Focus on the Agents of Whooping Cough

# Vaccination During Pregnancy to Prevent Early Infant Pertussis

Dr Helen Campbell, Lead Scientist
UK Health Security Agency, Immunisation and vaccine preventable diseases division
5th November 2024

# Intended Learning Objectives

Specific objectives of this session:

1. Learn about the rationale for maternal vaccination
2. Learn about the drivers for the introduction of maternal pertussis vaccination
3. A case study based on the UK experience
4. Understand what we know about safety and effectiveness of maternal pertussis vaccination
5. Understand the continued importance of maternal pertussis vaccine programmes

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# Do you have a maternal pertussis vaccination programme in your country?

ⓘ Start presenting to display the poll results on this slide.

# Rationale for maternal vaccination

- Pregnant women
  - Increased risk of severe disease from some pathogens due to pregnancy-induced immunological changes to avoid rejection of the fetus
  - Due to a combination of decreased lung capacity and tidal volume alongside increased oxygen consumption, respiratory infections like influenza, increase the risk of maternal mortality. Especially in late pregnancy
- Neonates
  - Immune system is not fully developed so increased risk of infection
  - Risk is reduced with trans-placental IgG antibody transfer to the fetus later in pregnancy
  - Risk is reduced through maternal IgA antibodies in the breast milk

# Rationale for maternal vaccination cont.

The benefits are derived from:

- Prevention of maternal morbidity and mortality
  - Benefit to mother
  - Benefit to the fetus
- Reduction of in utero infection or fetal disease
- Passive immunity in the neonate/ young infant
- Indirect protection in the neonate/ young infant through prevention of maternal disease

# Rationale for maternal vaccination cont.

- Neonatal tetanus (WHA target for elimination since 1988)
  - Contamination of the umbilical cord stump when hygiene is poor
  - In the absence of medical treatment case-fatality ~100%
  - vaccination of pregnant women or women of childbearing age, reduces neonatal mortality by 94%
- Influenza
  - USA first prioritised pregnant women in 1960. In 2004 flu vaccine was recommended for all pregnant women
  - 2009 H1N1 influenza pandemic – In the USA pregnant women accounted for:
    - 6.3% influenza-associated influenza admissions
    - 5.9% ICU admissions (29% in women aged 18-29 years)
    - 5.7% deaths (16% in women aged 18-29 years)
  - UK - increase in the stillbirth rate (27 per 1,000 with influenza vs 6 per 1,000 total births)
- COVID-19
- RSV

# Pertussis disease

Infants and young children are usually most severely affected by pertussis and most infants will require hospital treatment

Young infants are more likely to develop severe complications such as:

- pneumonia
- temporary pauses in breathing as a result of severe difficulty with breathing
- weight loss due to excessive vomiting
- seizures or brain damage
- encephalitis (an acute inflammation of the brain)
- Death in around 1% of confirmed infant cases

# Control of pertussis disease

- Wholecell pertussis vaccines were used from the 1950s
- Resultant fall in pertussis cases and deaths

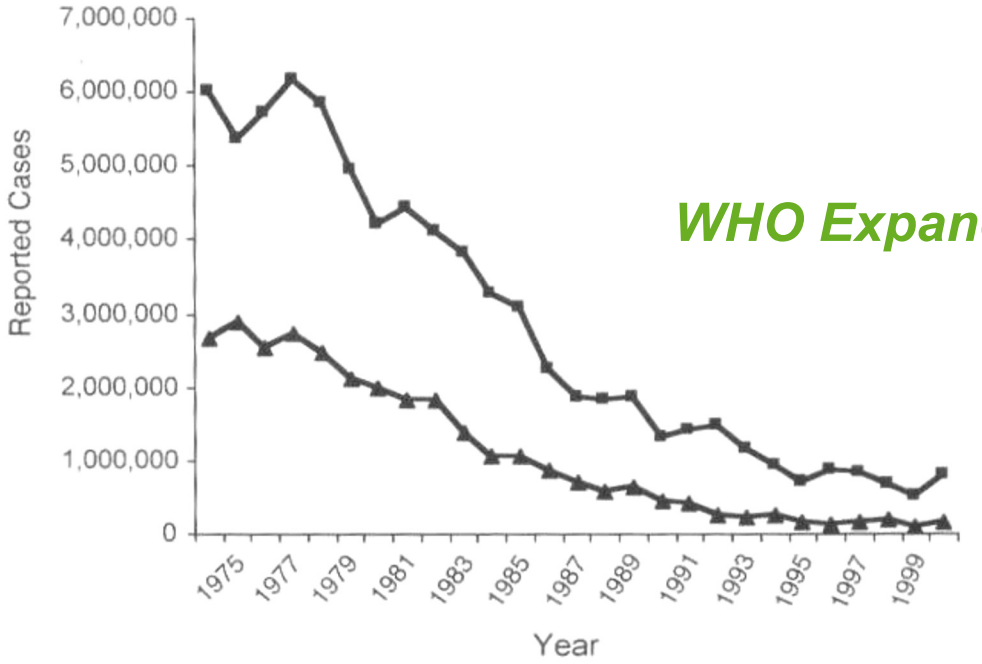



FIGURE 1 Measles (■) and pertussis (▲) cases reported to WHO, 1974–2000.

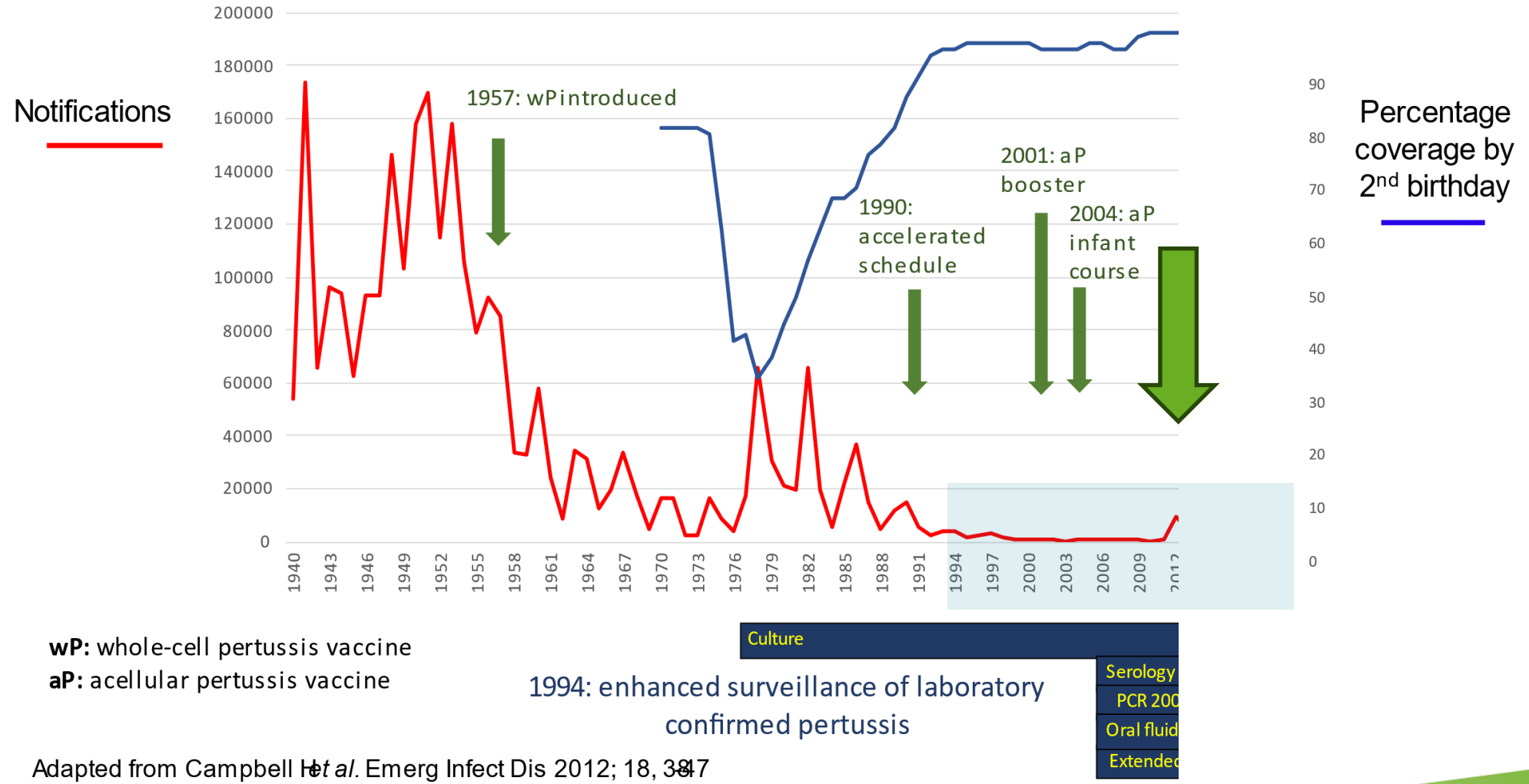
***WHO Expanded Programme on Immunization (EPI)***

