Acta Pædiatrica ISSN 0803–5253

REVIEW ARTICLE

Breastfeeding is an essential complement to vaccination

Josè G Dòrea (dorea@rudah.com.br)

Department of Nutrition, Universidade de Brasília, Brasília, Brazil

Keywords
Allergy, Asthma, Breastfeeding, Thimerosal, Vaccines

Correspondence
Josè G. Dòrea, Ph.D., C.P. 04322, Universidade de Brasilia, 70919-970 Brasilia, DF, Brazil.
Tel: +55-61-3368-3575 |
Fax: +55-61-3368-3575 |
Email: dorea@rudah.com.br

Received
27 February 2009; revised 4 April 2009; accepted 16 April 2009.

DOI:10.1111/j.1651-2227.2009.01345.x

Abstract

Aim: This article explores the role of breastfeeding in different aspects of vaccination in the first 6 months when infants are still developing: (1) pain management; (2) immunomodulation of infants' vaccine responses; (3)metabolism of thimerosal.

Methods: Major databases were searched for studies that addressed outcomes of related issues.

Results: Studies reveal that breastfeeding can: (1) help mothers and infants to cope with the stressful situations that accompany parenteral vaccines; (2) improve response to vaccines in the still maturing immunologic and enterohepatic systems of infants; (3) influence physiologic parameters that can change metabolism of ethylmercury derived from some vaccines.

Conclusion: Health promotion that supports vaccinations should also emphasize early initiation and maintenance of exclusive breastfeeding up until 6 months for maximum protection of the infants with a possible beneficial effect on the vaccine response. Paediatric professionals should inform mothers of the proven benefits of breastfeeding and its importance in complementing vaccination and lowering stress and the risk of untoward reactions on susceptible infants.

INTRODUCTION

Two of the most significant factors for disease prevention and child survival are breastfeeding and vaccination. Indeed, there is a dose response of increasing risk of neonatal mortality associated with decreasing breastfeeding (1). Maximum functional development and health of infants are intrinsically associated with breastfeeding. Field (2) has discussed the many mechanistic ways in which the breastfeeding protects infants, remarking that the maternal immune system continues to communicate with that of the infant after birth through breast milk; breast milk actively directs and educates the infant's immune system eliciting protection from pathogens, metabolic alterations and the microflora system within the infant (2). While the advantages of breastfeeding have been well recognized over decades of clinical and epidemiological research, some aspects of vaccines related to the stressful situation brought on by parenteral inoculations, such as pain and transient fever or more lasting side effects, have only recently been studied. Other aspects related to the putative effects of ethylmercury (etHg) derived from thimerosal-containing vaccines (TCV) have also been studied but with much controversy; the resulting heated debate has brought about changes in the schedule (3) and manufacture practices of vaccines in industrialized countries. In some of these countries, the rate of breastfeeding has been declining over the years. In addition to that, Wu et al. (4) found that mothers' knowledge about vaccination was poor; therefore, lactating mothers may need special attention from healthcare professionals, so that they feel confident that vaccination and breastfeeding go hand in hand as health-promoting actions.

Because most of these themes are novel aspects of the interaction of breastfeeding and vaccines, I chose the most relevant articles dealing with breastfeeding in coincident aspects of vaccination: nociceptive stimuli

Abbreviations
CNS, vulnerable central nervous system; etHg, ethylmercury; BCG, Bacille Calmette-Guérin; BBB, blood-brain barrier; TCV, thimerosal-containing vaccines; Hib, *Haemophilus influenzae* type b, DTP, diphtheria, tetanus, pertussis.

management; immunomodulation of infants' vaccines; metabolism of thimerosal (used as vaccine preservative); immune reactions to respiratory and food allergens.

STRESS AND PAIN

Immunizations engender discomfort and, mostly, distress and pain when administered parenterally. When the child is injected with immunogens, the pain of the needle in the flesh and the psychological distress, although thought to be relatively mild, is a painful experience that is frequently alleviated with medication. In this regard, there are reports showing that breastfeeding alleviated the pain caused by inoculations (5). A recent study by Dilli et al. (6) confirmed the soothing and analgesic effect brought by breastfeeding; thus reducing the need for medication (lidocaine–prilocaine treatment or sucrose solutions) to ease pain as a result of the vaccinations a nursing infant has to endure. Schechter et al. (7) discussed procedures that minimize the discomfort and pain associated with intramuscular injections, but did not discuss breastfeeding.

