WHO SAGE pertussis working group

Background paper

SAGE April 2014

14 March 2014

Composition of the Working Group:

- Elizabeth Miller (Working Group Chair until February 2014), Immunisation Department, Colindale, UK
- Claire-Anne Siegrist, (Working Group Chair since February 2014) Department of Pediatrics, University of Geneva, Switzerland
- Piyanit Tharmaphornpilas, National Immunization Program, Ministry of Public Health, Nonthaburi, Thailand
- Tom Clark, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, USA
- Kathryn Edwards, Vanderbilt Vaccine Research Program, Vanderbilt University School of Medicine, Nashville, USA
- Nicole Guiso, Institut Pasteur Research Unit, Institut Pasteur, Paris, France
- Scott A. Halperin, Canadian Center for Vaccinology, Dalhousie University, Halifax, Canada
- Teeranart Jivapaisarnpong, Institute of Biological Products, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.
- Daniel Levy-Bruhl, Infectious Diseases Department, Institut de Veille Sanitaire, Saint-Maurice, France
- Peter McIntyre, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Sydney, Australia
- Gabriela Moreno, Departments of Epidemiology and Immunizations, Ministry of Health, Santiago, Chile
- Carl Heinz Wirsing von König, National reference laboratory for *Bordetella* infections, Krefeld, Germany

WHO Secretariat:

- Philippe Duclos
- Ana-Maria Henao-Restrepo
- Melanie Schuster
- Cuauhtémoc Ruiz-Matus (replaced by Cristina Pedreira in February 2013)
- Mark Muscat

Contents

1. Introduction

In the light of the recent increase in reported pertussis cases from some countries, which were in some instances associated with an increase in infant deaths, SAGE and the WHO agreed that a new working group on pertussis would be established. This working group would first prepare for a SAGE review of the data and would then consider updating current pertussis vaccine recommendations as published in the 2010 pertussis vaccine position paper (http://www.who.int/wer/2010/wer8540.pdf). This also provided an opportunity to review newly available data on effectiveness of various vaccination strategies aimed at reducing infant mortality, as well as the pertussis-related outcomes of the vaccine schedule optimization project.

The terms of reference for the SAGE pertussis vaccines working group were:

1. Review epidemiological data on pertussis from selected countries using acellular pertussis (aP) and/or whole cell pertussis (wP) vaccines and evaluate the evidence for resurgence of pertussis, with an emphasis on severe pertussis in very young infants. In countries where the evidence supports resurgence, evaluate the evidence for the hypothesis that resurgence is due to shorter lived protection from aP relative to wP vaccines;
2. Review the evidence on effectiveness of 1 or 2 doses of pertussis vaccines against severe disease and death in young infants;
3. Review the evidence on effectiveness of three keys strategies aimed at reducing severe disease and death from pertussis in very young infants (cocooning, maternal immunization during pregnancy, and immunization of newborns);
4. Review the evidence for optimal primary vaccination scheduling and timing of booster dose(s);
5. Review the evidence that changes in circulating pertussis strains have had an adverse impact on the effectiveness of aP or wP vaccines;
6. Propose updated recommendations for SAGE consideration on the use of pertussis vaccines.

The working group has completed its review in relation with points 1, 2, 3, 5, of its terms of reference. The review of the optimal primary immunization schedules as per point 4 of the terms of reference is still ongoing and will be completed in the summer of 2014 and presented at the October 2014 SAGE meeting. This review entails a 4-component framework (epidemiology of the diseases, systematic review of the effectiveness and safety of the various schedules, operational considerations, and models & ICEA) following the model already applied to pneumococcal conjugate, rotavirus and *Haemophilus influenzae* type b (Hib) vaccines. Both combined diphtheria, tetanus toxoid and pertussis vaccine (DTP) and tetanus toxoid vaccine (TT) schedules will be reviewed by the pertussis working group in view of the impossibility of disentangling the primary vaccination schedule for pertussis from that of diphtheria and tetanus and the interrelation of the TT and DTP schedules. Point 6 of the terms of reference will only be fully completed after completion of point 4.

