Medicines Adverse Reactions Committee

Meeting date	12 March 2020	Agenda item	3.2.3
Title	**Boostrix in pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Product name Boostrix	**Active ingredients** diphtheria vaccine, pertussis vaccine, tetanus vaccine (Tdap)		**Sponsor** GlaxoSmithKline (GSK)
Funding	From 1 July 2019 funding widened to include pregnant women in their 2nd and 3rd trimester of pregnancy (previously funded between weeks 28 and 38 of gestation)		
Previous MARC meetings	Use of Boostrix in pregnancy was discussed at the 154th meeting on 13 June 2013 following PHARMAC's announcement to start funding Boostrix for pregnant women between gestational weeks 28 and 38 during epidemics (www.medsafe.govt.nz/profs/adverse/Minutes154.htm#3.2.2)		
Classification	Prescription medicine		
Usage data	Cumulative worldwide postmarket exposure up to 16 March 2017 based on number of doses distributed by the company (GSK): 155,719,727 doses		
Advice sought	**The Committee is asked to advise on the following:** • Is the benefit-risk profile for the use of Tdap (Boostrix) during the 2nd trimester (from week 16) of pregnancy favourable? • Does the data sheet require updating? • Is further communication required other than MARC's Remarks in *Prescriber Update*?		

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1 PURPOSE

Pertussis (whooping cough) is a highly infectious bacterial respiratory infection. Epidemics of whooping cough in New Zealand occur about every 3 to 5 years, with infants and children most at risk [1]. Immunisation with the pertussis vaccine is the best way to prevent pertussis infection [1, 2].

Infants aged under 12 months, particularly those too young to be immunised, are at high risk of contracting severe disease [1]. The pertussis immunisation programme therefore aims to protect infants in their first year of life. This includes maternal vaccination with pertussis vaccine during pregnancy through the passive transfer of maternal antibodies [2].

Pertussis vaccine is administered as a single injection that also contains diphtheria vaccine and tetanus vaccine (Tdap). There are two approved Tdap vaccines in New Zealand: Boostrix and Adacel. However, PHARMAC funding is for Boostrix and the criteria for funding during pregnancy recently changed – from 1 July 2019, women in their 2nd or 3rd trimester of each pregnancy are eligible for funded vaccine; it was previously funded for women between gestational weeks 28 and 38. This change aligns with the New Zealand Immunisation Handbook which recommends pregnant women are given the vaccine from 16 weeks of gestation of every pregnancy, preferably in the 2nd trimester, but at least 2 weeks before birth.

The Boostrix data sheet states its use may be considered during the 3rd trimester of pregnancy. Human data from prospective clinical studies on its use during the 1st and 2nd trimester of pregnancy are not available. Boostrix may be used during pregnancy when the possible advantages outweigh the possible risks for the fetus.

The purpose of this paper is to review the benefits and risks of Tdap vaccine (Boostrix) when administered to pregnant women in their 2nd trimester (from week 16).

2 BACKGROUND

2.1 Pertussis (whooping cough)

Pertussis (whooping cough) is a bacterial respiratory infection caused by *Bordatella pertussis*, a gram-negative bacillus [3]. Pertussis is highly transmissible and is one of the most infectious vaccine-preventable diseases [3]. Transmission occurs by aerosolised droplets with an incubation period of 7 to 10 days [3]. Pertussis is an epidemic disease with two- to five-yearly epidemic cycles [3]. Epidemics are frequently sustained over 18 months or more, during which there are marked increases in hospital admission rates [3]. Pertussis does not show the seasonal variability typical of other respiratory infections [3].

The endemic circulation of *Bordatella pertussis* in older children and adults provides a reservoir for spread of the infection and the development of severe disease in incompletely vaccinated infants [3]. Pertussis mortality rates are highest in the first year of life [4, 5]. Beyond age 3 years mortality rates are relatively low [3]. In immunised populations almost all deaths occur in the first two months of life and deaths in toddlers and preschool-aged children have largely disappeared [3].

Since the introduction of mass immunisation, countries with consistently high immunisation rates have consistently low pertussis incidence rates [6, 7]. However, despite high vaccination coverage, outbreaks have been reported in numerous countries since 2004. Waning immunity in adolescents and adults is thought to be a large contributing factor for these outbreaks [8], highlighting the need for continued protection through booster doses. There have also been improvements in diagnostic testing, active surveillance, changes in disease susceptibility and increased awareness which may have contributed to more cases being identified.

The decrease in incidence following the introduction of mass immunisation is most noticeable in those aged under 10 years [3]. Despite this, the reported pertussis disease rates have remained highest in infants and young children [9-11]. Infants aged under 3 months have the highest rate of notification and hospitalisation [12, 13].

2.1.1 Epidemiology in New Zealand [14]

Pertussis is a notifiable disease in New Zealand and data is collected by the Institute of Environmental Science and Research (ESR). For the 12-month period ending May 2019:

- A total of 2110 cases notified (43.2 per 100,000). Of the 2110 cases, 152 (7.2%) were aged <1 year of which 78 (51.3%) were hospitalised (Table 1).
- The highest reported pertussis rates were among those aged <1 year and 1 to 4 years (252.4 and 105.6 per 100,000, respectively). Pacific and Māori had the highest notification rates among those aged <1 year while the highest rate among children aged 1 to 4 years was in European or other (Figure 1).

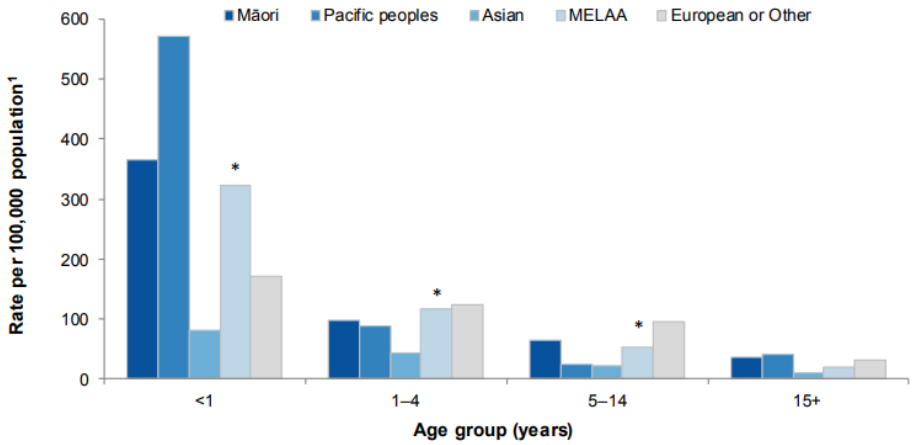
Table 1: Number of confirmed, probable and suspect pertussis notifications, rates and hospitalisations for the 12-month period ending May 2019, by age group

Age group (years)	Total			Hospitalised		
	May	Last 12 months	Rate[1]	May	Last 12 months	Percent[2]
<1	14	152	252.4	7	78	51.3
1–4	9	260	105.6	0	26	10.0
5–9	7	259	79.1	0	3	1.2
10–14	7	214	68.8	0	5	2.3
15–19	11	140	44.6	0	2	1.4
20+	59	1085	29.9	7	93	8.6
All ages	**107**	**2110**	**43.2**	**14**	**207**	**9.8**

[1] Annual rate for the 12 months ending May 2019 per 100,000 population, calculated using 2018 mid-year population estimates.
[2] Percentage of notified cases in the last 12 months that were hospitalised.

Source: ESR

Figure 1: Pertussis rates for the 12-month period ending May 2019, by age group and ethnicity



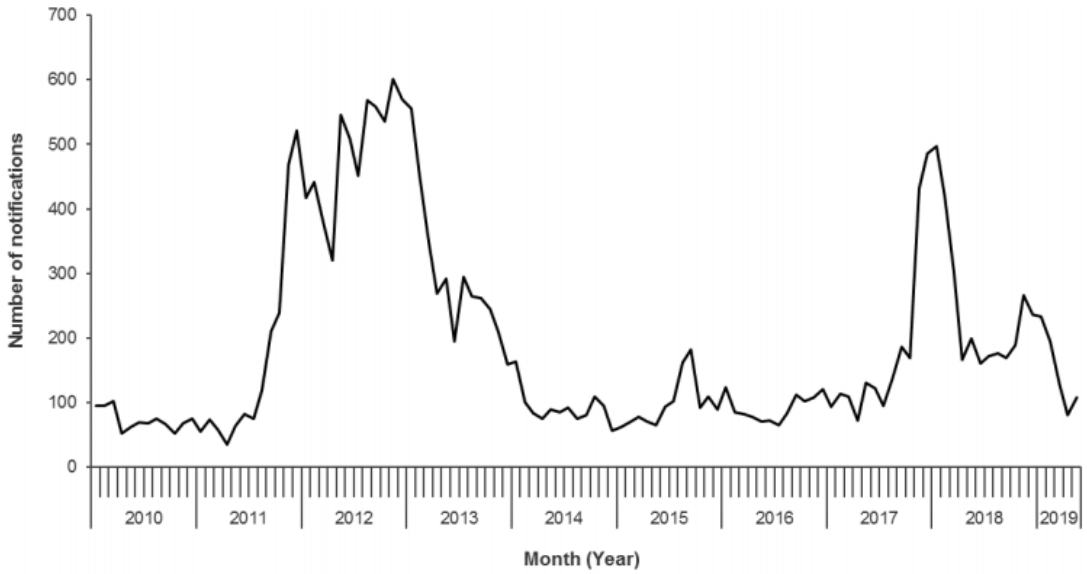
MELAA: Middle Eastern/Latin American/African.
[1] Annual rate for the 12 months ending May 2019.
* Rate based on fewer than five cases.

Notes:
- Includes confirmed, probable and suspect cases only. Cases still under investigation are excluded.
- Ethnicity is prioritised. Rates are based on the proportion of people in each ethnic group from the 2013 Census applied to the 2018 mid-year population estimates.

Source: ESR

From the beginning of the current national outbreak period (starting 16 October 2017) to the end of May 2019, there was a total of 4697 cases (2939 confirmed, 1636 probable, 122 suspect). Figure 2 shows pertussis notifications by month since January 2010. A four- to five-year cycle can be seen with large peaks in notifications in 2011/2012 and at the end of 2017/early 2018. Pertussis notifications had returned to expected levels as at May 2019.

Figure 2: Number of pertussis notifications by month and year, January 2010 to May 2019



Note: Includes confirmed, probable, and suspect cases only. Cases still under investigation are excluded.
Source: ESR

2.2 Pertussis vaccine

2.2.1 New Zealand immunisation schedule

Whole-cell pertussis vaccine was introduced in 1960 and replaced with acellular pertussis vaccine in 2000 [3]. The current schedule of three acellular pertussis-containing vaccines in the first year of life plus booster doses at ages 4 and 11 years has been in effect since 2006 [3]. The current recommended immunisation schedule for New Zealand is shown in Table 2.

Tdap is an adult vaccine containing a reduced-concentration of tetanus and diphtheria vaccine (denoted by the small letters in the abbreviation vs. capital letters in DTaP).

Table 2: Immunisation schedule for pertussis-containing vaccines (excluding catch-up) [3]

Age	Vaccine	Comment
6 weeks	DTaP-IPV-HepB/Hib	Primary series
3 months	DTaP-IPV-HepB/Hib	Primary series
5 months	DTaP-IPV-HepB/Hib	Primary series
4 years	DTaP-IPV	Booster
11 years	Tdap	Booster
Pregnant women (recommended from 16 weeks' gestation of every pregnancy, preferably in the second trimester, but at least two weeks before birth; funded when given any time in second or third trimester)	Tdap	Booster

Source: Immunisation Handbook 2017

Data on the protective effects of indirect strategies is currently incomplete [3]. Infants can be protected by immunisation of others at risk of developing pertussis, with whom the infant may come into contact (ie, 'cocoon strategy') [15]. This involves targeted immunisation of adult groups who have the most contact with young and vulnerable infants. Three identified groups are [3]:

1. New mothers who have not had recent immunisation, family, and close contacts of newborns
2. Healthcare workers
3. Early childhood workers.

2.2.2 Use in pregnancy

Newborn infants have immature immune systems and they don't acquire protective levels of antibodies until at least 3 months of age (usually after the second dose of pertussis vaccine) [16]. They are therefore reliant on IgG antibodies acquired through passive transplacental transfer [16]. The timing of maternal immunisation depends on many factors. These include whether the goal is to protect mothers, infants or both, the kinetics of maternal response to vaccination, the efficiency and timing of IgG transfer, and the half-life of antibodies [17].

Transplacental transfer of maternal antibodies

Immunoglobulin G (IgG) must cross several anatomical barriers in order to be transferred from the maternal to fetal circulation. This includes the syncytiotrophoblast and cytotrophoblast cell barriers, and then across the villous stroma to ultimately reach the lumen of fetal endothelial vessels [17].

The Fc neonatal receptor (FcRn) is a major histocompatibility complex (MHC) class I related molecule [18] that plays a central role in the regulation of IgG homeostasis and in IgG transport across polarised epithelial barriers [19, 20]. Studies have shown that FcRn expressed on syncytiotrophoblast cells is a key contributor to IgG transplacental transfer [21, 22]. However, there are several steps in IgG transport across the placenta that are incompletely understood.

The transplacental transfer of maternal IgG to the fetus begins during the 1st trimester of pregnancy and can be detected in cord blood as early as 8 to 10 weeks of gestation [23]. However, only small amounts of maternal IgG are transferred in the 1st trimester, with an estimated transplacental transfer of about 10% of maternal IgG concentrations by 17 to 22 weeks of gestation [24]. The concentration of maternal IgG in infant cord blood reaches about 50% of maternal IgG levels by 30 weeks gestation [24]. By 37 to 40 weeks of gestation, infant cord blood concentrations of maternal IgG often exceed that of maternal serum by the delivery time point in full term healthy pregnancies [24-27]. The majority of IgG transfer therefore occurs in the last trimester possibly due to an increase in the surface area of IgG uptake from maternal blood with higher gestational age [17].

Passively acquired maternal antibodies with different antigen-specificity have been reported to have distinct half-lives in infants [17]. An example is pertussis-specific IgG where levels in cord blood achieve >100% of maternal levels but maternal pertussis-specific IgG has a half-life of 6 weeks in infants and wane to undetectable levels as early as 4 months of age [28]. At 2 months of age, only 41% of infants have detectable levels of pertussis-specific IgG [29]. In contrast, maternal passively acquired measles-specific IgG remains near or above protective levels in 6-month-old infants and are still detectable by 1 year of age [30, 31].

The efficiency of IgG transfer can vary from one antigen-specificity to another (eg, up to 200% for pertussis vs. 70% for group B streptococcus) [32, 33]. Some reports indicate the IgG subclass is important in determining this efficiency – IgG_1 being the most efficiently transferred whereas IgG_2 is the least efficiently transferred [34, 35]. Vaccination with Tdap during pregnancy is thought to induce antibodies of the IgG_1 subclass [36].

Blunting

There is potential immune interference of Tdap vaccination during pregnancy with the protection afforded by infant vaccination schedules (also known as blunting) [37]. However, the benefits of Tdap vaccination during pregnancy and protecting a newborn generally outweigh the potential risk of blunting the infant's response to DTaP [38]. This is because infants are at greatest risk of severe disease and death from pertussis before 3 months of age when their immune systems are least developed [38].

Uptake of Tdap during pregnancy in NZ

The uptake of vaccination during pregnancy has been slow since its introduction to the immunisation schedule in 2013 (estimated to be somewhere from 13% to 44%) [39].

An audit conducted at Rotorua hospital in 2015 indicated a 35% immunisation uptake of Tdap vaccine in pregnant women between 28 to 38 weeks of gestation [40]. Steps were taken to improve coverage and the overall proportion of pregnant women vaccinated for pertussis from March to April 2017 was 44% [40]. This was compared to pregnant women in Taupo/Turangi where they were more likely to be vaccinated at a rate of 76% [40].

Recommended timing of Tdap vaccination during pregnancy

The timing of pertussis vaccination during pregnancy varies from country to country. A summary of current recommendations for the timing of Tdap vaccination in NZ, UK, Australia and the US is shown in Table 3.

Table 3: Summary of current recommendations for timing of Tdap vaccination during pregnancy in New Zealand, United Kingdom, Australia and United States

Country	Timing of Tdap vaccination during pregnancy
New Zealand	From 16 gestational weeks, preferably in 2nd trimester but at least 2 weeks before birth
United Kingdom	Between 16 and 32 gestational weeks, ideally after the fetal anomaly scan (usually around 20 weeks)
Australia	Between 20 and 32 gestational weeks
United States	Between 27 and 36 gestational weeks

The **United States** was the first country (in 2011) to recommend using Tdap in pregnant women who had not been previously vaccinated with Tdap in adulthood in addition to the cocooning strategy. This recommendation was made by the Advisory Committee on Immunisation Practices (ACIP) for the Centers for Disease Control and Prevention (CDC). The recommendation was subsequently updated in 2012 and states women should receive Tdap vaccination in every pregnancy irrespective of her prior history of Tdap vaccination [2]. The optimal recommended timing is between weeks 27 to 36 weeks [2].

Since the recommendation in the United States in 2011, recommendations for a pertussis booster vaccination during pregnancy have been implemented either temporarily or permanently in at least a further 21 countries.

The **United Kingdom** introduced a pertussis vaccination programme for pregnant women in October 2012 [41]. This was in response to a national pertussis outbreak. At that time, the greatest number of cases were in adolescents and young adults but the highest rates of morbidity and mortality occurred in infants too young to be protected through routine vaccination.

The recommendation for the timing of administration of prenatal pertussis containing vaccine to pregnant women was reviewed by the Joint Committee on Vaccination and Immunisation (JCVI). From 1 April 2016, pertussis containing vaccine should be offered to pregnant women from 16 weeks gestation, ideally after their fetal anomaly scan (usually at around 20 weeks) [41]. This will provide greater opportunity for pregnant women to access the vaccine, will provide additional benefit to the neonate where delivery is premature and will potentially improve neonatal antibody levels [41]. Babies born to vaccinated mothers are 90% less likely to get disease than babies whose mothers were unvaccinated [41].

The recommendation for the change in timing of the vaccine was made because [41]:

- During 2012 it was recommended that pregnant women should be vaccinated from weeks 28 to 38 of their pregnancy with the optimum time for transfer of maternal antibodies being between weeks 28 and 32.