# Control of pertussis disease cont.

- Relative efficacy trials of highly purified acellular pertussis and whole cell vaccines were undertaken in the 1990s
- The acellular pertussis vaccines were less reactogenic and (whilst different vaccines varied) were shown to be highly effective against mild and severe disease
- Acellular vaccines were used in national primary immunisation programmes from 1997 in the USA – other countries followed
- Despite high coverage, increases in pertussis disease were observed in a number of countries in the 2010s. With a pertussis outbreak in California in 2010-11, Australia and a number of European countries, including England in 2011-12

# Historical perspective of pertussis epidemiology

Figure 1: Historical pertussis notifications in England and Wales with laboratory confirmed cases from England only 2008 to 2023 (after confirmed exceeded notified cases) and vaccine coverage in England



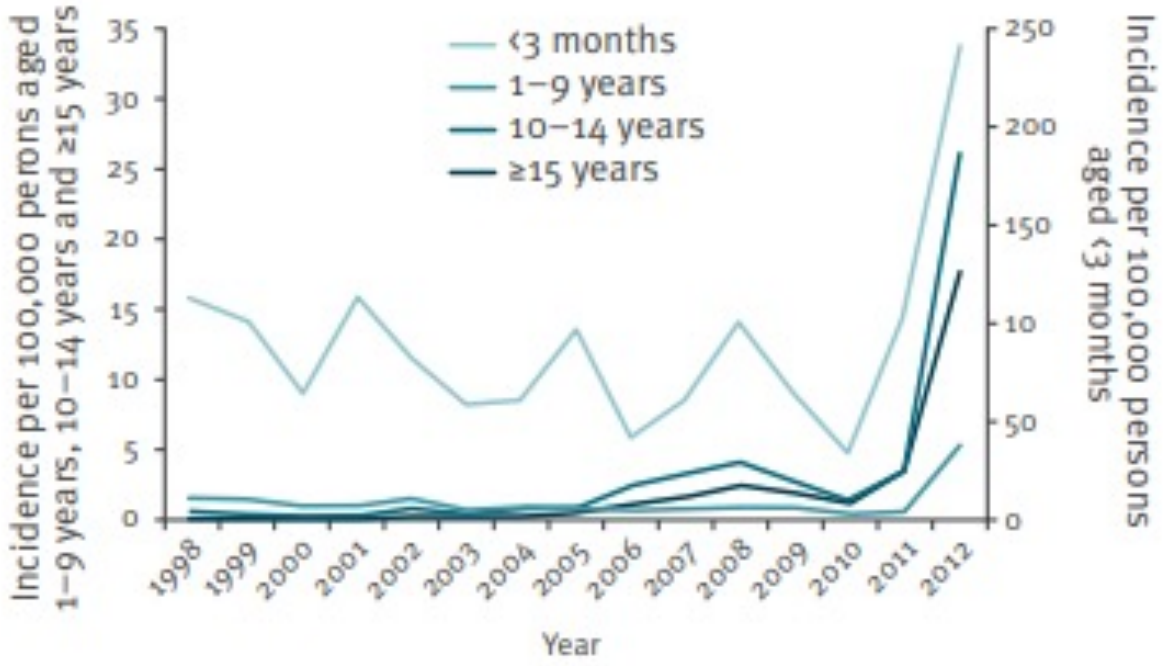

**wP:** whole-cell pertussis vaccine
**aP:** acellular pertussis vaccine

1994: enhanced surveillance of laboratory confirmed pertussis

Adapted from Campbell H *et al.* Emerg Infect Dis 2012; 18, 3-7

# The re-emergence of pertussis in the 2010s

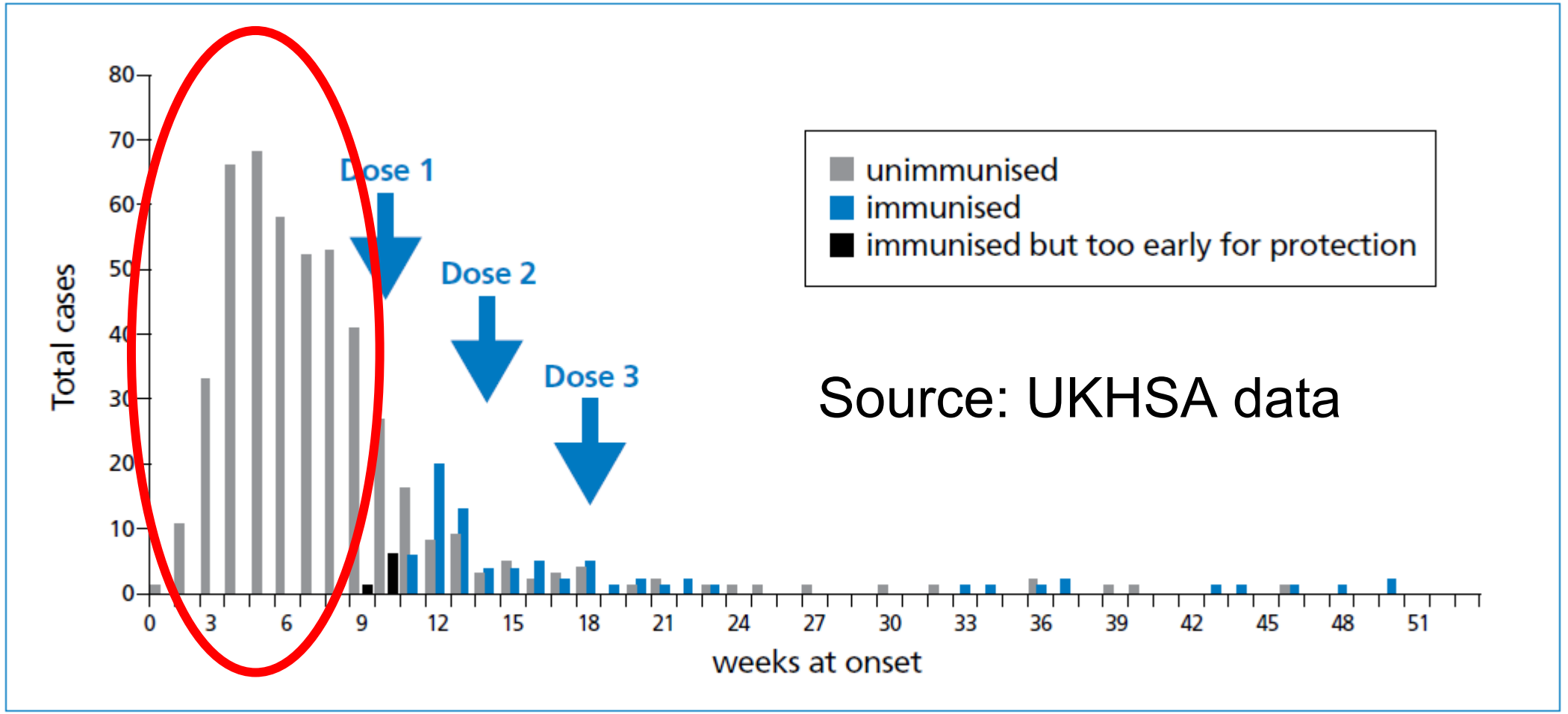
Incidence of laboratory-confirmed pertussis by age group, England and Wales, 1998–2012




Source: Health Protection Agency.

Amirthalingam G, Gupta S, Campbell H. Pertussis immunisation and control in England and Wales, 1957 to 2012: a historical review. Euro Surveill. 2013 Sep 19;18(38):20587. doi: 10.2807/1560-7917.es2013.18.38.20587. PMID: 24084340.