The 2010 pertussis position paper will be revisited only after the results of the review are available. In the meantime, a brief update to the position paper will be published, pending the decision made by SAGE at its April meeting.

2. Review of country specific information

Methods

A total of 21 countries (Argentina, Australia, Brazil, Canada, Chile, Colombia, Cuba, Denmark, Finland, France, Germany, Israel, Japan, Mexico, Norway, Portugal, Singapore, Sweden, Thailand, UK, and USA) were approached for detailed data collection. A standardized questionnaire developed by the working group (Annex 2) was used to capture information on pertussis incidence, vaccination coverage and schedule, surveillance methods, case definitions, and type of vaccine used. Relevant publications were also used to complete information from the questionnaire. The selected countries were not globally representative but were chosen on the basis that they were believed to have long-standing high vaccine coverage rates and effective disease control, and were able to provide high quality data on vaccine coverage and trends in pertussis disease burden over time. The countries selected were chosen to include representation from those with or without an apparent pertussis resurgence, those with wP or aP based programs, developing and industrialized countries, and different regions of the world. The working group defined the term "resurgence" as a larger burden of disease than expected, given the periodic variability of naturally recurring pertussis disease, when compared to previous cycles in the same setting.

Results

The working group was presented with evidence derived from 19 countries (Figure 1 and Figure 2) on various measures of pertussis incidence, vaccination coverage and schedules in the context of the surveillance methods, case definitions and type of vaccine used. 15 countries were high income countries, 4 were upper middle income countries.[1] Two countries (Argentina and Colombia) did not return the completed questionnaire.

---

[1] World Bank List of Economies – as of Nov 19, 2013. www.worldbank_list_of_economies.com [accessed 19.11.13].

