



Review

Breastfeeding after maternal immunisation during pregnancy: Providing immunological protection to the newborn: A review



Kirsten Maertens^{a,*}, Sara De Schutter^b, Tessa Braeckman^a, Lesley Baerts^b,
Pierre Van Damme^a, Ingrid De Meester^b, Elke Leuridan^a

^a Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium

^b Laboratory of Medical Biochemistry, Department of Pharmaceutical Sciences, University of Antwerp, Antwerp, Belgium

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ABSTRACT

Vaccination during pregnancy results in an augmentation of disease specific maternal antibodies. Immunoglobulin G (IgG) is mainly transferred through the placenta during the third trimester of pregnancy, while secretory Immunoglobulin A (sIgA) is passed through breast milk. At birth, newborns are partially protected against infectious diseases by these antibodies.

This review aims to provide an overview of the effect of vaccination during pregnancy on the immunological protection of the newborn by the presence of disease specific sIgA antibodies in breast milk and their possible protective function against disease.

Our search produced 11 relevant papers; 1 on pertussis, 7 on pneumococcus, 2 on influenza and 1 on meningococcus.

All of the studies in this review that measured disease specific antibodies in breast milk ($n = 8$ papers), stressed the beneficial effect of maternal vaccination during pregnancy on the amount of disease specific sIgA in breast milk. Only a few studies demonstrated a potential protective effect, particularly with influenza vaccines. In an era where maternal vaccination is increasingly considered as a valuable strategy to protect both the mother and infant, further research is needed to assess the effect on breast milk sIgA and to understand the potentially beneficial effects to the infant.

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1. Introduction

In industrialised countries, the use of vaccines in pregnant women has been controversial. Live attenuated vaccines are contraindicated in pregnant women because of the possible transplacental transmission of the attenuated virus to the foetus. However, this recommendation is based on a theoretical risk rather than on evidence [1]. In contrast, vaccination with killed or inactivated vaccines has not been shown to cause any risk to the foetus when administered during pregnancy [2–5]. Some of these vaccines are even recommended during pregnancy [5]. This strategy has the potential to protect the pregnant woman and foetus from serious illness during pregnancy (e.g., from influenza). In addition, it provides better protection to the infants after birth and during the first months of life when they are too young to be vaccinated for certain diseases (e.g., from tetanus, influenza and pertussis) [5]. The Centers for Disease Control and Prevention (CDC) have published a summary of vaccines that may be given during pregnancy, i.e., vaccines against typhoid fever infection, Japanese encephalitis,

tick-borne encephalitis, pneumococci (both conjugate and polysaccharide), hepatitis A, hepatitis B, meningococci (both conjugate and polysaccharide), cholera, inactivated polio, rabies, inactivated influenza, pertussis, tetanus and diphtheria [6].

As a rule, breastfeeding is not a contraindication to maternal vaccination nor is vaccination a contraindication to breastfeeding. The only exception is the yellow fever vaccination, as reports have demonstrated that the live attenuated virus may be transmitted through breast milk [7]. Vaccination with the yellow fever vaccine should therefore be avoided during breastfeeding.

According to the World Health Organization (WHO), colostrum is the perfect food for the newborn and should be given within the first hours of life. Furthermore, breast milk provides essential nourishment to the newborn and assures healthy growth and development. Breast milk is also known to have a protective effect against sudden infant death syndrome, infant mortality, allergic disease, necrotising enterocolitis, gastrointestinal tract infections and respiratory tract infections [8]. The WHO recommends exclusive breastfeeding up to the age of 6 months, followed by a combination of breast milk and supplementary food up to 2 years of age or older [9].

In general, the transfer of maternal antibodies from the mother to child via placental transport [10,11] has been well documented.

* Corresponding author. Tel.: +32 3 265 29 44; fax: +32 3 265 26 40.

E-mail address: kirsten.maertens@uantwerpen.be (K. Maertens).

