may provide higher protective efficacy in areas with high levels of maternal antibodies [24,25]. However, the impact of maternal antibodies on non-replicating vaccines also had conflicting results from different cohort studies of various pathogens. For the inactivated poliovirus vaccine, the vaccine efficacy was higher compared to the efficacy of a live poliovirus vaccine; however, the high titres of maternal antibodies have been proven to be associated with a lower immune response after immunization with the inactivated poliovirus vaccine [26]. For recombinant hepatitis B vaccines, Zhang L et al. found that the antibody responses were inhibited by high titres of maternal anti-HBs (>1000 mIU/ml) [27]. In contrast, the results of Zhang W et al. [28] showed that maternal immunization had no inhibitory effect on the immune response of neonates.

The discrepancy in the conclusion of different cohort studies could be due to the different criteria used to evaluate the level of pre-existing maternal antibodies and the final immunization efficiency. In particular, the individual effects of maternal antibodies from breastfeeding or the placenta could not be individually analysed in the cohort studies while avoiding the effects from each other. This situation results in a call for future studies in an animal model, which could not only be used to mimic the controlled production of maternal rotavirus-specific antibodies but also avoids the cross-effects between the breast milk antibodies and the placental antibodies.

In this study, the impact of maternal antibodies on the immune responses of live rotavirus or recombinant antigen was analysed in a mouse model. The dams were challenged with rotavirus EDIM three times to stimulate maternal antibody production, and the pups were exchanged for feeding after delivery to analyse the impact of placentally acquired and milk-acquired maternal antibodies. The pups were immunized with live rotavirus EDIM or with recombinant EDIM-VP4* as described in our previous studies [29]. The results show that the maternal antibodies inhibited the immune response elicited by the live rotavirus vaccines but enhanced the response elicited by recombinant VP4*.

2. Materials and methods

2.1. Viruses

The murine rotavirus strain EDIM (G16P[16]) was kindly donated by the Institute of Pathogen Biology at the Chinese Academy of Medical Sciences (Beijing, China). The EDIM strain was propagated in neonatal mice. BALB/c mice at approximately 7 days of age were orally inoculated, and their stool was collected every day after the challenge until they no longer had diarrhoea (approximately 7 days after the infection). The diarrhoea stool was resuspended in PBS (1:10 in volume), vortexed and centrifuged at 1000 rpm/min for 5 min. Then, the supernatant was divided into 500 μl sterile tubes and was stored at −80 °C until use.

2.2. Expression and purification of rotavirus VP4*

The EDIM and LLR-truncated VP4 protein (VP4*, aa residues 26–476) was produced in the *E. coli* expression strain BL21 (DE3) and was purified as previously described [29]. The purity of the proteins was assessed by SDS-PAGE, and the concentration was measured by a BCA assay (Thermo Fisher Scientific, Shanghai, China) according to the manufacturer's instructions.

2.3. Immunization of the dams

Seven-day-old BALB/c mice were divided into two groups and were immunized with rotavirus EDIM to mimic a natural infection, and PBS was used as a control. Fifty dams were orally infected with three doses of 200 μl EDIM virus containing 10 × 50% shedding dose (10 × SD_{50}), and 50 dams were inoculated with the same volume of PBS every two weeks before mating. Two dams that delivered on the same day were regarded as one pair. Finally, 18 pairs were chosen for immunization with EDIM virus, EDIM-VP4*, or PBS (n = 6). The serum samples were collected prior to the first dose of immunization and 2 weeks after each immunization.

2.4. Exchange of the pups and grouping

Two weeks after the last immunization, the dams were mated and delivered approximately 21 days later; half of the pups were exchanged after birth, as shown in Fig. 1, to generate four different maternal antibody groups. For each maternal antibody group, the pups were further divided into three groups and were vaccinated with live rotavirus EDIM, recombinant EDIM-VP4* or PBS (as a control) three times at postnatal days 7, 14 and 21.

2.5. Immunization of newborn mice.

For live rotavirus, it was orally vaccinated with 200 μl of rotavirus EDIM (10 × SD_{50}); for recombinant EDIM-VP4*, 10 μg of VP4* (100 μl) was mixed 1:1 (v:v) with an aluminium adjuvant, and the mice were vaccinated by intraperitoneal injection the first two times and were intramuscularly vaccinated the last time.

