World Health Organization

Report on
Safety of Immunization during Pregnancy

Global Advisory Committee on Vaccine Safety

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1 Introduction

Vaccine-preventable infectious diseases are responsible for significant maternal, neonatal, and young infant morbidity and mortality. Immune alterations, thought to be a consequence of allowing the woman to tolerate the semi-allogeneic fetus, may interfere with the normal development of specific response to pathogens in the mother and fetus. These immunological changes may alter their susceptibility to certain infectious diseases (Jamieson, Theiler & Rasmussen, 2006). In addition, they may be at risk of more serious outcomes of infections. The immature adaptive immune systems of neonates and premature infants make them one of the most vulnerable age groups for morbidity and mortality due to infections.

Maternal immunization can protect the mother directly against vaccine-preventable infections, and provide a cocooning effect that can potentially protect the fetus. It can also provide further direct fetal/infant protection against infection via the transport of specific antibodies to the fetus prior to birth.

At its meeting in December 2011, the Strategic Advisory Group of Experts (SAGE) asked GACVS to provide support to the review of current evidence on the safety of vaccinations in pregnant and lactating women. This request related to uncertainties about the safety of vaccination – whether intended or inadvertent – of pregnant women during mass vaccination campaigns. Such evidence would be particularly important in situations where manufacturers do not recommend the vaccination of pregnant women on solely precautionary grounds. However, evidence relating to this issue is limited. Clinical trials are not usually conducted among pregnant and lactating women prior to the licensure of vaccines. Experience from several countries suggests both a lack of available post-licensing data and a reluctance to include pregnant women in clinical trials. This in turn has limited the ability to make evidence-based decisions and provide optimal guidance for the use of vaccines in this population.

2 Methodology

This report presents an overview of the relevant literature including high quality publications. GACVS also consulted with regulatory authorities and pharmaceutical companies concerning results of on-going surveillance programs in pregnant women (pertussis containing and meningococcal vaccines) Data lock point for literature review was May 2013.

GACVS has assessed the availability and amount of data, as well as their overall quality in terms of consistency, strengths, and weaknesses and draws conclusions based on expert discussion and consensus rather than on a systematic review and a grading system (e.g. that put forth by the Grading of Recommendations Assessment, Development and Evaluation Working Group, GRADE). This report focuses on vaccines currently available. Given their broad spectrum, GACVS prioritized vaccines for review based on two key criteria: their potential to reduce morbidity for the pregnant woman and her fetus; and their use (or anticipated use) in vaccination campaign settings, where there is the potential for inadvertent vaccination of pregnant women.

Following the selection of specific vaccines for review, a standard framework was developed which addressed the following issues:

- demonstrated or potential benefit of maternal vaccination during pregnancy. This included evidence of morbidity from the disease in pregnant women and fetuses, as well as any evidence of efficacy/effectiveness of the vaccine in pregnant women;
- evidence of safety of vaccination or lack of evidence of adverse pregnancy outcomes. This was carried out by assessing clinical trial, observational study and passive surveillance data, as well as theoretical considerations and/or experimental data relating to potential harm caused to the fetus and the mother (e.g. type of vaccine, ability of the vaccine strain to cross the placenta, risk of infection related to gestational age).

The pregnancy outcomes considered in this review included maternal morbidity and mortality, miscarriage/stillbirth, pre-maturity, small size for gestational age, and congenital anomalies. The results were reported in the form of a summary of available literature and an outline of methodological issues to be considered when planning clinical trials and post-marketing studies of vaccines in pregnant women. Recommendations for further investigations are made at the end of the discussion of each vaccine reviewed. The aim of the review is to guide the standardization of both the process of policy formulation and the format for recommendations for pregnant women.

3 Vaccines reviewed

3.1 Inactivated vaccines

Immunization with inactivated vaccines or toxoids during pregnancy is not expected to be associated with any increased risks to the fetus. Inactivated vaccines with novel adjuvants, however, may require on a case by case basis further consideration and evaluation.

Safety data from vaccinated pregnant women were reviewed for seasonal influenza vaccines, H1N1 2009/2010 pandemic vaccines, tetanus toxoid vaccines, conjugated meningococcal vaccines, and inactivated polio vaccines.

3.1.1 Non-adjuvanted inactivated trivalent seasonal and monovalent pandemic influenza vaccines

Several publications have summarized the evidence of the risks of serious maternal influenza disease, particularly in the second and third trimester, and the safety and effectiveness of maternal immunization with inactivated influenza vaccines (Ortiz, Englund & Neuzil, 2011; Neuzil et al., 1998; Mosby, Rasmussen & Jamieson, 2011; Mak et al., 2008). There is widespread recognition that seasonal influenza disease is more severe in pregnant women with underlying medical conditions (Hartert et al., 2003). The increased severity of disease in pregnant women infected with the 2009 pandemic influenza strain has also been widely documented, with rates of serious adverse outcomes similar to, or higher than, those of any other risk group studied, including the very young or very old (Vankerkhove et al., 2011; Mosby, Rasmussen & Jamieson, 2011).