Indeed, breastfeeding is recognized as an analgesic procedure recommended in painful interventions for newborns and infants (8). Such effects could be either because of components in breast milk composition (9) or skin contact or both. Sajedi et al. (10) reported that heart rates during and 3 min after injection given to neonates in the 'kangaroo care' group were significantly lower than for neonates in the control group; blood oxygen saturation rates were also significantly higher for breast-fed infants than for neonates in the control group. It should be noticed that young babies are sensitive to the overall context of acute pain episodes when maternal soothing is fundamental (11).

FEVER, IRRITABILITY AND FEEDING DISTURBANCE

It is widely recognized that immunologic stimuli from vaccines can cause fever and irritability. Such reactions are accompanied by disinclination to feed or even anorexia; young children are more susceptible to these events. Yalçin et al. (12) have reported postvaccination (diphtheria, tetanus, pertussis-DTP) reaction rates for fever (53–63%), irritability (52–56%), drowsiness (33–37%) and anorexia (18–21%) in young children (15–20 months of age). Indeed, more than 20% of adverse events reported after DTP vaccines in the state of São Paulo (Brazil) were fever, which was more frequent in children aged under 7 months (13). There is hardly any study of the impact of these transient feeding-related episodes on infant nutrition. Anorexia or slight aversion to feed as a result of vaccination was studied by Lopez-Alarcon et al. (14,15); they reported that breast-feeding protects against decreased energy intakes.

In some countries, hepatitis B vaccine starts within the first postnatal day. In these circumstances Eales (16) observed that '*A baby suffering the common side effects of the hepatitis B vaccine is irritable and disinclined to feed*'*;* these concerns about the impact that early vaccination could have on breastfeeding rates of Australian infants were refuted by McIntyre and Wood (17). Nevertheless, fever remains a common adverse event following vaccination of preterm infants. Ellison et al. (18) reported that 33% preterm infants enrolled in a trial showed low-grade fever (>37.5°C) after vaccination. Yet impacts of transient events on early initiation of breastfeeding have not been sufficiently studied. To illustrate the importance of this issue, during early postnatal events, at least one form of jaundice is caused by 'postnatal starvation' that can be counteracted by effective breastfeeding initiation and maintenance. Therefore, it is important to keep in mind the need to start breastfeeding as soon as the baby wants to in order to prevent or attenuate some forms of hyperbilirubinaemia (19); keeping in mind that an increase in endogenous substances such as bilirubin is capable of displacing a competing substance (such as etHg) from albumin binding sites during the neonatal period, thus contributing to a higher fraction of substances (20) such as bilirubin or etHg to spread into neonates' vulnerable central nervous system (CNS).

IMMUNOMODULATION OF VACCINE RESPONSES

The role of breastfeeding on vaccine responses has been elegantly discussed elsewhere (21). Gut development and systemic immunity are intimately associated (22) and studies have showed that the infant's feeding method is important in the evaluation of various types of vaccines; that happens because the active immune response to specific antigens develops differently in breast-fed and formula-fed infants (23,24). Cell-mediated immune response to BCG (Bacille Calmette-Guérin) vaccine given at birth, but not at after 1 month, was significantly enhanced by breast-feeding (25); acquisition of cell-mediated immune response through breastfeeding has been confirmed by others (26,27). Also, antibody level responses to both peroral (poliovirus) and parenteral (diphtheria and tetanus toxoid) vaccines were significantly increased in breast-fed infants compared to formula-fed (28).

Compared to formula feeding, breast-fed infants immunized with *Haemophilus influenzae* type b (Hib) vaccine had significantly higher antibodies at the age of 7 months (26); but more important is the significant difference at 12 months and the consistent impact due to breastfeeding (29). Pabst et al. (30) reported that 14 days after live viral vaccination, only the breast-fed children had increased production of interferon-gamma, of percentages of CD56+ and CD8+ lymphocytes. The immunologic effects of breastfeeding on vaccines could also be detected much later after weaning (30). Indeed, Kanariou et al. (31) showed that IgA, an immunomodulatory component that boosts antibody titres during immunization, was significantly associated with breastfeeding.

It seems that breastfeeding duration is capable of eliciting a gradient of responses after vaccination; Silfverdal et al. (32) found that, compared to less breast-fed children, those exclusively breastfed for at least 90 days get a better serological protection after vaccination against Hib, and the pneumococcal serotypes 6B and 14. Other studies of the same research group had indicated that breastfeeding

enhanced the long-term IgG2 antibody response to Hib infections (33), suggesting that protection conferred by breastfeeding against *Haemophilus influenzae* meningitis could be traced 5–10 years later (34). These results concur that the duration of breastfeeding is related to higher levels of IgG2 anti-Hib above 18 months of age (35).

