Superior Health Council

# ADVISORY REPORT OF THE SUPERIOR HEALTH COUNCIL no. 8754

**Maternal Immunisation: Belgian guidelines**

In this scientific advisory report, which offers guidance to public health policy-makers, the Superior Health Council of Belgium provides recommendations for vaccination during pregnancy.

This report aims at providing general practitioners, gynaecologists, midwives and other health care workers, and pregnant women with specific recommendations on maternal immunisation.

This version was validated by the Board on July 2020

## I INTRODUCTION/SUMMARY

Vaccination of pregnant women is an increasingly used strategy to protect a pregnant woman, her unborn child and/or her infant from vaccine preventable diseases. The recommendation aims at informing all players in the field on the current practices, recommendations and guidelines. There are misconceptions on vaccine use in pregnancy and pregnant women are usually excluded from scientific research, yet there is increasingly interest and evidence on the safety, immunogenicity and effectiveness of vaccination during pregnancy.

## II RECOMMENDATIONS

Vaccination in pregnancy is safe with all vaccines; yet live attenuated vaccines are contraindicated on the basis of the theoretical risk of transmission to the foetus (Laris-Gonzalez et al, 2020). Tetanus, influenza and pertussis vaccines are recommended in pregnancy, other vaccines can be used if indicated for an individual or epidemiological reason.

Recommendations:

I. In case a woman has not/ never been vaccinated with a tetanus (containing) vaccine, 2 doses of tetanus vaccine should be administered during pregnancy, of which one containing a pertussis component, and a third dose in the post-partum period.
II. All pregnant women should be vaccinated against seasonal influenza during the influenza season, as stipulated in the influenza recommendation, regardless of gestational age at vaccination.
III. All pregnant women should be vaccinated against pertussis preferentially at gestational age 24 to 32 weeks, and with every new pregnancy.

Keywords and MeSH descriptor terms[1]

| MeSH terms* | Keywords | Sleutelwoorden | Mots clés | Schlüsselwörter |
|---|---|---|---|---|
| Humans | Vaccination | Vaccinatie | Vaccination | |
| | Immunisation | Immunisatie | Immunisation | |
| | Pregnancy | Zwangerschap | Grossesse | |
| Immunity, Maternally-Acquired | Safety | Veiligheid | Sécurité | |
| Pregnancy Complications, Infectious / immunology | Immungenicity | Immunogeniciteit | Immunogénicité | |
| | Lactation | Lactatie | Allaitement | |
| Pregnancy Complications, Infectious / prevention & control | Breast milk | Moedermelk | Lait maternel | |
| Humans | Vaccination | Vaccinatie | Vaccination | |

*MeSH (Medical Subject Headings) is the NLM (National Library of Medicine) controlled vocabulary thesaurus used for indexing articles for PubMed http://www.ncbi.nlm.nih.gov/mesh.*

[1] The Council wishes to clarify that the MeSH terms and keywords are used for referencing purposes as well as to provide an easy definition of the scope of the advisory report. For more information, see the section entitled "methodology".

## III TABLE OF CONTENTS

## IV METHODOLOGY

After analysing the request, the Board and the Chair of the area Vaccination identified the necessary fields of expertise. An *ad hoc* working group was set up which included experts in paediatrics, epidemiology, immunology, gynaecology, vaccinology and general medicine. The experts of this working group provided a general and an *ad hoc* declaration of interests and the Committee on Deontology assessed the potential risk of conflicts of interest.

This advisory report is based on a review of the scientific literature published in both scientific journals and reports from national and international organisations competent in this field (peer-reviewed), as well as on the opinion of the experts.

Once the advisory report was endorsed by the working group and by the standing working group Vaccination (NITAG) it was ultimately validated by the Board.

## V ELABORATION AND ARGUMENTATION

List of abbreviations used

| | |
|---|---|
| aP | Acellular pertussis |
| EPI | Expanded Programme on Immunisation |
| GBS | Group B streptococcus |
| HBsag | Hepatitis B surface antigen |
| Hep B | Hepatitis B |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| ONE | *Office de la naissance et de l'enfance* |
| RSV | Respiratory Syncytial Virus |
| SHC | Superior Health Council |
| Tdap | Tetanus, diphtheria, acellular pertussis |
| WHO | World Health Organisation |

### 1 Introduction

### 1.1 Rationale of maternal vaccination

Maternal Immunisation is a strategy increasingly used to protect pregnant women, their unborn children and/or young infants, from infectious diseases. The present guideline aims to provide an overview of the currently recommended vaccines, to be used in pregnancy.
Historically, tetanus vaccination has been implemented in pregnancy with success in combatting maternal and neonatal tetanus since the 1960ies. Maternal antibodies against tetanus toxin offer protection against disease in the neonate (Koenig et al., 1998). Influenza vaccination in pregnancy was implemented because pregnant women have a higher risk for more severe disease, and to combat the eventual consequences for the infants of maternal influenza infection during pregnancy, for example growth retardation, preterm delivery etc (Zaman et al., 2008).
Pertussis vaccination was more recently recommended and implemented in mainly high income countries, that are using the acellular pertussis vaccines in the vaccination programmes, on the basis of the epidemiological resurgence of pertussis cases and mortality among very young infants. Vaccination in pregnancy is currently the only option with the available pertussis vaccines, to protect neonates from severe pertussis infection and even

death. The vaccination in pregnancy is more cost effective compared to previously recommended cocoon vaccination, involving vaccination of household members in the immediate postpartum in order to protect infants (Amirthalingam et al., 2014).
Lessons have been learnt from these recommendations in a pregnant population with regards to safety aspects, immunogenicity, effectiveness, hurdles for implementation and acceptance of the strategy by both the general public as well as the healthcare providers. The research on vaccination in pregnancy, has opened the pathway for basic research on other and newly designed vaccines to be used in pregnancy.