2.6. Preparation of serum antibodies and recombinant VP4 complex and vaccination.

EDIM or LLR-VP4* antibody-containing serum was obtained from mice immunized as previously described [29], and the control mouse serum was obtained from neither the rotavirus-infected nor immunized mice. VP4* antibody-containing serum and the control mouse serum were heat-inactivated for 30 min at 56 °C, after which they were passed through a 0.22 μm filter and were stored at −80 °C until use.

EDIM-VP4* or LLR-VP4* antibody-containing serum was mixed with 10 μg LLR-VP4* in different molar ratios (Ag/Ab, 2:0.1, 2:1, 2:10) for 1 h at room temperature to allow the Ag/Ab complex conformation. The estimated levels of LLR-VP4* antibodies and EDIM-VP4* antibodies in the serum were 6 mg/ml and 3.5 mg/ml, respectively and were evaluated using ELISA (Supplementary materials).

Recombinant LLR-VP4* (10 μg) was mixed with serum samples in different molar ratios (2:0.1, 2:1, 2:10) and was incubated at room temperature for 1 h before mixing with the appropriate aluminium adjuvant. Five- to six-week-old female BALB/c mice were divided into groups, and each group contained 7 mice. Groups of mice were intramuscularly immunized with different molar ratios of Ag/Ab complexes containing the aluminium adjuvant (1:1) three times at 0, 14 and 28 days. The serum samples were collected

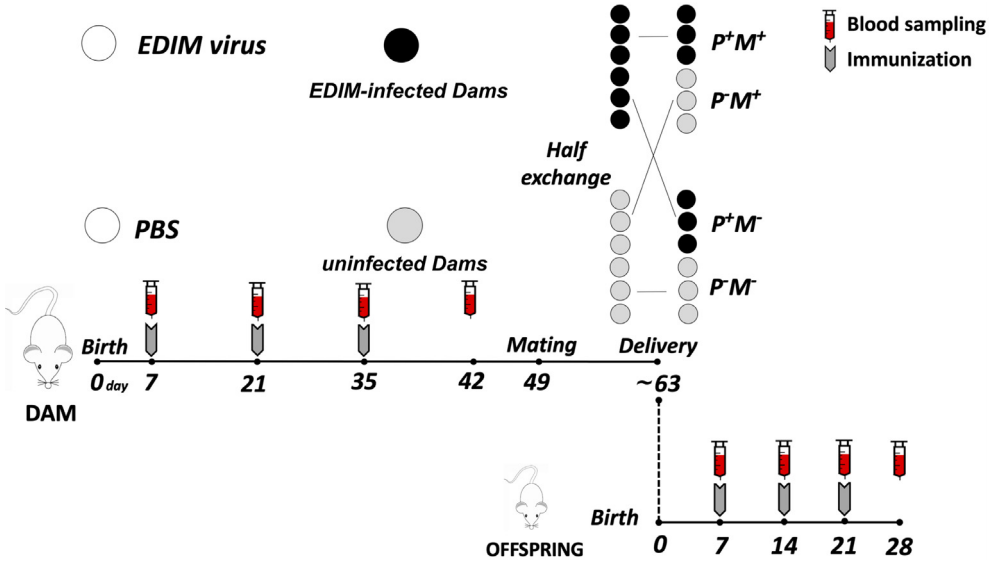

Fig. 1. The flowchart of the experiment. P^+M^+: maternal antibodies derived from both the placenta and the milk; P^-M^+, maternal antibodies derived from the milk only; P^+M^-, maternal antibodies derived from the placenta only; P^-M^-, no maternal antibodies.

individually from the mice before the first dose of immunization and 2 weeks after each dose of immunization.

2.7. Neutralization assay

The neutralizing antibody titres of each serum sample were determined by an ELISPOT assay similar to a previously described assay [30]. Briefly, an aliquot of 100 µl of 2-fold serially diluted serum samples was mixed with 100 µl of rotavirus EDIM, which was trypsin-activated by an incubation at 37 °C for 1 h. Then, this 200 µl mixture was added to a MA104 monolayer plated 20 h before and was then incubated for 14 h at 37 °C. The inhibition (%) was calculated as 100 × [1− (average number of spots in experimental wells/average number of spots in control wells)]. The reciprocal of the serum dilution with a 50% reduction in the spot number compared to that of the control was considered to be its neutralizing antibody titre.