# The re-emergence of pertussis in the 2010s
# The situation in England

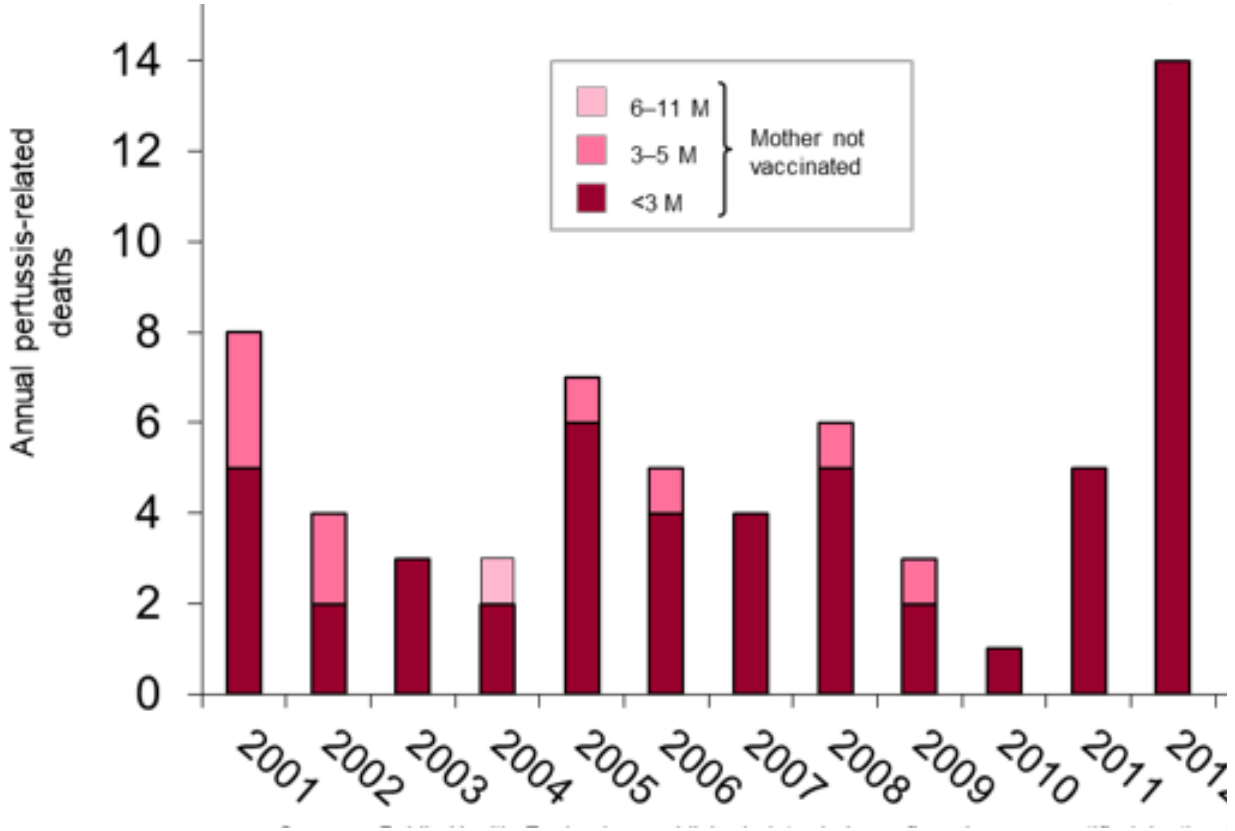



Confirmed cases in infants aged under one year, by week of age at onset (2011- August 2012).
Protection is assumed to accrue within the two weeks following immunisation.

# The re-emergence of pertussis in the 2010s

## The situation in England: deaths in infants with pertussis

Source: UKHSA data




Sources: Public Health England, unpublished data. Lab confirmed cases, certified deaths, Hospital episode statistics, GP registration details, HPZone

- Cocooning strategies were introduced in e.g. France, USA and Australia but these proved difficult to implement

# The evidence at the time that maternal vaccination was being considered – safety of Tdap in pregnancy

- Pregnant women were not included in prelicensure studies
- Data from Tdap manufacturers' (Sanofi Pasteur & GSK) pregnancy registers
- VAERS in the USA (reviewed by the Advisory Committee on Immunization Practices ACIP) and a couple of small published studies
- Td and T vaccines had been extensively used in pregnant women globally

# The evidence at the time that maternal vaccination was being considered – efficacy of Tdap in pregnancy

- Numerous studies evidencing efficient transplacental transfer of antibodies in cord blood and in infants born to vaccinated women
- The effectiveness of this antibody transfer in protecting against infant disease was not known as there is no correlate of protection for pertussis
- Considered likely that pertussis-specific antibodies would confer protection against severe disease in infants
- Vaccinated mother would also be less likely to infect her baby with pertussis

# The evidence at the time that maternal vaccination was being considered – the blunting effect

- Several studies suggested maternal pertussis antibodies could interfere with the infant response to primary pertussis vaccination
- It was not clear whether this "blunting" was of clinical importance
- Blunting was likely to be short-lived as maternal antibodies decline over weeks in infants
- It was expected that maternal antibodies would protect in the first weeks of life when babies were most at risk
- Even if there was slightly lower effectiveness when babies received their own vaccines, they would be older and at less risk

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# Would you introduce maternal vaccination in this scenario?

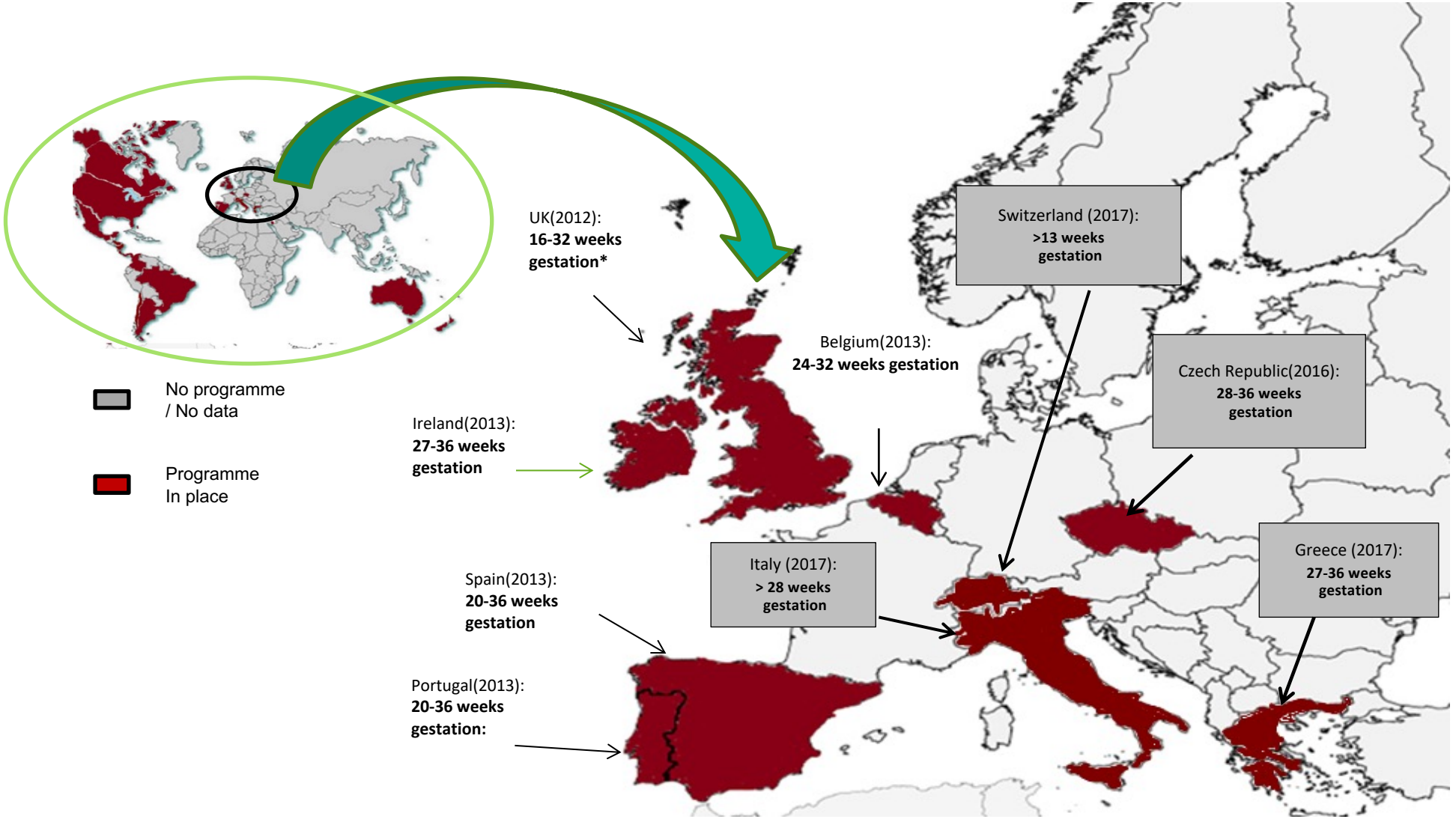
ⓘ Start presenting to display the poll results on this slide.