### 1.2 Immunobiology in pregnancy

Pregnancy is associated with immunological changes at the materno-fetal interface that are required for tolerance of the fetus. These immunological changes do not result in a state of immunodeficiency. Pregnant women develop robust immune responses to vaccines (Maertens et al, 2020). Studies comparing pregnant and non-pregnant women showed that the magnitude of vaccine responses is not affected by pregnancy. Evidence suggests that pregnancy is associated with modifications of the quality of antibodies that favour their transfer across the placenta and promote immunity of the newborn infant (Okuma et al., 2017). On the other hand, pregnant women have a higher susceptibility to severe infections caused by specific pathogens like influenza, *Listeria monocytogenes* or hepatitis E, as compared to non-pregnant women. This susceptibility is related to pathogen-specific factors and does not reflect a global susceptibility to infectious diseases (Leuridan et al., 2019). Pregnant women are as resistant as non-pregnant women to the majority of infectious pathogens.

### 1.3 Transfer of maternal antibodies to the newborn

Pathogen-specific maternal antibodies are actively transported to the fetus through binding to specific receptors (FcRn) expressed by placental cells and trafficking between the maternal and the fetal sides of the placenta (Jennewein et al., 2017). This active transport often results in a higher concentration of antibodies in the blood of the newborn as compared to the blood of the mother. The maternal antibodies transported across the placenta are almost exclusively immunoglobulin (Ig)G and not the other types of antibodies (IgM, IgA or IgE). Pathogen-specific IgA are transferred through breastmilk and provide immunity to the infant at the level of the mucosa (Brandtzaeg et al., 2010). Maternal IgG and IgA are high quality antibodies providing optimal protection against infectious pathogens. Transplacental transfer of IgG favours the IgG1 subclass that has potent anti-microbial activity. Transfer of maternal IgG starts in the first trimester and exponentially increases during the last trimester of pregnancy. Maternal antibodies induced by vaccination during the second and third trimester of pregnancy can therefore be transferred to the fetus (Maertens et al., 2020). However, vaccination during the second trimester of pregnancy increases the period of transfer and can result in higher levels of maternal antibodies in the newborn. On the other hand, preterm birth reduces the period of transfer and therefore results in lower levels of maternal antibodies in the newborn. Transplacental transport of maternal antibodies can also be reduced by chronic maternal infections, including HIV and malaria (Marchant et al., 2017). Disease control of maternal infections have the potential to improve the transfer of maternal immunity in the newborn.

### 1.4 Immunity of the newborn and the young infant

Maternal antibodies transferred to the newborn play a central role in protection against infectious pathogens in the first months of life (Kollmann et al., 2020). Studies indicate that the level of maternal antibodies at birth can be correlated with a reduced risk of infection after birth, supporting the notion that increasing the level of maternal antibodies by vaccination

during pregnancy is protective for the newborn. On the other hand, high levels of maternal antibodies have been associated with reduced vaccine responses in infants, a phenomenon that has been called 'blunting or interference' (Edwards et al, 2015). The magnitude of this effect is variable between studies and between vaccine antigens. Typically, limited interference is observed with tetanus or hepatitis B. Importantly, the reduction of infant vaccine response primarily affects the early synthesis of infant antibodies, as for example is the case for pertussis. In contrast, maternal antibodies have a more limited impact on infant memory responses to vaccines (Kollmann et al., 2020). This allows priming of infant responses that can be boosted by subsequent vaccinations. The possibility that reduced responses to infant vaccines may be associated with an increased susceptibility to infectious pathogens is carefully evaluated. To date, there is no evidence that maternal immunisation against pertussis, for example, is associated with an increased incidence of disease after primary infant immunization. Therefore, the effect of maternal immunisation on infant immunity is largely beneficial by reducing the risk of severe disease and death in the first months of life.
The interference effect and the importance of priming and boosting in infants, should be reflected in the infant vaccination schedule.

### 1.5 The role of breast milk

Immunoglobulins are one of the most important bioactive components in breastmilk. Maternal immunoglobulins opsonize pathogens, select favourable gut microbiota, control inflammation etc. IgA is the predominant antibody in breastmilk.
Increasing the levels of these protective immunoglobulins in breastmilk, through maternal immunization, can therefore have additional beneficial effects, especially to protect against common intestinal and respiratory pathogens.
After maternal vaccination, an increased amount of disease-specific maternal antibodies is observed in the breast milk up to several weeks postpartum (Orije et al., 2020).

### 1.6 Safety

Extended data are available on the safety of the strategy, when non-live vaccines are used in pregnancy. More detailed information can be found for flu and pertussis in the disease specific paragraphs.
Safety can be defined for 3 groups: The pregnant woman, the unborn fetus and the neonate/infant.
In general, all non-live vaccines have an excellent safety profile including pregnant women.
For interpretation of the safety data, uniform reporting is of utmost importance. Therefore, evidence is gathered on the safety of administration of vaccines in pregnancy through specific registries and surveillance systems. Guidelines have been developed, eg the *Global Alignment of Immunization safety Assessment in pregnancy* (GAIA) guidelines, on the safety definitions to be used to report in a uniform way on side effects and adverse events after vaccination in pregnancy. Not only in view of vaccine safety, yet also on general pregnancy outcomes. Since the first months of pregnancy represent a particularly vulnerable gestational time window for fetal organogenesis and development, it is extremely important to monitor birth outcomes after maternal vaccination in the first trimester.
Reporting is a responsibility for the entire community of health care workers in contact with pregnant women.