The placental transport of Immunoglobulin G (IgG) depends on the placental function and on the concentration of maternal antibodies in the pregnant woman [11,12]. The concentration of IgG in women at childbearing age is defined by the previous exposure to the antigen through either disease and/or vaccination. Increased levels of maternal IgG antibodies have been described after vaccination during pregnancy [13–15]. In contrast, little is known about the effect of vaccination during pregnancy on the transfer of vaccine-induced secretory Immunoglobulin A (sIgA) maternal antibodies via breastfeeding, which is the principal immunoglobulin in breast milk [16]. sIgA protects infants by binding and opsonising pathogenic microorganisms, thus inhibiting the colonisation and invasion of the mucosal membranes of the child [17]. Via this mechanism, sIgA functions as a first-line barrier protecting the epithelium from pathogens and toxins. Other factors that are responsible for the protective effect of breast milk are lactoferrin, oligosaccharides, interleukin-10, epidermal growth factor and other anti-inflammatory factors [17,18].

In this paper, we review the literature on the possible immunological protection provided through breastfeeding in women who were vaccinated during pregnancy. Animal studies were not selected because we cannot extrapolate the results to humans. The immune system and the role of breastfeeding in animals are entirely different from humans. In mice, for example, maternal antibodies are mainly transmitted to the offspring through breastfeeding and less often through placental transfer, as confirmed by foster feeding studies. These breast milk derived maternal antibodies of these animals provide a longer lasting protection in comparison to the antibodies transferred via the placenta [19].

The current recommendations for vaccination during pregnancy are based on evidence that vaccination during pregnancy or shortly before pregnancy has a positive effect on the amount of IgG antibodies transported through the placenta [13]. The question remains whether this vaccination also has a positive effect on the amount of maternal sIgA antibodies found in breast milk and if these breast milk antibodies will provide actual protection against infectious diseases.

2. Methods

2.1. Systematic literature review

A review of the literature on transfer of maternal antibodies through breastfeeding from mothers vaccinated during pregnancy was performed according to the MOOSE criteria (Meta-Analysis of Observational Studies in Epidemiology) [20]. A Medline search was conducted using the National Library of Medicine's PubMed online search engine with a combination of the following Medical Subject Headings (MESH) terms: Vacc*, Lact*, Breast milk, Breastfeeding, Colostrum, Preg*, Pertussis, Pneumo*, Influenza, Meningo*, Tetanus, Diphtheria, Hepatitis A, Hepatitis B and Polio. We only included studies on inactivated licensed vaccines for adults that are not contraindicated for administration during pregnancy. Supplemental information was consulted based on the available references of the selected papers. No language priority was chosen. No time limitations were set.

One study was obtained through personal communication and was presented during a meeting (Annecy, Fondation Mérieux) [21].

2.2. Inclusion and exclusion criteria

The abstracts and full articles were reviewed on October 3, 2013 and were selected based on the title and the available abstract.

If an abstract mentioned vaccination in combination with pregnancy and lactation, breast milk or breastfeeding, the full text was reviewed. Only human studies were included.

3. Results

3.1. Results of the search

The overall search produced a total of 208 papers, of which 70 papers were repeatedly selected. A searching of the bibliographies revealed 5 further publications. On the basis of the inclusion/exclusion criteria, 22 abstracts were selected and the full papers were obtained and read. A second selection was made using the same inclusion/exclusion criteria on the full text of the papers. Only 10 publications and 1 presentation were selected for the present review (Table 1).

A summary of the selected articles and test procedures used is presented in Table 2.

3.2. Tetanus, diphtheria, hepatitis A, hepatitis B, polio

The PUBMED search on tetanus, diphtheria, hepatitis A, hepatitis B and polio produced a total of 117 papers; however, none of these papers met the criteria for inclusion in this review.

3.3. Pertussis

One publication was found for pertussis. This was a US (United States) study (1938) with pregnant women ($n=28$) who were vaccinated with 3 doses of a vaccine containing *Haemophilus pertussis* (old nomenclature for *Bordetella pertussis*). To test whether colostrum had a positive influence on the phagocytic capacity in the blood of young infants, blood was taken before and after ingestion of colostrum in a limited subsample of infants ($n=5$). No influence was found on opsonophagocytic activity in the blood after colostrum intake [22].

3.4. Influenza

For influenza, two relevant articles from the same vaccine trial in Bangladesh were found. This trial assessed the effect of influenza vaccination during pregnancy on the transfer of maternal antibodies through breastfeeding.