Increased fetal risks associated with maternal influenza infection have also been documented for nearly a century following well-described pandemics (Harris 1919; Freeman & Barno, 1959; Ortiz, Englund & Neuzil, 2011; Neuzil, Griffin & Schaffner, 2001; McNeill et al., 2011; Mendez-Figueroa, Raker & Anderson,

2011; Pierce, 2011; Håberg et al., 2013). Specific effects of maternal influenza disease include fetal death due to maternal morbidity or premature onset of labour (ANZIC, 2010; Rasmussen, Jamieson & Uyeki, 2012; Steinhoff& Omer, 2012), as well as decreased birth weights or an increased proportion of infants born small for gestational age (McNeill et al., 2011; Mendez-Figueroa, Raker & Anderson, 2011, Pierce et al., 2011; Omer et al., 2011).

The benefits of influenza vaccination to the mother and newborn have been demonstrated, particularly in the second and third trimester for both seasonal influenza and during influenza pandemics. National immunization policies implemented in countries throughout the world recognize these benefits and incorporate influenza vaccination for pregnant women.

Adequate immunologic responses to inactivated influenza vaccines during pregnancy and the efficient transplacental transfer of antibodies have been demonstrated in several studies. One randomized controlled trial (RCT) and several non-randomized studies have also shown the effectiveness of seasonal inactivated influenza vaccination in pregnancy against morbidity in pregnant women and laboratory confirmed infection in their neonates (Zaman et al., 2008; Eick et al., 2011; Sheffield et al., 2012; Ortiz, Englund & Neuzil, 2011). Immunogenicity studies of the 2009 pandemic influenza vaccine and documented transplacental transfer of antibodies provide indirect evidence of protection against illness in mothers and their infants (Jackson et al., 2011).

Prospective trials, retrospective database assessments, post-marketing passive reporting systems, and pregnancy registries provide substantial data on the safety of non-adjuvanted inactivated influenza vaccines administered to pregnant women over many decades. For instance from 1990 to 2009 the Vaccine Adverse Event Reporting System (VAERS) database in the United States of America reported only twenty serious adverse events following trivalent influenza vaccine (TIV) administration to an estimated 11.8 million pregnant women (Moro et al., 2011). Studies have not found new, unusual, or unexpected patterns of serious acute events, adverse pregnancy outcomes, or congenital anomalies (Ortiz, Englund

& Neuzil, 2011, Heinonen et al., 1973, Heinonen, Slone & Shapiro, 1977; Hulka, 1964; Munoz, 2012; Tamma et al., 2009; Kharbanda et al., 2012; Bednarczyk, Adjaye-Gbewonyo & Omer, 2012). For example, the older study by Heinonen, which evaluated children born to nearly 2,300 women who had received influenza vaccine during pregnancy, documented only one malignancy during the first year of life; this is comparable to expected background rates (Heinonen et al., 1973; Bednarczyk, Adjaye-Gbewonyo & Omer, 2012). A recent review by Tamma et al., of pregnant women included 12 studies (10 observational and 2 randomized control trials) with safety outcomes for the mother and fetus. Inactivated influenza vaccines were administered to over 4400 women during all stages of pregnancy. No harmful effects of influenza vaccine in pregnant recipients were identified (Tamma et al., 2009). Ten studies that were part of this review addressed fetal health, and identified no increase in adverse birth outcomes or congenital fetal anomalies over reported background rates. Bednarczyk and colleagues' more recent review of the effects of maternal influenza immunization on the fetus included several additional studies and confirmed no increase in poor pregnancy outcomes or congenital anomalies among children born to vaccinated mothers. Similarly, the United States passive vaccine safety reporting system (Moro et al., 2011; Goodman & Nordin, 2006) notes very few influenza vaccine-associated fetal health complications with a reporting rate of one spontaneous abortion per 1.9 million pregnant women vaccinated (Moro et al., 2011). During the 2009–2010 influenza A (H1N1) vaccination programme, clinical trials were conducted and several monitoring systems were established or enhanced to assess whether adverse events were associated with H1N1 2009 monovalent vaccines. These evaluations did not identify any safety concerns in vaccinated pregnant women or in their infants (Mosby et al., 2011; Jackson et al., 2011; Omon et al., 2011;Bednarczyk, Adjaye-Gbewonyo & Omer, 2012; Moro et al., 2011; Moro et al., 2012; Mackenzie et al., 2011), even when higher doses of 2009-pandemic monovalent H1N1 vaccine were given (Horiya et al., 2011).