# Maternal pertussis vaccination

- In 2011 the USA was the first country to advise that pertussis-containing vaccine could be safely given to pregnant women (in those not previously vaccinated with Tdap)
- Offered after 20 weeks' gestation
  - From 2004 mean of ~3,000 infant cases and >19 death annually
  - Majority of pertussis cases, hospitalisations and deaths in infants aged <3 month

- In 2011 Argentina was the first country to recommend pertussis-containing vaccine for all pregnant women
- Offered from 20 weeks' gestation
  - In 2011 10,395 suspected cases and 76 deaths
  - 90% were infants <1 year and 60% infants aged <2 months

# Maternal Pertussis immunisation programmes globally



# International position

## 2015 WHO Position paper[1]

*' Vaccination of pregnant women is likely to be the most cost effective additional strategy for preventing disease in infants too young to be vaccinated …'*

Pertussis vaccines: WHO Position paper Aug 2015 (Pertussis vaccines: WHO position paper – August 2015)

# Recommendations for pertussis vaccination during pregnancy, 2019, 2023 and 2024

## 2019


7 countries

## 2023


17 countries

## 2024

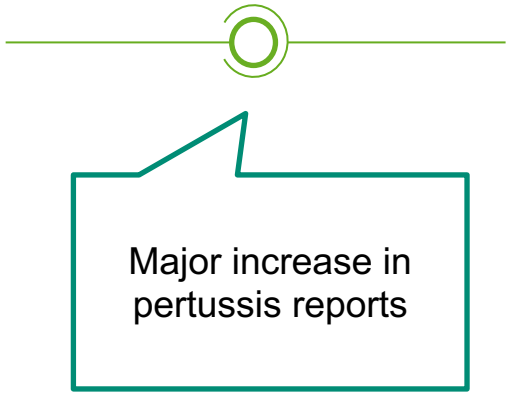

25 countries

# Maternal pertussis vaccination in England: a case study

# UK Maternal Programme was introduced as an outbreak response measure

- Primary infant immunisation: 8, 12, 16 weeks of age aP-containing vaccine since 2004.
- Booster with aP-containing vaccine at 3 years 4 months since 2001

**2011/12[1]**




Increase in deaths and hospitalisation, mainly in young infants before age of routine vaccination

Amirthalingam G *et al Clin Infect Dis* 2016;63:S236–243

*Clinical Infectious Diseases*

MAJOR ARTICLE

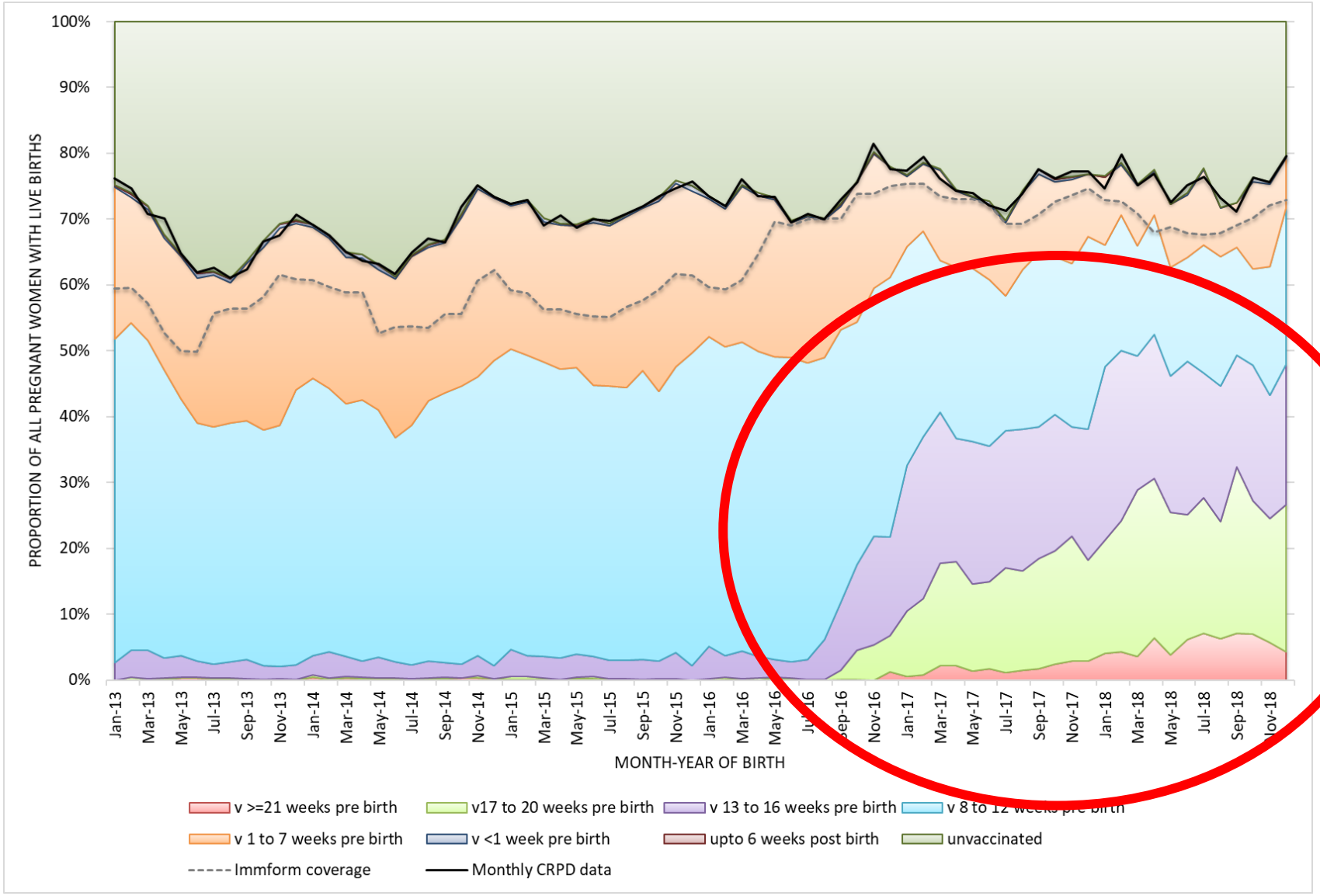
# Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis

**Christiane S. Eberhardt,[1,2] Geraldine Blanchard-Rohner,[3] Barbara Lemaître,[1] Meriem Boukrid,[4] Christophe Combescure,[5] Véronique Othenin-Girard,[4] Antonina Chilin,[4] Jean Petre,[6] Begoña Martinez de Tejada,[4] and Claire-Anne Siegrist[1,3]**

[1]Center for Vaccinology and Neonatal Immunology, Department of Pediatrics and Pathology-Immunology, Departments of [2]Neonatology and Pediatric Intensive Care, and [3]Pediatrics, Children's Hospital of Geneva, [4]Department of Gynecology and Obstetrics, and [5]Clinical Research Center, University Hospitals of Geneva and Faculty of Medicine, University of Geneva, Switzerland; and [6]BioNet-Asia Co, Ltd, Bangkok, Thailand

Early second-trimester maternal Tdap immunization significantly increased neonatal antibodies.

# Coverage of maternal pertussis immunisation programme in England, 2013-2018, based on CPRD, ImmForm data sources.




Gayatri Amirthalingam, Helen Campbell, Sonia Ribeiro et al *Clinical Infectious Diseases*, Volume 76, Issue 3, 1 February 2023, Pages e1129–e1139, https://doi.org/10.1093/cid/ciac651