In a first epidemiological paper from Bangladesh (2012), 340 pregnant women were vaccinated against influenza ($n=166$) or pneumococcus ($n=165$). A follow-up on the frequency of occurrence of respiratory illness with fever (RIF)-episodes in infants was performed from birth up to 6 months of age. All children received breastfeeding, but the duration of the breastfeeding period was variable. From the epidemiological results, there was a significant, independent protective effect of exclusive breastfeeding on the occurrence of RIF-episodes. In addition, infants of mothers who received the influenza vaccine had a reduced risk in the occurrence of RIF-episodes compared to infants from mothers who received the pneumococcal vaccine [23].

The second paper reports a subanalysis of the same Bangladesh study [24]. Of the 340 pregnant women who were vaccinated during pregnancy, breast milk samples from 57 women were analysed, 30 of which had received trivalent inactivated influenza vaccine, and 27 received a 23-valent pneumococcal polysaccharide vaccine. At different time points in the study, breast milk samples were collected and analysed for the presence of anti-influenza sIgA with a neutralisation assay and the total amount of sIgA using an ELISA technique. In addition to these laboratory parameters, the occurrence of RIF-episodes was also monitored. The mean specific anti-influenza sIgA antibody titer was higher in the breast milk

Table 1
Overview of the number of papers selected by the inclusion/exclusion criteria for this review.

	PUBMED search	Duplicates	Articles selected from reference list of other publications	Selected on abstract	Final selection on full paper
Pertussis	21 Papers	1 Paper	0 Papers	3 Papers	1 Paper [22]
Pneumococcus	29 Papers	5 Papers	3 Papers	11 Papers	6 Papers and 1 presentation [21,26–31]
Influenza	37 Papers	10 Papers	3 Papers	7 Papers	2 Papers [23,24]
Meningococcus	4 Papers	3 Papers	0 Papers	1 Paper	1 Paper [25]
Tetanus	37 Papers	17 Papers	0 Papers	0 Papers	0 Papers
Diphtheria	20 Papers	17 Papers	0 Papers	0 Papers	0 Papers
Hepatitis A	9 Papers	2 Papers	0 Papers	0 Papers	0 Papers
Hepatitis B	40 Papers	10 Papers	0 Papers	0 Papers	0 Papers
Polio	11 Papers	5 Papers	0 Papers	1 Paper	0 Papers
Total	208 Papers	70 Papers	6 Papers	23 Papers	10 Papers and 1 presentation

of women who received the influenza vaccine during pregnancy, and the effect lasted up to 6 months after birth. The highest titer was detected immediately after birth. The neutralisation antibodies were also higher and a decreased number of RIF-episodes was detected in children of women vaccinated with influenza vaccine during pregnancy [24].

3.5. Meningococcus

One relevant paper was selected concerning polysaccharide quadrivalent meningococcal vaccination (serotypes A, C, Y and W-135) during pregnancy and the effect on antibody concentration in breast milk. The article describes a study from Bangladesh, in which 55 pregnant women were vaccinated with either a pneumococcal or a meningococcal polysaccharide vaccine during pregnancy. In addition, all of the participants received a tetanus toxoid vaccine in the contralateral arm. At fixed time points in the study, up to 5 months after delivery, the mothers donated a breast milk sample that was analysed for the presence of anti-meningococcal group A sIgA. The results of this study clearly showed that vaccination of the mother during pregnancy had a positive effect on the amount of meningococcal antibodies detected in breast milk in comparison to the control group up to 6 months after delivery [25].

3.6. Pneumococcus

Most of the published manuscripts ($n=6$) on the transfer of maternal sIgA antibodies through breastfeeding have assessed the impact of pneumococcal polysaccharide vaccination in pregnant women. To our knowledge, no studies have been published on the use of conjugate pneumococcal vaccines during pregnancy.

The same group that reported on meningococcal vaccination during pregnancy [25], also described the impact of the pneumococcal vaccine (1995). Of the 55 pregnant women included in the study, 29 were vaccinated with the pneumococcal vaccine. Breast milk samples were collected at the same time points (Table 2), and the analysis revealed a significantly higher titer of specific sIgA in the breast milk samples of the study group compared to the control group up to 5 months after delivery [26].