Reports to VAERS following administration of H1N1 influenza vaccines were also studied (Moro et al., 2011; Bednarczyk, Adjaye-Gbewonyo & Omer, 2012). As with the seasonal influenza vaccine, there did

not appear to be an increase over expected levels of spontaneous abortion and stillbirths which are the most commonly reported outcomes (Moro et al., 2011, Bednarczyk, Adjaye-Gbewonyo & Omer, 2012).

Conclusion:

Pregnant women and infants suffer disproportionately from severe outcomes of influenza. The effectiveness of influenza vaccine in pregnant women has been demonstrated, with transfer of maternally-derived antibodies to the infant providing it with additional protection. The excellent and robust safety profile of multiple inactivated influenza vaccine preparations over many decades supports World Health Organization (WHO) recommendations that pregnant women be vaccinated to reduce complications of influenza disease during pregnancy. Ongoing clinical studies of influenza vaccination in pregnant women on effectiveness, safety, and benefits in diverse settings will provide additional data that will aid countries in assessing influenza vaccine use for their own populations.

3.1.2 Adjuvanted influenza vaccines

Newer influenza vaccine formulations that contain oil-in-water emulsions as adjuvants have been approved for seasonal and pandemic use in many countries. Evaluation of the reproductive and developmental toxicity of MF59 alone and of an MF59-adjuvanted H5N1 vaccine in animals demonstrated no evidence of teratogenicity or impact on fetal or early perinatal development (Tsai et al., 2010; Heikkinen et al., 2012). The results from three studies of MF59 adjuvanted vaccines in pregnancy are available. Tsai and colleagues used the Novartis Vaccines pregnancy database for reported exposures to MF59-adjuvanted influenza vaccines (n=43 pregnancies) to compare outcomes with exposures to non-adjuvanted influenza vaccines (n=60 pregnancies) and found no differences in pregnancy outcomes (Tsai et al., 2010). A cohort study of 2295 pregnant women who received influenza A (A/H1N1) vaccine adjuvanted with MF59 and pregnant women who were not vaccinated found no differences in pregnancy outcomes apart from fewer premature births among the vaccinated women

(adjusted proportional hazard, 0.69; 95% confidence interval, 0.51–0.92). No differences were observed in rates of congenital anomalies after vaccination in the first (2.1%), second (2.7%), or third (2.1%) trimesters (Heikkinen et al., 2012). Finally, a multi-centre trial of MF59-adjuvanted influenza vaccine in 7,293 vaccinated women in Argentina suggested no difference in pregnancy outcomes (Rubinstein et al., 2013).

Another H1N1 pandemic vaccine product by GlaxoSmithKline was adjuvanted with the oil-in-water emulsion ASO3. Effectiveness of the vaccine in second and third trimester pregnant women against H1N1 pandemic influenza was demonstrated in a large cohort study in Norway (Håberg et al., 2013). In a small study in the United Kingdom 77 pregnant women received AS03 (A)-adjuvanted vaccine in the second or third trimester and this was followed by transplacental transfer of passive immunity at titres consistent with clinical protection in three quarters of newborn infants (Puleston et al., 2013). A post-authorization safety study (also in the United Kingdom) of 267 pregnant women who received an AS03-adjuvanted monovalent H1N1 influenza vaccine, noted overall outcome rates corresponding to those observed in the general population (Tavares et al., 2011). In a separate safety surveillance study in Scotland, 117 pregnant women received an AS03-adjuvanted H1N1 influenza vaccine. No differences in birth outcomes across vaccinated or unvaccinated women were seen (Mackenzie et al., 2011). A Danish cohort study, of nearly 7000 pregnant women, did not find an association between exposure to an AS03-adjuvanted H1N1 monovalent vaccine during pregnancy and adverse pregnancy outcomes (Pasternak et al., 2012a). The study also provided preliminary evidence that excluded a large risk of adverse pregnancy outcomes in 345 women vaccinated in the first trimester because of pre-existing chronic diseases.

A second study in a similar Danish cohort also found no evidence of an increased risk of fetal death associated with vaccine exposure in pregnancy (Pasternak et al., 2012b). Fetal death following vaccination with mostly ASO3-adjuvanted H1N1 pandemic vaccines was also investigated in the United Kingdom (Sammon et al., 2012): 9445 women who were vaccinated before or during pregnancy were

compared to 30 218 pregnant women who had not been vaccinated. Influenza vaccination during pregnancy does not appear to increase the risk of fetal death. These data are in line with those from the large cohort study in Norway that used AS03-adjuvanted H1N1 vaccine and found no association with increased fetal mortality (Håberg al., 2013).

Finally data from the Swedish Medical Birth Register were used to evaluate the association between ASO3-adjuvanted H1N1 vaccine and pregnancy outcomes such as stillbirth, congenital anomalies, preterm birth, low birth weight, and small for gestational age. A total of 18 612 vaccinated women who delivered 18 844 infants were studied. Consistent with the other studies, the risk for stillbirth, preterm birth, and low birth weight was lower than in the comparison groups, and the risk for small for gestational age and congenital anomalies (after vaccination during the first trimester) did not differ from the comparison groups (Källén & Olausson, 2012).