Diphtheria-tetanus toxoid and pertussis (Tdap) immunization is reported to be associated with increased frequency of local reactions in general, but is generally well tolerated, also in pregnancy, even with repeat doses at subsequent pregnancies.

The seasonal influenza vaccines are well tolerated among pregnant women, with the majority of injection site and systemic reactogenicity reported as mild to moderate and self-limited, and similar to that observed in non-pregnant adults.

Accidental administration of live attenuated vaccines did not result in congenital disease or congenital infection or malformation, for any vaccine. Evidence exists that the rubella vaccine strain could transfer through the placenta, yet not cause infection, nor congenital rubella syndrome (Castillo-Solorzano et al., 2011). None of the other live attenuated vaccines shows transplacentally caused infection. Reassurance of the pregnant woman should be achieved at accidental exposure.

### 1.7 Future vaccines

Given the potential of maternal immunization for protection of both women and offspring, several new vaccines specifically designed for use in pregnancy are currently under development.
A first focus is on Respiratory Syncytial Virus (RSV), causing a significant global respiratory disease burden, especially in young infants.
Another target is Group B Streptococcus (GBS). GBS is a leading cause of neonatal and infant invasive neonatal bacterial disease, often causing death or neurological sequelae.
Finally, vaccine development against Cytomegalovirus (CMV) is also proceeding with potential use of the vaccine both before and during pregnancy to benefit both mother and neonate. CMV infection is a major public health priority which causes substantial long-term morbidity, particularly sensorineural hearing loss in newborns.
Additional vaccines that can offer protection against other infectious agents including Zika, Ebola, Herpes Simplex, malaria, COVID19, … are only in the developmental phase but certainly have the potential to be successful when being developed and on the market.

### 1.8 Measuring coverage in Belgium and implementation

#### *1.8.1 Brussels and Wallonia*

Coverage surveys of toddlers in 2019 (Robert et al., 2020).

Two vaccine coverage surveys of toddlers commissioned by the *Commission communautaire commune* (COCOM) and the *Office de la Naissance et de l'Enfance* (ONE) conducted by ULB took place in 2019. Those surveys have included interview of a representative sample of parents on pertussis and flu maternal vaccination during pregnancy in 2017.
For 2017, maternal vaccination coverage for pertussis during pregnancy was 31 % and 39 % respectively for Brussels region and in Wallonia.
Pertussis vaccinators were respectively for Brussels and Wallonia: Gynaecologist 44 % and 42 %, GP 37 % and 19 %, midwife 16 % and 9 %.
For flu vaccine during pregnancy, coverage was much lower either in Brussels or in Wallonia: 19 % and 10 %.
Flu vaccinators were respectively for Brussels and Wallonia: Gynaecologist 32 % and 30 %, GP 24 % and 41 %, midwife 19 % and 16 %.

Survey at birth (Avis de naissance): An ONE survey

In the beginning of 2019, a question was added to the questionnaire "*avis de naissance*" whether the mother was vaccinated against pertussis and/or flu during pregnancy. This survey (48 166) was taken by all mothers resident in Wallonia or Brussels AND attending any hospital in Wallonia or Brussels but the UZ.

Information on vaccination during pregnancy was available for 70.4 %.
37.5 % were vaccinated against pertussis during pregnancy and 40 % were informed about this vaccination.
Coverage data from Wallonia and Brussels report a vaccination coverage of influenza vaccination during pregnancy around 10 % in 2019 (personal communication).

#### *1.8.2 Flanders*

Coverage surveys of toddlers in 2016 allowed assessing coverage of the mothers during pregnancy.
Pertussis vaccination reached 69 % and flu 4 7%.
Vaccinators were respectively for pertussis: 19 % gynaecologist, 72 % GP, 4 % midwife and 2 % occupational physician. For flu: 11 % gynaecologist, 68 % GP, 15 % occupational physician and 1 % midwife (Maertens et al., 2018).

## 2 Vaccines routinely recommended during pregnancy

### 2.1 Pertussis vaccination

#### *2.1.1 Recommendation*

Vaccination with an acellular pertussis (aP) containing vaccine is recommended for all pregnant women during every pregnancy between 24 - 32 weeks of gestation. This timing is chosen since scientific evidence suggests that the transplacental transport is optimal from the second trimester of pregnancy onwards and hence can add protection to preterm born infants.

There is a strong preference of administering the tetanus diphtheria acellular pertussis (Tdap) vaccine within the recommended timeframe in pregnancy. However, when this timeframe is missed, there is no reason not to vaccinate in pregnancy. So, vaccination with an aP containing vaccine from 16 weeks gestational age onwards until the end of pregnancy is acceptable.

There is no need for cocoon vaccination (vaccination of close contacts) if the maternal vaccination coverage is high enough. Cocoon vaccination has been proven to be less cost effective and harder to implement compared to vaccination n pregnancy. However, when mothers are not vaccinated against pertussis during pregnancy, they should be vaccinated with an aP containing vaccine in the immediate postpartum. In this case, also vaccination of close household contacts is recommended.