2.8. Enzyme-linked immunosorbent assay

Three monoclonal antibodies (VP4-specific mAb: 8G3, 5B5; rotavirus-neutralizing mAb: E5), were used to determine the relationship of the absorbance with the level of antibodies, and the estimated level of VP4*-specific antibodies was quantified based on the absorbance. Next, 100 µl of 2-fold serially diluted monoclonal Abs was added to the microplates coated with VP4*, and the microplates were incubated at room temperature for 1 h. Next, the sample was reacted with an HRP-conjugated goat anti-mouse IgG (Abcam, Cambridge, UK) for detection. After TMB colorization and the termination of the reaction, the absorbance at 450 nm with a reference wave length of 630 nm was determined using the automated ELISA Reader TECAN, Männedorf, Switzerland). The estimated level of VP4*-specific antibodies in the sample was the average of the quantification outcome based on the three mAbs.

To detect the level of VP6-specific IgA antibodies after immunization, the serum samples were diluted 10-fold and were added to the microplates coated with VP6; then, the microplates were incubated at room temperature for 1 h. Next, the sample was reacted with an HRP-conjugated goat anti-mouse IgA (Abcam, Cambridge, UK). The absorbance at 450 nm with a reference wavelength of 630 nm was considered to be the level of VP6-specific IgA antibodies.

2.9. Statistical analysis

GraphPad PRISM™ version 5.0, (GraphPad Software, Inc. La Jolla, Calif., U.S.A.) was used for the analysis and mapping. The experimental results are expressed as the means ± the standard errors of the means. Significant differences between 2 groups were determined using an unpaired Student's *t*-test.

3. Results

3.1. Immunization of the dams and antibody transfer from the mouse dams to their pups

After three doses of oral immunization at 7, 21, and 35 days of age, the serum levels of neutralizing antibodies against EDIM in the infected dams were significantly higher than those in the control group (Fig. 2). After delivery, the pups were half exchanged for cross-fostering to determine the impact of trans-placentally acquired and milk-acquired maternal antibodies. The serum

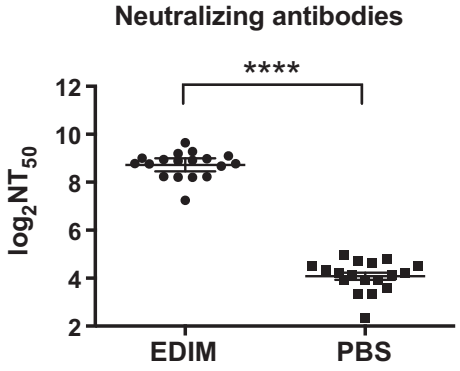

Fig. 2. The neutralizing antibody titres in the dams after three oral EDIM infections or PBS inoculation. The error bars represent the standard error of each group (n = 18). *** represents a significant difference between the EDIM group and the PBS group ($p < 0.0001$).

samples of the 7-day-old pups were analysed by a neutralization assay, and the results showed that the maternal antibodies transferred from the dams to the pups, mainly through breastfeeding (Fig. 3). In addition, in pups inoculated with PBS, the maternal antibody levels waned with the growth of the pups, but the levels were still higher than those in the no maternal antibody group and were especially higher in the milk antibody group (P^-M^+) and the total maternal antibody group (P^+M^+) (Fig. 3C). No serum neutralizing activity was detected in the P^-M^- group inoculated with PBS throughout the experimental period (Fig. 3C).

3.2. The impact of maternal antibodies on the immunogenicity of live rotavirus

To evaluate the impact of maternal antibodies on the immunogenicity of live rotavirus, the pups were orally inoculated with live EDIM virus three times at 7, 14 and 21 days of age. Serum samples were collected one week after each immunization, and neutralizing antibodies against EDIM were detected. Compared with those in the PBS group, increasing titres of neutralizing antibodies were detected in the immunized group (Fig. 3A). As the maternal antibodies did not completely disappear after three doses of immunization, the antibody level in the PBS group was deducted. After adjustment, it was found that the neutralizing antibody titres in the P^+M^+ and P^-M^+ groups were significantly lower than those in the P^-M^- group; however, in the P^+M^- group, the neutralizing antibody titres were slightly lower than those in the no maternal antibody group (Fig. 4A). Similar results were also found for anti-VP6 IgA antibody titres (Supplementary Fig. 1). Thus, the presence of maternal antibodies, especially breast milk antibodies, significantly inhibited the immune response after inoculation with live rotavirus EDIM.