Conclusion:

The data on vaccination during pregnancy with oil-in-water adjuvanted H1N1 vaccines appear to indicate no harmful effects on pregnancy outcomes. While no concerns have emerged after the use of influenza vaccines adjuvanted with oil-in-water emulsions in pregnancy, the data are largely confined to monovalent H1N1 vaccines.

3.1.3 Meningococcal vaccines

Each year, 450 million people in the region of sub-Saharan Africa known as the "meningitis belt" are at risk of death and disability from epidemic meningitis caused by serogroup A *Neisseria meningitidis*. A number of different meningococcal polysaccharide vaccines and meningococcal conjugate (mono and combined) vaccines are available and administered to populations worldwide, including women of childbearing age.

In 6 small studies (3 prospective RCTs, 1 prospective cohort and 2 retrospective studies), a total of 335 pregnant women received polysaccharide meningococcal A and C vaccines. The main focus of the studies was placental transfer of meningococcal antibodies and antibody titres in the infants, not pregnancy outcomes; however, no concerns were identified (O'Dempsey et al., 1996; Obaro et al., 2004; McCormick et al., 1980; Makris et al., 2012).

Between 2010 and 2011, the first conjugate serogroup A meningococcal conjugate vaccine (PsA-TT) developed solely for Africa was introduced in Burkina Faso, Mali, and Niger during mass campaigns. The vaccine is indicated for persons aged 1–29 years. National post-marketing enhanced passive surveillance was successfully conducted during a vaccination campaign in Burkina Faso. Adverse events following immunization (AEFIs) were collected up to 42 days after the end of the mass campaign using standardized forms (Ouandaogo et al., 2012). Overall reporting rates for any AEFI were higher than for previous vaccine introductions (12.8 compared to 5.9 AEFIs per 100 000 meningococcal polysaccharide vaccines given in the last mass campaign), although very few severe AEFIs (2 possible and 2 probable) were noted. No harmful effects on the women or their birth outcomes were reported.

Conjugated meningococcal C vaccines and quadrivalent conjugated meningococcal vaccines have been used in the United Kingdom and the United States in adolescents and young adults. Inadvertent vaccination during pregnancy can thus occur. A recent review of 103 reports to the US VAERs system after inadvertent MenACWY-D conjugate vaccination in pregnancy found no signals suggesting harm comparing the proportion of adverse pregnancy outcomes or congenital anomalies compared to those of inactivated trivalent influenza vaccination in pregnancy (Zheteyeva et al 2013). Pregnancy registries have been implemented for some of the vaccines and these are currently ongoing.

Conclusion:

Existing evidence is limited and derived mostly from passive surveillance data for meningococcal vaccines and small studies of polysaccharide meningococcal A and C vaccines. The available data suggest

that vaccination of pregnant women is safe and is not associated with increased risk for adverse pregnancy outcomes. However, the low statistical power of the studies, lack of sufficient follow-up of infants, and the known limitations of passive surveillance data need to be considered. Further active surveillance is warranted.

3.1.4 Tetanus toxoid vaccines

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by *Clostridium tetani*. Neonatal tetanus may occur in neonates exposed to tetanus that have low or absent levels of antitetanus antibody due to a lack of passively-transferred maternal antibody. Therefore, tetanus toxoid (TT) vaccines are recommended for use in pregnancy, particularly in developing countries where elimination of maternal and neonatal tetanus (defined as less than one case of neonatal tetanus per 1000 live births in every district) remains a goal. According to WHO estimates there were 59 000 neonatal tetanus deaths in 2008, a 92% reduction from the late 1980s and an indicator of how widely maternal TT immunization is being used. Although 34 countries had not reached maternal and neonatal tetanus elimination status by February 2012, TT vaccination coverage during the antenatal period has been increasing in developing countries, reaching > 95% in some countries. Based on rough estimates of birth cohorts and coverage, at least 100 million doses of TT vaccine were given to pregnant women in 2011 (compared to 64 million women immunized between 1995 and 2004).

The effectiveness of TT vaccination of pregnant women in the prevention of neonatal tetanus deaths is well established (Demicheli, Barale & Rivetti, 2008). The WHO position paper on tetanus, published in 2006, suggests that 3 doses of DTP be given in infancy, with boosters in childhood and adolescence along with a 6th dose at first pregnancy or entry into military service. If a good immunization history is not available, pregnant women should receive 2 doses of vaccines 4 weeks apart and at least 2 weeks before

delivery. This recommendation has resulted in widespread use of the vaccine in pregnancy, particularly in developing countries.

