Vaccine 30 (2012) 4921–4926

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

State of the art: Could nursing mothers be vaccinated with attenuated live virus vaccine?

Sophie Alain[a,*], Marie-Aliette Dommergues[b], Anne Carole Jacquard[c], Evelyne Caulin[c], Odile Launay[d]

[a] Service de Bactériologie-Virologie-hygiène, CHRU, Limoges, INSERM 1092, Université de Limoges France
[b] Service de Pédiatrie, Centre Hospitalier de Versailles Le Chesnay, France
[c] Sanofi Pasteur MSD, Lyon, France
[d] Université Paris Descartes, Assistance Publique Hôpitaux de Paris, Groupe Hospitalier Cochin Saint Vincent de Paul, Inserm, CIC BT 505, Paris, France

ARTICLE INFO

Article history:
Received 25 February 2012
Received in revised form 10 May 2012
Accepted 19 May 2012
Available online 31 May 2012

Keywords:
Breast-feeding
Infant
Vaccine attenuated
Viral vaccine

ABSTRACT

Recently two cases of vaccine-associated neurologic disease have been reported in breastfed infants whose mothers had received live attenuated yellow fever vaccine. These two cases have focused attention on the transmission of attenuated yellow fever vaccine virus from mother to infant via breastfeeding, and more generally of all other live attenuated viruses used to immunize nursing mothers. This article provides an overview of the rare literature on possible virus excretion in breast milk after vaccination of nursing mothers with live attenuated virus vaccine and on cases of infection via breastfeeding in infants whose mothers had been vaccinated postpartum. Before implementing postpartum vaccination in a nursing mother, the vaccinator needs to weigh up the risk of transmission to and adverse effects in the baby from live vaccine virus against the beneficial effects of the vaccine for the mother, taking into account her need for vaccination.

1. Introduction

It is generally accepted that lactating mothers may safely receive live virus vaccines without interrupting their breastfeeding schedule [1]. However, recently two cases (one confirmed and one probable) of vaccine-associated meningo encephalitis have been reported in infants whose mothers had received live attenuated yellow fever vaccine. Both infants were less than one month old at exposure, and were exclusively breastfed. Yellow fever vaccine virus was recovered from the cerebrospinal fluid in the confirmed case, and specific IgM antibodies against yellow fever in the probable case [2–4]. These reports did not preclude nursing women vaccination. However, both before (as a precautionary measure due to the theoretical risk of vaccine virus transmission to breastfed infants) and after the two cases, caution was recommended when vaccinating nursing mothers against yellow fever in vaccine guidelines [3]. Nursing mothers can be vaccinated when living in or moving to areas at very high risk of wild-type yellow fever virus transmission [4]. However, the two cases focused attention on transmission of yellow fever attenuated vaccine virus from mother to infant via breastfeeding, and more generally of all other live attenuated viruses potentially used to immunize nursing mothers (i.e., measles, mumps, rubella, and varicella-zoster virus).

The aim of this article is thus to present the published data on possible vaccine virus excretion in breast milk after vaccination of nursing mothers with live attenuated virus vaccine and on cases of infection via breastfeeding in infants whose mothers had been vaccinated postpartum. No analysis of the literature on the risk of transmission from nursing mothers to breastfeeding children has been carried out for live attenuated influenza vaccine, because this vaccine is currently marketed only for use in children and is not used in Europe; for those places where it is marketed for young adults, data are scarce and with little follow-up. By way of introduction, rubella, measles, mumps, varicella and yellow fever vaccine recommendations in breastfeeding women and the burden of these vaccine-preventable diseases in infants are discussed.

2. Are there specific recommendations for the use of live attenuated virus vaccines in nursing mothers?

According to the WHO position paper on rubella, two different approaches are recommended for the use of rubella vaccine [5]. In countries planning to reduce congenital rubella syndrome, only adolescent and adult females should be vaccinated, while in countries undertaking rubella elimination, vaccination should be introduced during childhood (between 9 and 12 months of age). Measles immunization is recommended by the WHO [6] for

* Corresponding author at: Service de Bactériologie-Virologie-Hygiène, Hôpital Dupuytren, 2 avenue Martin-Luther-King, 87042 Limoges cedex, France.
Tel.: +33 5 55 05 67 28; fax: +33 5 55 05 61 25.
E-mail address: sophie.alain@unilim.fr (S. Alain).

0264-410X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2012.05.047

all susceptible children and adults in whom it is not contraindicated. Finally, according to the WHO [7], mumps should be a lower vaccination priority than measles or rubella, and routine mumps vaccination of children is recommended in countries with a well-established childhood vaccination program. The WHO's contraindications for these three vaccinations, usually administered concomitantly, are a history of anaphylactic reaction to vaccine components, immunodeficiency, and pregnancy due to the theoretical risk of transmission of the live attenuated virus to the fetus. Breastfeeding is not mentioned as a contraindication.

As regards varicella [8], in addition to childhood immunization in several countries, immunization may be offered in any country to individual adolescents and adults without a history of varicella, and in particular those at elevated risk of infection. The WHO's contraindications for varicella vaccination are a history of anaphylactic reaction to vaccine components, immunodeficiency, and pregnancy. Breastfeeding is not a contraindication.