# Effectiveness of maternal vaccination given at different times pre-birth

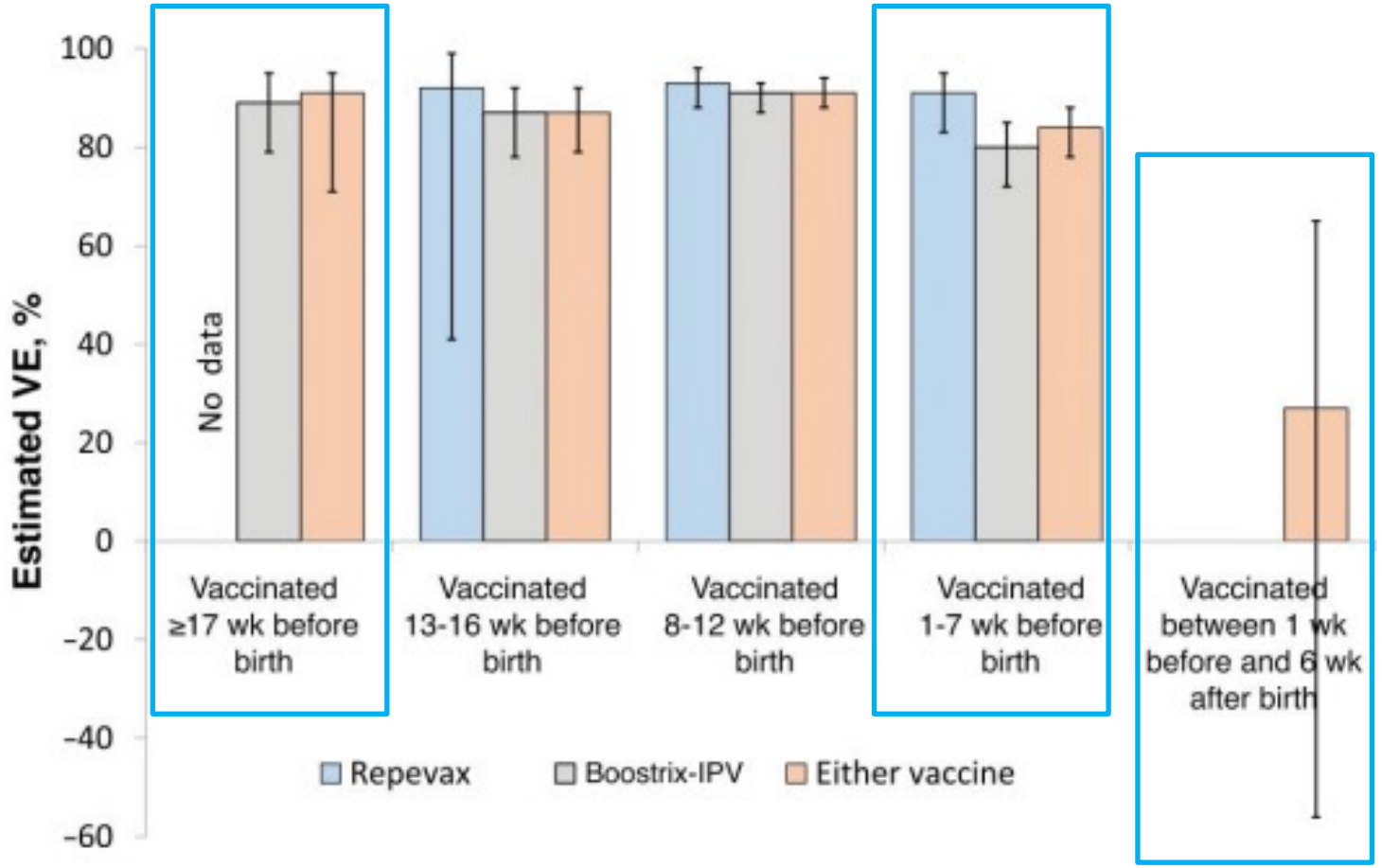



**Figure 4.** Estimates of the effectiveness of maternal vaccination in the prevention of laboratory-confirmed pertussis in infants aged <93 days by vaccine product and timing of maternal vaccination. Abbreviation: VE, vaccine effectiveness.

# Impact of moving to a recommendation of earlier vaccination from April 2016 on pertussis hospitalisations

**Byrne et al 2017, Tessier et al CID 2(**

Before the policy change, 25% of pertussis cases were in preterm infants—only 7.8% of infants nationally were preterm ($P < .001$). After the policy change, the proportion of preterm infants fell to 12.7% and was no longer significantly higher than birth statistics ($P = .12$).

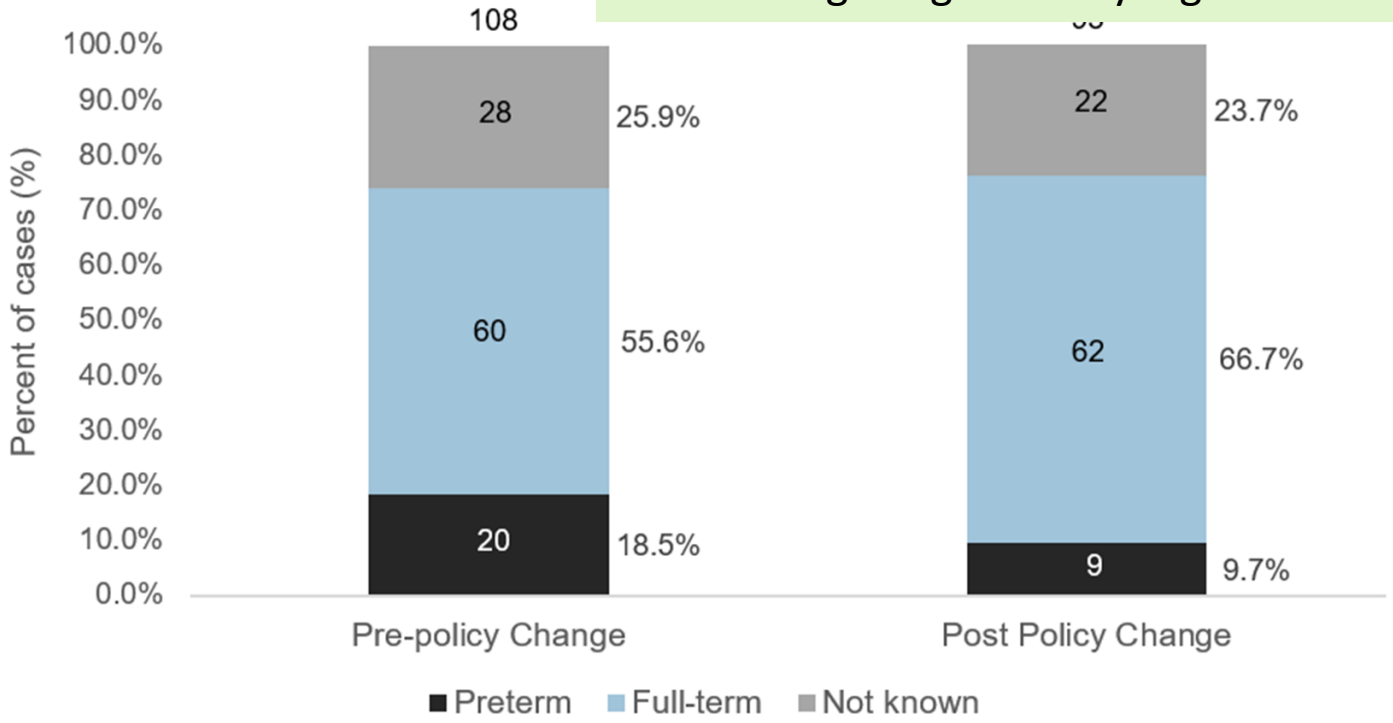
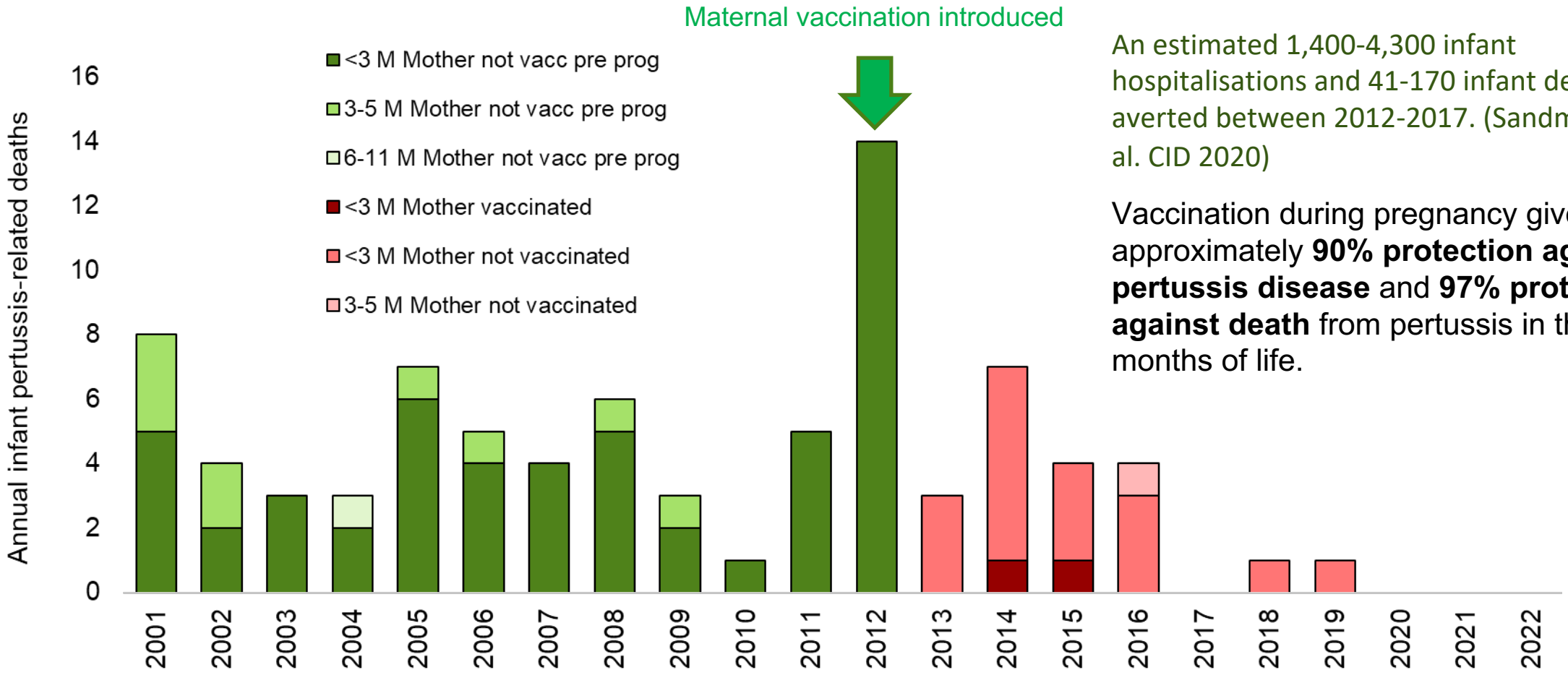



**Figure 1.** Distribution of infants ≤ 60 days old by gestational age between 1 September 2014 – 31 March 2016 (pre-policy change) and 1 September 2016 – 31 March 2018 (post-policy change) in England.