3.3. The impact of maternal antibodies on the immunogenicity of recombinant VP4*

To evaluate the impact of maternal antibodies on the immunogenicity of recombinant VP4*, the pups were parenterally injected with EDIM-VP4* three times at 7, 14 and 21 days of age. Serum samples were collected one week after each immunization, and neutralizing antibodies against EDIM were detected. Consistent with the EDIM virus immunization group, an increase in the titres of neutralizing antibodies was also detected compared with those of the PBS group (Fig. 3B). After adjustment, it was found that the neutralizing antibody titres in the P^+M^+ and P^-M^+ groups were significantly higher than those in the P^-M^- group (Fig. 4B). Thus, the presence of maternal antibodies, especially breast milk antibodies, significantly boosts the immune response after vaccination with recombinant VP4*.

3.4. The impact of VP4*-specific antibodies on the immunogenicity of recombinant VP4*

To evaluate whether the enhancement in the immunogenicity of recombinant VP4* was due to the formation of the antigen-antibody complex, recombinant VP4* was mixed with serum samples immunized with EDIM-VP4* or LLR-VP4* in three molar ratios (Ag/Ab, 2:0.1, 2:1, 2:10) or with serum samples from mock-immunized mice. After three doses of immunization, it was found that the serum neutralization titres in the groups of VP4* mixed

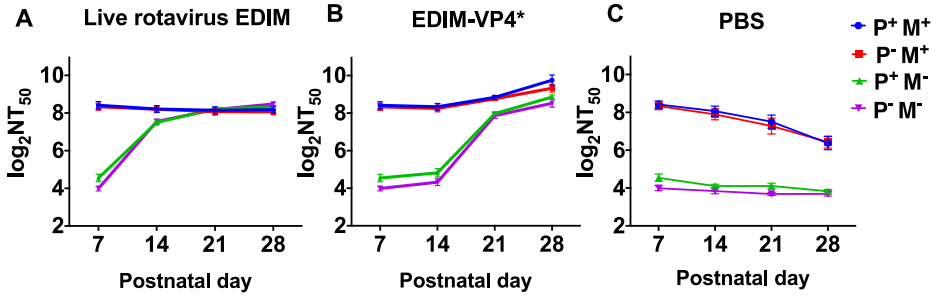

Fig. 3. The neutralizing antibody responses after immunization in different maternal antibody groups. (A) Oral, live rotavirus (EDIM)-infected group; (B) Intraperitoneal/intramuscular recombinant EDIM-VP4* immunization group; (C) PBS control group. The error bars represent the standard error of each group (n = 6).

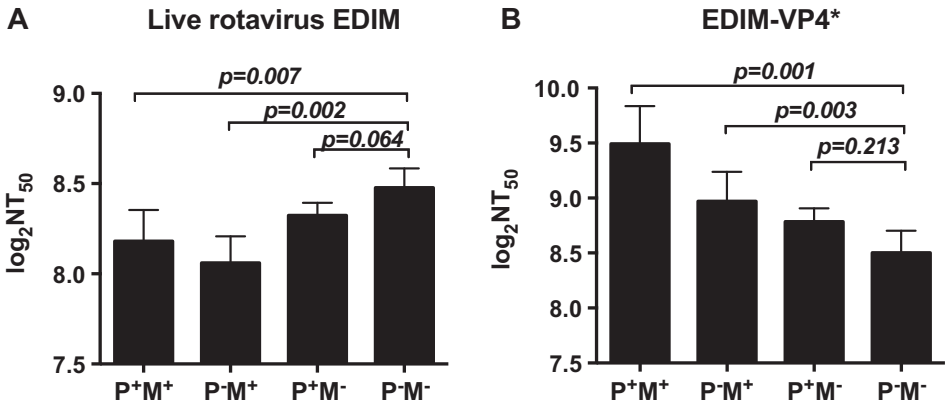

Fig. 4. The impact of maternal antibodies on the immunogenicity of rotavirus vaccines in the pups. (A) Oral immunization with live rotavirus (EDIM). (B) Intraperitoneal/intramuscular immunization with EDIM-VP4*. The neutralizing antibody titres were adjusted by subtracting the antibody titres in the PBS-immunized group, and the error bars represent the standard error of each group (n = 6).