- However a study by Eberhardt et al 2016a [42] showed that reasonable levels of pertussis antibodies were demonstrated in neonates through transplacental transfer from mothers vaccinated earlier in pregnancy.
- Based on study results, the JCVI recommended that women should be offered pertussis-containing vaccine between gestational weeks 16 and 32 to maximise the likelihood that the baby will be protected from birth.
- Offering the vaccine from week 16 of pregnancy gives pregnant women greater opportunity to take up the offer of vaccination and will offer some protection to infants born prematurely who may be particularly vulnerable to complications from pertussis.
- For operational reasons vaccination is probably best offered on or after the fetal anomaly scan at around 18 to 20 weeks. Offering at this time will also avoid any associations with unrelated adverse events identified up to or at the routine anomaly antenatal scan being made.
- Women may still be immunised after week 32 of pregnancy until delivery but this may not offer as high a level of passive protection to the baby.

The vaccine used in the UK is Boostrix-IPV (dTaP/IPV), which is Boostrix + inactivated poliovirus.

According to the **New Zealand** immunisation handbook, pregnant women from 28 to 38 weeks' gestation became eligible for funded Tdap vaccine under the outbreak policy in 2013 [3]. Subsequently in 2015, pregnant women from 28 to 38 weeks' gestation became eligible for funded Tdap vaccine for every pregnancy [3]. Funding of Tdap vaccine for pregnant women changed again on 1 July 2019. It is now recommended to be given from 16 weeks' gestation of every pregnancy, preferably in the second trimester, but at least two weeks before birth [3]. This updated recommendation was made based on the Eberhardt et al 2017 study [43] and the Amirthalingam et al 2016 study [44]. Tdap should be given during each pregnancy to protect the mother and so that antibodies can pass to the fetus; post-partum maternal vaccination will reduce the risk of a mother infecting her baby but does not have the added benefit of providing passive antibodies [3].

PHARMAC is responsible for considering any changes to the funded vaccines in NZ, including eligibility criteria. Their original proposal for the change in funding during pregnancy included any stage of pregnancy to prevent funding being a barrier to accessing Tdap if further evidence became available supporting earlier vaccination. However, based on feedback received during their consultation process, the criteria was amended to align with use from the 2nd trimester of pregnancy.

The **Australian** immunisation handbook recommends pregnant women receive a single dose Tdap vaccine in each pregnancy [45]. The optimal time for pertussis vaccination in pregnancy is between mid 2nd trimester and early 3rd trimester (between 20 and 32 weeks gestation) [45]. This is because:

- levels of pertussis antibodies that are likely to be protective are detected in infants born to mothers vaccinated in the 2nd and 3rd trimesters
- maternal antibodies are actively transported to the fetus from 13 weeks [46] with maximum transfer 30 weeks gestation onwards [47]
- pertussis antibody levels do not peak until about 2 weeks after vaccination [48].

Pregnant women typically have a routine morphology scan by ultrasound at around 20 weeks gestation and present to a maternity care provider in relation to this scan. Providers may use the 20 week scan as a prompt to provide pertussis vaccine or schedule a vaccination visit. There are no safety concerns if a pregnant woman receives pertussis vaccine before 20 weeks gestation.

If pregnant women are not vaccinated between 20 and 32 weeks, they should receive the vaccine as soon as possible and at any time up to delivery. If given within 2 weeks of delivery, the newborn may not be adequately protected [42].

If pregnant women receive the vaccine earlier than 20 weeks, they do not need a repeat dose during the same pregnancy. Evidence shows transfer of pertussis antibodies to the infant in women who received Tdap vaccine as early as 13 weeks gestation [42].

The Tdap vaccine used in Australia is either Boostrix or Adacel.

Comments:

The goal of the pertussis immunisation programme is to protect infants in their first year of life as they are at highest risk of developing severe disease. This includes administration of Tdap vaccine during pregnancy to allow passive transfer of maternal antibodies to provide protection up to 4 months of age.

The recommended timing of Tdap vaccination during pregnancy is different in the US, UK, Australia and NZ. Administration later in pregnancy (during the 3rd trimester) appears to have been the original recommendation. Since then, a recommendation for pertussis vaccine to be administered earlier in pregnancy has been adopted by the UK and NZ (from 16 weeks), and Australia (from 20 weeks). The studies most often cited to support this recommendation are those conducted by Eberhardt et al (see sections 3.1.4 and 3.1.7). One of the reasons the UK cited for changing the recommendation is to give pregnant women greater opportunity to have the vaccination. In NZ, contact with the health system from week 14 of pregnancy includes an anatomy scan at 18 to 20 weeks, and diabetes screening up to 20 weeks and again at 24 to 28 weeks. PHARMAC funding of Tdap from week 16 could be a prompt for vaccination at the 18 to 20 week anatomy scan.

Administration of Tdap vaccine earlier in pregnancy could also provide better protection against pertussis for preterm babies by allowing more time for passive antibody transfer to occur. In 2017, a total of 4,503 (7.5%) of babies were born preterm in New Zealand: 777 (1.3%) were born <32 weeks gestation and 3,726 (6.2%) were born at 32-36 weeks gestation [49]. The proportion of preterm babies showed little variation between 2008 and 2017: babies born at<32 weeks gestation ranged from 1.2% to 1.3% of all births, and babies born at 32-36 weeks gestation ranged from 5.9% to 6.3% of all births [49].

2.2.3 Boostrix [37]

Composition: Boostrix is a combined diphtheria, tetanus, acellular pertussis (Tdap) vaccine. It contains diphtheria toxoid, tetanus toxoid and three purified antigens of *Bordatella pertussis* (pertussis toxoid, pertussis filamentous haemagglutinin and pertussis 69 kilodalton outer membrane protein) adsorbed onto aluminium salts [37].

Dose and administration: Boostrix is administered by deep intramuscular injection, preferably in the deltoid region. Repeat vaccination against diphtheria, tetanus and pertussis should be performed at intervals as per official recommendations (generally 10 years).

Pertussis efficacy (general): There is currently no correlate of protection defined for pertussis; however, the protective efficacy of DTaP (Infanrix) vaccine against WHO-defined typical pertussis was demonstrated in 3 studies conducted in children:

1. Prospective blinded household contact study performed in Germany (3, 4, 5 months schedule). Protective efficacy of the vaccine was 88.7%.
2. NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). Vaccine efficacy was 84%.
3. In a follow-up of the NIH study cohort, efficacy was confirmed up to 5 years after completion of primary vaccination without administration of a booster dose of pertussis. A similar duration of protection can't be assumed to apply to older children or adults given a single dose of Boostrix, regardless of previous vaccination against pertussis.

Although the protective efficacy of Boostrix has not been demonstrated in adolescents and adult age groups, vaccines in this age groups who received Boostrix achieved anti-pertussis antibody titres greater than those in the German household contact study where the protective efficacy of Infanrix was 88.7%.

Pertussis efficacy (pregnancy): Boostrix or Boostrix-IPV vaccine effectiveness was evaluated in 3 observational studies in UK, Spain and Australia. The vaccine was used during the 3rd trimester of pregnancy to protect infants <3 months of age against pertussis disease, as part of a maternal vaccination programme. Vaccine

effectiveness against pertussis in these 3 studies are shown in Table 4. If maternal vaccination occurs within 2 weeks before delivery, vaccine effectiveness in the infant may be lower than the figures in Table 4.

Table 4: Vaccine effectiveness against pertussis for infants <3 months of age born to mothers vaccinated during the 3rd trimester of pregnancy with Boostrix or Boostrix-IPV

Study Location	Vaccine	Study design	Vaccination Effectiveness (VE)
UK	BOOSTRIX-IPV	Retrospective, screening method	88% (95% CI: 79, 93)
Spain	BOOSTRIX	Prospective, matched case-control	90.9% (95% CI: 56.6, 98.1)
Australia	BOOSTRIX	Prospective, matched case-control	69% (95% CI: 13, 89)

CI: confidence interval

Source: Boostrix New Zealand Data Sheet

Persistence of immunity: Table 5 shows the persistence of immunity (seroprotection/seropositivity rates) to diphtheria, tetanus and pertussis after vaccination with Boostrix in children, adolescents and adults.

Table 5: Seroprotection/seropositivity rates following vaccination with Boostrix

Antigen	Seroprotection/ seropositivity	Adults and adolescents from the age of 10 years onwards (% vaccinees)						Children from the age of 4 years onwards (% vaccinees)	
		3-3.5 years persistence		5 years persistence		10 years persistence		3-3.5 years persistence	5 to 6 years persistence
		Adult	Adole-scent	Adult	Adole-scent	Adult	Adole-scent		
Diphtheria	≥ 0.1 IU/ml*	71.2%	91.6%	84.1%	86.8%	64.6%	82.4%	97.5 %	94.2 %
	≥ 0.016 IU/ml*	97.4%	100%	94.4%	99.2%	89.9%	98.6%	100 %	Not determined
Tetanus	≥ 0.1 IU/ml	94.8%	100%	96.2%	100%	95.0%	97.3%	98.4 %	98.5 %
Pertussis									
Pertussis toxoid		90.6%	81.6%	89.5%	76.8%	85.6%	61.3%	58.7 %	51.5 %
Filamentous haemagglutinin	≥ 5 EL.U/ml	100%	100%	100%	100%	99.4%	100%	100 %	100 %
Pertactin		94.8%	99.2%	95.0%	98.1%	95.0%	96.0%	99.2 %	100 %

* Percentage of subjects with antibody concentrations associated with protection against disease (≥ 0.1 IU/ml by ELISA assay or ≥ 0.016 IU/ml by an in-vitro Vero-cell neutralisation assay).

Source: Boostrix New Zealand Data Sheet

Comment

Boostrix is an inactivated vaccine. The CDC states there is no evidence of theoretical risks to the developing fetus from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids [50].

Serologic correlates of protection against pertussis in infants are unknown, but it is thought that high concentrations of maternal antibodies to pertussis toxin are important in preventing severe pertussis.

2.3 Pertussis vaccine data sheets

Relevant information on use of Tdap vaccine during pregnancy is shown below. Most of this information is contained in the pregnancy section of data sheets (ie, section 4.6).

2.3.1 New Zealand

Boostrix (dated 28 February 2019) – Section 4.6 Fertility, pregnancy and lactation

Pregnancy

(Category B1)

The use of Boostrix may be considered during the third trimester of pregnancy.

For data relating to the prevention of pertussis disease in infants born to women vaccinated during pregnancy, see section 5.1 Pharmacodynamic properties.

Safety data from a prospective observational study where Boostrix was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from postmarketing surveillance where pregnant women were exposed to Boostrix or to Boostrix-IPV (dTap + inactivated poliovirus vaccine) indicate no vaccine related adverse effect on pregnancy or on the health of the fetus/newborn child.

Human data from prospective clinical studies on the use of Boostrix during the first and second trimester of pregnancy are not available.

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with Boostrix during pregnancy. The clinical relevance of this observation is unknown.

Non-clinical data obtained with Boostrix reveal no specific hazard for humans based on conventional studies of embryo-fetal development in rats and rabbits, and also of parturition and postnatal toxicity in rats (up to the end of the lactation period).

Boostrix may be used during pregnancy when the possible advantages outweigh the possible risks for the fetus. When protection against tetanus is sought, consideration should be given to tetanus or combined diphtheria-tetanus vaccines.

2.3.2 Australia

Boostrix (dated 11 December 2019) – Section 4.6 Fertility, pregnancy and lactation

Use in pregnancy

(Pregnancy Category B1)

Safety data form a prospective observational study where Boostrix was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from post-marketing surveillance where pregnant women were exposed to Boostrix or to Boostrix-IPV (dTpa-inactivated poliovirus vaccine) do not suggest any elevated frequency or unusual patterns of adverse events in pregnant women and their newborn child following pertussis vaccination.

The use of Boostrix may be considered during the third trimester of pregnancy.

Human data from prospective clinical studies on the use of Boostrix during the first and second trimester of pregnancy are not available.

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with Boostrix during pregnancy. The clinical relevance of this observation is unknown.

Combined embryo-fetal development studies in which rats or rabbits were IM administered Boostrix twice before mating and several times during gestation (and once during lactation in rats) with 2/5x (rats) or 1x

(rabbits) the human dose showed no effects on embryo-fetal development, nor on postnatal development in rats.

Boostrix may be used during pregnancy when the possible advantages outweigh the possible risks for the fetus. When protection against tetanus is sought, consideration should be given to tetanus or combined diphtheria-tetanus vaccines.

2.3.3 United Kingdom

Boostrix-IPV (dated 2 January 2019) – Section 4.6 Fertility, pregnancy and lactation

Pregnancy

The use of Boostrix-IPV may be considered during the third trimester of pregnancy.

For data relating to the prevention of pertussis disease in infants born to women vaccinated during pregnancy, see section 5.1.

Safety data from a prospective observational study where Boostrix (dTpa component of Boostrix-IPV) was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from passive surveillance where pregnant women were exposed to Boostrix-IPV or to Boostrix in the 3rd and 2nd trimester have shown no vaccine related adverse effect on pregnancy or on the health of the fetus/newborn child.

Human data from prospective clinical studies on the use of Boostrix-IPV during the first and second trimester of pregnancy are not available. However, as with other inactivated vaccines, it is not expected that vaccination with Boostrix-IPV harms the fetus at any trimester of pregnancy. The benefits versus the risks of administering Boostrix-IPV during pregnancy should be carefully evaluated.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or post-natal development (see section 5.3).

Limited data indicate that maternal antibodies may reduce the magnitude of the immune response to some vaccines in infants born from mothers vaccinated with Boostrix-IPV during pregnancy. The clinical relevance of this observation is unknown.

2.3.4 United States

Boostrix (dated 25 April 2019) – Section 8.1 Use in specific populations – Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Boostrix during pregnancy. Healthcare providers are encouraged to register women by calling 1-888-452-9622.

Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognised pregnancies is 2% to 4% and 15% to 20%, respectively. There are no adequate and well-controlled studies of Boostrix in pregnant women in the U.S.

Available data suggest that the rates of major birth defects and miscarriage in women who received Boostrix within 28 days prior to conception or during pregnancy are consistent with estimated background rates *(see Data)*.

A developmental toxicity study was performed in female rats administered Infanrix prior to mating and Boostrix during gestation, 0.1 mL at each occasion (a single human dose is 0.5 mL). In a second study, female rats were administered 0.2 mL of Boostrix prior to mating and during the gestation and lactation period. In a third study, female New Zealand white rabbits were given 0.5 mL (full human dose) of Boostrix (non-U.S.

formulation) prior to mating and during gestation. These studies revealed no evidence of harm to the fetus due to Boostrix. *(See Data)*

Data

Human Data: An assessment of data from the ongoing U.S. pregnancy registry over approximately 13 years (2005-2018) included 1,388 prospective reports of exposure to Boostrix within 28 days prior to conception or during pregnancy. Of these reports, 240 had known pregnancy outcomes available. After excluding those with exposure in the third trimester (n=186) and those with an unknown exposure timing (n=9), there were 45 pregnancies with known outcomes with exposure within 28 days prior to conception through the second trimester. Outcomes among these prospectively followed pregnancies included 3 cases of miscarriage in women exposed in the first trimester and no major birth defects in infants born to women with exposure within 28 days prior to conception or during pregnancy.

An assessment of spontaneous and postmarketing data through August 2018 included 595 prospective reports of exposure to non-U.S. formulations of Boostrix/Tdap or Boostrix-Polio/Tdap-IPV within 28 days prior to conception or during pregnancy. Of these reports, 146 had known pregnancy outcomes available. After excluding elective terminations (n=3), those with exposure to the third trimester (n=56), and those with an unknown exposure timing (n=4), there were 83 pregnancies with known outcomes with exposure during the 28 days prior to conception through the second trimester. Outcomes among these prospectively followed pregnancies included 1 live infant with a major birth defect born to a woman with exposure during the first trimester, 1 stillbirth in a woman exposed in the first trimester, and 4 cases of miscarriage in women exposed in the first trimester.

Animal Data: Developmental toxicity studies were performed in female rats and New Zealand white rabbits. In one study, female rats were administered 0.1 mL of Infanrix (a single human dose is 0.5 mL) by intramuscular injection 30 days prior to mating and 0.1 mL of Boostrix (a single human dose is 0.5 mL) by intramuscular injection on Gestation Days 6, 8, 11, and 15. The antigens in Infanrix are the same as those in Boostrix, but Infanrix is formulated with higher quantities of these antigens. In a second study, female rats were administered 0.2 mL of Boostrix by intramuscular injection 28 days and 14 days prior to mating, on Gestation Days 3, 8, 11, and 15, and on Lactation Day 7. In these studies, no adverse effects on embryo-fetal or pre-weaning development up to Postnatal Day 25 were observed; there were no fetal malformations or variations observed. In a third study, female New Zealand white rabbits were administered 0.5 mL (full human dose) of Boostrix (non-U.S. formulation) by intramuscular injection on Premating Days -28 and -14 and on Gestation Days 3, 8, 11, 15, and 24. In this study, no adverse effects on embryo-fetal development related to Boostrix were observed; postnatal development was not evaluated.

Comments:

The current wording in the NZ data sheet does not prevent its use during the 2nd trimester of pregnancy.

In summary, information in NZ and Australian data sheets is very similar. The UK data sheet has an additional sentence stating "However, as with other inactivated vaccines, it is not expected that vaccination with Boostrix-IPV harms the fetus at any trimester of pregnancy".

Note that the recommended timing for Tdap during pregnancy in NZ and UK is from 16 weeks, and in Australia is from 20 weeks (ie, from the 2nd trimester in all 3 countries).

3 SCIENTIFIC INFORMATION

3.1 Published literature – Optimal timing for Tdap vaccination during pregnancy

Recent studies exploring the optimal timing for Tdap vaccination during pregnancy are presented in this section (section 3.1). A summary of these studies, including their results and conclusions are shown in Table 6.