Another paper describes a study in the US where 60 pregnant women were enrolled and vaccinated with either a pneumococcal (serotypes 6B, 14, 19F and 23F) vaccine (study group) or a *Haemophilus influenzae* type b (Hib) conjugate vaccine (control group) (2001). Breast milk samples were analysed for pneumococcal and Hib specific sIgA and IgG at 2 and 7 months after delivery. The investigators found a significantly higher antibody level for both anti-pneumococcus sIgA and IgG in the study group when compared to the control group. The levels of sIgA remained higher in the study group until 7 months postpartum, while the differences in the IgG levels had disappeared at the same time point [27].

In The Gambia [28], 113 pregnant women were randomised and vaccinated with a pneumococcal ($n=56$) or meningococcal ($n=57$) polysaccharide vaccine between 24 and 32 weeks of pregnancy. Breast milk samples were collected at 0, 2, 4 and 6 months after birth. The samples were assessed for sIgA subclass distribution and avidity of pneumococcal antibodies. The ratio of the sIgA concentration to pneumococcal polysaccharide antigens in colostrum was at least three times higher in subjects vaccinated against pneumococcus when compared to subjects vaccinated against meningococcus. The antigen-specific sIgA concentration remained higher for at least 6 months after birth [28].

A sub-study [29] of the previous study in The Gambia [28] describes an analysis of the colostrum samples from 16 women who were vaccinated during pregnancy with either a pneumococcal vaccine (study group) or a meningococcal vaccine (control group). Both the concentration and the avidity of pneumococcal sIgA antibodies were higher in the study group when compared to the control group [29].

Other research was conducted in Papua New Guinea where a total of 258 pregnant women were recruited [30]. In this study, 177 women were immunised with the pneumococcal vaccine, and the control group contained 81 non-immunised women. In addition to colostrum, the concentration of anti-pneumococcal sIgA antibodies in breast milk samples from 1–3 and 4–6 months postpartum were analysed. Vaccination induced a humoral immune response that was measurable in both the colostrum and breast milk. The antibody concentrations were generally higher in the vaccinated group than the control group [30].

Another article describes a study in Brazil [31]. A total of 139 pregnant women were randomised and divided into 3 study groups as follows: (1) received 23-valent polysaccharide vaccination during pregnancy (group 1), (2) received the same vaccination after pregnancy (group 2) and (3) received no vaccination at all (group 3). From those 139 women, 65 women (22 in group 1, 19 in group 2 and 24 in group 3) were exclusively breastfeeding until 6 months after birth. In the infants who were exclusively breastfed, the occurrence of acute respiratory infection (ARI)-episodes was monitored during the first 6 months of life. No effect was found of exclusively breastfeeding on the occurrence of ARI-episodes in either group or on pneumococcal nasopharyngeal colonisation [31].

In Australia (2012), a vaccine trial was conducted on 227 pregnant women who were divided into the following three study groups: (1) received a pneumococcal vaccination during pregnancy, (2) received a vaccination at delivery and (3) received a vaccination 7 months after delivery. Breast milk specimens were taken at delivery and at month 1, 2 and 7. The amount of pneumococcal specific sIgA was measured in the breast milk samples and the highest titer was found in the group that had been vaccinated during pregnancy [21].

Table 2
Summary of the selected articles and used test procedures.