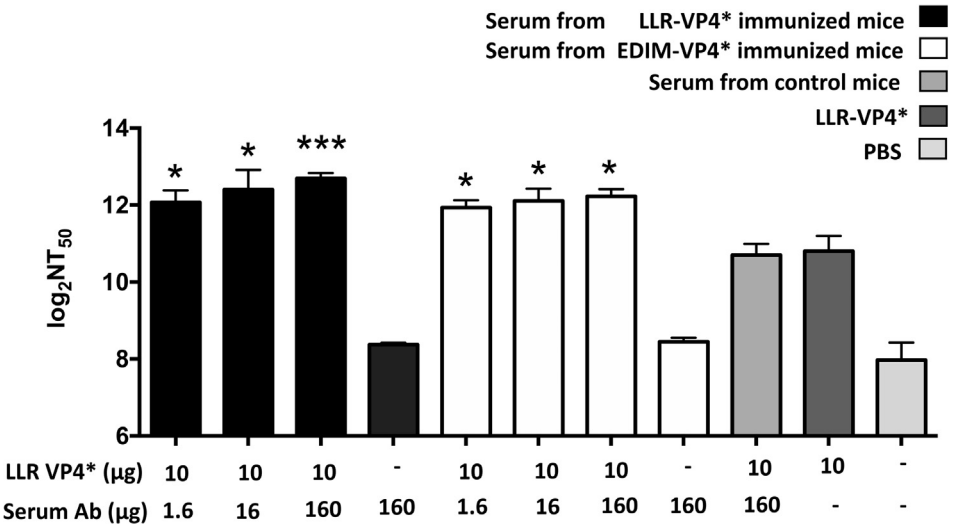

Fig. 5. The neutralizing antibody titres after three doses of immunization with different molar ratios of LLR-VP4* plus homologous (LLR) or heterologous (EDIM) serum antibodies. The error bars represent the standard error of each group (n = 7). * and ***represent a significant difference between the indicated group and the VP4* group (*: $P < 0.05$, ***: $P < 0.001$).

with the immunized serum samples were significantly higher than those mixed with the control serum (Fig. 5). In addition, no significant differences were observed in the serum samples from mice that were immunized with EDIM-VP4* or LLR-VP4* (Fig. 5). These data suggest that the pre-formation of the antigen-antibody complex could enhance the immune response of recombinant VP4*.

4. Discussion

In this study, the impact of maternal antibodies on the immune responses elicited from live and recombinant rotavirus vaccines was evaluated in a mouse model for the first time. It was demonstrated that the presence of maternal antibodies, especially milk antibodies, inhibited the immune responses after immunization with live rotavirus EDIM but enhanced that of recombinant EDIM-VP4* (Fig. 4).

Dams were infected orally with wild-type murine (EDIM) rotavirus for the first time at the age of 7 days to mimic a natural rotavirus infection in infants. All the dams developed rotavirus-specific neutralizing antibodies after three doses of infection, and the antibodies were transferred to the pups. The maternal antibodies waned as the animals grew. In infants, the maternal antibodies wane at approximately 6 months, and the vaccine should be administered before 6 months as the morbidity is high after 6 months [31]. Thus, immunization of the pups at their early life can reflect the impact of the maternal antibodies on the vaccines in maximum. In mice, the maternal antibodies waned at approximately 28 days; so in this study, the pups were immunized at 7, 14 and 21 days old.