Finally, according to the WHO position paper on yellow fever [9], the recommended vaccine strategy in at-risk countries is to include yellow fever vaccine in national childhood immunization programs (all children between nine and 12 months of age receiving the 17D live virus vaccine) and mass preventive vaccination campaigns to protect susceptible older children and adults. In addition, yellow fever vaccine is also recommended for travelers to at-risk areas aged over nine months. Contraindications to yellow fever vaccination are age less than six months, severe allergy to egg antigens, and immunodeficiency. Vaccination is also not recommended during pregnancy. Children between six and nine months of age and pregnant women may be vaccinated during epidemics when the risk of yellow fever is very high. Breastfeeding is not a contraindication.

These WHO recommendations are followed in most developed countries. Table 1 summarizes national recommendations for breastfeeding women in Australia, Canada, France, Switzerland, the United Kingdom, and the United States. Postpartum vaccination of seronegative women against rubella is a standard practice and measles, mumps or varicella is sometimes recommended, which would increase the probability of attenuated live virus vaccination of nursing mothers. Conversely, the summaries of product characteristics (SmPCs) usually recommend delaying vaccination with live attenuated vaccines until after breastfeeding.

The SmPC labeling for use in nursing women of some live attenuated vaccines, such as measles, mumps and rubella vaccine (e.g., M-M-R VAX PRO®, Sanofi Pasteur MSD and Priorix®, GlaxoSmithKline), differ slightly with the vaccine and the country. According to the French SmPC, vaccination with Priorix® must be avoided during breastfeeding, and preferably replaced by the corresponding monovalent vaccine in an epidemic situation (http://afssaps-prd.afssaps.fr/php/ecodex/extrait.php?specid=61896473). However, according to the UK SmPC, Priorix® can be administered to breastfeeding women where the benefit outweighs the risk (http://www.medicines.org.uk/emc/document.aspx?documentid=2054). According to the European SmPC, caution should be exercised when M-M-R VAX PRO® is administered to a breastfeeding woman (http://www.medicines.org.uk/emc/medicine/20968/SPC/mmrvaxpro/). Finally, it appears that vaccination recommendations do not necessarily match licensed indications of the products. Consequently, the risk versus benefit of each vaccine must be considered.

3. What could be the clinical consequences of wild virus infection with these vaccine-preventable diseases for infants?

To the best of our knowledge there is little information on the clinical consequences of infection with these vaccine-preventable diseases in breastfeeding infants, as most of the infants are protected against these diseases by maternal antibodies.

However, it seems that, apart from congenital infection, rubella is a mild, self-limiting illness that usually occurs during childhood, and that most mumps infections in children under two years of age are subclinical. Conversely, the risk of developing severe fatal measles increases for children under five years of age living in overcrowded conditions, who are malnourished (vitamin A deficiency), or who have immunological disorders [18]. In addition, neonatal or congenital measles, although rare, can be very severe with a mortality rate up to 30% [19]. Finally, the early onset of measles (congenital or before the age of one year) increases the risk of subacute sclerosing panencephalitis [20–22].

Varicella is a widespread and usually benign disease of childhood. However, in some instances, such as neonatal varicella, varicella can be severe and eventually fatal. Neonatal varicella that occurs in the first 10–12 days of life is caused by intrauterine transmission of varicella-zona virus (VZV). Varicella that occurs after the 10th or the 12th day of the neonatal period is most likely acquired by postnatal VZV infection and has a low morbidity rate as most neonates are protected by maternally derived antibodies. In fact, varicella severity is inversely correlated with the level of anti-VZV maternal antibodies [23–26]. In France, where varicella vaccines are not recommended on a routine basis, it has been shown that only 5% of infants under one month of age [24] and 2% of pregnant women [25] had anti-VZV antibody titers below the threshold considered to be protective. These results suggest that only a small proportion of children are at risk of congenital and neonatal varicella syndrome.

In the case of yellow fever, the incubation period lasts approximately three to six days and is followed by subclinical infection, nonspecific illness, transient influenza-like illness, febrile illness with jaundice, or fatal hemorrhagic fever. Fatal cases are more frequent among young children and the elderly [27].

4. Current state of knowledge on virus excretion in milk and infant infection with live attenuated virus vaccine via breastfeeding

4.1. Materials and methods

This literature review addresses the following question: what findings in the scientific literature tend to demonstrate vaccine virus excretion in breast milk after vaccination of nursing mothers and/or infection in infants whose mothers were vaccinated postpartum during the breastfeeding period?

The search strategy involved an electronic search (Medline database via PubMed) and cross-references. Only articles in French and English were selected. No other limit was applied: *all types of articles were selected*. Keywords [MeSH] were on the one hand "breastfeeding", "milk, human", and "milk", and on the other hand "yellow fever", "yellow fever virus", or "yellow fever vaccine", "measles", "measles virus", or "measles vaccine", "mumps", "mumps virus", or "mumps vaccine", or "rubella", "rubella virus", or "rubella vaccine", or "measles-mumps-rubella" vaccine, "chickenpox", "herpesvirus 3, human", or "chickenpox vaccine", and "morbillivirus" or "morbillivirus infection". A total of 84 papers were identified, of which 30 (with or without Abstracts) were selected to be read. The 54 other articles did not answer the question, most of them demonstrating the benefit of maternal vaccination on infant seroprotection. Ultimately only seven papers addressed the study question precisely, most ($n=4$) being case reports (see Table 2). Lastly, the international reference book on vaccines by Plotkin and Orenstein [1] was also consulted.