#### *2.1.2 Rationale*

Neonates are more susceptible to severe pertussis disease and death than any other age group. Despite high vaccination coverage of pertussis-containing vaccines globally, pertussis incidence has increased, particularly in high-income countries. Immunization of pregnant women with aP containing vaccines has been implemented in an increasing number of countries to protect newborns from pertussis disease during the first months of life, the only option with the currently available vaccines (Marchant et al., 2017). Vaccinating pregnant women with an aP-containing vaccine induces a rise in the titer of disease-specific antibodies. These maternal antibodies are then transported from the mother to the fetus via the placenta and breastmilk providing protection to the neonate until infant vaccination is started and

thereby closing the susceptibility gap for infection in the first months of life (De Schutter et al., 2015; Maertens et al., 2016a; Maertens et al., 2016b).

### *2.1.3 Epidemiology*

Pertussis epidemiology has a cyclic nature, peaking every 3 - 5 years. However, during recent years, some countries using Tdap with high vaccination coverage, have experienced an increase in the incidence of pertussis with the highest incidence, disease burden and case fatality rate in infants below one year of age (Tan et al., 2015).

In Belgium, pertussis is under mandatory notification to the health authorities. However, the pertussis surveillance system is not exhaustive. Pertussis infection is symptomatic and often severe in early life but can be pauci or asymptomatic in older children and adults. A study published in 2016 calculated that the mandatory notification systems only captures about 56 – 72 % of the total number of pertussis cases in Belgium, leading to a serious underestimation of the real burden of diagnosed pertussis cases (Braeye et al., 2016).
Despite high routine vaccination coverage, pertussis infections were on the rise in Belgium since 2011. From 2014 onwards, there was a sort of steady state of the number of pertussis cases whilst in 2018 the number of pertussis cases clearly decreased. Despite this decrease, the number of yearly reported pertussis cases is still higher than before the start of the pertussis outbreak in 2011 (Litzroth et al., 2020).

In 2018, 1232 pertussis cases were reported. The highest incidence is noted in children below one year of age and most pertussis cases are reported in the first four months of life, when children are too young to be completely protected by infant vaccination (Litzroth et al., 2020). In 2018, a total of 23 pertussis cases were reported in infants below one year of age (compared to 61 cases in 2017 and 102 cases in 2016, accounting for 45 and 48 % of all cases in children). The peak in the number of pertussis cases was seen at 4 months of age in 2018. Before 2018, this peak was seen at an earlier age of 1 - 2 months of age.

Between 2012 - 2016, approximately 100 infants/year required hospitalization for pertussis. The most recent hospitalization data from 2017 show a slight decrease in the number of hospitalization with 61 children below one year of age needing hospitalization (Litzroth et al., 2020).

### *2.1.4 Timing of vaccination*

The consideration on when to vaccinate with a Tdap vaccine in pregnancy is dependent on several factors including safety, effectiveness, uptake and timing of antenatal care visits. Ideally, the vaccine should be administered when optimal transplacental transfer of antibodies is guaranteed to ensure maximal protection against pertussis in early infancy. When determining the ideal timing, premature infants also need to be taken into account since this population is at increased risk for severe infections in early life.

Recent data indicate that maternal immunization in the second trimester is associated with higher pertussis-specific antibody levels in cord blood compared to third trimester vaccination, both in term and preterm born infants (Eberhardt et al., 2016; Eberhardt et al., 2017). Another recently conducted study also showed that a longer interval between Tdap vaccination and delivery induces higher pertussis-specific antibody titers in cord blood and that vaccination at least 8 weeks prior to delivery is necessary to maximize pertussis-specific antibody titers in infants at birth (Wanlapakorn et al., 2018).

Given the currently available evidence, we assume that vaccination earlier in pregnancy, even second rather than third trimester, is the best option since this timing offers the necessary interval to develop and transport maternal antibodies towards the unborn child and also offers the opportunity to better protect infants in case of preterm births.

On a practical basis, vaccination short after the 20 weeks ultrasound investigation is recommended.

There is strong preference of administering the Tdap vaccine within the recommended timeframe during pregnancy. However, when this timeframe is missed, there is no reason not to vaccinate in pregnancy after the recommended timeframe. Although, the antenatal period forms the ideal opportunity to educate women on the need for a pertussis containing vaccine during pregnancy whereas the postpartum period is an opportunity to catch-up and vaccinate both parents with a Tdap vaccine if the mother was not vaccinated during pregnancy. Also vaccination of close household contacts within the cocoon strategy is recommended in that case.

Scientific evidence suggest that there is a rapid waning of pertussis-specific antibody titers after maternal Tdap vaccination. So, in order to have enough maternal antibodies to confer sufficiently high titers of maternal antibodies to the offspring, pregnant women should be vaccinated with a Tdap vaccine at every pregnancy.

Concomitant administration of Tdap and influenza vaccines is tolerated well, but immunogenicity data are missing.

#### *2.1.5 Safety*

Data are reassuring regarding the tolerability and safety of pertussis vaccination during pregnancy. Various studies conducted in different countries including >100 000 pregnant women reported no significant increase in the risk for severe adverse events in the mother, fetus or infant has been seen when vaccinating pregnant women with a Tdap (Tetanus, Diphtheria, aP) vaccine in pregnancy. (Donegan et al., 2014; Kharbanda et al., 2016; McMillan et al., 2017).