Few studies have investigated the safety of TT vaccines in pregnancy. In an animal study on the reproductive effects of TT vaccine, a decrease in fecundity was found to be dependent on the adjuvant and not the vaccine (Zivkovic et al., 2012). A study using a single dose high-potency vaccine in women undergoing a first pregnancy identified no risk to mother or infant (Dastur et al., 1993). A Hungarian study detected no association between TT immunization and congenital anomalies (Czeizel & Rockenbauer, 1999). Similar results were reported from South America (Silveira et al., 1995) in a study that included nearly 70 000 mothers. In comparing diphtheria toxoid (DT) and TT in pregnant women, no differences were found in local or systemic side-effects (Salama et al., 2009). A search of the VAERS database from 2005 to 2010 did not identify any concerns in maternal, infant, and fetal outcomes following tetanus toxoid with a reduced amount of diphtheria, tetanus toxoid, and acellular pertussis vaccine (dTap) vaccination (Zheteyeva et al., 2012). Recently, dTaP-IPV vaccination has been recommended for pregnant women in the UK (http://transparency.dh.gov.uk/2012/09/28/jcvi-pertussis/).

In the United States, moderate to severe local reactions have been associated with high levels of tetanus and diphtheria antitoxin when tetanus toxoid with a reduced amount of diphtheria toxoid (Td) is administered. However, due to the potential benefits of maternal pertussis immunization and the lack of monovalent acellular pertussis vaccine, the ACIP has recently recommended that pregnant women receive Tdap boosters during each pregnancy (MMWR 2013;62:131-5). The American Congress of Obstetricians and Gynecologists also recommends giving diphtheria toxoid, tetanus toxoids, and acellular pertussis (DTaP) vaccination to pregnant women (Committee on Obstetric Practice, 2012).

Conclusion:

Although data from studies are limited, widespread use of TT-containing vaccines in many countries has not provided any signal of possible harm to pregnant women and fetuses. The safety of widespread tetanus toxoid vaccine use over the past 40 years as well as the substantial decrease in neonatal tetanus and increase in neonatal survival supports vaccine use.

3.2 Live attenuated vaccines

Theoretically, live attenuated virus vaccines might be capable of crossing the placenta and infecting the fetus. Owing to this concern, most live attenuated vaccines are contraindicated during pregnancy. However, because live attenuated viral vaccines are used in mass vaccination campaigns, inadvertent vaccination of pregnant women has been documented.

3.2.1 Rubella-mono and combined live attenuated vaccines

The rubella vaccine, containing a live attenuated virus, has been licensed for general use since the late 1960s. The vaccine can be given alone or, more commonly, in combination with measles and mumps vaccines (MMR). Congenital rubella syndrome (CRS) manifested in a neonate occurs when a susceptible (non-immune) woman is infected with rubella during the first trimester of pregnancy. The occurrence of congenital anomalies is as high as 85% if maternal infection occurs during the first 12 weeks of gestation, 54% if infection occurs during weeks 13 to 16 of gestation, and 25% if infection occurs at the end of the second trimester.

Since the introduction of vaccination in the late 1960s, the incidence of rubella and CRS has decreased dramatically and large-scale epidemics of rubella have been eliminated in immunized populations.

The incidence of CRS following inadvertent vaccination of pregnant women has been evaluated through rubella registries in the United States and Europe (e.g. UK, Sweden, Germany), a prospective controlled study from Israel and through surveillance for cases during more recent mass vaccination campaigns in Latin America and Iran (Bar-Oz et al., 2004; Da Silva e Sa, 2011; Badilla 2007; Minussi et al., 2008; Pardon et al., 2011; Soares et al., 2011; Hamkar, 2006; Sato et al., 2011). The combined data from the registries were reviewed by the United States Advisory Committee on Immunization Practices (ACIP) (Centers for Disease Control and Prevention, 2006). A total of 680 live births to rubella-susceptible women were evaluated. None of the infants was found to have CRS. The same was true in a smaller prospective controlled study of 94 women in Israel who had received rubella/MMR vaccination in early pregnancy (n=38) or 3 months prior to conception (Bar-Ozet al., 2004).