Some of the effects of breastfeeding on immunomodulation are exerted through the enteric system, albeit not fully understood. Gut colonization with specific probiotics increased the capacity to raise immune responses to protein antigens, especially in infants that were breastfed for less than 6 months (22). Oyedele et al. (36) showed that Nigerian mothers transferred measles-specific IgG in colostrum and breast milk that could protect breast-fed infants for at least the first 2 weeks. The rate of antibody waning, however, showed that 58% of these children had lost the protective maternal antibody by the age of 4 months.

However, for reasons not yet known, opposite results in antibody concentrations in response to vaccinated breastfed infants have been reported. Lower titres have been found for parenteral conjugate Hib (37) and per oral administration of rhesus rotavirus vaccine (38). However, it is clear from Hanson and Silferdal's (24) discussion that immunological responses to vaccines given to children are modulated by many factors related to constitutional (genetics, birth weight, gestational age) and environmental (helminth infestation and climate) factors; breastfeeding is also an important factor positively influencing immunization.

METABOLISM OF THIMEROSAL-HG FROM VACCINES

The number of vaccines given to infants has increased significantly over the last 20 years. Some of these vaccines are still formulated to contain small amounts of thimerosal (sodium ethyl mercury thiosalicylate), which is a water-soluble substance that degrades or metabolizes into etHg; this metabolite is lipid soluble but in animal tissues binds to protein matrices and is excreted through the gut (39). Because of the early exposure and the number of doses a young child takes, it is especially important for paediatric health workers in countries that have to use TCVs in newborns and infants to know the metabolism of alkylated forms of Hg.

Unlike older children, neonates and young infants lack the necessary barriers and detoxifying mechanisms (in the immature enterohepatic system) that exert a selective action on substances arriving through milk; for the exclusive breast-fed infant, these functions are carried out in the maternal system. Because of the mammary-gland barrier, exposure to Hg is handled without untoward consequences in the breast-fed infant (39). Indeed, Newland et al. (40) have discussed the occurrence of organic and inorganic forms of milk-Hg exposure, concluding that only a fraction of maternal blood-Hg is present in breast milk and only a fraction of that is absorbed by the infant. Even then, the amount of milk-Hg taken is proportional to the milk feeding. In the case of Hg exposure derived from TCV, the unimpeded dose of thimerosal reaching circulation is the same for a newborn, an infant or an older child (with a developed entero-hepatic system). It should be made clear that, to date, no unacceptable side-effects found for vaccines have been attributed to thimerosal; on the other hand, given the increasing concern about environmental mercury contamination (in tandem with increased recommendations to avoid methylmercury in seafood) it is only natural that we should discuss the exposure of TCV-etHg at vulnerable ages.

Studies of TCV-etHg metabolism in infants are very recent; half-life of EtHg in immunized infants was estimated as 6 days (41) or half of that (42). Recent studies, however, are showing that vaccine-etHg exposure can accumulate in infant's hair from serial exposure to thimerosal (43,44). Because parents may prefer multiple injections to be given at the same visit (7), if vaccinated with TCV children could be exposed to even higher doses of thimerosal.

A recognized impact of breastfeeding on infant health is that it reduces illnesses and attendant antibiotic treatments. The later engenders unwanted effects on infants' gut colonization; along with infant feeding (45), these are the most important determinants of the microbiotic composition in the infant gut (46). It has been shown in animal studies (47) that antibiotics changed the intestinal microflora and impaired demethylation of methylmercury, thus increasing tissue retention of Hg. The blood-brain barrier (BBB) stops toxic substances in the blood stream from reaching the highly vulnerable nervous cells and biochemical structure of the CNS. An immature BBB could be sensitive to changes in mercury metabolism brought about by delayed Hg excretion. In compensation, putative neurobehavioural effects resulting from maternal (ante-natal) exposure (that includes fish-meHg) are counteracted by breastfeeding (48); possible associations of neurodevelopmental delays with thimerosal in exposed infants are also overcome by exclusive breastfeeding (49). Indeed, studies have shown that intelligence tests (which included school performance in late adolescence or young adulthood) was higher in individuals that had been breastfed (50). Recent strong evidence based on a large randomized trial indicates that prolonged and exclusive breastfeeding improves children's cognitive development (51).