Also, repeated Tdap vaccination in consecutive pregnancies is well tolerated with no increased risk for large local reactions or any other adverse events following immunization when repeated Tdap booster doses are given with intervals of 2 years, between 2 and 5 years, or greater than 5 year intervals (Sukumaran et al., 2015).

Furthermore, concomitant administration of Tdap and influenza vaccines in pregnancy has also been shown to be safe with no increased risk of adverse events compared to sequential vaccination (Sukumaran et al., 2015).

#### *2.1.6 Effectiveness*

The effectiveness of maternal Tdap vaccination for the prevention of pertussis in infants has been well studied during the last years. In the UK, the vaccine effectiveness of maternal pertussis vaccination in the reduction of laboratory-confirmed pertussis in infants below 3 months of age was 91 % and even 93 % in the prevention of laboratory-confirmed cases in infants less than 8 weeks of age (Amirthalingam et al, 2014; Dabrera et al, 2015). In the US, a vaccine effectiveness between 85 – 91 % in the prevention of pertussis in infant below 8 weeks of age was found amongst different studies. Additionally, when infants developed

pertussis despite their mothers being vaccinated in pregnancy, the disease was less severe than in infants from unvaccinated women (Baxter et al, 2017; Winter et al, 2017a; Winter et al, 2017b).

#### *2.1.7 Implementation and coverage*

Maternal Tdap vaccination has been implemented in Flanders in 2013 and became free of charge to all vaccinators since 2014. The latest coverage data from the Flemish region (April - August 2016) reported a coverage of maternal Tdap vaccination of almost 70 % (Maertens et al., 2018).

In Wallonia/Brussels, the recommendation has been implemented in September 2015 and was immediately free of charge to all vaccinators. Since January 2018, Tdap vaccines can also be ordered and performed by midwives in the French speaking community in case of a "normal" pregnancy. Coverage data from Wallonia and Brussels report a vaccination coverage for Tdap vaccination in pregnancy around 30% to 39% (Robert et al., 2020).

Additional strategies and special attention is needed to reach the underserved populations of pregnant women (e.g. women with lower socio-economic background, women of non-European origin, multiparous women, …), such as increasing knowledge and awareness, both in health care workers and the target populations, and diminishing hurdles to vaccinate and reach the complete population of pregnant women.

### 2.2 Influenza (flu) vaccination

#### *2.2.1 Recommendation*

Pregnant women are prioritized and categorised as the highest risk group for influenza immunization by the Superior Health Council. All pregnant women, regardless of their trimester of pregnancy, should receive one dose of an inactivated influenza vaccine, as soon as the vaccine is available, or definitely between mid-October and mid-December, or until the peak of annual seasonal flu epidemic is reached.
More information on the exact timing of seasonal influenza vaccination can be found in the annual influenza recommendation from the Superior Health Council.
Any licensed inactivated influenza vaccine may be used to vaccinate pregnant women.

#### *2.2.2 Rationale*

Influenza virus affects all age groups and causes generally mild to severe disease. However, influenza infection during pregnancy is associated with an increased risk of severe disease and complications (Mertz et al., 2017) including higher rates of hospitalization, ICU admission and even death in this population. Additionally, infants below 6 months of age also have an elevated risk for severe influenza and associated complications like hospitalizations and mortality (Nair et al., 2011).
Despite the risk of influenza infection for both pregnant women and infants, it should be stressed that the primary target for influenza vaccination during pregnancy is the protection of the pregnant women. However, the vaccination of pregnant women with inactivated influenza vaccines also has a clear benefit for the unborn child and the infant.
Influenza vaccination during pregnancy mounts a robust immune response with an increase in influenza-specific antibodies within two weeks following vaccination. These vaccine-induced influenza-specific antibodies are efficiently transferred across the placenta during

pregnancy (Steinhoff et al., 2010) resulting in protection of her infant during the first months of life.

### *2.2.3 Epidemiology*

The World Health Organization estimates that during normal seasonal epidemics, 5 – 15 % of the population is infected each year resulting in 3 - 5 million cases of severe illness and up to 650 000 influenza-associated deaths each year. In Belgium, a moderate influenza epidemic affects about 5 % of the total population, i.e. 550 000 people.
For example, during the 2017 - 2018 influenza season, based on the surveillance of the sentinel network of GPs, it is estimated that approximately 697 000 Belgians visited their GP for influenza-like illness and that approximately 470 000 Belgians had a clinical infection with the influenza virus. That same season, influenza caused around 3100 deaths in Belgium. In the first phase of the epidemic, mostly children got infected, whilst in a second phase, the virus affected all age groups (Bossuyt et al., 2018).

No epidemiology data for influenza infection during pregnancy are available from Belgium.

### *2.2.4 Timing of vaccination*

Vaccination of all pregnant women during any trimester of pregnancy before the start of the influenza season or between mid-October and mid-December is currently recommended by the Superior Health Council.

However, in literature, there is still debate on the optimal timing of influenza vaccination in pregnancy in view of the protection of both the pregnant women and the infant. Most studies suggest to vaccinate pregnant women once the vaccine is available in order to protect themselves as soon as possible during their pregnancy. These vaccine-induced influenza-specific maternal antibodies will be transported to the foetus to provide protection to the infant during the first months of life (Cuningham et al., 2019). However, when you vaccinate early in pregnancy, there is a chance that the maternal antibodies already waned resulting in a reduced amount of influenza-specific maternal antibodies transported across the placenta.
On the other hand, there is a consensus that vaccination should occur at least 15 days before delivery to provide protection to the newborn (Blanchard-Rohner et al., 2013).