# Reconciled deaths from pertussis in infants, 2001-2022, England only (UKHSA data)

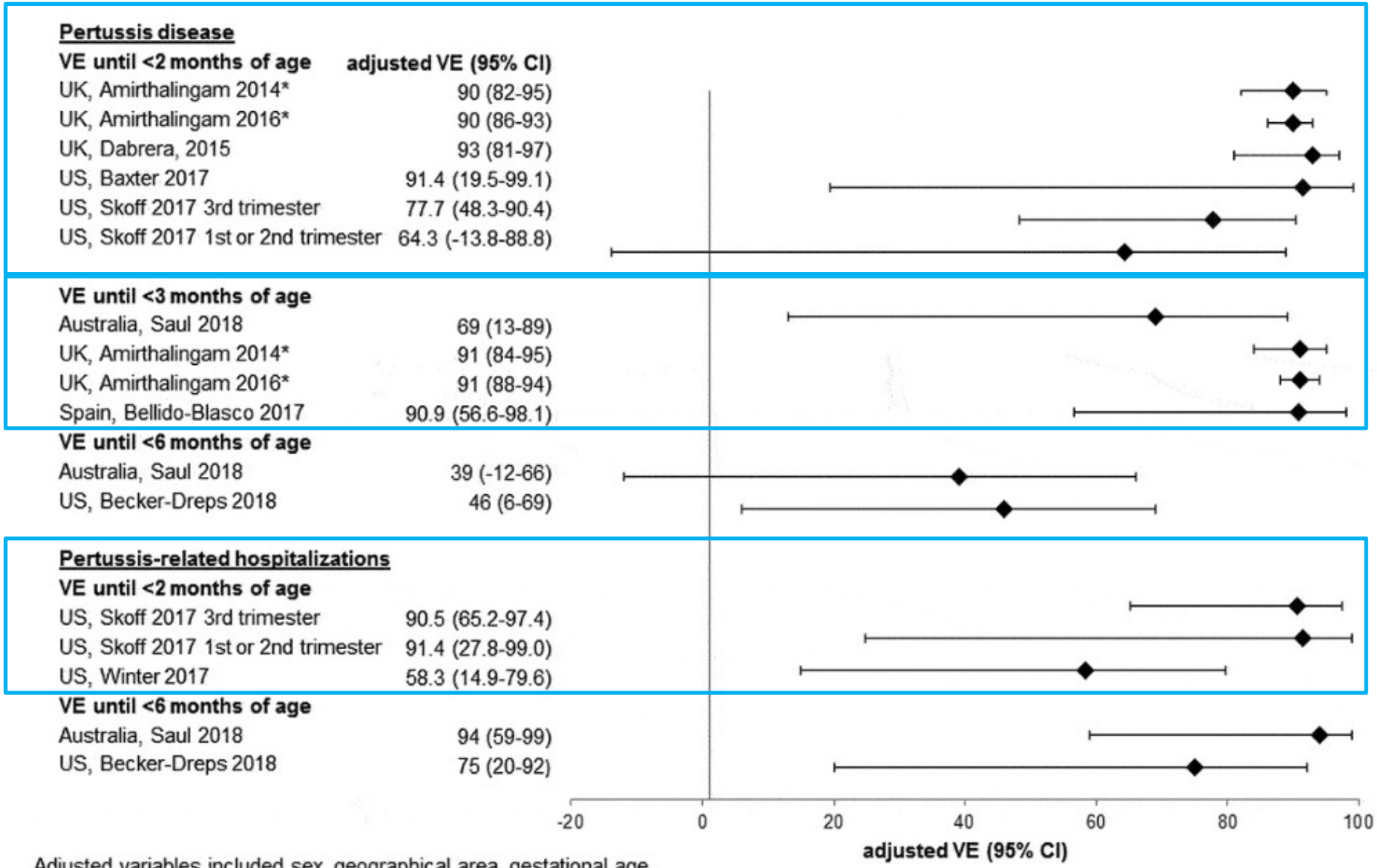



An estimated 1,400-4,300 infant hospitalisations and 41-170 infant deaths averted between 2012-2017. (Sandmann et al. CID 2020)

Vaccination during pregnancy gives approximately **90% protection against pertussis disease** and **97% protection against death** from pertussis in the first 2 months of life.

Sources: laboratory confirmed cases, certified deaths, Hospital episode statistics, GPs, HPZone

# Effectiveness of maternal vaccination against disease and hospitalisation in their infants




Adjusted variables included sex, geographical area, gestational age, birth period, number of DTaP doses, delivery hospital, race,breastfeeding, household size

**Figure 5: Effectiveness of maternal Tdap vaccination against pertussis disease and hospitalizations in infants up to 6 months of age**


Kandeil, W., van den Ende, C., Bunge, E. M., Jenkins, V. A., Ceregido, M. A., & Guignard, A. (2020). A systematic review of the burden of pertussis disease in infants and the effectiveness of maternal immunization against pertussis. *Expert Review of Vaccines*, *19*(7), 621–638. https://doi.org/10.1080/14760584.2020.1791092

# Blunting

**Table 5: Vaccine effectiveness of a maternal dose of pertussis vaccine given at least 7 days before birth for children who received each of the primary doses**

| Cases included | Exact number of primary doses at onset/sample date | Cases' mothers vaccinated / total | Average matched coverage | VE (95% CI) |
|---|---|---|---|---|
| PCR /culture | 1 | 27/102 (26.5%) | 69.6% | 85% (77% to 91%) |
| PCR / culture | 2 | 19/39 (48.7%) | 71.4% | 62% (29% to 80%) |
| PCR /culture and serology (post 80 weeks) | 3 | 154/234 (65.8%) | 69.9% | 17% (-9% to 37%) |
| PCR/culture With an onset date | 3 | 111/169 (65.7%) | 69.5% | 16% (-15% to 39%) |

Gayatri Amirthalingam, Helen Campbell, Sonia Ribeiro et al *Clinical Infectious Diseases*, Volume 76, Issue 3, 1 February 2023, Pages e1129–e1139, https://doi.org/10.1093/cid/ciac651

# Extensive data show that Tdap and Tdap/IPV have reassuring safety profiles in maternal immunisation

› Pediatrics. 2021 May;147(5):e2020042507. doi: 10.1542/peds.2020-042507. Epub 2021 Apr 19.

## Health Outcomes in Young Children Following Pertussis Vaccination During Pregnancy

Meghan Laverty [1], Natasha Crowcroft [2 3], Shelly Bolotin [3 4], Steven Hawken [1 2 5 6], Kumanan Wilson [1 2 5], Gayatri Amirthalingam [7], Anne Biringer [3 8], Jocelynn Cook [9], Vinita Dubey [3 10], Romina Fakhraei [5 6], Scott A Halperin [11], Frances Jamieson [3 8], Jeffrey C Kwong [2 3 4 12], Manish Sadarangani [13 14], Ewa Sucha [2], Mark C Walker [1 5 15], Deshayne B Fell [16 2 6]

**Results:** Of 625 643 live births, 12 045 (1.9%) were exposed to Tdap in utero. There were no significant increased risks of adverse childhood outcomes and prenatal Tdap exposure; however, we observed inverse associations (adjusted incidence rate ratio [95% confidence interval]) with upper respiratory infections (0.94 [0.90-0.99]), gastrointestinal infections (0.85 [0.79-0.91]), and urgent and inpatient health service use (0.93 [0.91-0.96]).

https://www.bmj.com/content/349/bmj.g4219

rth America) investigated:

A range of maternal, foetal and infant outcomes

comes in vaccinated

n others has been a small cally relevant sequelae

Vaccine
Volume 42, Issue 21, 30 August 2024, 126152

Review

# Timing of pertussis vaccination during pregnancy: Evidence and implementation – A systematic review

Louise De Weerdt [a], Sereina A. Herzog [b], Pierre Van Damme [a], Kirsten Maertens [a]

**Results**

"Overall, the selected publications did not indicate increased safety concerns associated with timing of pertussis vaccination in pregnancy. Immunogenicity studies often suggested optimal protection at birth after early third trimester vaccination...