Disease	Number of participants	Administered vaccine	Time of administration	Country of execution	Methodology and parameter analyzed	Time of sampling and storage conditions	Outcome
Pertussis Lichty [22]	5	Hemophilus pertussis (Bordetella pertussis) containing vaccine	Third trimester of pregnancy	USA	Measurement of the opsono-cytophagic reaction for H. pertussis bacilli in blood of the infant	Blood from newborn in first period of nursing and end of first week of life Storage conditions not specified	No effect of colostrum on phagocytic reaction in the blood of the newborn
Meningococcus Shahid [25]	55	Meningococcal polysaccharide vaccine (<i>n</i> = 26; study) or 23-valent pneumococcal polysaccharide vaccine (<i>n</i> = 29; control) and tetanus toxoid vaccine (all)	30–34 weeks of pregnancy	Bangladesh	<i>In-house</i> ELISA anti-meningococcal group A sIgA ^a (coated Ag ^b : meningococcus group A)	Colostrum at 0–3 days after delivery. Breast milk at 1 and 2 weeks and 1,3 and 5 months after delivery Storage of defatted milk at –20 °C until analysis (transported on dry ice)	Higher sIgA levels in vaccinated group, both in colostrum (2.6 times higher) and breast milk at 3–6 months of age (4 times higher)
Influenza Schlaudecker [24]	57	Trivalent inactivated influenza vaccine (<i>n</i> = 30; study) or 23-valent pneumococcal polysaccharide vaccine (<i>n</i> = 27; control)	Third trimester of pregnancy	Bangladesh	(1) <i>In-house</i> ELISA anti-influenza sIgA (coated Ag: recombinant hemagglutinin derived from H1N1 strain) (2) <i>In-house</i> ELISA total sIgA (coated Ag: Rabbit anti-human IgA) (3) Neutralization assay for influenza (H1N1) (4) Epidemiological study to detect RIF-episodes ^c	Breast milk at birth, 6 weeks, 6 and 12 months Storage of defatted milk at –70 °C until analysis	(1) Anti-influenza sIgA was significantly higher in influenza vaccinees up to 6 months postpartum (2) Total sIgA in breast milk was similar between vaccine groups (3) Neutralization titers significantly higher in influenza vaccinees at birth (4) Reduction of RIF-episodes in exclusively breastfed children of influenza vaccinees up to 6 months
Henkle [23]	331	Trivalent inactivated influenza vaccine (<i>n</i> = 166; study) or 23-valent pneumococcal polysaccharide vaccine (<i>n</i> = 165; control)	Third trimester of pregnancy	Bangladesh	Epidemiological study to detect RIF-episodes	Anamnestic follow-up of RIF-episodes from birth up to 6 months at weekly intervals	Exclusively breastfeeding and maternal influenza vaccination independently result in significant reduction of RIF-episodes in infants
Pneumococcus Munoz [27]	60	23-Valent pneumococcal polysaccharide vaccine (<i>n</i> = 20; study) or Hib ^d conjugate vaccine (<i>n</i> = 40; control)	30–36 weeks of pregnancy	USA	<i>In-house</i> ELISA pneumococcal IgG and sIgA (coated Ag: types 6B, 14, 19F or 23F pneumococcal capsular polysaccharide)	Breast milk at 2 and 7 months Storage of defatted milk at –70 °C until analysis	At 2 months postpartum PV ^e vaccinees had higher SIgA and IgG levels in breast milk while sIgA remained higher up to 7 months postpartum

Table 2 (Continued)