Table 6: Summary of results from studies contained in section 3.1 of this report exploring optimal timing for Tdap vaccination during pregnancy, by study

Study (country)	Timing of Tdap and sample size	Results	Conclusions
Abu Raya et al 2014 (Israel)	23-26 weeks: n=3 27-30^{+6} weeks: n=21 31-36 weeks: n=30 >36 weeks: n=7 Controls (unimmunised): 20	Umbilical cord GMCs of IgG to PT in newborns of women immunised at: • 27-30^{+6} weeks: 46.04 IU/mL (95% CI 24.29 to 87.30) • 31-36 weeks: 8.69 IU/mL (95% CI 3.66 to 20.63) • >36 weeks: 21.12 IU/mL (95% CI 7.93 to 56.22) Umbilical cord GMCs of IgG to FHA in newborns of women immunised at: • 27-30^{+6} weeks: 228.86 IU/mL (95% CI 182.34 to 279.76) • 31-36 weeks: 178.31 IU/mL (95% CI 134.59 to 237.03) • >36 weeks: 138.03 IU/mL (95% CI 97.61 to 195.16) Umbilical cord GMCs of IgG to PT, FHA and PRN, respectively, for 3 women vaccinated between 23-26^{+6} weeks: 1. 23^{+1} weeks: 0.5 IU/mL, 42.6 IU/mL and 148.3 IU/mL 2. 23^{+2} weeks: 57.0 IU/mL, 429.6 IU/mL and 114.9 IU/mL 3. 26^{+5} weeks: 21.5 IU/mL, 387.5 IU/mL and 269.2 IU/mL	Immunisation of pregnant women with Tdap between 27-30^{+6} weeks was associated with the highest umbilical cord GMCs of IgG to PT and FHA compared with immunisation beyond 31 weeks gestation. *Note: Those in the 23-26 week group were excluded from sub-analysis of Tdap receipt by gestational age due to small numbers (n=3)*
Abu Raya et al 2015 (Israel)	All women and newborns were enrolled in their 2014 study. 23-26^{+6} weeks: n=3 27-30^{+6} weeks: n=20 31-36 weeks: n=22 >36 weeks: n=7 Controls (unimmunised): 8	RAI of umbilical cord IgG to PT in newborns of women immunised at: • 27-30^{+6} weeks: 79.53%±5.61 (95% CI 76.91 to 82.16) • 31-36 weeks: 71.56±12.58 (95% CI 65.89 to 77.14) • >36 weeks: 63.93%±17.98 (95% CI 47.31 to 80.56) RAI of umbilical cord IgG to PT for 3 women vaccinated between 23-26^{+6} weeks: 1. 23^{+1} weeks: 65.04% 2. 23^{+2} weeks: 79.74% 3. 26^{+5} weeks: 78.78%	Gestational Tdap immunisation between 27 and 30^{+6} weeks resulted in highest avidity of IgG to PT conveyed at delivery as compared with immunisation beyond 31 weeks gestation. *Note: Those in the 23-26 week group were excluded from sub-analysis of Tdap receipt by gestational age due to small numbers (n=3)*
Maertens et al 2015 (Belgium, Vietnam) Letter to the editor	Belgium: • <27 weeks: n=12 • 27-30 weeks: n=24 • 31-36 weeks: n=20 • Mean gestational age at vaccination was 28.8 weeks	Mean RAI in women of Belgium study: • <27 weeks: 50.8 • 27-30 weeks: 52.3 • 31-36 weeks: 54.4 Mean RAI in cord samples of Belgium study: • <27 weeks: 44.8 • 27-30 weeks: 46.4 • 31-36 weeks: 48.3	Compared to Abu Raya et al 2015, there was no correlation between RAI and gestational age at vaccination in maternal samples or cord samples in the Belgium study.

	Vietnam: • <27 weeks: n=24 • 27-30 weeks: n=8 • 31-36 weeks: n=0 • Mean gestational age at vaccination was 24.5 weeks	Mean RAI in women of Vietnam study: • <27 weeks: 27.2 • 27-30 weeks: 38.12	Mean RAI in cord samples of Vietnam study: • <27 weeks: 36.9 • 27-30 weeks: 45	Compared to Abu Raya et al 2015, there was an inverse trend for correlation found between gestational age and RAI in maternal samples but not in cord samples in the Vietnam study. Differences in laboratory technique could explain the differences in findings with those of Abu Raya et al 2015.
Eberhardt et al 2016a (Switzerland) Annex 1	Term neonates (born after gestational week 36) 2nd trimester (13-25 weeks): n=122 3rd trimester (≥26 weeks): n=213 Controls (unimmunised): n=90	Anti-PT GMCs: • 2nd trimester: 57.1 EU/mL (95% CI 47.8 to 68.2) • 3rd trimester: 31.1 EU/mL (95% CI 25.7 to 37.7) Anti-FHA GMCs: • 2nd trimester: 284.4 EU/mL (95% CI 241.3 to 335.2) • 3rd trimester: 140.2 EU/mL (95% CI 115.3 to 170.3) Adjusted GMC ratios of 2nd to 3rd trimester: • Anti-PT: 1.9 (95% CI 1.4 to 2.5) • Anti-FHA: 2.2 (95% CI 1.7 to 3.0) Expected infant seropositivity rates: • 2nd trimester: 80% • 3rd trimester: 55% • Adjusted odds ratio: 3.7 (95% CI 2.1 to 6.5)		Early 2nd trimester maternal Tdap immunisation significantly increased neonatal antibodies. Recommending immunisation from the 2nd trimester onward would widen the immunisation opportunity window and could improve seroprotection.
Eberhardt et al 2017 (Switzerland) Annex 2	Preterm neonates (born before gestational week 37) 2nd trimester (13-25+6 weeks): 37 3rd trimester (after 25+6 weeks): 48	Birth antibody GMCs of anti-PT: • 2nd trimester: 41.3 EU/mL (95% CI 29.6 to 57.5) • 3rd trimester: 22.1 EU/mL (95% CI 14.3 to 34.2) Birth antibody GMCs of anti-FHA • 2nd trimester: 201.1 EU/mL (95% CI 149.7 to 2710.1) • 3rd trimester: 120.2 EU/mL (95% CI 80.6 to 179.2) Adjusted GMC ratios of 2nd to 3rd trimester: • Anti-PT: 2.05 (95% CI 1.15 to 3.61) • Anti-FHA: 1.57 (95% CI 0.93 to 2.67		Transplacental transfer of maternal antibodies is effective sufficiently early in gestation so that the majority of preterm neonates born between 30 and 36+6 gestational weeks benefit from a maternal Tdap immunisation during the 2nd trimester.

Amirthalingam et al 2016 (England) Annex 3	28 days before delivery: n=31 7-27 days before delivery: n=4 0-6 days before delivery or 1-13 days after delivery: n=3	Vaccine effectiveness: • 28 days before delivery: 91% (95% CI 88 to 94) • 7-27 days before delivery: 91% (95% CI 80 to 96) • 0-6 days before delivery or 1-13 days after delivery: 43% (-35 to 76)	This analysis suggests similarly high levels of protection are conferred to infants whose mothers received vaccine at least 4 weeks and 1-4 weeks prior to delivery.
Naidu et al 2016 (Australia)	28-32^{+6} weeks: 38 33-36^{+6} weeks: 44 Control (unimmunised): 39	Cord antibody levels PT (log transformed): • 28-32^{+6}: 4.18 (1.10) • 33-36^{+6}: 3.50 (1.25) • Control: 2.80 (1.2) Cord antibody levels FHA (log transformed): • 28-32^{+6}: 5.56 (0.99) • 33-36^{+6}: 5.03 (1.19) • Control: 4.21 (1.06) Cord antibody levels PRN (log transformed): • 28-32^{+6}: 5.83 (0.93) • 33-36^{+6}: 5.31 (1.17) • Control: 4.9 (1.04)	The optimal window of vaccination to confer the highest level of pertussis antibody protection to the infant appears to be between 28-32 weeks gestation.
Winter et al 2017 (United States)	1st or 2nd trimester: 6092 27-36 weeks: 32,445 >36 weeks but before delivery: 3681 Postpartum: 31,563	Adjusted overall VE of Tdap at 27-36 weeks compared with postpartum: • Infants <8 weeks of age: 85% (95% CI 33 to 98) • Infants ≤12 weeks of age: 72% (95% CI 30 to 89) Adjusted VE of Tdap at any time during pregnancy compared with postpartum: • Infants <8 weeks of age: 64% (95% CI 11 to 85) • Infants ≤12 weeks of age: 53% (95% CI 8 to 76) Infants whose mothers received Tdap at 27-36 weeks were less likely to have pertussis at ≤12 weeks of age than infants whose mothers received Tdap during pregnancy but outside the 27-36 week window (OR 0.22, 95% CI 0.08 to 0.63).	Prenatal Tdap at 27-36 weeks was 85% more effective at preventing pertussis in infants <8 weeks of age compared with postpartum Tdap. Vaccination at 27-36 weeks was more protective than vaccination before or after this window.

Healy et al 2018 (United States) Annex 4	Tdap-exposed during weeks 27-36 of pregnancy (n=312, mean gestation 31.2 weeks) Tdap-unexposed during pregnancy (n=314)	GMC of neonatal cord PT antibodies: • Exposed: 47.3 IU/mL (95% CI 42.1 to 53.2) • Unexposed: 12.9 IU/mL (95% CI 11.7 to 14.3) • GMC ratio of 3.6 (95% CI 3.1 to 4.2). GMCs of PT antibodies were highest when Tdap was administered during weeks 27-30 and declined thereafter, with peak at week 30 (57.3 IU/mL, 95% CI 44.0 to 74.6).	Immunisation with Tdap vaccine during the 3rd trimester of pregnancy, compared with no immunisation, was associated with higher neonatal concentrations of PT antibodies. Immunisation early in the 3rd trimester was associated with the highest concentrations.
Becker-Dreps et al 2018 (United States)	Total of 675,167 mother-infant pairs in the cohort Prenatal Tdap >2 weeks before delivery (n=90,445): • Tdap ≥27 weeks: n=74,172 • Tdap <27 weeks: n=16,273 Postpartum Tdap (n=42,342): • Tdap 2 weeks prior to delivery (n=5872) • Tdap on day of delivery or within 7 days (n=36,470)	Rates of pertussis: • Prenatal Tdap vs. no Tdap: HR_{adj} 0.57 (95% CI 0.35 to 0.92) • Prenatal Tdap ≥27 weeks vs. no Tdap: HR_{adj} 0.42 (95% CI 0.23 to 0.78) • Prenatal Tdap <27 weeks vs. no Tdap: HR_{adj} 1.10 (95% CI 0.54 to 2.25)	Prenatal Tdap provided a substantial reduction in infant pertussis during the period of life with the highest pertussis burden.

Tdap = pertussis-containing vaccine; GMC = geometric mean concentration; IgG = immunoglobulin G; PT = pertussis toxin; CI = confidence interval; FHA = filamentous hemagglutinin; PRN = pertactin; RAI = relative avidity index; VE = vaccine effectiveness; OR = odds ratio; HR_{adj} = adjusted hazard ratio

3.1.1 Abu Raya et al 2014 – The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – A prospective study [33]

Purpose and setting: In 2012, the CDC's advice was for pregnant women to be immunised with Tdap preferably at 27 to 36 weeks of each pregnancy. This recommendation is the same as the recommendation by Israel's Ministry of Health. The purpose of this prospective study was to reaffirm in a larger cohort of pregnant women that immunisation with Tdap at variable gestational ages during the late 2nd and 3rd trimester of pregnancy provides transplacental passive pertussis-specific antibody transfer to the newborn. In addition, the authors sought to ascertain whether there is a preferential period of maternal Tdap immunisation that results in the highest concentrations of pertussis-specific antibodies to the newborn at delivery.

Methods: Women at Bnai Zion Medical Center in Israel who delivered between November 2013 and May 2014 were assessed for participation in the study. Inclusion criteria were women with singleton births at gestational age ≥36 weeks who received Tdap (Boostrix) after the 20th week of the current pregnancy.

Results: 61 women were immunised with Tdap between 23 and 38 weeks gestation. Of these, 3 were immunised at 23-26 weeks, 51 at 27-36 weeks, 7 at >36 weeks gestation. 20 unimmunised women served as controls. Tdap was administered to pregnant women between 6 and 115 days before delivery (mean 50 days, median 46 days). There were no statistical differences between the Tdap-immunised and unimmunised women and their newborns in maternal and pregnancy morbidity, gestational age, delivery mode and birth weight.

Three women received Tdap between 20 and 26^{+6} gestation. Of these 3 women, one was vaccinated at 23^{+1} weeks gestation and had umbilical cord IgG to PT, filamentous hemagglutinin (FHA) and pertactin (PRN) of 0.5 IU/mL, 42.6 IU/mL and 148.3 IU/mL, respectively. The second woman was vaccinated at 23^{+2} weeks gestation and had IgG to PT, FHA and PRN of 57.0 IU/mL, 429.6 IU/mL and 114.9 IU/mL, respectively. The third woman was vaccinated at 26^{+5} weeks gestation and had IgG to PT, FHA and PRN of 21.5 IU/mL, 387.5 IU/mL and 269.2 IU/mL, respectively. This small number of subjects precluded their inclusion in the sub-analysis of Tdap receipt by gestational age.

The magnitude of transplacental transfer of pertussis-specific IgG by maternal immunisation status and gestational timing of Tdap administration is shown in Table 7. Umbilical cord geometric mean concentrations (GMCs) of IgG to PT were significantly higher in newborns of women immunised at 27-30^{+6} weeks gestation compared with newborns of women immunised at 31-36 weeks and >36 weeks. Umbilical cord GMCs of IgG to FHA were also higher in newborns of women immunised at 27-30^{+6} weeks gestation compared with newborns of women immunised at 31-36 weeks and >36 weeks. The umbilical cord GMCs of IgG to PRN did not differ significantly between newborns of women in the 3 gestational groups.

[redacted]

The data were further analysed by looking at pertussis-specific antibody concentrations as a function of time elapsed between Tdap administration and delivery (Table 8). Six women who received Tdap >85 days prior to delivery were excluded from this analysis due to the small sample size. There were significant differences in the GMCs of IgG to PT and FHA in this analysis. Post hoc testing, adjusting for multiple comparisons, revealed significantly higher umbilical cord GMCs of IgG to PT in newborns of women immunised 57-84 days prior to delivery compared with 1-28 days prior to delivery.

[redacted]

The authors also examined whether the finding of Tdap immunisation between 27 and 30^{+6} weeks gestation was expected to persist over time. Using a half-life of 36 days, the anticipated GMC of IgG to PT at different postpartum times according to immunisation status and timing of Tdap immunisation were calculated (Figure 3). Newborns of women immunised with Tdap at 27-30^{+6} weeks gestation were expected to sustain the highest GMCs of IgG to PT over time compared with the newborns of women immunised at 31-36 and >36 weeks.

[redacted]

The authors conclude optimal timing of maternal antepartum Tdap immunisation may enhance pertussis control. They found women immunised with Tdap between 27 and 30^{+6} weeks gestation conveyed the highest umbilical cord IgG to PT and FHA. They also found Tdap immunisation 8-12 weeks prior to delivery provides newborns with the highest IgG to PT and FHA.

Comments:
There were only 3 women who received Tdap prior to 27 weeks of gestation. These women were excluded from sub-analysis of Tdap receipt by gestational age, but the authors reported their umbilical cord IgG to PT, FHA and PRN.

3.1.2 Abu Raya et al 2015 – Immunization of pregnant women against pertussis: The effect of timing on antibody avidity [51]

Antibody affinity is the strength of the reaction between a single antigenic determinant and a single combining site on the antibody, whereas avidity is a measure of the overall binding strength of many antigenic determinants to multivalent antibodies. Antibody avidity increases with time after antigen exposure since it is the result of a process that selects high-affinity memory B cells, thereby serving as a marker for long-term humoral immunity against a pathogen.

The authors aimed to measure the relative avidity index (RAI) of IgG to pertussis toxin (PT) in the newborn cord sera of women immunised with Tdap during late pregnancy and compare it with the RAI of newborns born to unimmunised women. They also sought to explore whether there was an optimal timeframe for immunising pregnant women with Tdap that will induce the highest avidity of IgG to PT at delivery.

The final cohort included 52 women who were immunised with Tdap (Boostrix) between 23 and 38 weeks gestation (3 at 23-26, 43 at 27-36 and 6 at >36 weeks gestation) and 8 unimmunised women who were controls. All were previously enrolled in the authors' previous study (Abu Raya et al 2014, above) [33]. Tdap vaccine was administered antepartum 6 to 115 days prior to delivery (mean 52 days, median 50 days).

The RAI of umbilical cord IgG to PT was significantly higher for newborns of women immunised at 27-30^{+6} weeks gestation (n=20) compared with newborns of women immunised at 31-36 weeks (n=22) and >36 weeks (n=7), 79.53% ± 5.61 (95% CI 76.91 to 82.16) vs. 71.56% ± 12.58 (95% CI 65.98 to 77.14) vs. 63.93% ± 17.98 (95% CI 47.31 to 80.56), Kruskal-Wallis test, $p<0.03$. This was further analysed by looking at the RAI of umbilical cord IgG to PT as a function of time elapsed between Tdap administration to the pregnant woman and delivery (Figure 4). The RAI of umbilical cord IgG to PT increased linearly as a function of time between Tdap boosting and delivery. Six women who received Tdap >85 days prior to delivery were excluded from further analysis given the small sample size.

Newborns of women immunised with Tdap 57-84 days before delivery (n=16) had higher RAI of umbilical cord IgG to PT as compared with 1-28 days (n=11) and 29-56 days (n=19) before delivery, 78.53 ± 7.01 (95% CI 74.79 to 82.26) vs. 69.26 ± 15.90 (95% CI 58.57 to 79.94) vs. 71.16 ± 13.07 (95% CI 64.86 to 77.46), Kruskal-Wallis test, $p=0.127$.

The authors conclude defining the preferential timing of gestational Tdap immunisation may augment pertussis control among young infants. This study found that women immunised with Tdap between 27 and 30^{+6} weeks gestation transferred the highest umbilical cord levels and avidity of IgG to PT.

Comments:

The findings of this study are consistent with the authors' previous study including the same group of women where immunisation between 27 and 30^{+6} weeks gestation was the optimal time for vaccination.

3.1.3 Maertens et al 2015 – Avidity of maternal pertussis antibodies after vaccination during pregnancy [52]

Following the article of Abu Raya 2015 [51] (above), Maertens et al wrote a letter to the Editor since they observed contrasting antibody avidity results when compared with the poster abstract they presented at the European Society for Paediatric Infectious Diseases (ESPID) congress in 2014. The study results presented at the congress are summarised as follows.

In two trials in Vietnam and Belgium, the authors vaccinated pregnant women with a Tdap vaccine (Adacel in Vietnam, Boostrix in Belgium). None of the women received a pertussis vaccine in the 5 years prior to delivery. Relative avidity index (RAI) of anti-PT antibodies was measured.