RATES OF IMMUNE REACTIONS TO RESPIRATORY AND FOOD ALLERGENS

The frequency and severity of immune reactions triggered by food or respiratory allergens, also called allergies, are increasing despite international variation (52); currently, in Sweden, Alm et al. (53) reported that one in five infants suffer from eczema during the first year of life. The coincidence of increased rates of allergic diseases and increased number of vaccines in recent times has been intensely studied and can be found in specialized reviews.

Anderson et al. (52) discussed the rationale (for either positive or negative effects) of immunization on the incidence of allergic diseases. They expressed the central idea that 'immunization might increase atopic disease either by a direct effect on the immune system or by a reduction of the burden of infection in early childhood'. They discussed

relevant epidemiological studies that dealt with the main types of vaccines used in childhood (pertussis, measles, tuberculosis) in different countries (52); they found that the results for pertussis vaccines as a risk factor for atopy were inconsistent. Collectively, it was concluded that the weight of evidence suggests that vaccines do not increase atopic disorders (52).

More recent studies, however, indicate positive, negative or no association between vaccines and an increase in allergic disorders. There are results suggesting a weak association of vaccine with allergy in adults (54) or in children (55). Indeed, a study in Canada did indicate a negative association between delay in administration of the first dose of whole-cell DPT immunization in childhood and the development of asthma; the association was greater with delays in all of the first three doses (56). However, large and small studies have shown no association of vaccine status of children with changes in rates of atopic allergy or asthma in the United States (57) United Kingdom (55,58) and the Netherlands (59–61). Both DeStefano et al. (57) and McKeever et al. (58) attributed significant associations to statistical bias inherent to the analysed databases. To complicate matters, Dilli et al. (62) found that BCG vaccine at birth and hepatitis B vaccine at 2 months could be protective against recurrent wheezing but could not prevent atopy.

Most vaccines used in nonindustrialized countries are still preserved with small amounts of thimerosal. This vaccine preservative can sensitize children (63) and vaccine-thimerosal can account for high sensitization to thimerosal in adults (64). It has been speculated that thimerosal allergy in the general population has decreased in Denmark because it was excluded from vaccines (65). Nevertheless, studies have shown that thimerosal-sensitive individuals can receive intramuscular inoculations (66). Despite the fact that Glutathione S-transferase M1 deficiency was significantly more frequent among patients sensitized to thimerosal (67), epidemiological studies have yet to address this issue.

Although studies have not always concurred, main reviews and paediatric medicine boards recognize breastfeeding as having a positive effect on allergic diseases; the reasons to expect breast-fed children showing a reduced occurrence of asthma and atopic disease are discussed elsewhere (68). A comprehensive review through May 2006 has found that a history of breastfeeding was associated with a reduction in the risk of atopic dermatitis and asthma in young children (69). Indeed, Thygarajan and Burks (70) reviewed the American Academy of Pediatrics' statement on the effects of early nutritional interventions on the development of atopic disease in infants and children (71) and concluded that, in high-risk infants, exclusive breastfeeding for at least 4 months prevents or delays atopic dermatitis, cow milk allergy and wheezing early in life. In France, for this targeted population, as well as for the general population, there are also recommendations of exclusive breastfeeding until the age of 6 months (72). Breastfeeding can prevent a high proportion of asthma in childhood (73), maybe because it directs actions on helping lung function; a recent work of Ogbuanu et al. (74) shows that breastfeeding for at least 4 months enhances lung volume in children that affects airflow.

This topic is still debatable. Recently, Duncan and Sears (75) reviewed studies of the epidemiology of allergic diseases (especially atopic dermatitis in infants and asthma) associated with breastfeeding; they concluded that studies do not confirm the 'conventional wisdom' that breastfeeding is protective against allergy and asthma. However, studies that were not discussed in the main reviews published in 2008 indicate the difficulties in dealing with the issue. Larsson et al. (76) found that the main risk factors for incident asthma were male gender and short period of breastfeeding (rhinitis and eczema as well as allergic symptoms in parents were also strong risk factors); they pointed out that when comparing incident rates of asthma between different studies it is important to take into account the healthy baseline of the population. Others have also recently (77) identified breastfeeding as a protective factor among the determinants of the incidence of childhood asthma assessed for the prenatal, perinatal and childhood periods in Canada. However, in Japan studies indicated different results; Karino et al. (78) studied the prevalence of allergic diseases in young adults and reported that the effect of breastfeeding is negligible when compared with genetic factors. While in infants no statistically significant relationship between breastfeeding duration and the risk of wheezing or asthma was reported in a longitudinal study (79), prolonged breastfeeding was associated with a higher prevalence of atopic eczema in children in a cross-sectional study (80).

