Maternal Immunization

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6.1 Live Viral Vaccines

In general, the use of live-attenuated vaccines is contraindicated or not recommended during pregnancy based on a theoretical risk of transmission of the virus through the placenta resulting in an infection of the fetus.

Live attenuated rubella vaccine virus can cross the placenta but is not known to cause congenital rubella nor, in fact, any symptoms in the fetus or newborn. Nevertheless, rubella vaccine is contraindicated in pregnancy. Single rubella vaccine is no longer available, but the same applies for MMR (measles-mumps-rubella) vaccine although the measles and mumps components are not known to pass transplacentally. If MMR vaccine is indicated for women of childbearing age, pregnancy should be excluded before vaccine administration, and contraceptive precautions should be advised for 1 month following vaccination.

However, if MMR vaccine is given inadvertently, no specific measures need to be taken. The vast clinical experience of inadvertent administration of rubella and MMR vaccination suggests that these vaccines will not cause any harm to the fetus.

Live attenuated varicella and MMRV vaccines should be treated like MMR, i.e., not given in pregnancy but, if given accidentally, no specific measures taken.

Live intranasal influenza vaccine should not be given in pregnancy, while non-live vaccine is widely recommended.

6.2 Tetanus Immunization

Maternal and neonatal tetanus is an important cause of maternal and neonatal morbidity and mortality. Neonatal tetanus was estimated to be responsible for 787,000 deaths globally in the early 1980s. Therefore, the WHO (World Health Organization) launched the Maternal and Neonatal Tetanus Elimination program in 1989.

WHO recommends that unimmunized pregnant women or pregnant women without documentation of previous tetanus vaccination should receive two doses of tetanus toxoid at least 4 weeks apart. The first dose should be given as early as possible during pregnancy, and the last dose should be given at least 2 weeks prior to delivery.

The program has been a great success: in 2001, it was estimated that the mortality had fallen to 180,000 deaths annually and in 2018 to only 25,000.

The vast experience accumulated in the global effort to eliminate neonatal tetanus by vaccination during pregnancy provides valuable evidence of general safety of non-live vaccines in pregnant women and in this way has been part of the foundation for current immunizations in pregnant women with Tdap vaccines in Europe and elsewhere.

6.3 Pertussis Immunization

Infant immunization program in Europe starts at 2 or 3 months of age, and protection is insufficient after one dose. Thus, infants remain susceptible to pertussis for several months at the age when pertussis is most dangerous. With the introduction of acellular pertussis vaccines, the immunity level in young people surrounding the newborn, and indeed in young mothers, will be lower than before and the risk to newborn infants of severe pertussis even greater.

In the UK, a resurgence of pertussis in newborns with an increase of deaths was observed in 2012, and the authorities responded quickly by offering vaccine to pregnant women. The program has been highly successful and had reached around 80% coverage. The program has successfully prevented pertussis deaths in neonates, and the only two reported pertussis deaths where vaccine was used were in infants of mothers immunized only shortly before delivery (Fig. 6.1).

Immunizing pregnant women with a tetanus, diphtheria, and acellular pertussis (aP) (Tdap) vaccine results in an increase in pertussis-specific antibodies in the pregnant women. Since these pertussis-specific antibodies wane quite rapidly, Tdap immunization is recommended in every pregnancy to augment the transport of antibodies across the pla-