All women in Belgium received at least a priming schedule with a whole-cell (wP) vaccine during childhood and sometimes an acellular (aP) booster dose later in life. Mean gestational age at vaccination was 28.8 weeks, while the article of Abu Raya et al 2015 the mean gestational age at vaccination was 52 days before delivery. Maertens' team categorised vaccinated women according to gestational age at vaccination: group 1 was vaccinated <27 weeks, group 2 between 27 and 30 weeks and group 3 between 31 and 36 weeks. Mean RAI in women was 50.8, 52.3 and 54.4 in group 1 (n= 12), 2 (n=24) and 3 (n=20) respectively and 44.8, 46.4 and 48.3 in cord samples. In contrast to Abu Raya et al 2015, Maertens' team saw no correlation between RAI and gestational age at vaccination, neither in maternal samples nor in cord samples.

For the Vietnamese women, mean gestational age at vaccination was 24.5 weeks; no woman was vaccinated after week 30 of gestation. Compared to Abu Raya et al 2015, an inverse trend for correlation was found between gestational age and RAI in maternal samples, yet not in cord samples. Mean RAI in women was 27.2 and 38.12 in group 1 (n=24) and group 2 (n=8) respectively and mean RAI in cord samples was 36.9 and 45.

Maertens' team stated the difference in laboratory technique could be an explanation for the differences in their results with those of Abu Raya et al 2015. Vaccination history as well as the composition of vaccines used in the past (aP or wP) could play a role in the avidity of the maternal antibodies at birth. Furthermore, neither the study of Abu Raya et al 2015 nor this study were statistically powered to detect the effect of timing of vaccination in pregnancy on RAI in maternal and cord samples.

3.1.4 Eberhardt et al 2016a – Maternal immunisation earlier in pregnancy maximises antibody transfer and expected infant seropositivity against pertussis [42] (Annex 1)

Purpose: This was a prospective observational non-inferiority study conducted in Switzerland where the recommendation for maternal Tdap immunisation is during the 2nd or 3rd trimester. The study was designed to test the non-inferiority of antibody transfer following 2nd trimester (gestational week 13 to 25) vs. 3rd trimester (gestational week ≥26) maternal Tdap immunisation by comparing geometric mean concentrations (GMCs) and expected infant seropositivity rates. Secondary objectives were to define potential differences among populations and the influence of the time interval between maternal immunisation and delivery on infant cord GMCs.

Population: Eligible participants were consenting pregnant women vaccinated with Tdap after gestational week 13 and delivering after gestational week 36 at the University Hospitals of Geneva after 15 July 2014. Cord blood samples of 90 neonates of non-vaccinated mothers recruited in a similar study in 2011 (prior to maternal Tdap recommendation) were used as negative controls.

Data collection: A sample of umbilical cord blood was collected immediately after birth and analysed by ELISA. Information was collected on maternal medical and social histories (including employment resulting in exposure to young children), date of Tdap (Boostrix) immunisation, gravidity, parity, and maternal and

gestational age at delivery. Socioeconomic status (SES) was calculated as the sum of maternal educational level and paternal profession. Neonatal characteristics included birth weight and height, sex, and health status.

Definitions: The antibody concentration required for seroprotection against pertussis is unknown. It is postulated that anti-PT (anti-pertussis toxin) antibodies have an important role against severe infant pertussis. Therefore, the cutoff for expected infant seropositivity was based on the anti-PT half-life of 36 days in adults, which was confirmed in infants of mothers immunised during pregnancy. "Expected infant seropositivity" was defined from a calculation that birth anti-PT concentrations >30 EU/mL would be associated with seropositivity (antibody persistence >5 EU/mL) until at least 3 months of age. Due to the absence of similar data for anti-FHA antibodies, results were only expressed as GMCs and their 95% confidence interval.

Sample size & stats: The sample size was calculated to show non-inferiority with a margin of 10% in expected infant seropositivity rates among women immunised in the 2nd vs. 3rd trimester. The sample size was initially calculated at 210 women per group. This sample size exceeded the number of patients required to show non-inferiority in the anti-PT GMC ratio (133 women per group). Ultimately, the paucity of women immunised in the 2nd trimester led to a final inclusion of 122 women in this group. Due to uncertainties in the required minimal sample size and to avoid introducing potential pertussis exposure bias, recruitment was terminated on 30 May 2015. A 95% confidence interval of the GMC ratio above 0.67 determined GMC non-inferiority in the 2nd trimester group. Similarly, non-inferiority was reached if the 2-sided 95% confidence interval around the difference in expected infant seropositivity rates (2nd minus 3rd trimester) was entirely above -10% or equivalently if the 2-sided 95% confidence interval around the odds ratio (OR) was entirely above 0.44.

Descriptive analyses were performed to identify potential differences between the 2 study groups using the Mann-Whitney, Student *t*, Fisher exact, and χ^2 tests. The association between trimester of immunisation and the GMCs of anti-PT and anti-FHA were assessed with the base-10 log function (log) and compared between study groups. Linear regression models were used with adjustment for characteristics that were either unbalanced among the 2 groups or could potentially impact maternal vaccine responses to assess associations. As the titres were not normally distributed, they were transformed with the base-10 logarithm function. The regression coefficients were then back-transformed and expressed as ratios of GMCs. The normality of the distribution of residual was visually inspected. In addition to the differences in antibody GMCs, expected infant seropositivity was assessed via logistic regression. The logistic model's goodness of fit was tested using the Hosmer-Lemeshow test.

To assess the influence of timing of maternal vaccination on birth GMCs and expected infant seropositivity rates, multivariate regression analyses were performed to calculate adjusted GMC ratios/ORs for various intervals of gestational week at vaccination. Results were displayed as reverse cumulative distribution curves.

A *P* value <0.05 was considered statistically significant.

Results: The study included 335 women immunised with Tdap and delivering term newborns between 15 July 2014 and 30 May 2015. Of these, 122 (36%) were immunised with Tdap in the 2nd trimester and 213 (64%) immunised in the 3rd trimester. At baseline, the two groups differed significantly only with regard to parity and two socioeconomic scores (overall mean and maternal education level).

Birth anti-PT GMCs in cord blood were significantly higher following 2nd vs. 3rd trimester immunisation (57.1 EU/mL; 95% CI 47.8 to 68.2 vs. 31.1 EU/mL; 95% CI 25.7 to 37.7, respectively) and anti-FHA (284.4 EU/mL; 95% CI 241.3 to 355.2 vs. 140.2 EU/mL; 95% CI 115.3 to 170.3, respectively). Adjusted GMC ratios for anti-PT (1.9; 95% CI 1.4 to 2.5) and anti-FHA (2.2; 95% CI 1.7 to 3.0) confirmed that GMCs were significantly higher following 2nd trimester immunisation (Table 9).

[redacted]

The authors assessed the influence of the time interval between vaccination and delivery. Cord sera of 90 offspring born to nonimmunized women were used as controls for the 68 newborns whose mothers were immunised <2 weeks prior to delivery. Valid ELISA results were obtained for 69 (anti-PT) and 51 (anti-FHA) samples. Cord blood anti-PT GMCs were similar in infants whose mothers were immunised <2 weeks prior to delivery or not immunised (Figure 5). This finding is consistent with the known lack of protection following vaccination within 14 days of delivery. The same applied to anti-FHA. Antibody concentrations markedly increased with intervals >14 days, reaching optimal GMCs with intervals between 30 and 120 days. Unexpectedly high GMCs were observed in neonates of 37 women immunised >150 days prior to delivery.

[redacted]

To further assess the impact of timing of maternal immunisation, the authors calculated neonatal GMCs by gestational age at maternal Tdap immunisation. Similar neonatal anti-PT and anti-FHA GMCs were observed following immunisation between gestational weeks 13 and 33 (Table 10). Calculating the expected waning of anti-PT antibodies confirmed that immunisation in this period should confer seropositivity (anti-PT >5 EU/mL) to all infants up to 3 months of age.

Seropositivity was frequent: Anti-PT antibodies were >5 EU/mL in 119 of 122 (98%) vs. 182 to 213 (86%) neonates after 2nd vs. 3rd trimester immunisation, respectively. The seroprotection rate reached 80% (97/122) and 55% (116/213) after 2nd and 3rd trimester immunisation, respectively. This 25% (95% CI 14.8% to 35.6%) difference in seroprotection rates not only reached non-inferiority criteria for 2nd trimester immunisation but demonstrated superiority. The unadjusted OR for neonatal seroprotection after 2nd vs. 3rd trimester immunisation was 3.2 (95% CI 2.0 to 5.4) similar to the adjusted OR of 3.7 (95% CI 2.2 to 6.5) (Table 9).

[redacted]

As the cutoff for expected infant seropositivity was extrapolated, sensitivity analyses were conducted by modifying the limit of cord blood anti-PT antibodies to >20 EU/mL and >10 EU/mL. This did not eliminate the superiority of 2nd trimester immunisation (>20 EU/mL: 107/122 (88%) vs. 145/213 (68%); 10 EU/mL: 115/122 (94%) vs. 165/213 (78%)). Similarly, restricting the 3rd trimester to the current recommended gestational week 26 to 36 found expected infant seropositivity rates of 75/118 (64%) vs. 97/122 (80%) after 2nd trimester immunisation.

The authors state the finding that immunisation in early pregnancy results in higher cord blood GMCs is contradictory with the observed progressive increase of IgG transfer efficiency in late gestation. It suggests that a prolonged maternofetal transfer cumulatively results in a higher amount of transferred IgG than a shorter exposure at the time of peak transfer efficacy (gestational week 32 to 33). Although unexpected, this is in line with the active, saturable nature of FcRn-mediated transfer. Despite antibody detection with a genetically detoxified PT whose immunogenicity is closest to that of native PT, seroprotection rates are lower than the first reported vaccine effectiveness. Whether this reflects a contribution of indirect protection is yet to be defined.

The authors conclude that 2nd trimester maternal Tdap immunisation significantly increased neonatal antibodies, and therefore they recommended immunisation from the 2nd trimester onward to widen the immunisation opportunity window and improve seroprotection.

Comments:

Unlike the studies by Abu Raya et al, this study by Eberhardt et al had a larger population of women exposed to Tdap vaccine during the 2nd trimester and sample size calculations were performed. Antibody persistence in infants was not measured but was instead calculated.

Two letters to the Editor were written following publication of this study (see sections 3.1.5 and 3.1.6)

3.1.5 Abu Raya et al 2016 – Optimal timing of immunisation against pertussis during pregnancy

Abu Raya et al replied to the article of Eberhardt 2016a by writing to the Editor where they referred to several issues that needed further discussion.

Firstly, it remains to be known if Tdap immunisation in early pregnancy is associated with higher vaccine-specific IgG transfer efficiency compared with immunisation later in pregnancy. The predominant IgG transplacental transfer occurs during the 3rd trimester of pregnancy via the neonatal Fc receptor. The efficiency of vaccine-specific IgG transplacental transfer corresponds to the cord-maternal ratio (CMR) of vaccine-specific antibody levels at delivery rather than the cord absolute antibody levels. Several factors, including the concentration of total and vaccine-specific IgG in the maternal sera, affect the efficiency of transfer across the placenta.

Secondly, it is not known if cord pertussis antibody levels measured at delivery are the result of cumulative transplacental transfer of antibodies during gestation or limited to the transfer that occurs mainly in close proximity to delivery. Earlier studies have shown maternally derived IgG levels in the fetal blood increase as gestation advances. Notably, the amount of maternally derived pertussis antibodies in fetal blood is thought to be affected by the established adult's pertussis antibodies' half-life; specifically, 36 days for anti-PT IgG and 40 days for anti-FHA IgG, with comparable data on infants yet to be established. Therefore, maternally derived pertussis-specific antibodies accrued in fetal blood during early pregnancy following immunisation in early gestation do not assure higher cord pertussis antibody levels at term delivery compared with immunisation later in pregnancy.

Lastly, although anti-PT IgG >5 EU/mL is assumed as the seropositivity cutoff, the minimal protective level of pertussis-specific antibodies at delivery required to confer protection from pertussis disease in infants remains unknown. What is known is that higher pertussis antibody levels are associated with enhanced clinical protection from disease.

Additional studies exploring the effect of timing of Tdap immunisation during pregnancy on the clinical protection of young infants from pertussis disease is required.

3.1.6 Eberhardt et al 2016b – Reply to Abu Raya et al

Eberhardt et al replied to the letter of Abu Raya et al. Abu Raya focused on IgG transfer efficiency. Higher cord titres following 2nd vs. 3rd trimester immunisation might result from the induction of maternal antibodies at higher titres or of higher affinity, or from more effective neonatal Fc receptor (FcRN)-mediated transport.

Although data comparing maternal responses to 2nd vs. 3rd trimester pertussis immunisation are lacking, similar titres were reported in pregnant women immunised between 20 and 36 gestational weeks in a Spanish study [53]. The influence of the timing of immunisation on antibody avidity is unclear. Abu Raya et al reported a higher avidity of antipertussis antibodies following early 3rd trimester immunisation [51], although this was not confirmed by Maertens et al [52]. Both studies were insufficiently powered for this aim and included 3rd trimester immunisation only.

Based on previous studies, Eberhardt et al propose that higher antibody titres following early maternal immunisation essentially result from a more prolonged and thus more effective cumulative antibody transfer. This is expected to be general and the duration of transfer to be eventually confirmed as the main driver of cord blood titres following maternal immunisation against other pathogens.

Eberhardt et al state regardless of the exact mechanisms at play, 2nd trimester immunisation will increase the titre and thus likely the persistence of protective antibodies, increase immunisation opportunities and minimise the proportion of women delivering too early after immunisation for sufficient antibody transfer.

Comments:

The Spanish study referred to in this letter looked at antibody persistence in infants whose mothers received Tdap vaccine (Adacel) during pregnancy. The study included 37 infants whose mothers received the vaccine between 21 and 38 weeks, of which only 3 received Tdap at 21 to 26^{+6} weeks.

3.1.7 Eberhardt et al 2017 – Pertussis antibody transfer to preterm neonates after second- versus third-trimester maternal immunisation [43] (Annex 2)

Purpose and setting: The authors sought to extend on their previous results in term neonates. This single-centre (University Hospitals of Geneva) prospective observational study took place between 15 July 2014 and 29 February 2016. Eligible participants were pregnant women delivering before gestational week 37 (ie, preterm) who had previously been vaccinated with Boostrix according to official Swiss recommendations (any time after gestational week 13). Exclusion criteria and data collection methods were described in their previous study [42].

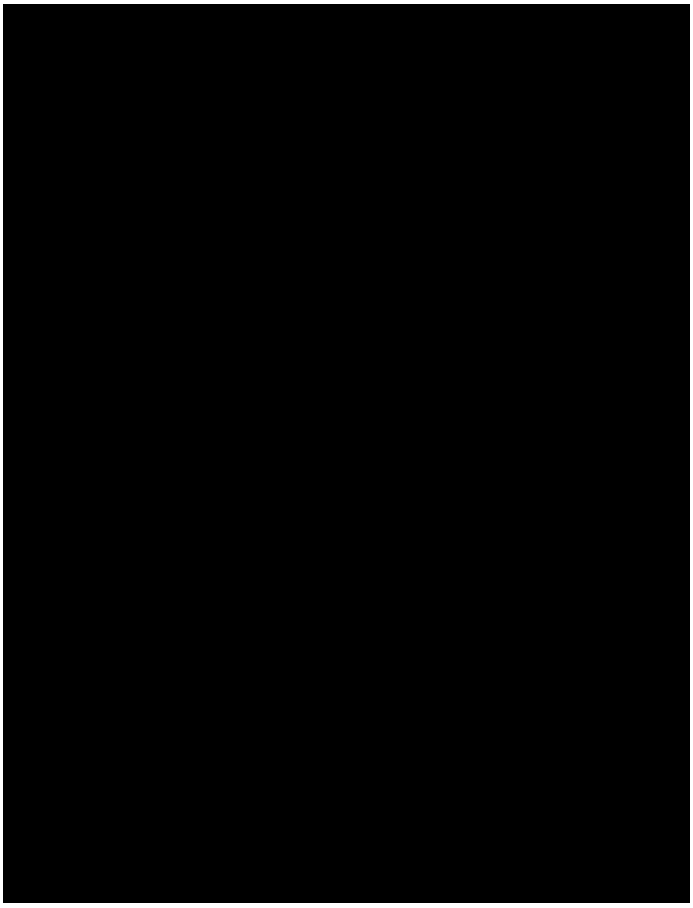
Methods: The sample size was based on the expected number of preterm births in the study hospital within a continuous 19-month period to avoid influence of a potential change in pertussis prevalence over time. Therefore, the intention was to include 100 patients.

Cord blood samples of preterm neonates were collected after maternal Tdap immunisation performed between gestational week 13 and 25^{+6} (2^{nd} trimester) or after gestational week 25^{+6} (3^{rd} trimester). Anti-PT and anti-FHA antibodies were measured by ELISA and GMCs were calculated with 95% confidence intervals. Seronegativity was defined as anti-PT ≤5 EU/mL.

Multivariable linear regression analysis was performed to compare GMC ratios using potential confounding factors identified in their previous study of term neonates, and clinical considerations; all unbalanced epidemiological characteristics between the 2^{nd} and 3^{rd} trimester term groups (maternal age, parity, socioeconomic status) and gestational age at birth were introduced in the model.

Results: 544 women delivered before term at the University Hospitals of Geneva between August 2014 and February 2016. The distribution of gestational ages in these women followed the general epidemiology pattern of preterm births in Switzerland. 85 consenting Tdap-immunised mother-preterm newborn pairs were included: 68 (80%) were born between gestational week 34 and 36^{+6} and 17 (20%) between gestational week 30 and 33^{+6}. Among these 85 mothers, 37 had been immunised during the 2^{nd} trimester and 48 during the 3^{rd} trimester. There were no statistically significant differences between the baseline clinical characteristics in the 2^{nd} trimester and 3^{rd} trimester groups.

Birth antibody GMCs were significantly higher after 2^{nd} compared to 3^{rd} trimester immunisation for both anti-PT (41.3 EU/mL (95% CI 29.6 to 57.5) vs. 22.1 EU/mL (95% CI 14.3 to 34.2)) and anti-FHA antibodies (201.1 EU/mL (95% CI 149.7 to 2710.1) vs. 120.2 EU/mL (95% CI 80.6 to 179.2)). This is shown in Figure 7.