Disease	Number of participants	Administered vaccine	Time of administration	Country of execution	Methodology and parameter analyzed	Time of sampling and storage conditions	Outcome
Shahid [26]	55	23-Valent pneumococcal polysaccharide vaccine ($n = 29$; study) or meningococcal polysaccharide vaccine ($n = 26$; control) and tetanus toxoid vaccine (all)	30–34 Weeks of pregnancy	Bangladesh	<i>In-house</i> ELISA pneumococcal IgG and sIgA (coated Ag: Types 6B or 19F pneumococcal capsular polysaccharide)	Colostrum 0–3 days after delivery. Breast milk samples at 1 and 2 weeks and 1,3 and 5 months after delivery Storage of breast milk at -20°C until analysis (transported on dry ice)	Colostrum of PV vaccinees contained higher anti-type 6B sIgA ($3\times$) and anti-type 19F ($7\times$) sIgA compared to controls sIgA remained higher ($3\times$) in breast milk until 5 months postpartum
Deubzer [29]	16	Polyvalent (two types) pneumococcal polysaccharide vaccine ($n = 8$; study) or meningococcal polysaccharide vaccine A and C ($n = 8$; control)	Late second to early third trimester of pregnancy	The Gambia	(1) Adherence of <i>S. pneumonia</i> serotype 6B and 14 polysaccharides to human pharyngeal epithelial-cell line (Detroit 562) (2) <i>In-house</i> ELISA pneumococcal sIgA and avidity (coated Ag: Types 6B or 14 pneumococcal capsular polysaccharide)	Colostrum first week after delivery Storage of defatted milk at -20°C until analysis	(1) Colostrum of PV vaccinees induced a higher inhibition of adherence (2) Significantly higher concentration and avidity of sIgA were observed in colostrums of PV vaccinees
Lehmann [30]	258	14-Valent pneumococcal polysaccharide vaccine ($n = 177$; study) and no vaccine ($n = 81$; control)	Between 28 and 38 weeks of pregnancy	Papua New Guinea	<i>In-house</i> ELISA pneumococcal sIgA (coated Ag: Types 5, 7F, 14 or 23F pneumococcal capsular polysaccharide)	Colostrum immediately postpartum. Breast milk at 1–3 months and 4–6 months postpartum Whole milk transported at -20°C , storage of defatted milk at -70°C until analysis	Breast milk of vaccinated women contained higher ($1.1\text{--}1.8\times$) sIgA levels against the four serotypes up to 90 months postpartum No differences in sIgA levels from 90 days until 6 months postpartum
Obaro [28]	113	23-Valent pneumococcal polysaccharide vaccine ($n = 56$; study) or meningococcal polysaccharide vaccine ($n = 57$; control)	Between 24 and 32 weeks of pregnancy	The Gambia	<i>In-house</i> ELISA pneumococcal sIgA and avidity (coated Ag: Types 4, 6B, 14, 19F or 23F pneumococcal capsular polysaccharide)	Breast milk at 0, 2, 4 and 6 months postpartum Storage of defatted milk at -20°C until analysis	Colostrum sIgA concentrations specific to all pneumococcal polysaccharide Ag were significantly higher among PV vaccinees Titers for serotypes for 4, 6B and 14 remained significantly higher during 6 months, and those for 19F were higher up to 4 months
Lopes [31]	65	23-valent pneumococcal polysaccharide vaccine ($n = 41$); and no vaccine ($n = 24$)	After pregnancy ($n = 19$) or between 30 and 34 weeks of pregnancy ($n = 22$)	Brasil	Epidemiological study to detect ARI-episodes [†] and nasopharyngeal colonisation	Follow-up of ARI-episodes(through questionnaire) from birth up to 6 months	No effect of exclusively breastfeeding on the occurrence of ARI-episodes, nor on nasopharyngeal colonisation

Table 2 (Continued)

Disease	Number of participants	Administered vaccine	Time of administration	Country of execution	Methodology and parameter analyzed	Time of sampling and storage conditions	Outcome
Andrews [22]	227	Pneumococcal polysaccharide vaccine during pregnancy (<i>n</i> = 75), pneumococcal vaccine at birth (<i>n</i> = 75), pneumococcal vaccine at 7 months (<i>n</i> = 77)	Between 30 and 36 weeks of pregnancy	Australia	Method not specified, sIgA levels to pneumococcal polysaccharide serotype 6B, 10A, 19A and 33F were measured.	Colostrum at delivery. Breast milk at 1,2 and 7 months postpartum. Storage conditions not specified	Higher amount of sIgA against all serotypes in breast milk from PV vaccinees

^a sIgA is the secretory Immunoglobuline A.

^b Ag is the antigen.

^c RIF-episode is the respiratory illness with fever-episode.

^d Hib is the haemophilus influenzae type b.

^e PV is the pneumococcal polysaccharide vaccine.

^f ARI-episode is the acute respiratory infection-episode.

4. Discussion

Based on this review, we conclude that very little data are available on the effect of vaccination during pregnancy on the composition of breast milk and, in particular, on the presence of disease specific sIgA antibodies.

The concept of providing protection to children through breast milk is not new. Considering the US article on pertussis [22], it is obvious that there is a long history of research on the possible protective effects of breast milk. However, most research does not focus on the transfer of antibodies through breast milk that is induced by vaccination during pregnancy.