### *2.2.5 Safety*

An extensive body of literature on the safety of seasonal influenza vaccination during pregnancy shows that the use of inactivated influenza vaccines in pregnant women is well tolerated without unexpected side effects in pregnant women, foetuses or infants.
The reactogenicity profile of influenza vaccines, as well as the occurrence of unsolicited and serious adverse events during pregnancy is similar to that observed in the general adult population. Additionally, no concerns regarding birth outcomes or congenital malformations in the offspring have been reported after maternal influenza vaccination (Giles et al., 2019).
Since influenza vaccination during pregnancy is recommended from the first trimester onwards, studies have specifically monitored immunization during this potentially vulnerable period. A systematic review, a meta-analysis and observational studies have failed to show increased risks for birth defects in infants born to women vaccinated in early pregnancy (Baum et al., 2015; Chambers et al., 2016).
When focusing on pediatric health outcomes beyond the first 6 months of life in infants born to vaccinated mothers, studies have showed no differences in developmental scores, infection-related physician visits or healthcare services utilisation.

Also, concomitant administration of Tdap and influenza vaccines in pregnancy has also been shown to be safe with no increased risk of adverse events compared to sequential vaccination (Sukumaran et al., 2015).

### *2.2.6 Effectiveness*

Maternal influenza vaccination protects both pregnant women and newborns against the disease. However, up till now, it is hard to estimate the exact effectiveness of the strategy since studies are conducted in different epidemiological settings, use influenza vaccines with a different composition and are inconsistent in measuring endpoints as there is laboratory-confirmed influenza, influenza like illness or respiratory infections symptoms, …
Several observational studies and clinical trials already demonstrated that maternal influenza vaccination is effective in preventing laboratory-confirmed influenza in pregnant women (Quach et al., 2020). The effectiveness of maternal influenza vaccination against laboratory-confirmed influenza in pregnancy varies between 30 and 71 % amongst different randomized controlled and observational studies (Sullivan et al., 2019). Additionally, influenza vaccination of pregnant women also has a benefit on preventing hospitalisation.
The duration of passive protection against influenza in the infant on the other hand depends on the maternal level of antibodies, the amount of antibodies transferred from mother to infant and how quickly these passively acquired antibodies wane during the first months of life. Several studies describe a half-life of vaccine-induced maternal influenza antibodies in the infant of 42 - 50 days corresponding with a protection of approximately 2 - 3 months (Steinhoff et al., 2010; Nunes et al., 2015).
A recent meta-analysis including 19 studies supports maternal influenza vaccination as a strategy to reduce laboratory-confirmed influenza and influenza-related hospitalisations in infants less than 6-month old (Jarvis et al., 2020). Also, maternal influenza vaccination in pregnancy has been associated with protection against low-birth weight, small for gestational age deliveries, preterm births and stillbirths.

### *2.2.7 Implementation and coverage*

Since 2009, influenza vaccination is recommended and implemented for all pregnant women by the Superior Health Council. However, the influenza vaccine is not included in the vaccination schedule and influenza vaccines have to be bought by the pregnant women at the pharmacy followed by a partial reimbursement by the health insurances.

The latest coverage data from the Flemish region (April - August 2016) report a coverage of maternal influenza vaccination of 45 % (Maertens et al., 2018). Coverage data from Wallonia and Brussels report a vaccination coverage of influenza vaccination during pregnancy around 10 to 19 % (Robert et al., 2020).

As for maternal Tdap vaccination, additional strategies are needed to increase the coverage of influenza vaccination in pregnancy. Special attention is needed to reach the underserved populations of pregnant women (e.g. women with lower socio-economic background, women of non-European origin, multiparous women…), such as increasing knowledge and awareness, both in health care workers and the target populations, and diminishing hurdles to vaccinate and reach the complete population of pregnant women.

## 3 Maternal immunisation in women with preexisting conditions

Maternal immunisation can be performed in women with pre-existing conditions: HIV infected women, women with diabetes, immunocompromised women or women on

immunocompromising medication etc. For the latter category, the general guidelines on immunisation of adult population should be followed (SHC 9158, 2019).
Live attenuated vaccines might be contraindicated in some conditions. HIV infection is no contraindication for vaccination. On the contrary, vaccination with flu and pertussis vaccines has beneficial effects on the protection and health of both women and infants.

## 4 Other vaccines that can be administered to pregnant women

### 4.1 Rationale

For the vaccines mentioned above (see point 2), the risk/benefit ratio clearly favours vaccination for the general pregnant population in Belgium. For other vaccines, the potential benefits and whether or not they outweigh (theoretical) risks will depend highly on the epidemiological circumstances and the personal risk of the pregnant woman. Vaccination is likely to be beneficial if the likelihood of the disease is high, when infection would pose an important risk to mother or fetus, and when the vaccine is unlikely to cause harm (CDC, 2011). In general, live attenuated virus vaccines are contra-indicated due to the theoretical risk they pose to the fetus.