The ratio of 2^{nd} to 3^{rd} trimester anti-PT antibodies was significantly higher (1.87; 95% CI 1.06 to 3.29) even after adjustment for maternal age, gestational age at birth, parity and socioeconomic status (2.05; 95% CI 1.15 to 3.61). For anti-FHA antibodies the GMC ratio was 1.67 (95% CI 1.00 to 2.81) with an adjusted ratio of 1.57 (95% CI 0.93 to 2.67).

None of the 37 preterm neonates born after 2^{nd} trimester maternal immunisation were seronegative compared with 11 of the 48 in the 3^{rd} trimester group. Following 3^{rd} trimester immunisation, the proportion of seronegative preterm neonates was high in both age groups.

The authors also assessed the time interval between vaccination and delivery required to maximise maternofetal antibody transfer. An interval of 15 day was sufficient to observe significantly higher cord antibody titres in this preterm population.

Conclusions: The authors conclude the transplacental transfer of maternal antibodies is effective sufficiently early in gestation so that the majority of preterm neonates born between 30 and 36 weeks benefit from a maternal Tdap immunisation administered during the 2^{nd} trimester of pregnancy. This extends their previous results in term neonates.

Comments:

This is one of the studies referenced in the NZ Immunisation Handbook to support the recommended timing of Tdap from 16 weeks of pregnancy, preferably in the 2nd trimester but 2 weeks before birth.

3.1.8 Amirthalingam et al 2016 – Sustained effectiveness of the maternal pertussis immunisation program in England 3 years following introduction [44] (Annex 3)

Purpose and setting: In 2012, the pertussis-containing vaccine used during pregnancy in the United Kingdom was low-dose diphtheria-tetanus-5-component acellular pertussis-inactivated polio combination vaccine (dT5aP-IPV). This changed to diphtheria-tetanus-3-component acellular pertussis (dT3aP-IPV) in 2014.

According to the authors, one of the key remaining questions is the impact of interference from maternally derived antibodies on the infants' immune response and the resultant risk of disease among older fully vaccinated infants and toddlers. The authors sought to update the previously published estimates of vaccine effectiveness (VE) of the maternal program in England, 3 years following its introduction, and provide the first estimates for the effectiveness of the maternal program on infant deaths and the comparative effectiveness of dT5aP-IPV and dT3aP-IPV on infant disease.

Data sources: The first data source was the routine collection (Immform) which measures coverage at national and subnational levels on a monthly basis using data held on computerised general practice records. Since April 2014 it has moved from a manual to automated extraction with >90% general practices in England participating. In each survey month, the denominator is the number of pregnant women with an estimated date of delivery in that month and the numerator is the number of women who received pertussis vaccine after 28 weeks of gestation.

The second data source is the CPRD sentinel primary care data source. It represents about 6% of the UK population and includes 520 English general practices. Data from the CPRD were extracted in November 2015 and coverage was calculated by week of the child's birth for the period 1 October 2012 to 31 August 2015. The cohort was defined as any woman with a READ code for a live birth from 1 October 2012. For each week, the denominator was the number of women from participating practices that delivered a live infant in that week; the numerator was the number of women who received a pertussis vaccine during pregnancy. Only pertussis vaccines recorded as administered between 300 days prior to a birth and up to 8 weeks after birth were counted.

Public Health England is responsible for national surveillance of vaccine-preventable infections. All laboratory-confirmed cases are followed up with the patients' GP to collect additional clinical and epidemiological data including vaccination history and, for infants born after 1 October 2012, the maternal vaccination status.

Statistical analysis: Vaccine effectiveness (VE) against laboratory-confirmed infant disease was calculated using the screening method where VE is 1 minus the odds of vaccination in cases (maternal vaccine status) divided by the odds of vaccination in the matched population. Statistically this was done by logistic regression with an offset for the logit of the matched population coverage.

For the analysis, the expected coverage in the mother was determined for each confirmed case using the CPRD dataset matched on the week of birth of the baby and the birth cohort of the mother (pre-1985, 1985-1989, 1990 and later). If mother's date of birth was unknown, the average coverage was used. For the primary analysis, when calculating expected vaccine coverage, any vaccine given within 7 days of birth was excluded from the calculation. Similarly, any cases whose mothers were vaccinated within 7 days of birth were not included. Cases were included if the age at onset was known, or otherwise if date of specimen collection was before the age of 24 months (≤731 days). VE was assessed for cases with onset/sample aged ≤62 days and cases with onset/sample aged ≤93 days as long as they had not received their first routine dose within 7 days of onset/sample.

To account for differences observed between CPRD coverage and Immform coverage, a sensitivity analysis was done with coverage reduced by a relative 20% (eg, 70% reduces to 56%) to more closely match Immform coverage.

Analysis was undertaken to calculate the following VE measures: maternal VE against infant disease; maternal VE by timing of vaccination; maternal VE against infant death from pertussis; and maternal VE against infant disease for dTaP7-IPV and dTaP3-IPV vaccines.

To address the question of whether maternal vaccination may have a detrimental effect on responses to primary vaccination, the VE of maternal vaccine in children who have received primary vaccine doses was assessed. An infant dose was counted if given >7 days prior to onset/sample date. Sample date may be weeks after onset date, so children with only a sample date may have had onset prior to vaccine doses. Children up to 23 months of age were included and maternal VE was assessed after the infant had received 1, 2 and 3 primary doses. An additional analysis using only cases with a known onset date was done to reduce possible misclassification of vaccination status.

Results (maternal vaccine coverage): From CPRD, a total of 72,781 live births from 1 October 2012 until 31 August 2015 were obtained. Following introduction of the vaccine programme, the majority (more than two-thirds) of women vaccinated received vaccine at least 8 weeks prior to delivery.

Results (maternal pertussis vaccine effectiveness by timing of vaccination): Vaccine effectiveness was also calculated for vaccination at least 4 weeks before delivery, 1-3 weeks before delivery, and within a week of delivery to 2 weeks after delivery (Table 11). For these analyses, cases from week 40 of 2012 were included. Vaccine effectiveness was 91% for infants whose mothers received vaccine at least 4 weeks prior to delivery (95% CI 88% to 94%) and 1-3 weeks prior to delivery (95% CI 80% to 96%). For the small number of infants whose mothers received vaccine up to 1 week before delivery and within 1-2 weeks following delivery, vaccine effectiveness declines to 43% (95% CI -35% to 76%).

Results (maternal vaccine effectiveness in infants commencing primary infant series): A total of 73 children had received a childhood vaccine and were born after week 40 of 2012. Of these 73 children, the mothers of 26 had been vaccinated. Of the 73 children, 43 had received 1 dose, 12 had received 2 doses, and 18 had received 3 doses of their primary pertussis vaccines.

Estimated vaccine effectiveness (Table 12) indicates that maternal vaccine continues to offer protection to children who have received a first primary dose (VE 82%; 95% CI 65% to 91%). For infants who have received 2 doses, the protection conferred through maternal immunisation declines to 69% (95% CI 8% to 90%), and after completion of the primary infant schedule the protection from maternal immunisation which is based on small numbers, declines further, although the point estimate remains above 0%. With these lower effectiveness estimates, the effect of reducing coverage by a relative 20% is greater, with the estimated effectiveness from maternal vaccination declining from 69% to 43% for infants who have received 2 doses of their primary series.

[redacted]

Discussion: Although evidence of high effectiveness and safety of the maternal pertussis program in England has been extremely encouraging, a number of questions still remain. This includes the influence of timing of maternal vaccination on protection against disease in infants. The authors' analysis suggests similarly high levels of protection are conferred to infants whose mothers received vaccine at least 4 weeks and 1-4 weeks prior to delivery. The levels of protection decline significantly for the relatively low number of infants whose mothers received vaccine around the time of delivery.

Another area of continuing discussion is clinical significance of blunting. The analysis of additional protection conferred through maternal immunisation for infants who have commenced their primary infant schedule suggest high levels of protection are conferred to infants who have received their 1st dose of the primary series. After the 3rd infant dose, numbers are small and there is no longer evidence of protection.

Comments:
This is one of the studies referenced in the NZ Immunisation Handbook to support the recommended timing of Tdap from 16 weeks of pregnancy, preferably in the 2nd trimester but 2 weeks before birth. The authors conducted many different analyses to assess Tdap vaccine effectiveness.

3.1.9 Naidu et al 2016 – The optimal gestation for pertussis vaccination during pregnancy: a prospective cohort study

This prospective study sought to determine the optimal gestational window for vaccination in the 3rd trimester. Three groups of women were recruited: an early group vaccinated between 28 to 32^{+6} weeks' gestation; a late group vaccinated between 33 to 36^{+6} weeks' gestation; and an unvaccinated control group. Maternal venous blood was taken prior to pertussis vaccination. At birth, infant cord blood was collected to determine antibody levels to pertussis toxin (PT), pertactin (PRN) and filamentous hemagglutinin (FHA).

154 women were recruited from April to September 2014 (53 in the early group, 62 in the late group and 39 controls). There were 82 paired maternal and infant cord blood samples from Tdap-immunised mothers and 27 unimmunised mothers for analysis. There was no significant difference between maternal PRN and FHA antibody levels among the 3 groups, however PT was higher in the early compared to late group. Cord blood antibody levels to PT, PRN and FHA were significantly higher in those born to vaccinated women compared with controls. Vaccination between 28 to 32^{+6} weeks' gestation resulted in significantly higher cord blood PT and FHA antibody levels than vaccination between 33 to 36^{+6} weeks' gestation (Table 13).

When adjusted for maternal prevaccination antibody levels, PT levels in early vs. late vaccination approached significance. PRN levels were significantly higher in the early vaccination group. There was no significant difference for FHA antibody levels between the 2 groups (Table 14).

The authors conclude maternal vaccination during the 3rd trimester is effective in affording higher levels of pertussis antibody protection to newborns. Vaccination early in the 3rd trimester appears more effective than later in pregnancy.

3.1.10 Winter et al 2017 – Effectiveness of prenatal versus postpartum tetanus, diphtheria, and acellular pertussis vaccination in preventing infant pertussis [54]

The authors sought to evaluate the effectiveness of the ACIP recommendation in the United States to vaccinate pregnant women with Tdap at the start of the 3rd trimester of each pregnancy to optimise transplacental transfer of antibodies to the fetus. A cohort of mothers with documented Tdap vaccination histories in the California Immunisation Registry (CAIR) were evaluated to determine whether infants whose mothers received Tdap vaccine at 27-36 weeks gestation had a lower risk of pertussis at <8 weeks of age than infants born to women who received Tdap vaccine within 14 days post partum.

A total of 74,791 women had a live birth during 2013 or 2014 in California and a recorded Tdap vaccine dose in CAIR administered during the pregnancy or within 14 days after delivery. After exclusions, 74,504 mothers remained and of these, 42,941 (58%) were vaccinated during pregnancy and 31,563 (42%) post partum. In the cohort, 119 infants were reported with pertussis at <1 year of age for an incidence of 1.6 cases per 1000 births, suggesting the cohort was representative of the source population with respect to risk of pertussis.

Among the 42,218 women vaccinated during pregnancy with known data, 77% (32,445) received Tdap during the recommended window of 27-36 weeks gestation, 14% (6092) were vaccinated in the 1st or 2nd trimester, and 9% (3681) received Tdap after 36 weeks gestation but before delivery. Infants whose mothers received

Tdap vaccine at 27-36 weeks gestation were less likely to have pertussis at ≤12 weeks of age than infants whose mothers received Tdap during pregnancy but outside the window of 27-36 weeks (OR 0.22, 95% CI 0.08 to 0.63).

In multivariate regression models, receipt of Tdap between 27 and 36 weeks gestation or at any point during pregnancy remained highly protective against infant pertussis at age <8 weeks and ≤12 weeks when other covariates were controlled for.

Vaccine effectiveness estimates when Tdap was administered during pregnancy compared with postpartum administration is shown in Table 15. The overall vaccine effectiveness for Tdap vaccination at 27-36 weeks gestation was 85% (95% CI 33% to 98%) for preventing pertussis in infants <8 weeks of age and 72% (95% CI 30% to 89%) for preventing it in infants ≤12 weeks of age, compared with postpartum Tdap and with adjustment for maternal and infant covariates. The vaccine effectiveness at any point during pregnancy was 64% (95% CI 11% to 85%) for preventing pertussis in infants <8 weeks of age and 53% (95% CI 8% to 76%) for preventing it in infants ≤12 weeks of age, compared with postpartum Tdap and with adjustment for maternal and infant covariates.

Among the 15 case patients ≤12 weeks of age whose mothers were vaccinated during pregnancy, 6 (40%) were vaccinated at 27 to 36 weeks gestation. In the subanalysis of mother-infant pairs who received Tdap during pregnancy and ≥14 days before delivery, infants whose mothers were vaccinated during the 2nd trimester were significantly more likely to have pertussis at age <8 weeks (OR 8.1, 95% CI 1.3 to 49.0) or ≤12 weeks (OR 4.6, 95% CI 1.39 to 15.25) when controlling for the age of the mother, number of prior births and preterm birth (Table 16).

The authors conclude prenatal Tdap at 27-36 weeks gestation was 85% more effective at preventing pertussis in infants <8 weeks of age compared with postpartum Tdap. Vaccination at 27-36 weeks gestation was more protective than vaccination before or after this window.

Comments:

The number of pertussis cases in this study was low which could explain the wide confidence intervals and imprecise findings seen in the analyses.

3.1.11 Eberhardt et al 2017b – Cautious interpretation of optimal timing of maternal pertussis immunisation [55]

This was a letter to the editor in response to the Winter et al 2017 study which reported that Tdap immunisation between 27 and 36 gestational weeks was more effective to protect young infants from pertussis than immunisation postpartum. Based on subgroup analysis, Winter et al concluded immunisation was more beneficial during the 3rd than during the 2nd trimester.

The OR reported by Winter et al was adjusted for 3 potential confounders in a multivariate regression model. However, the low number of cases in their study (5 cases out of a sample size of 35,964 patients) not only results in a risk of overfitting of the model but also precludes the inspection of the assumptions underlying to the model (eg, linearity of logit). The model is potentially mis-specified and the reported association between trimester immunisation and infant pertussis is potentially overestimated.

After Winter et al concluded that vaccination between 27 and 36 weeks was most beneficial, they cited the Eberhardt et al 2016a study [42]. In this letter, Eberhardt et al were concerned with the selective citation of their work by Winter et al.

Eberhardt et al caution against drawing firm conclusions from the Winter et al study due to the low number of cases. They agree that further studies are needed to decipher the optimal timing of vaccination as the transfer of maternal antibodies is described to be higher in early vaccination.

3.1.12 Healy et al 2018 – Association between third-trimester Tdap immunisation and neonatal pertussis antibody concentration [56] (Annex 4)

Purpose and setting: This prospective, observational, cohort study of term neonates was conducted in Houston, Texas. The authors sought to determine pertussis toxin antibody concentrations in cord blood from neonates born to women immunised and unimmunised with Tdap vaccine in pregnancy and optimal gestational age for immunisation to maximise concentrations of neonatal antibodies.

Methods: The study population was term newborns born at the Pavilion or Women at Texas Children's Hospital in Houston (tertiary referral centre for obstetrics with about 5000 deliveries each year). Participants were eligible for inclusion if they delivered at term (≥37 weeks gestation), there was documentation that the mother received Tdap vaccine during gestation weeks 27 through 36 and 14 days or more before delivery (Tdap exposed), or there was specific documentation that the mother hadn't received Tdap vaccine during pregnancy (Tdap unexposed).

Cord serum samples were collected from infants from 9 December 2013 through 15 March 2014. Maternal age, self-reported race/ethnicity, date and gestation at Tdap vaccine administration, infant date of birth, and length of gestation were obtained from medical records.

The primary outcome was pertussis toxin antibody concentrations in cord blood from infants of Tdap-immunised mothers vs. infants of Tdap-unimmunised mothers. The secondary outcome was optimal gestation to administer Tdap vaccine that resulted in maximum infant pertussis toxin antibody concentration at birth. For both primary and secondary outcomes, the estimated pertussis toxin antibody concentrations in infants of Tdap-immunised mothers at age 2 months, when the infant primary immunisation series starts, was calculated using the published half-life of passively acquired maternal levels (36 days).

The proportions of cord samples with pertussis toxin antibody concentrations ≥15 IU/mL, ≥30 IU/mL, and ≥40 IU/mL were calculated. Using the published half-life, pertussis toxin antibody concentrations at the start of the primary immunisation series were estimated to be ≥3.75 IU/mL when concentration at birth was ≥15 IU/mL, ≥7.5 IU/mL when concentration at birth was ≥30 IU/mL, and ≥10 IU/mL when concentration at birth was ≥40 IU/mL.

The association of timing of maternal Tdap vaccine administration with infant cord concentrations of pertussis toxin antibodies was determined by calculating the GMC. Two separate regression models were run with mean GMC as the outcome variable and gestation week for immunisation as the independent variable for gestation <30 weeks and ≥30 weeks.

Differences in antibody concentrations at birth between infants who received Tdap vaccine during the early 3rd trimester (gestation weeks 27-31) vs. late 3rd trimester (gestation weeks 32-36) were also determined. This post hoc comparison was chosen because the biology of placental transport suggests early 3rd trimester as the optimal time to administer a vaccine in pregnancy and it is the midpoint of the recommended gestational window for Tdap administration. These immunisation windows also allow for at least 2 healthcare visits.

Generalised linear mixed models were used for estimating adjusted GMCs and corresponding 95% CIs. Results were adjusted for age and ethnicity which are known to be associated with variations in pertussis incidence and could therefore affect antibody levels through natural infection. Results were also adjusted for gestation at delivery.

Results (patient population): Of 954 patients evaluated for eligibility, 328 were excluded (no cord sample, delivery <37 weeks gestation, no documentation of Tdap status, Tdap administered outside of recommended gestation period etc.). Umbilical cord sera were collected from 626 neonates – those whose mothers had received Tdap vaccine (n=312) and those whose mothers were unimmunised (n=314). Immunised women were older, more likely to be white, and less likely to be black than unimmunised women. There were no differences in infant birth weight or gestation at delivery.

The mean gestation at maternal Tdap vaccine administration was 31.2 weeks (range 27.3 to 36.4). Most women (80%) received Tdap vaccine during weeks 28-32 of gestation. The mean interval between immunisation and delivery was 57 days (range 21-90 days). 77% of women received Tdap vaccine ≥8 weeks before delivery.

Results (primary outcome): GMC of neonatal cord pertussis toxin antibodies from the Tdap-exposed group was 47.3 IU/mL (95% CI 42.1 to 53.2) compared with 12.9 IU/mL (95% CI 11.7 to 14.3) in the Tdap-unexposed group, for a GMC ratio of 3.6 (95% CI 3.1 to 4.2) (Figure 7). This ratio remained significant after controlling for maternal age, ethnicity and gestational age at delivery.