The results of this study showed that maternal antibodies could inhibit immune responses after vaccination with live rotavirus. This is consistent with the results in infants that demonstrate that the immune response after vaccination with live attenuated rotavirus vaccines was negatively correlated with the level of maternal antibodies. During the first 6 months, the maternal antibodies could protect the infants from rotavirus-induced morbidity [32,33]. In mice, it was also found that maternal antibodies could protect the pups from rotavirus-induced diarrhoea [34] in a maternal antibody model. Compared to the impact of trans-placentally acquired maternal antibodies, the impact of breastfeeding-acquired antibodies was much higher (Fig. 4). This is not surprising because most of the maternal antibodies were acquired from milk, and the antibody levels in the milk antibody group were significantly higher than those in the placental antibody group (Fig. 3). In addition, the diarrhoea in the pups of the placental antibody group was more serious than that in the milk antibody group after the first inoculation of live rotavirus (data not shown). In previous studies, similar results were also observed [35,36]. In infants, withholding breastfeeding did not improve the performance of live attenuated rotavirus vaccines [21-23]. This may be because the milk antibody levels were highest in the colostrum, and these levels decrease sharply [37]. The infants had already acquired most milk antibodies from the colostrum and milk before immunization, and the impact of withholding breastfeeding was too weak.

Non-replicating rotavirus vaccines were developed as an alternative to the current oral, live vaccines, and it was supposed that the efficacy of non-replicating rotavirus vaccines could not be inhibited by maternal antibodies [24]. In previous studies, Trang et al. found that the high titres of circulating maternal antibodies from the passive injection of serum suppressed the response to parenteral immunization with VLP in the piglet model [38], and no inhibitory effect was observed in their study on low titres of circulating maternal antibodies [39]. The results of Johansson and colleagues also showed the inhibitory effect of maternal antibodies in a mouse model [40]. In our study, we found that the immunogenicity of recombinant EDIM-VP4* was not inhibited by maternal antibodies and was actually enhanced. The conflicting results from different studies could be explained by previous observations that the impact of pre-existing circulating antibodies depends on the relative ratio of antibodies to antigens, the characteristics and dose of the antigen [41], the immunization time [42] and the routes of immunization [40]. In this study, we found that the immunogenicity of VP4* could be enhanced by the formation of an antigen–antibody complex (Fig. 5). In previous studies, Wen et al. also found that the immunogenicity of HBsAg could be enhanced by assembling it into antibody-antigen complexes before immunization [43]. It was possible that the formation of an antigen-antibody complex could enhance the recognition of antigens by Fc receptors on antigen-presenting cells. In addition, it has also been proposed that immunocytes transferred to the foetal circulation have also been found to increase the specific immune response in studies of HBV vaccines [28]).

There were some limitations in the present work. First, the maternal antibody levels in the milk were not determined because we could not collect enough milk for detection. It has been

reported that the antibody levels in the milk were extremely low [44]. However, in other studies, it has also been found that even low levels of milk antibodies, but not placental antibodies, could confer protection in maternal antibody models [36]. Thus, it was not surprising that milk antibodies inhibit the immune response after live rotavirus immunization because the viruses were neutralized in the intestine before infection. Second, the immune response in gut-associated lymphatic tissue (GALT) was not directly analysed. However, the serum IgA levels could reflect the induction of local immunity in GALT [45,46]. After the EDIM challenge of the pups, the serum IgA levels were determined, and the IgA levels were significantly lower in the P^+M^+ and P^-M^+ groups but were not lower in the P^+M^- group without adjustment (Supplementary Fig. 1). These results suggested that milk antibodies could inhibit the immune responses after live rotavirus vaccination. Third, the impact of maternal antibody subclass should be further studied. Moreover, the results in mice may not completely reflect the results in humans due to the differences in the immune system and the main routes of acquiring maternal antibodies [47]. Although we found that the immunogenicity of recombinant VP4* was enhanced by maternal antibodies, whether recombinant rotavirus vaccines can stimulate high levels of antibodies in humans and confer a higher protection efficacy should be evaluated by clinical trials.

Taken together, we found that maternal antibodies could inhibit immune responses after immunization with live rotavirus in a mouse model. For the recombinant rotavirus vaccine EDIM-VP4*, the neutralizing antibody responses were not inhibited and were enhanced by the maternal antibodies, especially the milk antibodies. This finding provides a basis for the development of non-replicating rotavirus vaccines as an alternative to live attenuated vaccines to improve rotavirus vaccine efficacy in low- and middle-income countries.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.086.

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