CONCLUSIONS

1 Breastfeeding is essential to complete postnatal development by promoting and priming neonatal immunologic, gastrointestinal and central nervous systems.
2 Stressful reactions to pain and immunogenic effects of vaccines are alleviated by breast feeding.
3 Appetite disruption caused by fever and transient neurobehavioural reactions of vaccines can be attenuated by breastfeeding.
4 Compared to conventional and low protein formula, breastfeeding has showed a positive effect on postvaccine immunomodulation; in most studies breastfeeding increased infant vaccine responses.
5 So far, studies indicate no conclusive association between vaccines and changes in rates of allergic diseases, but there are evidence-based recommendations that breastfeeding is protective.
6 Breastfeeding should be communicated as an effective tool to complement immunization, especially in those situations that require thimerosal-containing vaccines. Healthcare professionals should inform mothers of the proven benefits of breastfeeding and its importance in complementing vaccines, lowering risks of untoward effects on susceptible infants.

ACKNOWLEDGEMENTS

This work was supported by The National Research Council of Brazil-CNPq (grants 556985/2005–2 and 555516/2006–7).

References

1. Edmond KM, Zandoh C, Quigley MA, Amenga-Etego S, Owusu-Agyei S, Kirkwood BR. Delayed breastfeeding initiation increases risk of neonatal mortality. *Pediatrics* 2006; 117: e380–e6.
2. Field CJ. The immunological components of human milk and their effect on immune development in infants. *J Nutr* 2005; 135: 1–4.
3. Offit PA, Moser CA. The problem with Dr Bob's alternative vaccine schedule. *Pediatrics* 2009; 123: e164–e169.
4. Wu AC, Wisler-Sher DJ, Griswold K, Colson E, Shapiro ED, Holmboe ES, et al. Postpartum mothers' attitudes, knowledge, and trust regarding vaccination. *Matern Child Health J* 2008; 12: 766–73.
5. Efe E, Ozer ZC. The use of breast-feeding for pain relief during neonatal immunization injections. *Appl Nurs Res* 2007; 20: 10–6.
6. Dilli D, Küçük IZ, Dallar Y. Interventions to reduce pain during vaccination in infancy. *J Pediatr* 2009; 154: 385–90.
7. Schechter NL, Zempsky WT, Cohen LL, McGrath PJ, McMurtry CM, Bright NS. Pain reduction during pediatric immunizations: evidence-based review and recommendations. *Pediatrics* 2007; 119: e1184–98.
8. Gray L, Miller LW, Philipp BL, Blass EM. Breastfeeding is analgesic in healthy newborns. *Pediatrics* 2002; 109: 590–3.
9. Walker CD. Nutritional aspects modulating brain development and the responses to stress in early neonatal life. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; 29: 1249–63.
10. Sajedi F, Kashaninia Z, Rahgozar M, Noghabi FA. The effect of Kangaroo Care on physiologic responses to pain of an intramuscular injection in neonates. *Iran J Pediatr* 2007; 17: 339–44.
11. Axia G, Bonichini S. Are babies sensitive to the context of acute pain episodes? Infant distress and maternal soothing during immunization routines at 3 and 5 months of age. *Infant Child Dev* 2005; 14: 51–62.
12. Yalçin SS, Gümüş A, Yurdakök K. Prophylactic use of acetaminophen in children vaccinated with diphtheria-tetanus-pertussis. *World J Pediatr* 2008; 4: 127–9.
13. Freitas FR, Sato HK, Aranda CM, Arantes BA, Pacheco MA, Waldman EA. [Adverse events following diphtheria, pertussis and tetanus vaccinations and factors associated with severity]. *Rev Saude Publica* 2007; 41: 1032–41.
14. Lopez-Alarcon M, Garza C, Habicht JP, Martinez L, Pegueros V, Villalpando S. Breastfeeding attenuates reductions in energy intake induced by a mild immunologic stimulus represented by DPTH immunization: possible roles of interleukin-1beta, tumor necrosis factor-alpha and leptin. *J Nutr* 2002; 132: 1293–8.