More Tdap-exposed than Tdap-unexposed neonates had pertussis toxin antibody concentrations of ≥15 IU/mL (86% vs. 37%), ≥30 IU/mL (72% vs. 17%), and ≥40 IU/mL (59% vs. 12%). When adjusted for potential confounders, all results remained significant ($p<0.001$).

Results (secondary outcome): The GMC of pertussis toxin antibodies in cord sera increased sequentially each week when Tdap vaccine was administered during 27 through 29 weeks of gestation, and was highest when given at week 30 (GMC 57.3 IU/mL, 95% CI 44.0 to 74.6, range 7.5-424) and declined thereafter (Figure 8). Analysis indicated that after 30 weeks, GMC decreased significantly with increasing gestation age at immunisation. Proportions of samples with pertussis toxin antibody concentrations of ≥15 IU/mL, ≥30 IU/mL, and ≥40 IU/mL were highest when Tdap vaccine was administered between weeks 28 through 31.

The estimated GMC of serum pertussis toxin antibody at age 2 months was 11.8 IU/mL (95% CI 10.5 to 13.3) among infants born to Tdap-immunised mothers and 3.2 IU/mL (95 % CI 2.9 to 3.6) among those born to Tdap-unimmunised mothers for a GMC ratio of 3.7 (95% CI 3.2 to 4.2) ($P<0.001$). Estimated GMC of pertussis toxin antibodies at infant age 2 months was highest when Tdap vaccine was administered during week 30 (14.3 IU/mL, 95% CI 11.0 to 18.7).

[redacted]

Results (post hoc analysis): The GMC ratio of pertussis toxin antibodies was 1.4 (95% CI 1.1 to 1.7, p=0.02) when mothers were immunised at weeks 27 through 31 (52.5 IU/mL, 95% CI 45.5 to 60.6, range 7.5-960) compared with weeks 32 through 36 (39.0 IU/mL, 95% CI 32.1 to 47.4, range 7.5-433). When adjusted for maternal age, ethnicity and gestation at delivery, the GMC ratio was 1.4 (95% CI 1.1 to 1.8, p=0.007).

Conclusion: The authors conclude immunisation with Tdap vaccine during the 3rd trimester of pregnancy, compared with no immunisation, was associated with higher neonatal concentrations of pertussis toxin antibodies. Immunisation early in the 3rd trimester was associated with the highest concentrations.

Comments:

Although the authors sought to determine the optimal gestational age for immunisation to maximise concentrations of neonatal pertussis toxin antibodies, inclusion criteria for the Tdap-immunised group was from 27 weeks of gestation.

3.1.14 Becker-Dreps et al 2018 – Effectiveness of prenatal tetanus, diphtheria, acellular pertussis vaccination in the prevention of infant pertussis in the U.S. [57]

This was a nationwide cohort study of pregnant women with deliveries in 2010-2014 and their infants. The cohort was from Truven Health Analytics MarketScan Commercial Claims and Encounters Databases which contains insurance enrolment and billing data for commercially insured employees, spouses and dependents from about 100 large employers around the US.

The objective was to examine clinical effectiveness of prenatal Tdap and whether effectiveness varies by gestational age at immunisation. Pertussis occurrence was compared between infants of mothers who received prenatal Tdap (overall and stratified by gestational age at administration) and infants of unvaccinated mothers.

There were 675,167 mother-infant pairs in the cohort. Of these, 90,445 (13.4%) women received prenatal Tdap (vaccinated during pregnancy >2 weeks before delivery), 5872 (0.9%) were vaccinated in the 2 weeks prior to delivery and were included in the postpartum Tdap group along with 36,470 (5.4%) women who received the vaccine on the day of delivery or in the 7 days after.

Among infants whose mothers received prenatal Tdap, the rate of pertussis was 43% lower (HR 0.57, 95% CI 0.35 to 0.92) than infants whose mothers did not receive prenatal or postpartum Tdap. This reduction was consistent across pertussis definitions. Pertussis rates were also lower for infants whose mothers received Tdap during the 3rd trimester. Infants whose mothers received Tdap at <27 weeks of gestation did not experience reductions in pertussis rates (HR 1.10, 95% CI 0.54 to 2.25). Although these infants tended to have lower rates of pertussis hospitalisations and possible pertussis (Table 17), inferences were imprecise due to limited numbers of mothers receiving Tdap at <27 weeks.

The authors conclude infants of mothers who received prenatal Tdap experienced half the rate of pertussis compared with infants of unimmunised mothers. These results do not provide evidence to support changing the currently recommended timing of Tdap administration in pregnancy (27 to 36 weeks of gestation).

[redacted]

Comments:

The number of pertussis cases in infants born to women who were vaccinated with Tdap <27 weeks of gestation are low (n=10). Therefore, the finding that infants born to mothers who received Tdap <27 weeks of gestation did not experience reductions in pertussis rates compared to unimmunised women should be interpreted with caution.

3.2 Published literature – Safety of Tdap immunisation during pregnancy

The studies in this section (section 3.2) evaluated the safety of Tdap immunisation during pregnancy. Note that this section only presents some safety studies, not all. Studies conducted in New Zealand are presented first (sections 3.2.1 to 3.2.4), followed by other studies that were more frequently referenced. A recent systematic review is also shown in section 3.2.8.

3.2.1 Petousis-Harris et al 2016 – Safety of Tdap vaccine in pregnant women: an observational study [58]

The Pertussis Immunisation in Pregnancy Safety (PIPS) studies were 3 observational studies in NZ examining the safety of Tdap immunisation during pregnancy. This is the first component of the PIPS study evaluating reactogenicity for maternal outcomes.

The authors conducted a prospective observational study (active safety surveillance) to assess safety of Tdap in pregnant women in two New Zealand regions after vaccination with Boostrix. The two regions as well as participant characteristics and recruitment are detailed as follows:

- Northern: Primarily Auckland but includes other North Island centres. Women administered Tdap between 28 and 38 weeks gestation were identified by staff from 21 out of 24 participating general practices and maternal clinics of three DHBs. Referrals were faxed to the study team from 30 January 2014 to 30 June 2014.

  Participants were given a study envelope containing an information sheet, consent form, clear plastic measuring tool to measure any local reactions and a 3-day diary card to record any symptoms or events. They were contacted by phone 48-72 hours post vaccine administration. Consent was obtained and an interview conducted at this time. The 2nd phone interview was conducted at 4 weeks post administration.

- Canterbury: Recruitment for this arm was from late September 2012 to late June 2014. Participants aged 18-40 years and administered Tdap between 30 and 36 weeks gestation were identified via claims submitted by general practices (within 1 week of vaccination) for reimbursement from the local DHB for each vaccination service delivered.

  Participants were contacted by phone within 2 weeks of identification. Consent was obtained and an interview conducted at this time. A follow-up questionnaire was mailed at 4 weeks post vaccination.

793 women participated in this study. 79% of participants reported mild or moderate pain and 2.6% severe pain. Onset of pain occurred within 24 hours in 83.9% of participants. Any swelling was reported by 7.6%, induration by 12.0%, erythema by 5.8% and fever was reported by 2.1% participants. Headache, dizziness, nausea, myalgia or arthralgia was reported by <4% of participants, respectively, and fatigue by 8.4%.

CARM data was reviewed for reports during the study period. There were 115 adverse events (AEs) in 113 participants, most of which were minor. 31 events (3.9%) were classified as serious. Of these 31 events, 23 required hospitalisation during pregnancy for the following reasons: obstetric bleeding (4), hypertension (2), infection (4), tachycardia, preterm labour (9), exacerbation of pre-existing condition (2) and pre-eclampsia (1) (Table 18). All had variable onset time from vaccination. The remaining 8 serious adverse events (SAEs) occurred during labour and delivery (Table 19). Of these 8 SAEs, 2 were perinatal deaths (congenital abnormality and unexplained, respectively). None of the SAEs were considered by clinical review as likely to be caused by exposure to Tdap vaccine.

The authors concluded that vaccination with Tdap in pregnant women was well tolerated and with no SAE likely caused by the vaccine.

[redacted]

[redacted]

Comments:

The women included in this first component of an NZ PIPS study were vaccinated from gestational week 28, which was within recommended window for Tdap at the time of the study.

3.2.2 Walls et al 2016 – Infant outcomes after exposure to Tdap vaccine in pregnancy: an observational study [59]

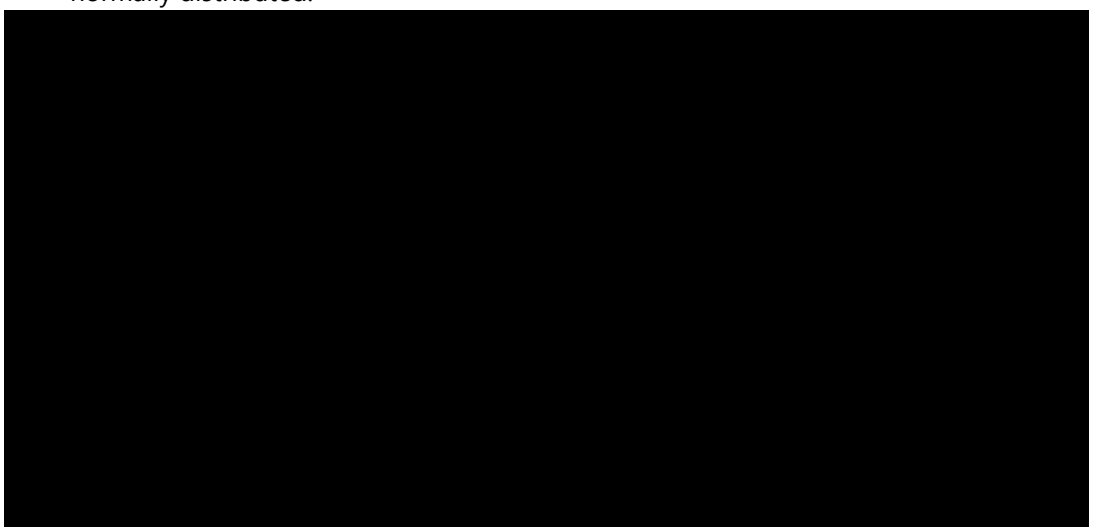
This is the second component of the PIPS study evaluating the safety of Tdap vaccine for infants exposed during pregnancy. The study is also called Safety Monitoring of Adverse Reactions to Tdap Vaccine in Pregnancy (SMART VIP). The study was conducted in the Canterbury region and specifically focuses on longitudinal infant outcomes. Infants were followed for between 6 and 12 months after birth with 84% completing 12 months of follow-up.

470 of the 1211 women who had received Tdap vaccine during pregnancy were recruited. 86% were NZ European, 4% Māori and 8% Asian. 62 women also received trivalent influenza vaccine during their pregnancy, often given at the same time as Tdap vaccine.

Follow-up data were obtained from 403 women on 408 infants (403 singleton infants, 6 sets of twins and 1 stillbirth). Of these 408 infants, 345 were followed through to 12 months of age and 63 through to 6-12 months of age. There were no significant differences in birth weight, gestational age at birth, congenital anomalies or infant growth as compared with baseline population data. Infants of mothers who had received the vaccine were more likely to receive their vaccinations on time during infancy. No cases of pertussis occurred in this cohort despite high rates of disease in the community. Birth outcomes, growth parameters and rates of congenital anomalies were very similar to baseline rates in NZ.

Ten infants (2.5%) were identified as having medical events of significance or congenital anomalies. One infant was stillborn and despite a postmortem examination (there were no congenital abnormalities identified) the reason for this is unknown.

A total of 303 infants completed their 6-week check and 278 completed their 5-month check. Figure 9 shows the z-scores for weight at birth, at the 6-week check, and between 5 and 7 months of age, each of which is normally distributed.



Nine infants had contact with a confirmed case of pertussis during the follow-up period. 67 infants were household contacts of a person with a prolonged cough illness and 64 infants were reported to have had a cough lasting >10 days themselves. None of these infants were subsequently diagnosed with pertussis. Nine infants were admitted to hospital during the follow-up period. Of these, 3 had respiratory tract illness, one of whom had proven influenza infection and all 3 tested negative for pertussis.

The proportion of infants in this cohort receiving their immunisation on time were 97.8%, 98.5% and 94.2% at 6 weeks, 3 and 5 months, respectively. For each vaccination event, this was significantly better than the overall Canterbury infant cohort during the same time period (Table 20).

The authors conclude these data add to the growing pool of evidence that administration of Tdap vaccine during pregnancy is an appropriate strategy for reducing the burden of pertussis in infants. No difference was found in infant outcomes in those who have been exposed to the vaccine in pregnancy when compared with

the overall population. However, the data on vaccine safety remain limited and the need for ongoing surveillance and reporting of adverse events relating to Tdap vaccination during pregnancy remains.

[redacted]

Comments:

As with the first component of this PIPS study (Petousis-Harris et al 2016), women received Tdap vaccine during gestational weeks 28 and 38.

3.2.3 Griffin et al 2018 – Pertussis immunisation in pregnancy safety (PIPS) study: A retrospective cohort study of safety outcomes in pregnant women vaccinated with Tdap vaccine [60]

This study reports maternal outcomes following Tdap vaccination during pregnancy as part of NZ's national immunisation programme. The study was a national retrospective observational study using linked administrative NZ datasets. The study population consisted of pregnant women eligible to receive funded Tdap vaccination from 28 to 38 weeks gestation in 2013.

Primary study outcomes were based on prioritised adverse events for the assessment of vaccine safety in pregnant women as defined by WHO and Brighton Collaboration taskforces. Except for duration of pregnancy, outcomes were taken from the National Minimum Data Set (NMDS) and defined dichotomously by the presence of specified ICD-10-AM codes. Demographic data were obtained from the NHI database, the mortality dataset (MORT) was used to obtain information on fetal deaths including stillbirths, data on primary maternity services and inpatient and day-patient health event data from 9 months before and 3 months after birth were obtained from the National Maternity Collection (MAT), and the Immunisation Subsidies Collection (IMMS) was used to identify fee-for-service payments made to GPs for providing government-funded immunisations.

Cox proportional hazards regression with a time-dependent Tdap exposure was used to estimate the effect of Tdap on key maternal outcomes. For regression analysis, time to event was defined at the start of 28 weeks gestation for all women.

In the cohort of 68,550 women eligible to receive funded antenatal Tdap vaccination during 2013, 8178 (11.9%) were vaccinated and 60,372 (88.1%) were unvaccinated (Table 21). Of those receiving Tdap vaccine, 95% received the vaccine within the funded timeframe of 28 to 38 weeks gestation, 3.7% at <28 weeks gestation, and 1.3% after 38 weeks gestation. The median gestation at first vaccination was 33 weeks. Among the cohort of women eligible to receive Tdap, 11.5% of vaccinated women were of Māori ethnicity, while 24.6% of the total population of women eligible were Māori.

[redacted]

Table 22 reports the relationship between Tdap exposure and priority maternal outcomes. Tdap did not increase the hazard rate of priority outcomes to assess the safety of vaccines in pregnancy in the adjusted models, including gestational hypertension, pre-eclampsia, pre-eclampsia with severe features, fetal growth restriction, preterm labour, or post-partum haemorrhage. There were insufficient numbers of events for the authors to examine the effect of Tdap on chronic hypertension with superimposed pre-eclampsia (n=8 in Tdap exposed), eclampsia (n=2 in Tdap exposed) and stillbirth (n=9 in Tdap exposed). There was one maternal death (Tdap unexposed) in the cohort. Among priority outcomes, there was a significant protective effect of Tdap on pre-eclampsia with severe features and preterm labour.

[redacted]

Table 23 shows the relationship between Tdap exposure and secondary maternal outcomes, including those classified as 'outcomes' and 'suggested outcomes' by Brighton Collaboration and WHO. Tdap was associated with an increased rate of hospitalisation for lactation disorders in the unadjusted and adjusted models, with Tdap exposed women having 1.6 times the rate of hospitalisation in the adjusted model (95% CI 1.15 to 2.33). Tdap increased the rate of fetal distress in the unadjusted model, however this association was not significant in the adjusted model (AHR 1.04, 95% CI 0.97 to 1.12). Tdap exposed women had 0.61 times the hazard of hospitalisation for antenatal bleeding (95% CI 0.49 to 0.78) and 0.86 times the hazard of hospitalisation for preterm delivery (95% CI 0.75 to 0.99) compared to Tdap unexposed women. There were insufficient cases to examine the effect of Tdap on DVT, uterine rupture and maternal cardiomyopathy.

The authors did not detect any biologically plausible adverse maternal outcomes following Tdap vaccination in pregnancy. Their results provide further support for the safety of Tdap vaccination during pregnancy for maternal outcomes.

[redacted]

3.2.4 Petousis-Harris et al 2019 – A retrospective cohort study of safety outcomes in New Zealand infants exposed to Tdap vaccine in utero [61]

This publication reports infant outcomes following the Griffin et al 2018 publication which reported maternal outcomes. The authors examined the difference in birth and hospital-related outcomes of infants with and without fetal exposure to Tdap.

The study population and data sources have been described above in the Griffin et al 2018 study. Infants were followed from birth up to one year of age. Study outcomes were prioritised according to categories and definitions by the WHO and the Brighton Collaboration task force. Priority outcomes were stillbirth, perinatal death, neonatal death, infant death, preterm birth, small for gestational age (SGA), congenital anomalies (major and minor), asphyxia, infection, and sudden infant death syndrome.

A total of 69,389 infants were eligible. Of these, 8299 infants were born to 8178 mothers exposed to Tdap (12%) primarily between 28 and 38 weeks gestation according to the national schedule. Of the Tdap vaccinations during pregnancy, 5% occurred outside of the 28 to 38 week gestation window. Infants of European ethnicity comprised 67% of the vaccine-exposed group while infants of Māori ethnicity comprised 13.2%.

Continuous outcomes (birthweight and Apgar score at 5 min after birth) were analysed using linear regression models. Those outcomes diagnosed at delivery with no follow-up time were considered as a binary variable and analysed using logistic regression models.

There were insufficient numbers of cases in the vaccine-exposed group to assess the association between Tdap exposure and stillbirth (n=9), extreme (n=0) and very preterm birth (n=9), and extreme (n=0) and very low birth weight (n=9). There were insufficient events (n=4) in the Tdap exposed group to allow examination of the effect of Tdap on infant death.