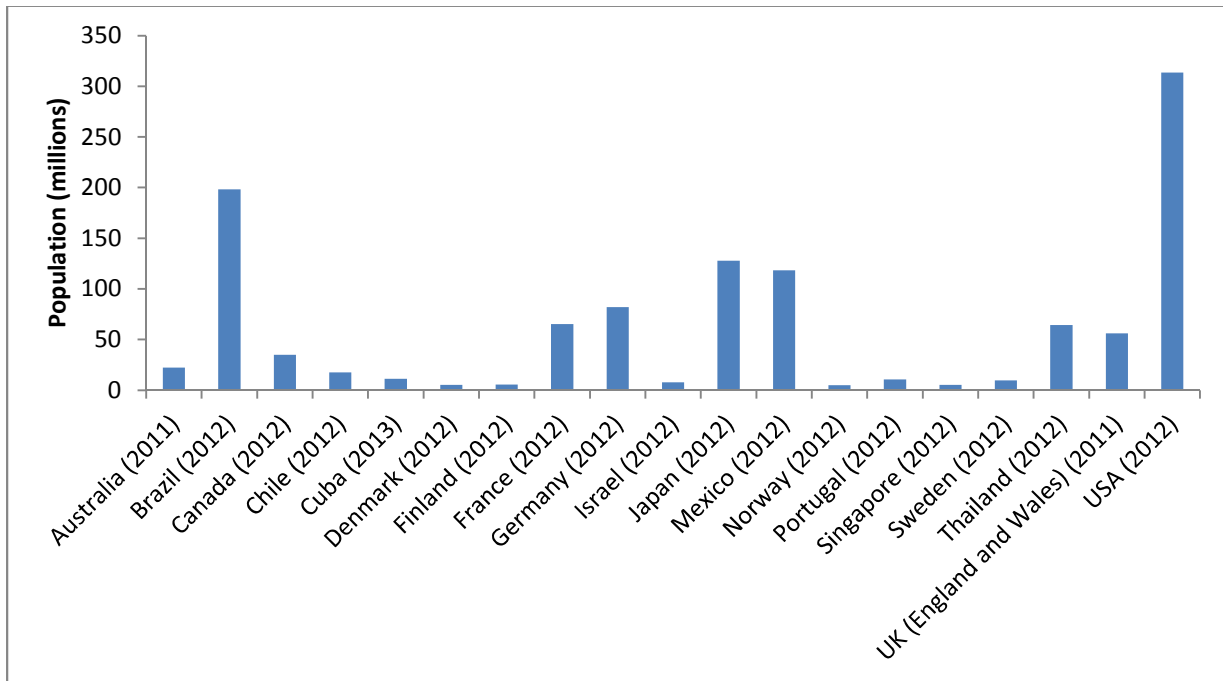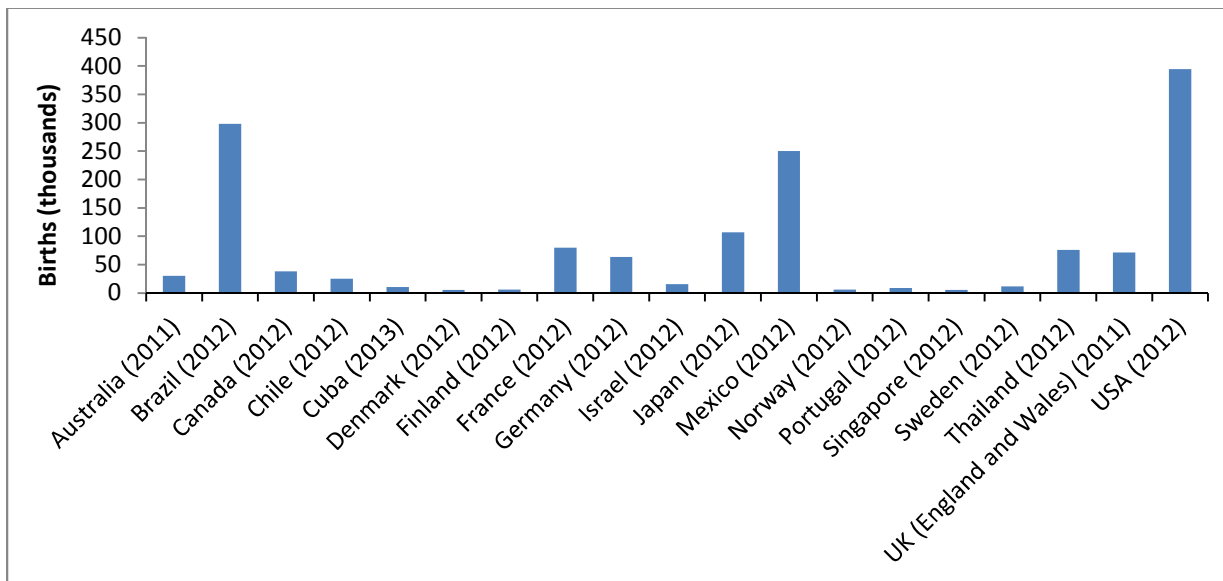**Figure 1: Total country population by year**


Figure 2: Total country birth cohort by year

Australia (total population in 2012: 23.05 M)

Surveillance	Mandatory universal laboratory (public & private) reporting since 1993.
Laboratory confirmation	Culture (all years), immunofluorescence (from 1980s), serology (from 1990s) and PCR (from 2000, in hospitals). Reimbursement changes led to PCR tests being readily available in primary care from 2007, with an estimated 7 fold increase in use in this sector. All reports based on PCR or culture are deemed confirmed irrespective of clinical symptoms; individual follow up of cases is largely restricted to children under 5 years of age.
Vaccination coverage	95% for the full primary series (DPT3) at the age of 24 months at the national level, but there are pockets of low coverage (<85%), predominantly in alternate lifestyle regions outside capital cities.
Current vaccine in use	aP (3 component)
Vaccination recommendations	Australia used a locally manufactured wP from 1975 to 1996; a booster dose at 18 months was re-introduced in 1983 and a pre-school dose was introduced in 1995. Acellular pertussis vaccine (DTaP) has been used for booster doses since 1997 and exclusively since 1999. Until September 2003, the recommended primary schedule was 3 doses at 2, 4 and 6 months, with boosters at 18 months and 4 years. In 2003, the 18 month dose was removed in favour of an adolescent booster dose, which was given in schools at varying ages (11-17 years) from 2004. Recommendations for adults (Health Care Workers (HCW), those with contact with infants, child-care personal, pregnant women) exist but doses are not funded by the national immunization program. However, a number of Australian States have provided funding for free of charge adult vaccination in the context of "cocoon" programs during outbreaks from 2009.