15. Lopez-Alarcon M, Garza C, Del Prado M, Garcia-Zuniga PA, Barbosa L. Breastfeeding's protection against illness-induced anorexia is mediated partially by docosahexaenoic acid. *Eur J Clin Nutr* 2008; 62: 32–8.
16. Eales SJ. Hepatitis B vaccine at birth–just another barrier to breastfeeding? *Aust Mid* 2003; 16: 4–5.
17. McIntyre P, Wood N. Does universal hepatitis B vaccination at birth have a negative impact on breastfeeding? *Aust Mid* 2004; 17: 4–5.
18. Ellison VJ, Davis PG, Doyle LW. Adverse reactions to immunization with newer vaccines in the very preterm infant. *J Paediatr Child Health* 2005; 41: 441–3.
19. Alex M, Gallant DP. Toward understanding the connections between infant jaundice and infant feeding. *J Pediatr Nurs* 2008; 23: 429–38.
20. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Drug therapy: developmental pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; 349: 1157–67.
21. Hanson LA. Breastfeeding provides passive and likely long-lasting active immunity. *Ann Allergy Asthma Immunol* 1998; 81: 523–33.
22. West CE, Gothefors L, Granström M, Käyhty H, Hammarström M-L, Hernell O. Effects of feeding probiotics during weaning on infections and antibody responses to diphtheria, tetanus and Hib vaccines. *Pediatr Allergy Immunol* 2007; 19: 53–60.
23. Pabst HF. Immunomodulation by breast-feeding. *Pediatr Infect Dis* 1997; 16: 991–5.
24. Hanson LA, Silfverdal SA. Vaccination immunology. *Scand J Infect Dis* 2008; 40: 696–701.
25. Pabst HF, Godel J, Grace M, Cho H, Spady DW. Effect of breast-feeding on immune response to BCG vaccination. *Lancet* 1989; 1: 295–7.
26. Ogra SS, Weintraub D, Ogra PL. Immunologic aspects of human colostrum and milk. III. Fate and absorption of cellular and soluble components in the gastrointestinal tract of the newborn. *J Immunol* 1977; 119: 245–8.
27. Schlesinger JJ, Covelli HD. Evidence for transmission of lymphocyte responses to tuberculin by breast-feeding. *Lancet* 1977; 2: 529–32.
28. Hahn-Zoric M, Fulconis F, Minoli I, Moro G, Carlsson B, Bottiger M, et al. Antibody responses to parenteral and oral vaccines are impaired by conventional and low protein formulas as compared to breast-feeding. *Acta Paediatr Scand* 1990; 79: 1137–42.
29. Pabst HF, Spady DW. Effect of breast-feeding on antibody response to conjugate vaccine. *Lancet* 1990; 336: 269–70.
30. Pabst HF, Spady DW, Pilarski LM, Carson MM, Beeler JA, Krezolek MP. Differential modulation of the immune response by breast- or formula-feeding of infants. *Acta Paediatr* 1997; 86: 1291–7.
31. Kanariou M, Petridou E, Liatsis M, Revinthi K, Mandalenaki-Lambrou K, Trichopoulos D. Age patterns of immunoglobulins G, A and M in healthy children and the influence of breast feeding and vaccination status. *Pediatr Allergy Immunol* 1995; 6: 24–9.
32. Silfverdal SA, Ekholm L, Bodin L. Breastfeeding enhances the antibody response to Hib and Pneumococcal serotype 6B and 14 after vaccination with conjugate vaccines. *Vaccine* 2007; 25: 1497–502.
33. Silfverdal SA, Bodin L, Ulanova M, Hahn-Zoric M, Hanson LA, Olcen P. Long-term enhancement of the IgG2 antibody response to *Haemophilus influenzae* type b by breastfeeding. *Pediatr Infect Dis J* 2002; 21: 816–21.
34. Silfverdal SA, Bodin L, Olcen P. Protective effect of breastfeeding: an ecological study of *Haemophilus influenzae* meningitis and breastfeeding in a Swedish population. *Int J Epidemiol* 1999; 28: 152–6.
35. Silfverdal SA, Bodin L, Ulanova M, Hahn-Zoric M, Hanson LA, Olcén P. Expression of idiotypic antibodies -1 and -2 and breastfeeding in relation to antibody levels against *Haemophilus influenzae* type b in children. *Scand J Immunol* 2006; 63: 371–5.