There were insufficient observations available to allow examination of the effect of Tdap on extreme low birth weight (LBW) and very LBW. There was no mean difference in Apgar score between vaccine-exposed and unexposed groups (Table 24). A small but significantly higher mean birthweight was observed in the vaccine-exposed group with a mean difference of 35.59 g (95% CI 21.39 to 49.67). There were reduced risks in the Tdap exposure group for LBW (OR 0.78, 95% CI 0.65 to 0.94), SGA (OR 0.72, 95% CI 0.57 to 0.91) and large for gestational age (OR 0.57, 95% CI 0.36 to 0.89).

[redacted]

Two congenital anomalies that had enough cases to include in regression models were deformities of feet and ankyloglossia (tongue-tie). There was no association with deformities of feet (OR 0.96, 95% CI 0.61 to 1.52). There was an increased odds association with ankyloglossia (OR 1.24, 95% CI 1.04 to 1.47). There were three infants with microcephaly none of which were born to mothers exposed to Tdap.

Neonatal erythema toxicum was significantly associated with exposure to Tdap. After adjustment, the association remained significant (OR 1.66, 95% CI 1.16 to 2.37).

The authors conclude results from this NZ study of adverse outcomes in infants following maternal Tdap vaccination are consistent with other studies and provide support for the safety of Tdap vaccination during pregnancy.

3.2.5 Munoz et al 2014 – Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunisation during pregnancy in mothers and infants: A randomised clinical trial [62]

This was a phase 1 randomised double-blind placebo-controlled clinical trial conducted in private (Houston) and academic (Durham, Seattle) obstetric practices from 2008 to 2012. The objective was to evaluate the safety and immunogenicity of Tdap immunisation during pregnancy and its effect on infant responses to Tdap vaccine.

A total of 48 healthy 18 to 45-year-old pregnant women were randomised 2:1 and received Tdap (n=33) or placebo (n=15) at 30 to 32 weeks' gestation with crossover Tdap immunisation postpartum. Primary outcomes were maternal and infant adverse events, pertussis illness, and infant growth and development until age 13 months. Secondary outcomes were antibody concentrations in pregnant women before and 4 weeks after Tdap immunisation or placebo, at delivery and 2 months postpartum, and in infants at birth, at 2 months, and after the 3rd and 4th doses of DTaP.

The Tdap vaccine used during pregnancy was Adacel (Sanofi Pasteur). The DTaP vaccine used in infants was Pentacel (Sanofi Pasteur) plus inactivated poliovirus and *Haemophilus influenzae* type b conjugate (tetanus toxoid conjugate) administered at 2, 4, 6 and 12 months of age.

All participants delivered healthy newborns. Injection site reactions after Tdap immunisation were reported in 78.8% (95% CI 61.1% to 91.0%) and 80% (95% CI 51.9% to 95.7%) pregnant and postpartum women, respectively. Injection site pain was the predominant symptom. Systemic symptoms were reported in 36.4% (CI 20.4% to 54.9%) and 73.3% (CI 44.9% to 92.2%) pregnant and postpartum women, respectively. Malaise and myalgia were most common.

Serious adverse events were reported by 22 participants, including 7 women who received Tdap during pregnancy (21.2%, 95% CI 8.9% to 38.9%) and 6 of their infants (18.1%, 95% CI 7% to 35.5%), 2 women given Tdap postpartum (13.3%, 95% CI 1.7% to 40.5%) and 6 of their infants (40%, 95% CI 16.3% to 67.7%) and 1 non-pregnant woman (3.1%, 95% CI <0.1% to 16.2%).

Table 25 shows antibody responses. Infants born to mothers who received Tdap during pregnancy had significantly higher concentrations of pertussis antibodies at birth and at age 2 months. The concentration of pertussis antibodies in cord blood was higher than in maternal serum at delivery, with linear correlation between maternal and infant concentrations (Table 26). The ratio of concentrations of antibodies to Tdap antigens remaining at 2 months in infants is shown in Table 26. Antibody responses in infants of Tdap recipients during pregnancy were modestly lower after 3 DTaP doses, but not different following the 4th dose.

The authors conclude this preliminary safety assessment didn't find an increased risk of adverse reactions among women who received Tdap vaccine at 30–32 weeks' gestation or their infants. Maternal immunisation with Tdap resulted in high concentrations of pertussis antibodies in infants during the first 2 months of life and didn't substantially alter infant responses to DTaP.

[redacted]

3.2.6 Zheteyeva et al 2012 – Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women [63]

This study sought to characterise reports to the Vaccine Adverse Event Reporting System (VAERS) of pregnant women who received Tdap. A search was conducted in VAERS for reports of pregnant women who received Tdap from 1 January 2005 to 30 June 2010 (ie, before ACIP's recommendation to administer Tdap to pregnant women >20 weeks gestation).

VAERS is the US FDA's spontaneous reporting system. To assess for disproportionately higher reporting of adverse effects after Tdap administration to pregnant women, the authors calculated proportional reporting ratios (PRRs) compared to inactivated influenza vaccines which have been determined to have an acceptable safety profile in pregnancy. Clinical reviews were conducted for all MedDRA terms with a PRR ≥2.

A search of VAERS identified 132 reports of Tdap administered to pregnant women. Characteristics of the 132 reports are shown in Table 27. Of these 132 reports, 6 (4.5%) were classified as serious and included 2 reports of ruptured ectopic pregnancies that required laparotomy and 1 report each of still birth at 37 weeks gestation due to placental abruption, influenza, gastroschisis in a newborn, and laryngotracheomalacia in a 3-month-old infant. No maternal or infant deaths were reported.

The most frequent pregnancy-specific adverse event was spontaneous abortion in 22 (16.7%) reports. The median gestational age at the time of spontaneous abortion was 9 weeks (range 5-16 weeks). The median onset interval between vaccination and spontaneous abortion was 33 days (range 9-61 days). The authors didn't' observe any temporal clustering of these reports.

Two stillbirth cases were reported. One case occurred in a 20-year-old woman at 37 weeks gestation and was reported to be due to placental abruption. Tdap was administered several hours before the outcome. The other case was in a 27-year-old woman at 22 weeks of gestation (46 days after exposure to Tdap) with no other pregnancy complications reported before fetal demise.

[redacted]

Six (4.5%) reports indicated adverse infant outcomes including 1 report each of gastroschisis, patent foramen ovale and peripheral pulmonic stenosis, physiologic neonatal jaundice, transient tachypnoea and infiltrates in the lower lobes, bilateral hydrocele, and laryngotracheomalacia. The report of gastroschisis was the only one considered to be a major birth defect. This infant was born to a 15-year-old mother who received Tdap and HPV-4 vaccines concomitantly at about 8 weeks gestation.

Injection site reactions were the most frequent non-pregnancy-specific adverse event found in 6 (4.5%) reports. 55 reports (42%) described no adverse event. These were reported because the vaccine had been administered during pregnancy at a time period when Tdap in pregnancy was not routinely recommended.

The PRR screening criteria were met for higher proportional reporting after Tdap in pregnancy for the following MedDRA terms: anaemia, antepartum haemorrhage, gestational diabetes, oligohydramnios, and upper respiratory tract infection. No disproportionality was found in reporting spontaneous abortion, stillbirth or preterm deliveries.

The authors conclude during a time when Tdap was not routinely recommended in pregnancy, review of reports to VAERS in pregnant women after Tdap did not identify any concerning patterns in maternal, infant, or fetal outcomes.

3.2.7 Donegan et al 2014 – Safety of pertussis vaccination in pregnant women in UK: observational study [64]

This was an observational cohort study to examine the safety of pertussis vaccination in pregnancy. Following the UK's Joint Committee on Vaccination and Immunisation (JCVI) recommendation to vaccinate pregnant women between 28 and 38 weeks gestation, the MHRA undertook a tailored proactive approach to pharmacovigilance. This started as soon as the vaccination campaign began using the Clinical Practice Research Datalink (CPRD) to identify vaccinated women in as real time a manner as possible (on a monthly basis). This article describes the growing identified cohort after the first 6 months of the programme (1 October 2012 to 31 March 2013) and presents comparative analyses investigating the risk of a range of predefined events.

The main outcome measure was adverse events identified from the matched child record identified through mother-child linkage. The primary event of interest was stillbirth (intrauterine death after 24 weeks gestation).

20,074 pregnant women with a median age of 30 who received the pertussis vaccine during the first six months of the campaign were identified.

Short term risk of adverse events: 17,560 (87%) had ≥28 days follow-up data after their vaccination record of which 5 had a recorded stillbirth within 2 weeks of vaccination. The observed vs. expected incidence rate ratio was calculated to be 0.69 (95% CI 0.23 to 1.62). An additional 2 women with miscarriage after vaccination were identified and in both cases vaccination appeared to have occurred in the 2nd trimester.

There were 1135 pregnancy outcomes (live and stillbirths) within 2 weeks of vaccination compared with an expected 1115. Therefore the observed vs. expected incidence ratio is 1.02 (95% CI 0.96 to 1.08) indicating no signal of an increase in the number of pregnancy outcomes within 2 weeks of vaccination.

Overall risk of adverse events: As shown in Table 28, out of 6185 vaccinated women, there were 12 recorded instances of stillbirth after vaccination (0.19%, about 1 per 500 deliveries). Based on background data, 15.8 stillbirths would have been expected in this cohort. The observed vs. expected rate ratio is therefore 0.85 (95% CI 0.44 to 1.61). These women were matched to unvaccinated historical controls and the resulting conditional rate ratio for the overall risk of stillbirth in vaccinated vs. unvaccinated women was 0.85 (95% CI 0.45 to 1.61).

There were 2 cases of neonatal death (Table 28) within a week after delivery in addition to the 12 cases of stillbirth. The authors examined all further prespecified adverse events and there were no significant differences in the rates of any of these events. There were no records of maternal death, antepartum haemorrhage, uterine rupture, placental abruption, vasa praevia, fetal distress, or child renal failure after vaccination.

The authors conclude in women given pertussis vaccination in the 3rd trimester there is no evidence of an increased risk of any of an extensive predefined list of adverse events related to pregnancy. In particular, there was no evidence of an increased risk of stillbirth. Given the recent increases in the rate of pertussis infection and morbidity and mortality in neonates, these early data provide initial evidence for evaluating the safety of the vaccine in pregnancy for health professionals and the public and help to inform vaccination policy making.

3.2.8 Vygen-Bonnet et al 2020 – Safety and effectiveness of acellular pertussis vaccination during pregnancy: a systematic review [65] (Annex 5)

The authors searched for studies from 1 January 2020 to 10 January 2019 and evaluated the quality of evidence using the GRADE approach. To be eligible, a study had to match the PICO (population, intervention, comparator, outcome) criteria. Efficacy/effectiveness outcomes were: (1) laboratory-confirmed pertussis in infants ≤3 months of age, (2) hospitalisation due to (1), (3) death due to (1). Safety outcomes were: (4) fever

(≥38 °C) in pregnant woman, (5) pre-eclampsia/eclampsia, (6) chorioamnionitis, (7) preterm birth, (8) stillbirth, (9) low birth weight, (10) malformation, (11) neonatal intensive care unit (NICU) admission, (12) neonatal sepsis, (13) neonatal death.

1273 articles were identified and 22 studies were included (14 for safety, 8 for effectiveness) comprising 1.4 million pregnant women in safety studies and 855,546 mother-infant pairs in effectiveness studies.

No significant differences between vaccinated and unvaccinated women and their infants were observed for safety outcomes with the exception of fever (assessed in 4 studies) and chorioamnionitis (investigated in 6 non-randomised studies). The definition of fever varied considerably across studies. Overall, fever following immunisation was reported in 0.03 to 3% of pregnant women and occurred more frequently in Tdap-vaccinated women than in control women. Compared to no vaccination, 3 studies showed a significantly increased relative risk for the presence of the ICD-9 code for chorioamnionitis in electronic patient data after pertussis vaccination. However, no study reported an increased risk for clinical sequelae of chorioamnionitis after vaccination during pregnancy, such as preterm birth or neonatal intensive care unit administration.

Vaccine effectiveness against pertussis in infants of immunised mothers ranged from 69 to 91% for pertussis prevention, from 91 to 94% for prevention of hospitalisation and was 95% for prevention of death due to pertussis.

Risk of bias was serious to critical for safety outcomes and moderate to serious for effectiveness outcomes. GRADE evidence quality was moderate to very low, depending on outcome.

The authors conclude although an increased risk for a diagnosis of fever and chorioamnionitis was detected in pregnant women after pertussis vaccination, there was no association with a higher frequency of clinically relevant sequelae. Vaccine effectiveness for prevention of infant pertussis, hospitalisation and death is high. Pertussis vaccination during pregnancy has an overall positive benefit-risk ratio.

Comments:
For studies of safety outcomes, exposure to Tdap during pregnancy predominantly occurred from week 27 of gestation.

3.3 Company report – Boostrix PBRER covering 17 March 2012 to 16 March 2017

[redacted]

[redacted]

3.4 Company report – Boostrix US pregnancy registry (PASS study [redacted] cumulative report

[redacted]

o [redacted]

[redacted]

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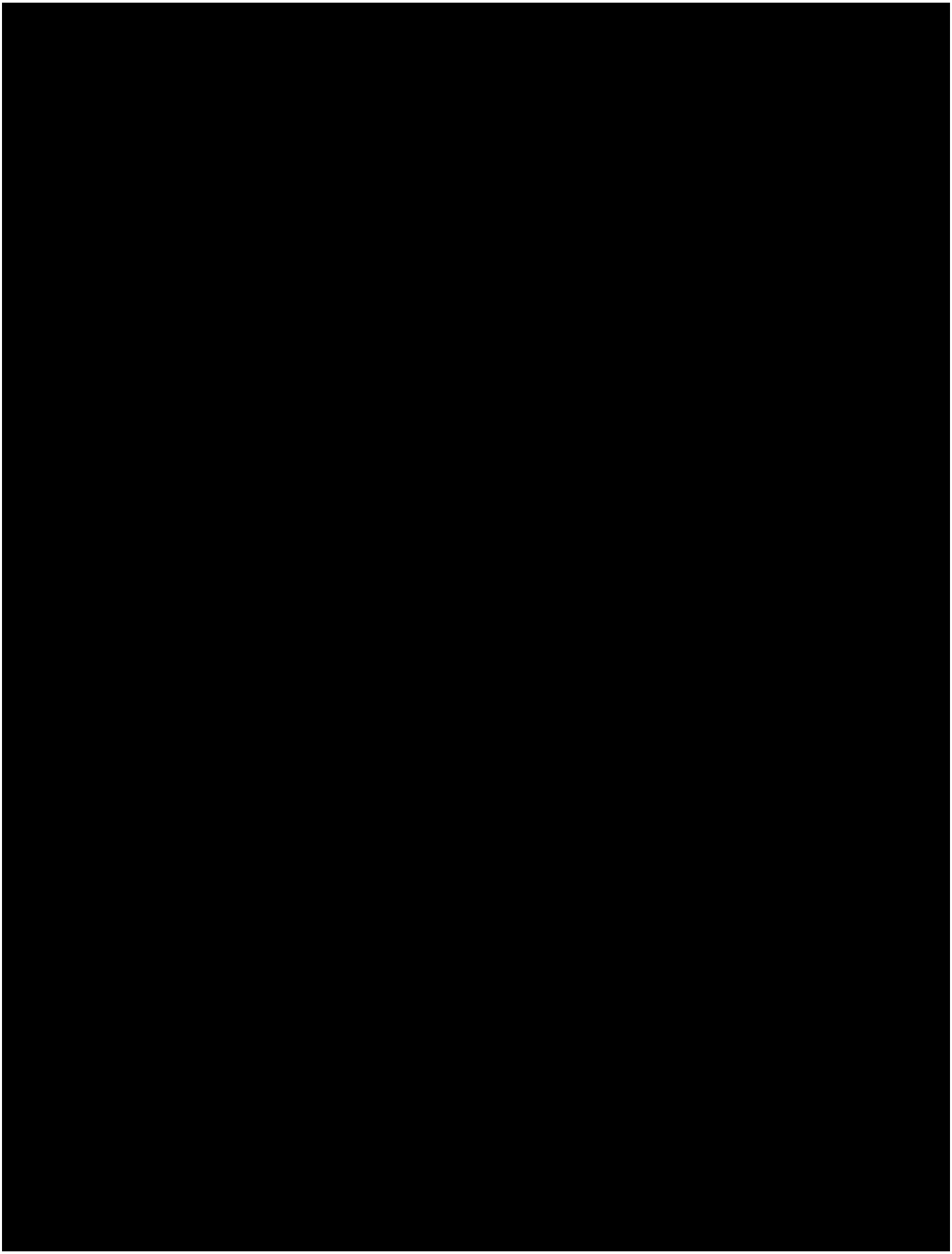