There has been a notable rise in pertussis incidence since 2008, with epidemic activity occurring at varying times in different areas of Australia (Figure 3). In contrast to previous epidemics in 2001 and 1997, the steepest increase was among children under 10 years. In children, the most notable increases in notified cases have been in 2 to 4 year olds and in 5 to 9 year olds. In persons over 15, the highest and most steeply increasing incidence of pertussis has been in those over 60 years of age.

Figure 3: Incidence of reported pertussis cases in Australia
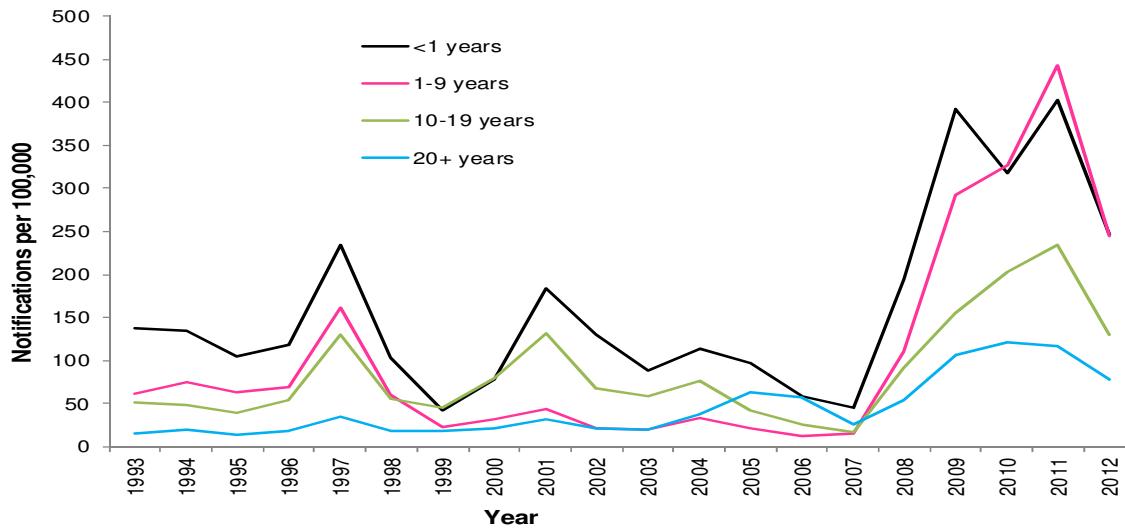
In the era before PCR was widely available, more hospitalizations than notifications were recorded in infants less than 1 year; since 2000, notification rates exceeded hospitalization rates in this age group (Figure 4), as reporting relies more on PCR positives from laboratories than clinicians. Despite greatly increased use of PCR, hospitalization rates have not increased over historical levels, suggesting that most of the observed increase has been in less severe cases. Reported deaths from pertussis have decreased in the most recent epidemic period. Mortality per 1 million births was 7.5 (95% CI: 4.5-11.7) from 1993 to 2002, but declined to 4.3 (95% CI: 2.2-7.5) from 2003 to 2012, despite PCR being available to increase diagnostic test sensitivity.

Figure 4: Incidence of pertussis hospitalisations in Australia, infants aged <1 year

Key conclusions	• Data quality from Australia was judged to be good. • Resurgence of pertussis was seen from 2008-2012 in children less than 10 years of age, in particular in 2-4 year olds and 7 to 9 year olds. • Pertussis is a major public health issue in Australia, with a continuous increase observed over a long period of time, first in adults related to availability of serologic tests, then in adolescents related to low historical vaccine coverage, and most recently in younger children consistent with waning immunity in the context of increased test availability and use. No other country using acellular vaccines has seen such a major increase in 2 to 3 year old children; other countries have seen increased cases from 6 years of age, but these apparent increases have been magnified by testing. • Cessation of the 18 month booster dose appears to be an important contributor to resurgence in 2 to 4 year olds, with early waning immunity following the last acellular vaccine dose at 6 months. As in the US, large increases in cases over 6 years of age have been observed, and there are Australian data to support a shorter duration of immunity among children who have received aP vaccines than in those who received the Australian-manufactured wP. • The resurgence was not associated with any increase in infant pertussis deaths, which have remained similar or lower to that of previous pertussis epidemics in the past 2 decades despite more sensitive diagnostic tests.