36. Oyedele OO, Odemuyiwa SO, Ammerlaan W, Muller CP, Adu FD. Passive immunity to measles in the breastmilk and cord blood of some Nigerian subjects. *J Trop Pediatr* 2005; 51: 45–8.
37. Hawkes JS, Makrides M, Roberton DM, Gibson RA. Responses to immunisation with Hib conjugate vaccine in Australian breastfed and formula-fed infants. *J Paediatr Child Health* 2007; 43: 597–600.
38. Pichichero ME. Effect of breast-feeding on oral rhesus rotavirus vaccine seroconversion: a metaanalysis. *J Infect Dis* 1990; 162: 753–5.
39. Dórea JG. Exposure to mercury during the first six months via human milk and vaccines: modifying risk factors. *Am J Perinatol* 2007; 24: 387–400.
40. Newland MC, Paletz EM, Reed MN. Lactational exposure to mercury in experimental models. *Neurotoxicology* 2009; 30: 161–3.
41. Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet* 2002; 360: 1737–4171.
42. Pichichero ME, Gentile A, Giglio N, Umido V, Clarkson T, Cernichiari E, et al. Mercury levels in newborns and infants after receipt of thimerosal-containing vaccines. *Pediatrics* 2008; 121: e208–e4.
43. Marques RC, Dórea JG, Fonseca MF, Bastos WR, Malm O. Hair mercury in breast-fed infants exposed to thimerosal-preserved vaccines. *Eur J Pediatr* 2007; 166: 935–41.
44. Park HJ, Kim DS, Moon JS, Yang WH, Son BS. Mercury level in hair of primary school children in Korea and China. *Mol Cel Toxicol* 2008; 4: 235–45.
45. Morelli L. Postnatal development of intestinal microflora as influenced by infant nutrition. *J Nut* 2008; 138: 1791S–1795S.
46. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* 2006; 118: 511–21.
47. Rowland IR, Robinson RD, Doherty RA. Effect of diet on mercury metabolism and excretion in mice given methylmercury: role of gut flora. *Arch Environ Health* 1984; 39: 401–8.
48. Dórea JG. Maternal smoking and infant feeding: breastfeeding is better and safer. *Matern Child Health J* 2007; 11: 287–91.
49. Marques, RC, Dórea JG, Bernardi JVE, Bastos WR, Malm O. Pre- and post-natal mercury exposure, breastfeeding and neurodevelopment during the first five years. *Cogn Beh Neurol* 2009; 22: 134–41.
50. Horta BL, Bahl R, Martinez JC, Victora CG. *Evidence on the long term effects of breastfeeding. Systematic reviews and meta-analyses*. Geneva: WHO, 2007: 1–51.
51. Kramer MS, Aboud F, Mironova E, Vanilovich I, Platt RW, Matush L, et al.; Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group. Breastfeeding and child cognitive development: new evidence from a large randomized trial. *Arch Gen Psychiatry* 2008; 65: 578–84.
52. Anderson HR, Poloniecki JD, Strachan DP, Beasley R, Björkstén B, Asher MI; ISAAC Phase 1 Study Group. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health* 2001; 91: 1126–9.
53. Alm B, Aberg N, Erdes L, Möllborg P, Pettersson R, Norvenius SG, et al. Early introduction of fish decreases the risk of eczema in infants. *Arch Dis Child* 2009; 94: 11–5.
54. Benke G, Abramson M, Raven J, Thien FC, Walters EH. Asthma and vaccination history in a young adult cohort. *Aust N Z J Public Health* 2004; 28: 336–8.
55. Bremner SA, Carey IM, DeWilde S, Richards N, Maier WC, Hilton SR, et al. Vaccinations, infections and antibacterials in the first grass pollen season of life and risk of later hayfever. *Clin Exp Allergy* 2007; 37: 512–7.
56. McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. *J Allergy Clin Immunol* 2008; 121: 626–31.
57. DeStefano F, Gu D, Kramarz P, Truman BI, Iademarco MF, Mullooly JP, et al. Vaccine Safety Datalink Research Group. Childhood vaccinations and risk of asthma. *Pediatr Infect Dis J* 2002; 21: 498–504.
58. McKeever TM, Lewis SA, Smith C, Hubbard R. Vaccination and allergic disease: a birth cohort study. *Am J Public Health* 2004; 94: 985–9.
59. Kummeling I, Thijs C, Stelma F, Huber M, Van Den Brandt PA, Dagnelie PC. Diphtheria, pertussis, poliomyelitis, tetanus, and *Haemophilus influenzae* type b vaccinations and risk of eczema and recurrent wheeze in the first year of life: the KOALA Birth Cohort Study. *Pediatrics* 2007; 119: e367–e3.
60. Bernsen RM, de Jongste JC, Koes BW, Aardoom HA, Van Der Wouden JC. Diphtheria tetanus pertussis poliomyelitis vaccination and reported atopic disorders in 8–12-year-old children. *Vaccine* 2006; 24: 2035–42.
61. Bernsen RM, Koes BW, de Jongste JC, Van Der Wouden JC. Haemophilus influenzae type b vaccination and reported atopic disorders in 8–12-year-old children. *Pediatr Pulmonol* 2006; 41: 463–9.
62. Dilli D, Bostanci I, Dallar Y. Do different vaccination regimens for BCG and hepatitis B affect the development of allergic disorders in early childhood? *J Asthma* 2008; 45: 155–9.
63. Osawa J, Kitamura K, Ikezawa Z, Nakajima H. A probable role for vaccines containing thimerosal in thimerosal hypersensitivity. *Contact Dermatitis* 1991; 24: 178–82.
64. Seidenari S, Manzini B M, Danese P, Motolese A. Patch and prick test study of 593 healthy subjects. *Contact Dermatitis* 1990; 23: 162–7.
65. Thyssen JP, Linneberg A, Menné T, Johansen JD. The epidemiology of contact allergy in the general population – prevalence and main findings. *Contact Dermatitis* 2007; 57: 287–99.
66. Aberer W. Vaccination despite thimerosal sensitivity. *Contact Dermatitis* 1990; 24; 6–10.
67. Westphal GA, Schnuch A, Schulz TG, Reich K, Aberer W, Brasch J, et al. Homozygous gene deletions of the glutathione S-transferases M1 and T1 are associated with thimerosal sensitization. *Int Arch Occup Environ Health* 2000; 73: 384–8.
68. van Rossum CTM, Büchner FL, Hoekstra J. Quantification of health effects of breastfeeding. Review of the litterature and model simulation. In: National Institute for Public Health and the Environment, Bilthoven: RIVM report 350040001. 2005:3–108. Available from: http: //www.rivm.nl/bibliotheek/rapporten/350040001.html (accessed April 03, 2008).
69. Ip S, Chung M, Raman G, Chew P, Magula N, DeVine D, et al. Breastfeeding and maternal and infant health outcomes in developed countries. *Evid Rep Technol Assess (Full Rep)* 2007; 153: 1–186.
70. Thygarajan A, Burks AW. American Academy of Pediatrics recommendations on the effects of early nutritional interventions on the development of atopic disease. *Curr Opin Pediatr* 2008; 20: 698–702.
71. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction,

breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008; 121: 183–91.
72. Chouraqui JP, Dupont C, Bocquet A, Bresson JL, Briend A, Darmaun D, et al.; Comité de nutrition de la Société française de pédiatrie. [Feeding during the first months of life and prevention of allergy]. *Arch Pediatr* 2008; 15: 431–42.
73. Karmaus W, Dobai AL, Ogbuanu I, Arshard SH, Matthews S, Ewart S. Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. *J Asthma* 2008; 45: 688–95.
74. Ogbuanu IU, Karmaus W, Arshad SH, Kurukulaaratchy RJ, Ewart S. Effect of breastfeeding duration on lung function at age 10 years: a prospective birth cohort study. *Thorax* 2009; 64: 62–6.
75. Duncan JM, Sears MR. Breastfeeding and allergies: time for a change in paradigm? *Curr Opin Allergy Clin Immunol* 2008; 8: 398–405.
76. Larsson M, Hägerhed-Engman L, Sigsgaard T, Janson S, Sundell J, Bornehag CG. Incidence rates of asthma, rhinitis and eczema symptoms and influential factors in young children in Sweden. *Acta Paediatr* 2008; 97: 1210–5.
77. Martel MJ, Rey E, Malo JL, Perreault S, Beauchesne MF, Forget A, et al. Determinants of the incidence of childhood asthma: a two-stage case-control study. *Am J Epidemiol* 2009; 169: 195–205.
78. Karino S, Okuda T, Uehara Y, Toyo-oka T. Breastfeeding and prevalence of allergic diseases in Japanese university students. *Ann Allergy Asthma Immunol* 2008; 101: 153–9.
79. Miyake Y, Arakawa M, Tanaka K, Sasaki S, Ohya Y. Cross-sectional study of allergic disorders associated with breastfeeding in Japan: the Ryukyus Child Health Study. *Pediatr Allergy Immunol* 2007; 18: 433–40.
80. Miyake Y, Tanaka K, Sasaki S, Kiyohara C, Ohya Y, Fukushima W, et al.; Osaka Maternal and Child Health Study Group. Breastfeeding and the risk of wheeze and asthma in Japanese infants: the Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2008; 19: 490–6.