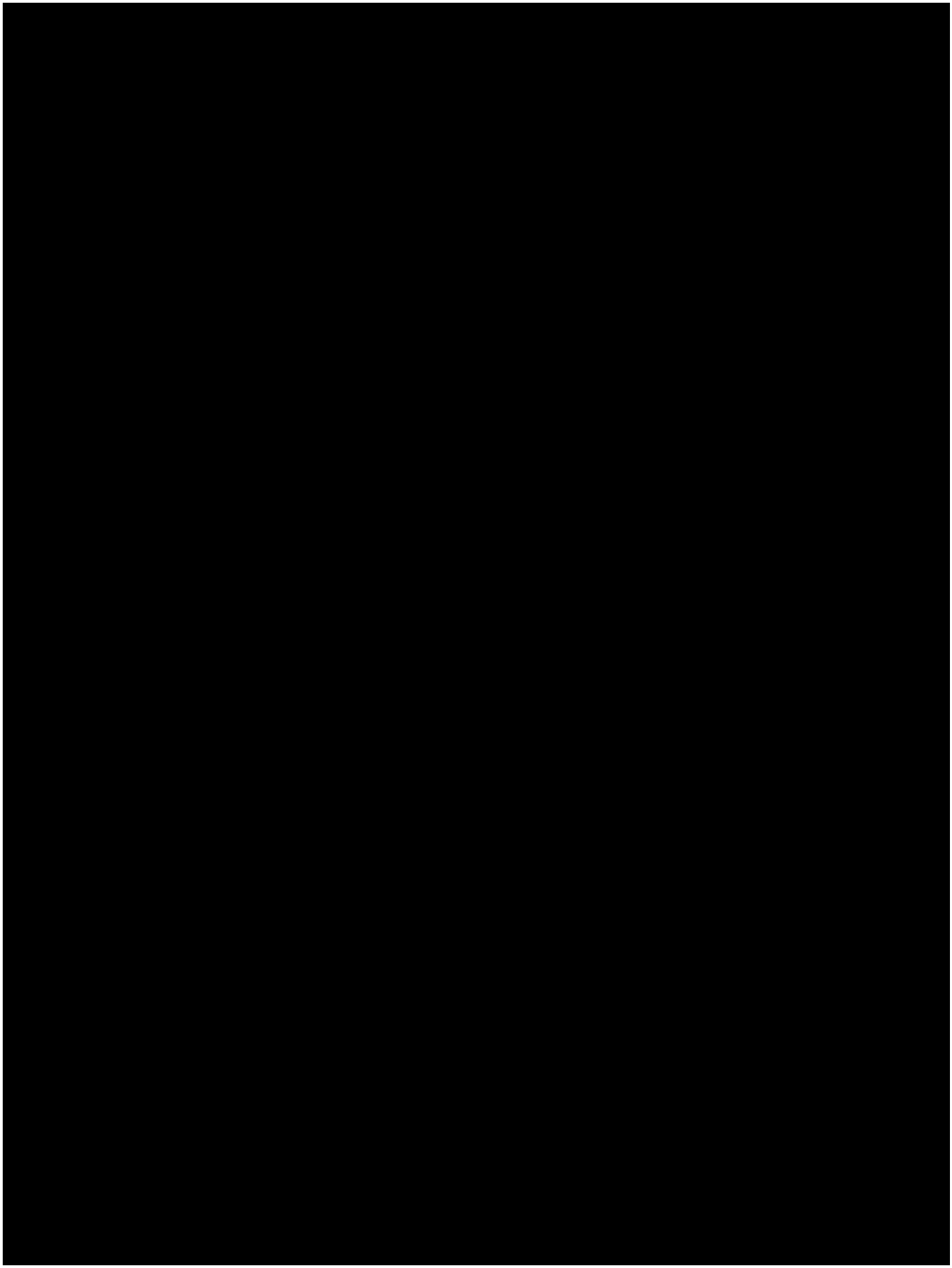

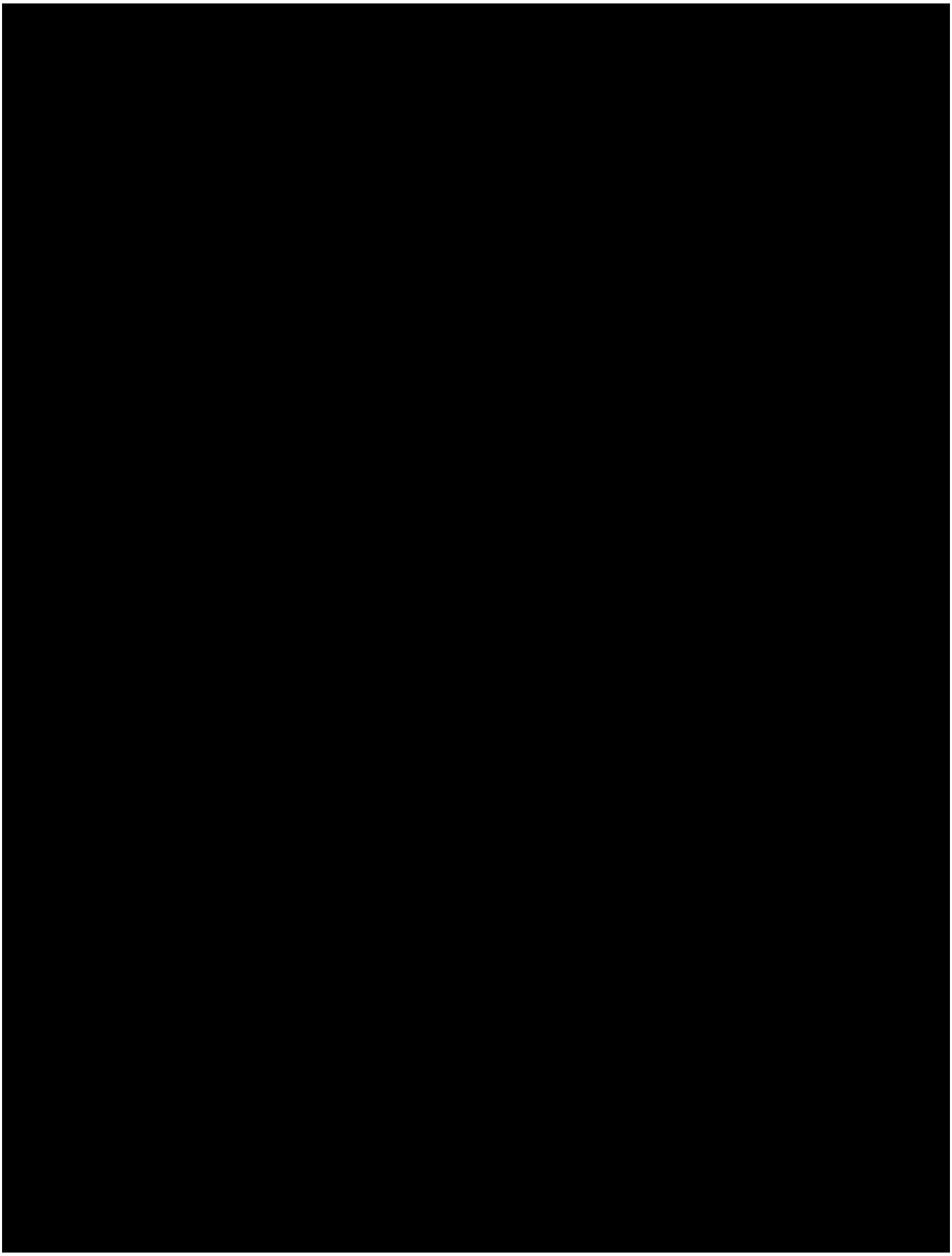

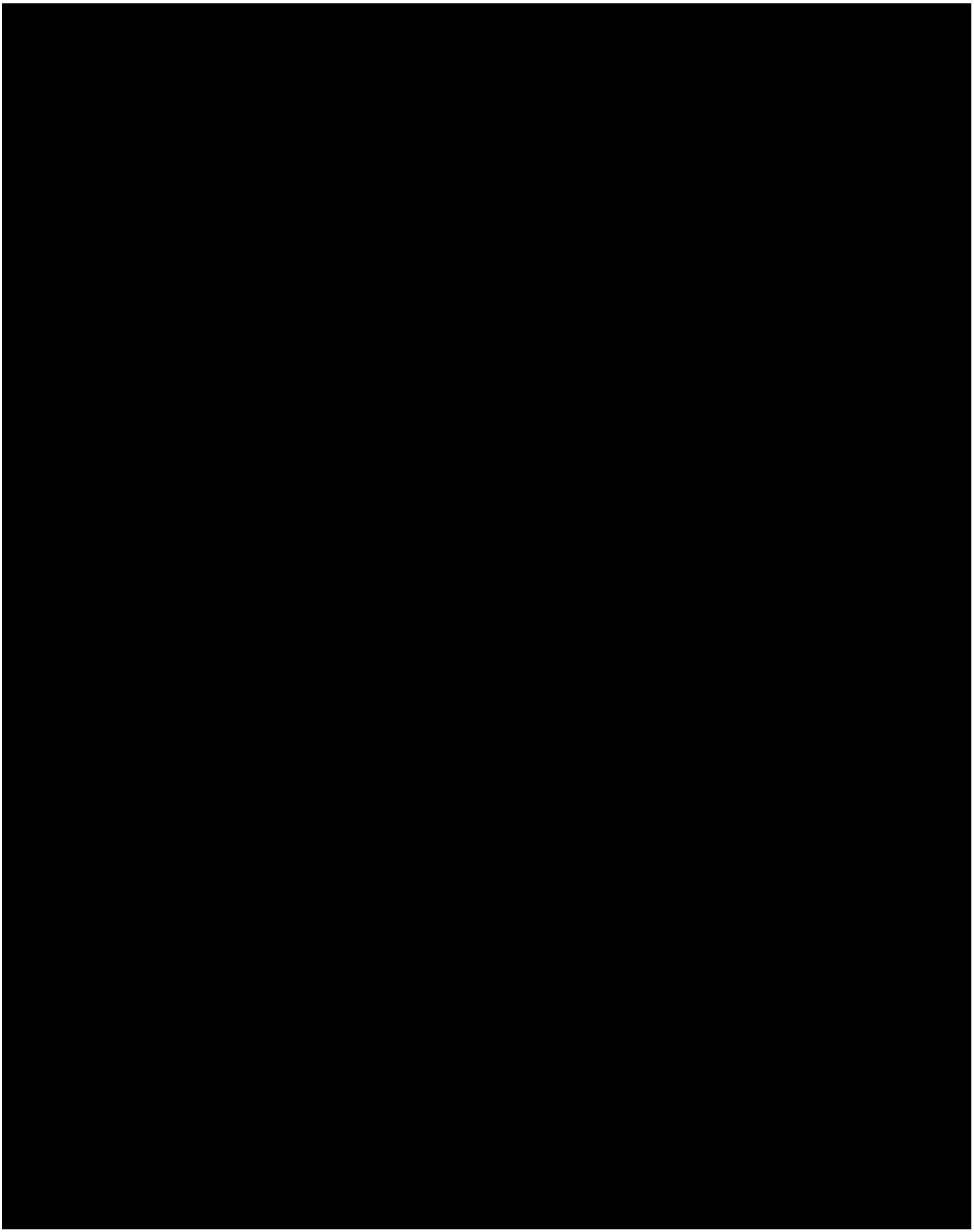

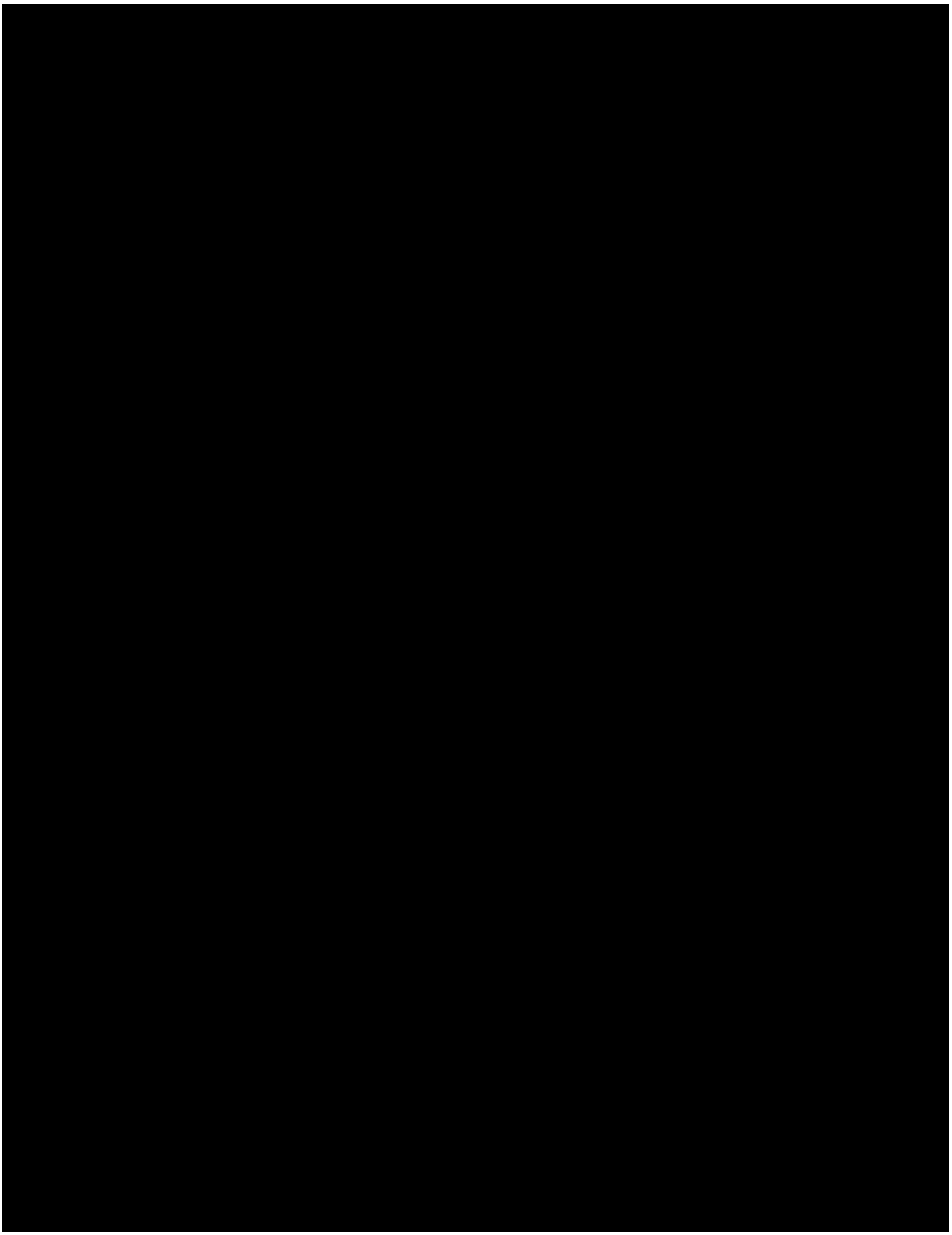

[redacted]

3.5 CARM data

Up to 31 December 2016, there are a total of 172 case reports to CARM where Boostrix was reported to be administered during pregnancy. Numbers of cases per trimester are:

- 1st trimester (first 12 weeks): 1
- 2nd trimester (weeks 12 to 26): 2
- 3rd trimester (≥27 weeks): 144
- Unknown: 25

A large number of these cases were related to the PIPS study (Petousis-Harris et al 2016 – section 3.2.1). The three cases reported where Tdap was administered during the 1st or 2nd trimesters of pregnancy were considered medication error reports as Tdap was administered outside the recommended window of gestational weeks 28 to 38. A listing of all 172 cases is shown in Annex 6.

4 DISCUSSION AND CONCLUSIONS

The recommended timing of Tdap vaccination during pregnancy is important in order to confer the best protection against pertussis for infants in their first year of life, particularly during the first 4 months. Many countries recognise the importance of maternal pertussis vaccination programmes and have implemented a programme accordingly. However, the recommended time period of when Tdap should be administered during pregnancy is not consistent, with the start of the time period ranging from 16 weeks in the UK and NZ to 27 weeks in the US.

The recommendation to vaccinate pregnant women earlier generally reference studies by Eberhardt et al. In these studies of both term and preterm neonates, the authors found that Tdap administration during the 2nd trimester (from 13 weeks) of pregnancy results in higher neonatal antibodies compared to administration during the 3rd trimester. This was measured by collecting samples of umbilical cord blood immediately after birth to measure anti-PT and anti-FHA antibodies, and calculating geometric mean concentrations and expected infant seropositivity.

It takes about 14 days to develop antibodies in response to Tdap, so Eberhardt et al's finding in preterm neonates is notable because the administration of Tdap earlier in pregnancy increases the amount of time to develop antibodies before birth. A longer time period where Tdap vaccine can be administered during pregnancy may also increase uptake of the vaccine. Both Australia and the UK mention that the fetal anomaly scan around 20 weeks of pregnancy should be a prompt for receiving Tdap.

It should be noted that serologic correlates of protection against pertussis in infants are unknown, but it is thought that high concentrations of maternal antibodies to pertussis toxin are important in preventing severe pertussis.

There have been numerous studies evaluating the safety of Tdap during pregnancy. Some of these have been conducted in NZ, but during the time when Tdap was administered between gestational weeks 28 and 38. The UK recommendation to vaccinate from 16 gestational weeks has been in place since 2016 and a safety concern hasn't been raised.

At first glance, it appears the change in funding of Boostrix during pregnancy to include women in the 2nd trimester (from 16 weeks) of pregnancy is contradictory to information in the NZ data sheet which includes the following:

> *The use of BOOSTRIX may be considered during the third trimester of pregnancy.*
>
> *Safety data from a prospective observational study where BOOSTRIX was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from post-marketing surveillance where pregnant women were exposed to BOOSTRIX or to BOOSTRIX-IPV (dTpa-inactivated poliovirus vaccine) indicate no vaccine related adverse effect on pregnancy or on the health of the foetus/newborn child.*
>
> *Human data from prospective clinical studies on the use of BOOSTRIX during the first and second trimester of pregnancy are not available.*
>
> *BOOSTRIX may be used during pregnancy when the possible advantages outweigh the possible risks for the foetus.*

However, on closer examination, the data sheet doesn't preclude the use of Boostrix during the 2nd trimester of pregnancy. This information is very similar to the Australian data sheet. The UK data sheet includes additional information as shown in red text below:

> *Safety data from a prospective observational study where Boostrix (dTpa component of Boostrix-IPV) was administered to pregnant women during the third trimester (793 pregnancy outcomes) as well as data from passive surveillance where pregnant women were exposed to Boostrix-IPV or to Boostrix in the 3rd and 2nd trimester have shown no vaccine related adverse effect on pregnancy or on the health of the fetus/newborn child.*

Human data from prospective clinical studies on the use of Boostrix-IPV during the first and second trimester of pregnancy are not available. However, as with other inactivated vaccines, it is not expected that vaccination with Boostrix-IPV harms the fetus at any trimester of pregnancy. The benefits versus the risks of administering Boostrix-IPV during pregnancy should be carefully evaluated.

There are many factors at play in determining the optimal timing of Tdap during pregnancy, including:

- Achieving the best level of protection for infants during the 1st year of life, especially during the first 4 months. This includes protection for preterm neonates.
- Accounting for the 14 days needed to develop antibodies in response to Tdap.
- The safety of administering Tdap during pregnancy and whether this differs based on timing of vaccine administration.
- Practical aspects, such as aligning with times when pregnant women have contact with the healthcare system as part of antenatal care.

5 ADVICE SOUGHT

The Committee is asked to advise on the following:

- Is the benefit-risk profile for the use of Tdap (Boostrix) during the 2nd trimester (from week 16) of pregnancy favourable?
- Does the data sheet require updating?
- Is further communication required other than MARC's Remarks in *Prescriber Update*?

6 ANNEXES

1. Eberhardt et al 2016a
2. Eberhardt et al 2017
3. Amirthalingam et al 2016
4. Healy et al 2018
5. Vygen-Bonnet et al 2020
6. CARM data

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