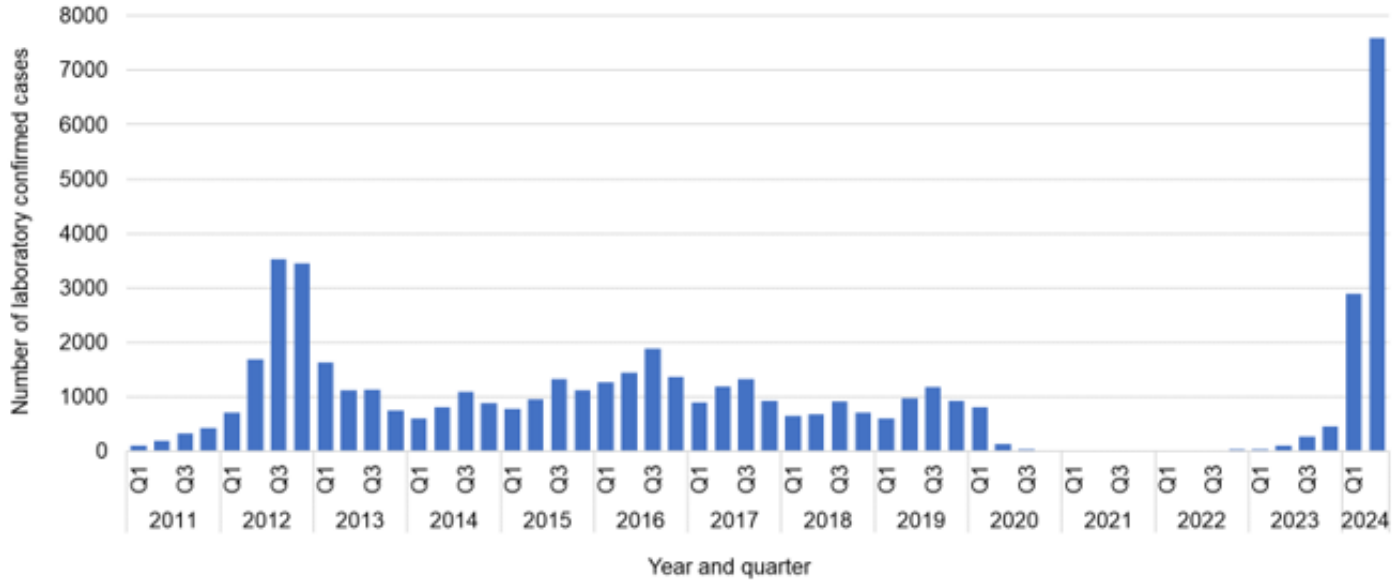
Effectiveness studies showed decreased vaccine effectiveness of late third trimester pertussis vaccination compared to vaccination earlier in pregnancy. Worldwide, a general recommendation for pertussis vaccination in pregnancy was found for 58 countries, with as many as 22 different recommended timings registered."

# Re-emergence of pertussis after the SARS-CoV-2 pandemic:

# The continued importance of maternal pertussis vaccination

# Re-emergence of pertussis after the SARS-CoV-2 pandemic

**Figure 3. Laboratory confirmed cases of pertussis by quarter in England: 2011 to June 2024 (note 1)**




Whooping cough kills another three babies

By Shaun Woolfer
Health Editor

PREGNANT women are being urged to get the whooping cough vaccine after three more babies

offer of the whooping cough vaccine so they can pass on protection to their babies, which should last until they are old enough to get vaccinated the

Dr Gayat gam, consu

Pregnant women urged to get whooping cough jab

EXPRESS

Cases of the whooping cough have risen sharply in France and the United Kingdom in recent months.

17:11, Wed, Jun 5, 2024 | UPDATED: 17:18, Wed, Jun 5, 2024

BBC NEWS

mirror.co.uk

Chilling rise of Victorian diseases in kids examined - and tragic whooping cough link

Exclusive:

The rise of Victorian-era diseases in the UK is 'extremely concerning' and fuelled by the cost of living crisis, one of the country's leading public health experts warns

Experts have issued a grave warning about the resurgence of Victorian diseases

THE Sun

Health,News Health,Childhood diseases and illnesses,Children parenting and family life,Health warnings,Medicines vitamins and vaccines,NHS,Parenting advice

CRITICAL Map reveals '100-day cough' hotspots amid fears of

# Pertussis cases rise in Denmark

**Denmark has experienced a substantial increase in cases of whooping cough, also known as pertussis, in the past few months. Sanjeet Bagcchi reports.**

In a report updated on Sept 26, 2023, Denmark's Statens Serum Institut (SSI) revealed that pertussis cases have increased in Denmark, from usually fewer than 80–100 detected cases per month to 104 in May, 293 in June, and approximately 228 in July. Case numbers were increased in the population due to lower natural boosting resulting in an increasing proportion of susceptible individuals."

Caused by *Bordetella pertussis*, pertussis is a respiratory infection that is prevented through vaccination. Since the launch of the pertussis vaccine in 1950–60, incidence and source of transmission to unprotected newborns, particularly in cases where routine vaccination during pregnancy was not conducted."

WHO states that pertussis is endemic in all countries. Laurence Luu (School of Life Sciences, University of Technology Sydney, NSW, Australia)

**This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on November 23, 2023**

For the **report from Statens Serum Institut** see https://essi.dk/news/epi-news/2023/27---2023

## Whooping cough hits Okotoks as Alberta outbreaks drag on

CBC

Wed, 13 March 2024 at 7:35 pm GMT · 3-min read

Alberta Health Services says 39 cases of pertussis, also known as whooping cough, have been confirmed in the Calgary zone since November, including 17 in the Okotoks area. (Winnipeg Health Region - image credit)

## Spike in whooping cough cases prompts warning from health officials and infectious disease expert

ABC Gold Coast / By Mark Rigby

Posted Thu 8 Feb 2024 at 3:48am

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## Pertussis deaths in New Zealand without community transmission—an infant immunity gap?

Peter B. McIntyre • Emma Best • Catherine A. Byrnes • Owen Sinclair • Adrian Trenholme • Cameron C. Grant

Open Access • Published: July 20, 2023 • DOI: https://doi.org/10.1016/j.lanwpc.2023.100850 • Check for updates

Attention was first drawn to development of a post-COVID "immunity debt" in children in