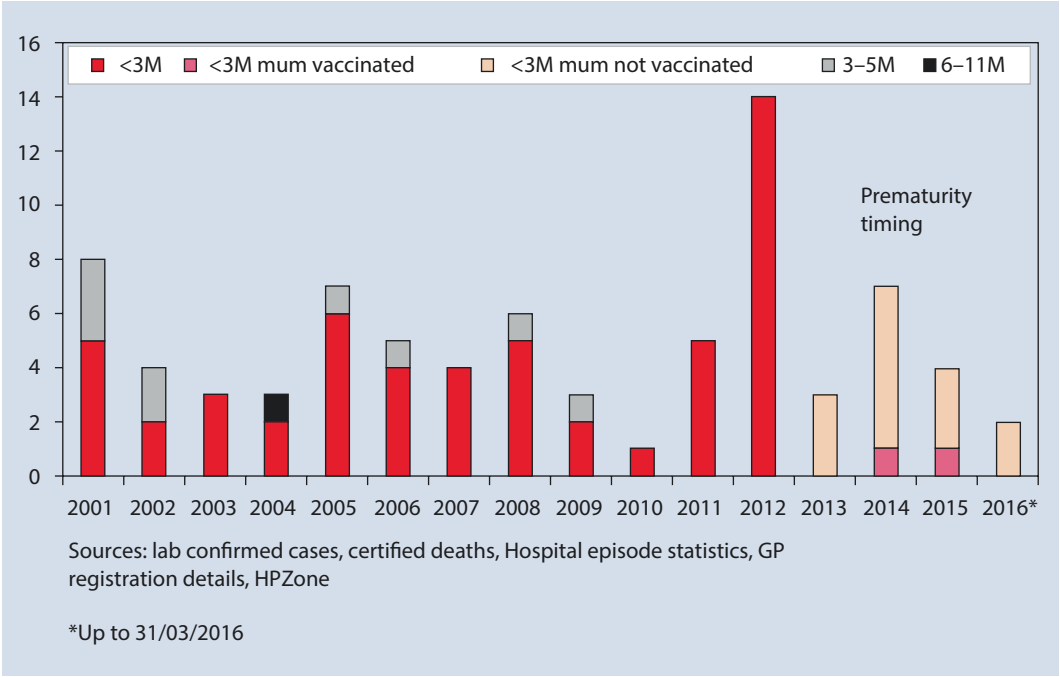

Fig. 6.1 Reconciled deaths from pertussis in infants, England 2001–2015. (From: ▶ https://www.gov.uk/government/publications/vaccination-against-pertussis-whooping-cough-for-pregnant-women. Vaccination against pertussis (whooping cough) for pregnant women: an update for healthcare professionals)

centa towards the fetus and to maximize passive neonatal immunity.

The presence of high levels of maternal antibodies induced by vaccination during pregnancy is associated with a modulation of the infant immune responses to childhood vaccination, a phenomenon called interference or blunting. Administration of Tdap during pregnancy results in a modulation of the infant immune response to their own routine childhood immunization, including pertussis, diphtheria, tetanus, and antibody responses to pneumococcal vaccines. Recent studies have shown that this modulation of the infant immune response did not result in a reduction of the percentage of children with seroprotective antibody levels, nor in an increase of the incidence of infectious diseases later in life. Therefore, clinical consequences of this modulation are highly unlikely.

While the UK program aims to prevent infant pertussis, in practice a Tdap-polio combination vaccine, such as Boostrix-IPV, is given to pregnant women. Other countries, notably Belgium in 2013, have followed the UK model and started vaccination of pregnant women with combination vaccine. However, Europe is divided in this regard, and the majority of countries do not (yet) recommend pertussis vaccination of pregnant women.

In the USA, a CDC-conducted case-control study showed that Tdap vaccination in the third trimester of pregnancy has a vaccine efficacy of 90.5% (CI 65.2–97.4%) for prevention of pertussis-associated hospitalizations in the newborn. This has led to a CDC recommendation that all mothers get a Tdap vaccination between 27 and 36 weeks of each pregnancy.

6.4 Influenza Vaccination

With the emergence of H1N1pdm09 pandemic, it was soon recognized that swine flu was serious and more often fatal in pregnant women. When monovalent H1N1pdm09 vaccines became available in late 2009, they were recommended and given to pregnant women