### 4.2 Overview of vaccines

In general inactivated vaccines can be used in pregnancy without any evidence of harm. The live attenuated vaccines are theoretically contraindicated because of a possible intrauterine infection with the vaccine strain, although congenital disease has not been reported for any available vaccine. More information on each of the vaccines can be found in the text below. If vaccines are not contra-indicated, they can be used in each trimester.

| **Disease** | **Current brand names available in Belgium** | **Vaccine type** | **Recommendation** |
|---|---|---|---|
| **Hepatitis A** | Havrix®<br>Avaxim®<br>Vaqta® | Inactivated | Use if needed |
| **Hepatitis B** | Engerix-B®<br>Fendrix®<br>Hbvaxpro® | Subunit | Use if needed |
| **Japanese Encephalitis** | Ixiaro® | Inactivated | Use if needed |
| **Meningococcus** | Menveo®<br>Nimenrix | Conjugated | Use if needed |
| **MMR** | MMR VaxPro®<br>Priorix® | Live attenuated | Contra-indicated |
| **Polio** | Imovax Polio® (IPV)<br>Boostrix Polio® (dTaP-IPV) | Inactivated | Use if needed |
| **Pneumococcus** | Pneumovax 23® | Polysaccharide non Conjugated | Use if needed |

| | | | |
|---|---|---|---|
| | Prevenar 13® | Polysaccharide Conjugated | |
| **Rabies** | Rabipur® | Inactivated | Use if needed |
| **Tetanus** | Boostrix ® (dTaP)<br>Triaxis ® (dTaP) | Toxoid / subunit | Recommended |
| **Tick-borne encephalitis** | FSME Immun® | Inactivated | Use if needed |
| **Varicella** | Varilrix®<br>Varivax® | Live attenuated | Contra-indicated |
| **Yellow Fever** | Stamaril® | Live attenuated | Medical waiver/ Use if needed<br><br>Contra-indicated during lactation |

General recommendations of the Superior Health Council regarding catch-up vaccinations for the adult population (rationale, schedule, etc) can be found here.

#### *4.2.1 Hepatitis A*

The hepatitis A vaccine (Havrix®/Avaxim®/Vaqta®) is an inactivated vaccine and hence theoretical risks are low. Use is therefore recommended for women at risk, e.g. travel to endemic areas. A combination vaccine with Hepatitis B (Twinrix®) can be used if protection against Hepatitis B is also required.
A review of adverse events in 110 women in the US and Switzerland showed no negative effects (D'Acremont et al., 2008;Moro et al., 2014).

#### *4.2.2 Hepatitis B*

The available vaccine contains non-infectious Hepatitis B surface antigen (HBsAg) and use in pregnancy has been proven to be safe in several trials (Sheffield et al., 2011; Moro et al., 2014;Gupta et al., 2003). Women who have not previously received the vaccine and are at risk of HBV infection during pregnancy (e.g. multiple sex partners, injection drug use, health care workers) should be vaccinated (Kim et al., 2016).

#### *4.2.3 Japanese encephalitis*

There are inactivated and live vaccines available and there is no data on use in pregnancy. However, the available vaccine in Belgium (Ixiaro ®) is an inactivated vaccine and disease can be severe (20 – 30 % case fatality rate) so that travelers to endemic areas should be vaccinated according to regional recommendations (WHO, 2015).

#### *4.2.4 Meningococcus*

Polysaccharide and conjugate vaccines, inactivated, are available against meningococcal diseases. Most evidence on safety of meningococcal vaccines exists for the polysaccharide

vaccine (MPSV4 - Mencevax ®) which is no longer available in Belgium as of November 2019. Pregnancy should not preclude vaccination with the conjugated MenACWY (Menveo®, Nimenrix®) (Okuma et al., 2017;Bilukha et al., 2005) if indicated. Observational data from use in 103 pregnant women in the US (Zheteyeva et al., 2013) and of a monovalent serotype A conjugate in 1730 pregnant women in Ghana (Wak et al., 2015) showed no safety concerns.
Meningococcal vaccines might be recommended in case of outbreaks or travel to endemic areas if indicated (e.g. Meningitis Belt, Hajj).

#### *4.2.5 MMR (measles-mumps-rubella)*

This is a live-attenuated vaccine and is contra-indicated during pregnancy. However, in case of accidental administration, the available evidence of inadvertent vaccination of over 3500 pregnant women showed no increased teratogenic risk (Castillo-Solorzano et al., 2011;WHO, 2014). The pregnant woman and her husband should therefore be reassured in case of accidental administration of the MMR vaccine. Unvaccinated women should start vaccination in the postpartum.
After vaccination of a woman of childbearing age, contraception should be advised for one month.
In the periconception period, Ig for rubella and varicella can be checked and vaccination can be planned before pregnancy.

#### *4.2.6 Pneumococcus*

Both polysaccharide and conjugate vaccines are available, all of them inactivated. Evidence shows that polysaccharide vaccines (Pneumovax ® in Belgium) in pregnancy are safe (Clarke et al., 2016). Less research has been done on conjugate vaccines (Prevenar ® in Belgium), although they appear to be safe on theoretical grounds.
There is currently no evidence that vaccination would benefit the newborn. A 2015 Cochrane review concluded there was insufficient evidence to assess the effect of maternal polysaccharide vaccination on newborns (Chaithongwongwatthana et al., 2015). The results of the PROPEL trial, a randomized controlled trial which included 600 pregnant women and aimed to asses safety and effectiveness of the 13-valent conjugate vaccine, are expected in 2020. (Clinicaltrials.gov, no date).
Vaccination of close contacts might be beneficial in case of an outbreak of invasive pneumococcal disease with a vaccine-preventable serotype (Basarab et al., 2011).