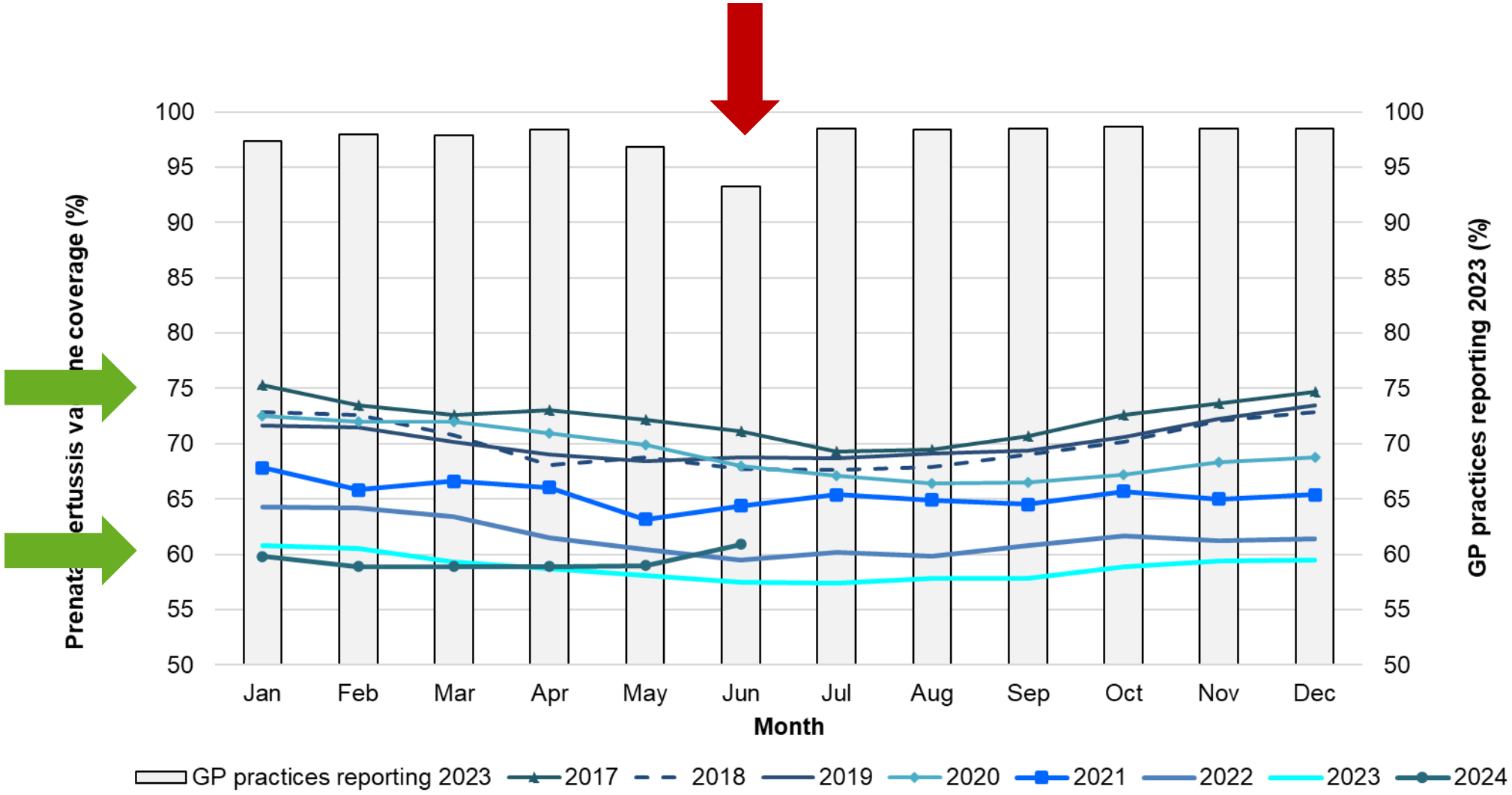
DutchNews 16 MARCH 2024

## Whooping cough killed four babies in last six weeks: RIVM

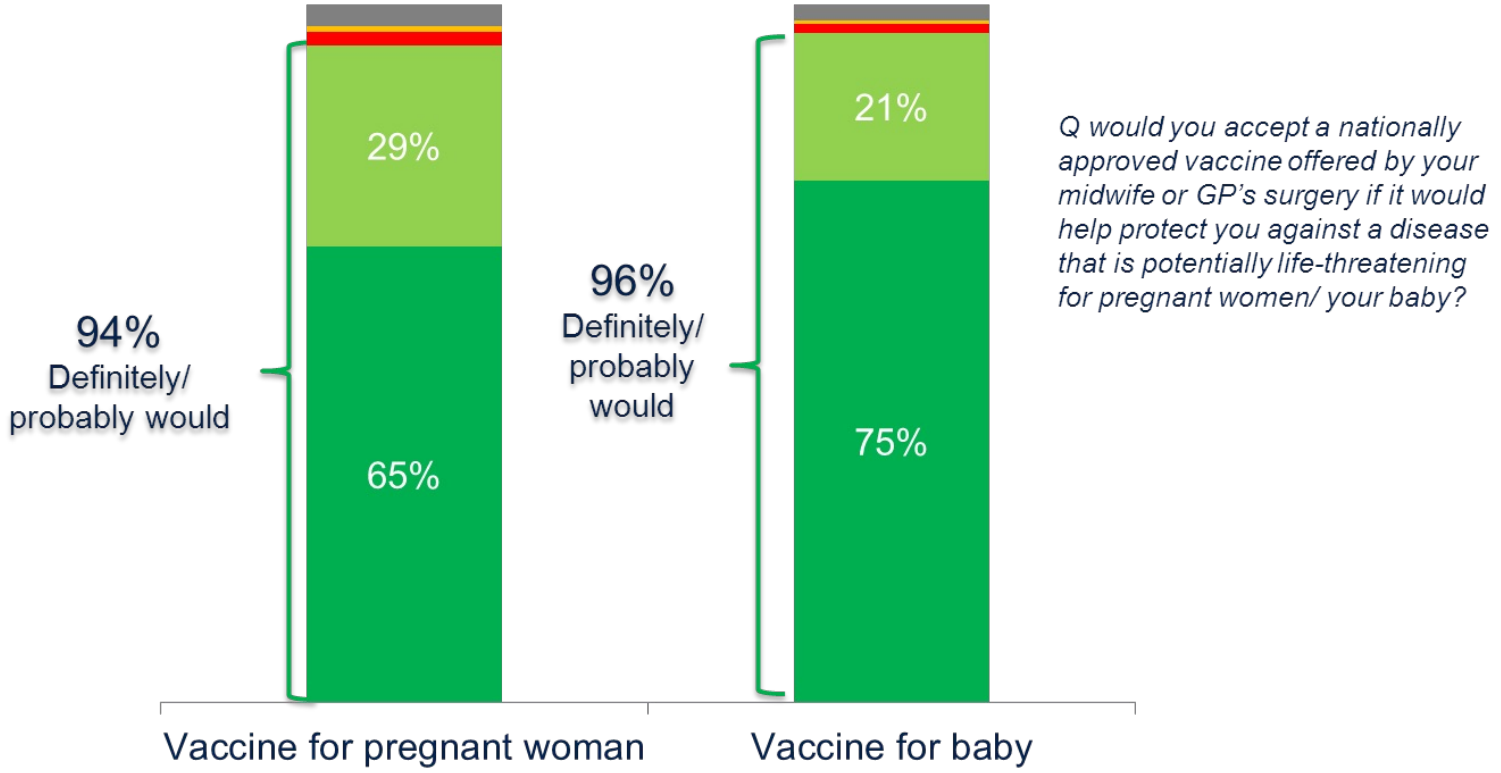
March 15, 2024

Four babies have died of whooping cough in the last six weeks as cases rise, national health institute RIVM has said.

# Monthly pertussis vaccination coverage (%) in pregnant women (England), 2017 to 2024



# Most mothers would accept vaccination in pregnancy




*Q would you accept a nationally approved vaccine offered by your midwife or GP's surgery if it would help protect you against a disease that is potentially life-threatening for pregnant women/ your baby?*

Base: All respondents (1,892)

Campbell et al (2014) British Journal of Midwifery

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**What do you think are the main reasons for relatively low pertussis vaccine coverage for pregnant women in many countries?**

ⓘ Start presenting to display the poll results on this slide.

PLoS One. 2024 Apr 19;19(4):e0298407. doi: 10.1371/journal.pone.0298407. eCollection 2024.

# Facilitators and barriers to vaccination uptake in pregnancy: A qualitative systematic review

Mohammad S Razai [1], Rania Mansour [1], Pahalavi Ravindran [2], Samuel Freeman [3], Charlotte Mason-Apps [1], Joan Morris [1], Azeem Majeed [4], Michael Ussher [1 5], Sally Hargreaves [1 6], Pippa Oakeshott [1]

Affiliations + expand

PMID: 38640190 PMCID: PMC11029626 DOI: 10.1371/journal.pone.0298407

Barriers include:

- concerns about vaccine safety and efficacy,
- lack of knowledge about vaccines' benefits and necessity,
- fear of adverse effects on the foetus or mother and
- low perception of disease severity.

Facilitators include:

- recommendations from trusted healthcare providers,
- easy access to vaccination,
- clear communication on the benefits and safety of vaccination, and
- positive social influences from family and friends.

Strategies for increasing vaccination uptake include:

- strong and proactive vaccine recommendations by trusted healthcare professionals,
- provision of vaccines during routine antenatal care, and
- clear and consistent communication about vaccines addressing pregnant women's concerns.

# Conclusions

- Despite success of childhood immunisation programmes, pertussis remains a global public health concern
- Immunising pregnant women has been shown to be a safe and highly effective strategy in protecting young infants in the first months of life, in high income settings
- Challenges remain in achieving high coverage in target group – high quality information from a trusted source, ease of access and training for health professionals are key
- there are some outstanding questions
- (1) optimal timing as demonstrated by clinical protection
- (2) longer term impact of approach – including blunting
- (3) vaccination in pregnancy after primary aP vaccination
- (4) optimal infant/ booster schedule

# Further reading


- Mackin DW, Walker SP. The historical aspects of vaccination in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2021 Oct;76:13-22. doi: 10.1016/j.bpobgyn.2020.09.005. Epub 2020 Oct 13. PMID: 33168428; PMCID: PMC7550856.
- Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep. 2011 Oct 21;60(41):1424-6. PMID: 22012116.
- Pertussis vaccines: WHO position paper – August 2015
- Klein, N. P. (2014). Licensed pertussis vaccines in the United States: History and current state. Human Vaccines & Immunotherapeutics, 10(9), 2684–2690. https://doi.org/10.4161/hv.29576
- Gayatri Amirthalingam, Helen Campbell, Sonia Ribeiro, Julia Stowe, Elise Tessier, David Litt, Norman K Fry, Nick Andrews, Optimization of Timing of Maternal Pertussis Immunization From 6 Years of Postimplementation Surveillance Data in England, Clinical Infectious Diseases, Volume 76, Issue 3, 1 February 2023, Pages e1129–e1139, https://doi.org/10.1093/cid/ciac651
- De Weerdt L, Herzog SA, Van Damme P, Maertens K. Timing of pertussis vaccination during pregnancy: Evidence and implementation - A systematic review. Vaccine. 2024 Aug 30;42(21):126152. doi: 10.1016/j.vaccine.2024.07.053. Epub 2024 Jul 31. PMID: 39088988.
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# Further reading


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- Increase of pertussis cases in the EU/EEA

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