The incidence of CRS and asymptomatic congenital rubella infection was also evaluated in the setting of large mass vaccination campaigns in Latin America and Iran (mostly with MR vaccines) (Castillo-Solórzanoet al., 2011; Hamkar et al., 2006). In these settings, rubella-susceptible women who were inadvertently vaccinated underwent cord blood testing for anti-rubella immunoglobulinM (IgM) as an indicator of maternal neonatal rubella transmission. If serologic testing was positive, infants were evaluated for clinical signs of CRS. In Latin America, 2894 women who were rubella-susceptible based on serum IgG titres and who became pregnant ≤ 1 month after receiving rubella vaccination were identified, and 1980 of these pregnancies resulted in a live birth. Cord blood serum was positive for anti-rubella IgM in 70/1980 (3.5%) cases. None of the infants showed signs or features of CRS. Based on these data, a maximum theoretical risk for CRS of 0.2% was estimated following inadvertent vaccination with rubella vaccine during pregnancy. In Iran, a study identified 117 rubella-susceptible women who were inadvertently vaccinated during pregnancy. All had normal pregnancies and deliveries, without evidence of CRS over a 6-month follow-up period. Cord blood rubella IgM testing was performed in 35 subjects and 2/35 (5.7%) were positive. These data are consistent with the rate of asymptomatic congenital

rubella infection following inadvertent vaccination of susceptible pregnant women in the above mentioned studies in Latin America (Castillo-Solórzano et al., 2011).

There are no individual case reports of confirmed CRS following inadvertent vaccination of pregnant women in the published literature. In one case, persistence of fetal antirubella IgM and constant vaccine strain virus shedding over a period of more than 8 months were observed during pregnancy until birth, consistent with the development of long-term persistent fetal infection as a consequence of immunization with the RA27/3 vaccine strain during pregnancy. Virus shedding ceased by 5 months of age (Hofmann et al., 2000).

In several studies rubella virus was isolated from the products of conception, obtained from women who had been inadvertently vaccinated with rubella vaccine during pregnancy and subsequently experienced a spontaneous or induced abortion (Wyll & Herrmann, 1973; Fleet et al., 1974; Larson et al., 1971; Ebbin et al., 1973; Phillips et al., 1970). In these case reports or case series, published in the 1970s, a presumptive identification of vaccine strain, as opposed to wild-type rubella virus, was made by comparing the growth characteristics of the isolate to reference strains in cell culture. Definitive identification of vaccine-strain virus by nucleotide sequencing was not performed. In one case series, presumptive vaccine-strain rubella virus was isolated from the products of conception from 7 of 119 abortions (spontaneous or induced), where 4 of 7 subjects were rubella-susceptible prior to vaccination and the pre-immune status of the other women was unknown. Histologic examination of the products of conception was not performed. None of the cases occurred in known recipients of the RA27/3 vaccine strain (Wyll & Herrmann, 1973).

In contrast to rubella and mumps, measles wild virus has not been shown to cross the placenta and infect the fetus and no teratogenic effects have been observed for measles or mumps virus infection during pregnancy (Plotkin, Orenstein & Offit, 2008). Measles infection in pregnancy is associated with an

increased risk for more severe pregnancy outcomes such as prematurity and miscarriage (Plotkin, Orenstein & Offit, 2008).

No studies have been conducted focusing on the pregnancy outcomes of women susceptible to measles or mumps who were vaccinated with measles- and/or mumps-containing vaccines. The observational studies from Latin America, Iran, and Israel, as well as the case series from the United States and several European countries in which MR or MMR vaccines were used, may provide some indirect evidence of the safety of the vaccines when given to pregnant women.

Data originating from spontaneous reporting with respect to MMR exposure prior to conception and during pregnancy do not indicate an increased risk of congenital malformation or spontaneous abortion, but there is not sufficient information to exclude such a risk.

Conclusion:

The attenuated rubella and mumps viruses can cross the placenta and infect the fetus (Plotkin, Orenstein & Offit, 2008). Fetal damage has not been documented when measles or mumps vaccines have been given to pregnant women. Although more than 3500 susceptible women had been, unknowingly, in the early stages of pregnancy when vaccinated against rubella, no cases of CRS had been reported by the end of 2012. Thus, available data from observational studies and spontaneous reports in passive surveillance systems do not demonstrate a teratogenic risk of rubella vaccination in pregnant women.

MMR vaccines are usually contraindicated in pregnant women because they are live attenuated vaccines, although this is considered a purely precautionary measure. Inadvertent administration of MMR vaccines, however, is not considered an indication for termination of the pregnancy as there is no evidence of harm to the fetus.