#### *4.2.7 Polio*

The monovalent inactivated polio virus vaccine (marketed in Belgium as Imovax Polio ®) contains the same amounts of the three polio antigens as the quadrivalent DTaP-IPV (Boostrix Polio ®). A review of 20 000 records of pregnant women who received the quadrivalent DTaP-IPV vaccine showed no increase in adverse events (Donegan et al., 2014).
Women not previously vaccinated and requiring protection against polio (e.g. in case of high-risk travel to endemic areas) should be vaccinated.

#### *4.2.8 Rabies*

Rabies vaccination consist of inactivated rabies virus. Several studies including around 350 pregnant women show no evidence of adverse pregnancy outcome after use of the rabies vaccine (Sudarshan et al., 1999a; Sudarshan et al., 1999b). Given the 100 % lethality of the diseases, post-exposure prophylaxis should be given and pre-exposure prophylaxis can be given in case of high-risk travel or occupational risks (ACIP, 2016).

#### *4.2.9 Tetanus*

Tetanus toxoid vaccination is only available for the moment in a combined vaccine in Belgium, with diphtheria, and pertussis. There is over 40 years of experience with the tetanus vaccine in pregnancy, showing no safety concerns (WHO, 2014). Like the general population, every pregnant woman should be protected against tetanus, thereby also protecting her child. Women requiring a booster dose of tetanus (e.g. after an injury) should receive the combination vaccine also containing acellular pertussis (ACIP, 2016), regardless of the trimester (no individual tetanus vaccine available in Belgium). For further info on the Tdap vaccine in pregnancy, see section 2.1. Women with no evidence of previous vaccination, should start the primary vaccination with 2 vaccines in pregnancy (of which one including pertussis) and one in the postpartum.

#### *4.2.10 Tick-borne encephalitis*

As it is an inactivated vaccine, theoretical risks are low. There are no data on use in pregnancy. The vaccine is recommended in case of travel to endemic areas.

#### *4.2.11 Varicella*

The varicella vaccine is a live-attenuated vaccine and is therefore contra-indicated. It is cost-effective to do serology testing in women who think they are non-immune, as the majority will have anti-varicella antibodies. Non-immune women should preferably be immunized pre-pregnancy (see SHC advice on Varicella). Varicella-specific immunoglobulins for post-exposure prophylaxis in non-immune pregnant women are no longer available in Belgium.

#### *4.2.12 Yellow fever*

The yellow fever vaccine is a live-attenuated vaccine and should therefore be avoided during pregnancy, if possible. There is however more than 60 years of experience with yellow fever vaccination and available evidence of over 500 women does not show an increase in adverse pregnancy outcomes, so that women travelling to endemic areas should be vaccinated if the risk of disease is high (WHO, 2013). The vaccine should be avoided during lactation as three cases of yellow-fever vaccine associated acute neurotropic disease have been reported in exclusively breastfed infants whose mothers were vaccinated (Traiber et al., 2011) (CDC 2010). If vaccination is solely a legal requirement, a medical waiver can be issued (ACIP, 2016).

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## VII COMPOSITION OF THE WORKING GROUP

The composition of the Committee and that of the Board as well as the list of experts appointed by Royal Decree are available on the following website: About us.

All experts joined the working group ***in a private capacity***. Their general declarations of interests as well as those of the members of the Committee and the Board can be viewed on the SHC website (site: conflicts of interest).

The following experts were involved in drawing up and endorsing this advisory report. The working group was chaired by **Elke LEURIDAN**; the scientific secretary was Veerle MERTENS.

| | | |
|---|---|---|
| **CARILLO Paloma** | Vaccinology, Public health | ONE |
| **CORNELISSEN Laura** | Epidemiology, Obstetrics, Gynaecology | Sciensano |
| **FRERE Julie** | Pediatrics, Infectiology | CHR citadelle |
| **LEURIDAN Elke** | Vaccinology, Maternal Immunization | UAntwerpen |
| **MAERTENS Kirsten** | Vaccinology, Maternal Immunization | UAntwerpen |
| **MARCHANT Arnaud** | Medical Immunology | ULB |
| **SWENNEN Beatrice** | Epidemiology, Vaccinology | ULB |

The following experts peer reviewed the advisory report but did not take part in endorsing it:

| | |
|---|---|
| DE CATTE Luc | VVOG |
| EMONTS Patrick | GGOLB |
| GOETGHEBUER Tessa | ULB |
| LANNOO Lore | UZLeuven |
| ROETS Ellen | VVOG |
| SMETS Karen | Domus Medica |
| SPODEN Julie | SSMG |

The standing working group Vaccination (NITAG) has endorsed the advisory report. The standing working group was chaired by **Yves VAN LAETHEM**; the scientific secretary was Veerle MERTENS.

**About the Superior Health Council (SHC)**

The Superior Health Council is a federal advisory body. Its secretariat is provided by the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC aims at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge.

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, staff members of scientific institutions, stakeholders in the field, etc.), 300 of whom are appointed experts of the Council by Royal Decree. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a Committee on Professional Conduct) as well as the final endorsement of the advisory reports by the Board (ultimate decision-making body of the SHC, which consists of 30 members from the pool of appointed experts). This coherent set of procedures aims at allowing the SHC to issue advisory reports that are based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

Once they have been endorsed by the Board, the advisory reports are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.hgr-css.be). Some of them are also communicated to the press and to specific target groups (healthcare professionals, universities, politicians, consumer organisations, etc.).

In order to receive notification about the activities and publications of the SHC, please contact: info.hgr-css@health.belgium.be.