In general, the evidence retrieved from the literature suggests that vaccination during pregnancy results in better protection of the offspring during the most vulnerable months of life. This is reflected by a higher concentration of sIgA to different diseases in the breast milk samples at different time points during the first months of life (Table 2) or by a lower incidence of RIF episodes in the young infants of influenza-vaccinated mothers [24]. There is particularly strong evidence to suggest a beneficial effect on breast milk composition when pregnant women are vaccinated against influenza [23,24].

For some diseases there is a “correlate of protection” defined by an immune response that is responsible for and/or related to protection against this specific disease [32]. For pertussis, there is no generally accepted correlate of protection defined as a specific threshold of anti-pertussis IgG antibodies in human serum [33]. As a consequence, we cannot be sure whether the amount of antibodies transferred to the child is sufficient to provide an accurate protection during the first months of life. For influenza, pneumococcus and meningococcus on the other hand, there is a known correlate of protection [32]. However, it is unclear whether we can extrapolate these correlates of protection in serological IgG assessments to sIgA titers in breast milk. Therefore, no conclusion can be drawn on protection through breastfeeding for vaccine preventable diseases unless other outcome measures are used in the study design. In the articles by Henkle et al. [23] and Schlaudecker et al. [24], the protective effect of breast milk is determined by the occurrence of RIF- or ARI-episodes and in Lopes et al. [31] by the effect on ARI and pneumococcal nasopharyngeal colonisation. Schlaudecker et al. and Henkle et al. proved that maternal influenza vaccination reduce significantly the number of RIF, although no effect was reported by Lopes et al. on ARI or nasopharyngeal carriage after maternal pneumococcal immunisation.

In some animal studies the protective effect of breast milk is proven by performing foster feeding studies. In these studies, the offspring of immunised mothers are nursed by non-immunised mothers and vice versa [34]. However, this study design is not feasible in humans due to ethical constraints.

This review has some limitations. Due to the limited number of articles on one specific disease and the limitations of the study designs (small number of participants), it is difficult to draw conclusions regarding the potential protective effect of breast milk after vaccination during pregnancy. Even for pneumococcal disease, which was the most studied vaccine according to the searching results, vaccination with polysaccharide pneumococcal vaccines results in a rise in the amount of maternal antibodies in breast milk that may have a protective effect on the child; however, no effect was found on ARI-episodes [31].

The studies analysed were conducted in different countries with different infectious disease epidemiology, which can result in a bias. Immunity is more likely to be naturally boosted in higher endemicity regions. Consequently these boosted women have a much higher titer of naturally acquired antibodies compared to women in other countries where the pathogen is no longer circulating. These women will therefore transfer a higher amount of antibodies to their children.

A caveat in sIgA research is the fact that, at this time, no validated commercial assay for the detection of sIgA exists. Most of the commercial assays used for the analysis of breast milk are only validated for the detection of IgA. In the various studies, breast milk samples were analysed with an *in-house* ELISA technique following site-specific procedures. For example, the pneumococcal antibodies in breast milk were determined with five different *in-house* ELISA methods. The major difference between these methods is the antigen that was coated on the microtiter plate. Furthermore, various secondary antibodies and substrates are used. The last two modifications can result in varying specificities and sensitivities. These variations can also be found in all of the other *in-house* methods. In addition, there is a lack of standardisation concerning the time of collection and storage of the breast milk samples. It is likely that there is a difference in the concentrations of antibodies in the different types of milk samples at different ages and at different points during feeding (start-middle-end of feeding). The storage temperature and handling of the sample before analysis has an influence on the amount of antibodies found in the samples [35]. For example, most of the breast milk samples were centrifuged to remove the fat layer, but the exact procedures are different for the various studies.

The potential roles of T cells and cellular immunity should be investigated in view of maternal vaccination during pregnancy. In particular, in colostrum, higher amounts of activated CD4+ T cells are encountered in comparison to peripheral blood, suggesting selective migration to breast milk [36]. However, we are not aware of information in the literature regarding the role of the cellular immune response and its effect on breast milk after maternal vaccination.

In view of the current recommendations on vaccination during pregnancy for influenza, pertussis and tetanus [6], additional research is necessary to determine the influence of vaccination on specific antibodies (and, if possible, other immunologically active substances) in breast milk and the possible effect of vaccination on the protection of the breastfed infant.

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