3.2.2 Oral polio vaccines

Oral polio vaccine (OPV) contains live-attenuated poliovirus types 1, 2, and 3 and has been shown to be highly effective in the prevention of polio. Live OPV, introduced in the early 1960s, was widely used to protect pregnant women and neonates against polio. The possible development of viremia following immunization (Horstmann et al., 1964) and cases suggestive of vaccination-associated anomalies were reported at the time (Burton et al., 1984). However, no population-based controlled studies are available from that period to confirm the significance of these individual reports. In contrast, mass immunization programmes that included thousands of pregnant women prompted by poliovirus epidemics in Finland (Harjulehto et al., 1989; Harjulehto-Mervaala et al., 1993) and Israel (Ornoy & Ishai, 1993; Linder et al., 1994) failed to show any association between maternal immunization with OPV and congenital anomalies or adverse pregnancy outcomes (Harjulehto-Mervaala et al., 1994;Harjulehto-Mervaala et al., 1995). In Finland, a wild-type poliovirus 3 epidemic broke out in autumn 1984, and in early 1985, OPV was given to 94% of the entire population, including pregnant women among whom the refusal rate was only 2% (Harjulehto-Mervaala 1997). In a retrospective cohort study, the outcome of 21 500 pregnancies was evaluated. In addition, data from the Finnish national Register of Congenital Malformations on 6500 children with anomalies in Finland, born during 1982–1986 were studied. No increase in the rates of growth retardation, perinatal deaths, prematurity or congenital anomalies was observed in the newborn infants exposed to OPV in utero when compared to the expected rates (Harjulehto-Mervaala 1997). In Israel, 90% of the population was given OPV in 1988 to protect against a wild-type 3 polio epidemic. In a pre-epidemic versus post-epidemic comparison of 15 021 and 15 696 live births, respectively, there were no significant differences in prematurity or anomalies (Ornoy et al., 1990; Ornoy & Ishai, 1993).

Conclusion:

Multiple large studies from different countries have demonstrated the safety of oral polio vaccine in infants born to women immunized against polio, although a theoretical risk for adverse effects as a result

of OPV immunization during pregnancy cannot be excluded. There is no evidence of increased rates of adverse pregnancy outcomes in immunized mothers. Adult immunization with poliovirus vaccine is not routinely recommended if a series of polio vaccinations has been completed in childhood. However, immunization of pregnant women at high risk from endemic or epidemic exposure is recommended by SAGE and several national immunization technical advisory groups (NITAGs). It is presently being carried out in several countries that still suffer from wild-type polio circulation.

3.2.3 Yellow Fever Vaccines in Pregnancy

Yellow fever vaccines are nowadays not recommended for pregnant women and lactating mothers, unless there is an epidemic or if women are traveling unavoidably to high risk areas (World Health Organisation 2012). Yellow fever vaccination is generally regarded as safe and effective, with mild reactions in vaccine naïve subjects being limited to low grade fever, mild headache, arthalgias and myalgia in 15-20% of vaccines and serious side effects of neurological syndromes and viscerotropic disease being described, but rarely reported and confirmed (Monath TP et al 2008).

Subsequent to a Nigerian campaign during an outbreak in 1986-1987, 101 pregnant women from 15-50 years who were inadvertently immunized with 17 D and the children born from these pregnancies were followed up for 4 years. No child showed any physical or psychological abnormality or growth retardation. There was no statement about data quality and no assessment of any clinical symptoms attributable to yellow fever vaccine. The results of neutralizing antibodies pre- and post-vaccination showed that the antibody responses of these pregnant women were much lower than those of YF-vaccinated, non-pregnant women in a comparable control group. There was poor response of the pregnant women to yellow fever vaccination (Nasidi A et al 1993).

After a campaign in Brazil in which over 2 million people were vaccinated, 312 pregnant women who had received 17D vaccine were followed up. Ten malformations were noted in 304 children born to vaccinated mothers (3.3%; 95% CI=1.7-14.6%, p=0.003) when compared to 10,961 births in the same region during 1997 to 1999. Down's syndrome (n= 3 babies exposed in utero) but no other malformations were significantly different among children exposed to yellow fever vaccine during pregnancy. Minor dysmorphisms, especially naevus, were significantly more frequent ($P < 0.001$) than in the reference population. the association found between YFV during pregnancy and minor dysmorphisms, especially pigmented naevus, seems to be a bias of evaluation (Cavalcanti DP et al 2007).

In another report from Brazil, 480 pregnant women who received 17DD yellow fever vaccine were followed by with at least three antenatal visits and their children were examined at 3, 6 and 12 months. A 12-month serological follow-up for newborns, and an examination to detect congenital abnormalities was offered to pregnant women, who signed a consent form. For a subsample of 86 babies born at a universal hospital, a more detailed neonatal protocol was used e.g. examination of placental and umbilical cord blood by PCR. A total of 480 pregnant, immunized women were identified, who had received the vaccine at a mean of 5.7 weeks (95% CI 5.2-6.2) of gestation. After a minimum 6-week interval, 98.2% pregnant women were IgG positive. A total of 19.6% of women reported mild adverse events (headache, fever or myalgia). No IgM antibodies were detected at birth and no placental or umbilical cord blood was positive according to PCR. At 12 months follow-up, 7% of samples were seropositive. However, after 12 months, only one child was seropositive. The frequency of malformations (2.3% or 7/304 babies), miscarriages (2.5% or 11/441 pregnancies), stillbirths (0.7%) and premature delivery (7.8%) was similar to that found in the general population. Rates of miscarriage, malformations, fetal deaths, early neonatal deaths and premature deliveries were similar to those seen in the general population. Mild AEs within 15 days of vaccination were reported by 19.8 % of mothers (Suzano CE et al 2006).