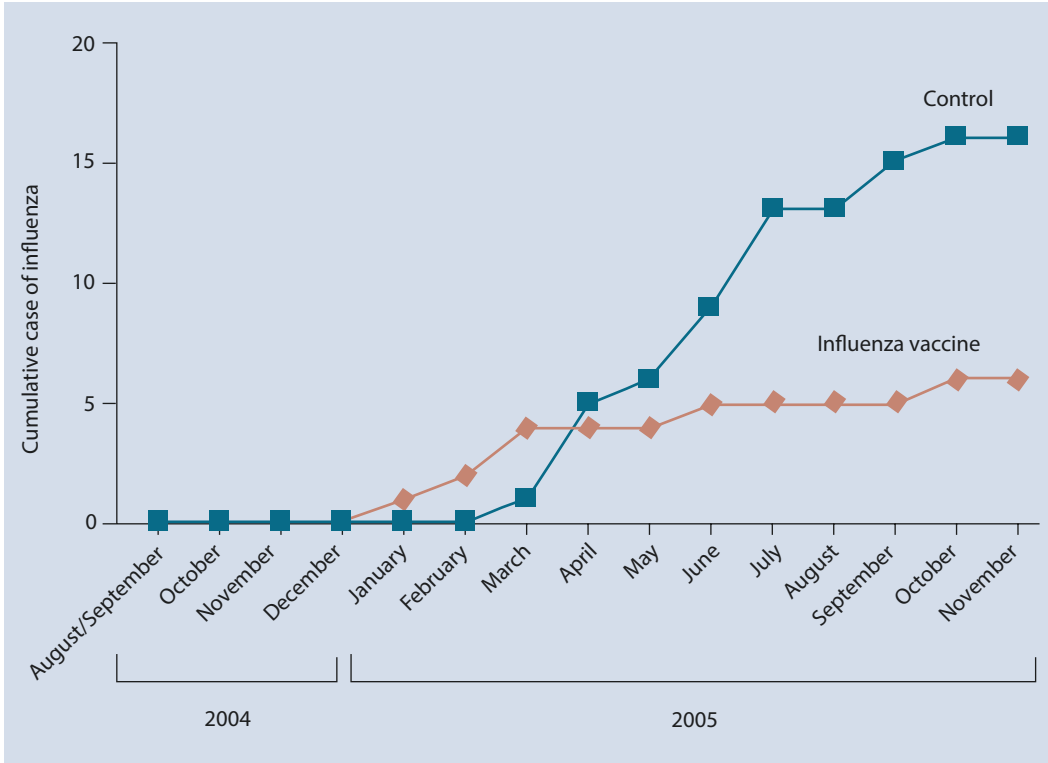

Fig. 6.2 Prevention of influenza up to 6 months of age in infants whose mothers received influenza vaccine during pregnancy. (From: Zaman et al. (2008))

to protect them against severe pandemic influenza. Several studies were conducted on safety and efficacy of this practice, and it was confirmed that the vaccine protected pregnant women and was not only safe for the fetus but actually decreased fetal complications.

Meanwhile, in 1998, Neuzil and coworkers had already shown that influenza vaccination reduces the risk of severe complications of seasonal influenza in pregnancy. This had already led to consideration of influenza vaccination of pregnant women, and the good experience of H1N1pdm09 vaccination formed another stimulus for the US ACIP in 2010 to reinforce recommendations for influenza vaccination for all women who are pregnant during influenza season. In 2012 WHO stated that influenza vaccination of pregnant women is a "highest priority." Several European countries have adapted the recommendation, and others may follow as there is no clear opposition to this recommendation in contrast to pertussis vaccine.

Influenza vaccine can be given during any trimester of pregnancy. Influenza vaccination reduces the risk of prematurity and the risk of low birth weight.

Influenza vaccination for pregnant women has also been documented to protect infants against influenza up to 6 months of age (Fig. 6.2). This is of particular importance, because young infants are a high-risk group for influenza deaths and there is no influenza vaccination policy in sight for direct protection of infants younger than 6 months of age.

6.5 Future Prospects

Maternal immunization is one option under investigation for prevention of severe respiratory syncytial virus (RSV)-associated disease

in the infant. A proof-of-principle efficacy trial was recently published and gives an idea of the effectiveness of this approach.

The vaccine that has reached phase 3 trial is RSV fusion (F) protein nanoparticle vaccine produced in insect cells (Novavax). The vaccine contains the epitope that is the target of palivizumab monoclonal antibody and other epitopes. In the trial about 4500 pregnant women were vaccinated between 28 and 36 weeks of gestation, and infants were followed for RSV disease for 90 days and up to 180 days. In the 90-day follow-up, 3.7% infants in the placebo group and 2.1% in the vaccine group were hospitalized for RSV-associated lower respiratory tract disease (VE 44.4%, 95% CI 19.6–61.5%).

It remains to be seen if this level of protection will be sufficient for licensure. Secondly maternal immunization will be compared to prevention of RSV disease in the infant by new immunoglobulins.

Other vaccines are in development with a potential to be given during pregnancy to prevent severe neonatal bacterial infections including group B streptococcal vaccine (see related chapters in Part IV).

Further Reading

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