To determine whether yellow fever (YF) vaccine administered in pregnancy causes fetal infection, women who were vaccinated during unrecognized pregnancy in a mass campaign in Trinidad were studied retrospectively. Maternal and cord or infant blood were tested for IgM and neutralizing antibodies to YF and dengue viruses. One of 41 infants had IgM and elevated neutralizing antibodies to YF virus, indicating congenital infection. The infant who was exposed through maternal infection during maternal immunization in the first trimester was delivered after an uncomplicated full-term pregnancy and appeared normal (Tsai TF 1993).

Six pregnant women who had attended a travel clinic in Switzerland and received yellow fever and other vaccines had no adverse outcomes in the mother or child (D'Acremont V 2008).

In 58 pregnant women who received 17 D vaccine and had follow up information in the European Network of Teratology Information Services, there were 3-4% major malformations among 46 live births and 7 spontaneous abortions (Robert E 1999).

In a Brazilian university hospital, following a campaign where some pregnant women inadvertently received yellow fever vaccine, 39 women with spontaneous abortions were compared with a control group of 79 women at the antenatal clinic. The odds ratio for spontaneous abortion after yellow fever vaccine was 2.29 (95% CI=0.65-8.03) after controlling for potential confounders. No serology was reported and the statistical power was low (Nishioka Sde A 1998).

These seven studies have also been discussed in systematic review of adverse events associated with yellow fever vaccine in vulnerable populations including pregnant women (Thomas RE 2012).

Conclusion: Yellow fever vaccination appears to have been documented several hundred pregnant women. The risks of adverse outcome of pregnancy and childbirth appear to be similar to the population, except in one study with use passive surveillance data and had low statistical power. There is

clearly a small risk of transmission to the infants when the mother is immunized for the first time during or immediately after pregnancy, which needs to be documented whenever such events and normal birth occur following inadvertent immunization.

4 Gaps preventing accurate assessment of risk

Any assessment of vaccine safety in pregnancy must be evaluated in the context of the substantial risk of infections to the pregnant woman and to the fetus in the absence of immunization. In addition, it may be difficult to dissociate inherent pregnancy risks from any risk associated with a vaccine. Knowledge of background rates of adverse pregnancy outcomes is critical when assessing adverse events that occur after the administration of any vaccine to pregnant women in order to interpret data for causality. Such background rates are non-existent in many parts of the world (Orenstein et al., 2012).

While there are theoretical reasons for considering certain vaccines safe for the mother and fetus, as well as emerging scientific evidence, policy formulation is challenging because the evidence base to guide decisions is still limited for some vaccines. With newer vaccines, the data are even more limited due to the exclusion of pregnant women from clinical trials and the lack of systematic investigation of the post-licensing experience.

GACVS has noted a number of methodological challenges of post-licensing safety studies – low statistical power due to limited sample sizes notwithstanding – inherent to different adverse pregnancy outcomes such as preterm birth, anomalies (major and minor), caesarean section, and the risk of pregnancy loss (miscarriages/stillbirths). Variation in both exposure to infection or vaccination and incidence of outcomes over the gestational period also may create challenges due to the changing risk during the course of a pregnancy. For instance a substantial percentage of conceptions are lost prior to clinical recognition. Thus a primary problem when studying miscarriages is the large scope for bias introduced by

the incomplete and varying ascertainment of implantation failures and early embryonic deaths. (Sammon et al 2012). Long term follow-up of the infant and post-natal care needs is also required to assess congenital anomalies. For example, minor heart malformations may only be detected by cardiac ultrasound, and developmental delay may be diagnosed months or years after birth. If these issues are not appropriately assessed and accounted for in study analysis, risk estimates may be profoundly biased.

5 Summary and overall recommendations

GACVS has evaluated the data on the safety of immunization of pregnant women for several inactivated and live attenuated vaccines. There is no evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated virus, bacterial vaccine, or toxoid. Therefore, pregnancy should not preclude women from immunization with these vaccines if medically indicated.

Live vaccines may pose a theoretical risk to the fetus. However, there is a substantial literature describing the safety of live-attenuated vaccines including monovalent rubella vaccines, combined measles mumps rubella vaccines, and oral polio vaccines. No significant adverse effects to the fetus following these live attenuated vaccines have been reported. Thus, the contraindication of MMR-containing vaccines is considered a purely precautionary measure. Inadvertent vaccination of pregnant women with MMR-containing vaccines is not considered an indication for termination of the pregnancy.

The benefits of vaccinating a pregnant woman generally outweigh the potential risks if she is at high risk of being exposed to a particular infection and the disease would pose a risk for her or her fetus/newborn, and if the vaccine is unlikely to cause harm. The use of selected vaccines in pregnancy is an important aspect of prenatal care, which not only improves maternal health but also benefits the neonate.

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