Brazil (total population in 2012: 198.66 M)

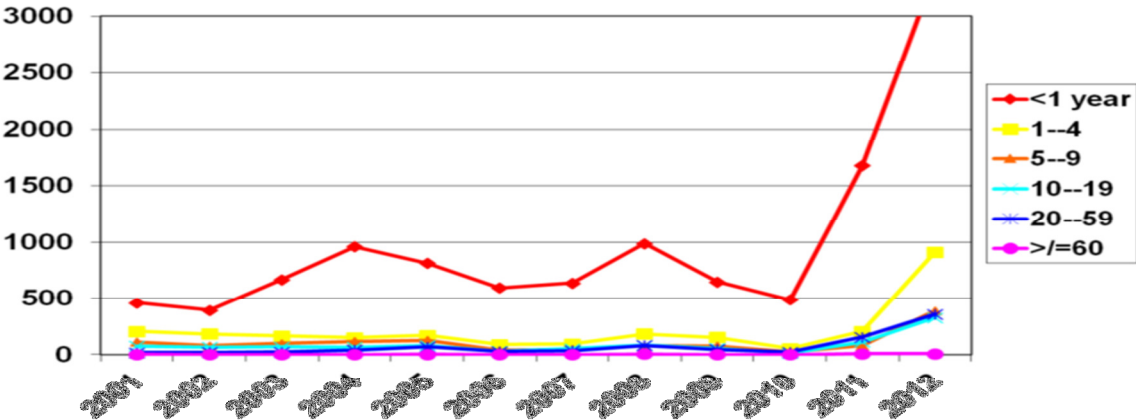| Surveillance	Mandatory universal passive notification; hospitalization and mortality data are obtained through the reporting system and/or taken from hospital records (ICD coded).
Laboratory confirmation	In the past, laboratory confirmation was obtained using culture; in 2008 PCR was introduced and is currently being implemented nationwide. In 2012, 41% of the cases in 2012 were lab confirmed (PCR or culture), 47% were clinical and 11% were epi-clinically confirmed (1% not provided). Sensitivity of the surveillance system increased in 2011.
Vaccination coverage	From 2001-2011, national vaccination coverage in infants <1 year with DTP3 was high (>95%). In 2012, a decrease was observed due to supply issues. From 2006 to 2012, the number of municipalities with >95% DTP3 coverage decreased from 83% to 55% with non-homogenous coverage throughout the country. Causes for the decline were mainly operational issues as social acceptance of vaccination in Brazil is high.
Current vaccine in use	wP (private sector is using combination aP vaccines; this market targets around 10% of the population)
Vaccination recommendations	Brazil introduced a wP primary 3 dose schedule plus a booster at 15 months in 1977 (DTwP). A 2nd booster was introduced at age of 4-6 years in 2004. Pentavalent wP vaccine (Crucell; Serum Institute India) was introduced in 2012, with retention of DTwP for booster dose. Pentavalent vaccine is used as a 3-dose primary schedule at 2, 4, and 6 months of age; the booster doses of

	DTwP (Butantan) are recommended at 15 months of age and 4 years of age (Sanofi Pasteur). The country will recommend Tdap in the routine immunization programme for pregnant women from 2014 onwards.

The number of pertussis cases increased from 2001- 2012 (Figure 5). In 2011 and 2012, there was an apparently large increase in morbidity and mortality among infants less than 1 year of age. In mid-2011, there was a sudden increase of the number of cases starting from the epidemiologic week 30, attributed to improvement in the sensitivity of the surveillance. Between 2007 and 2012, 51% of the reported pertussis cases under 6 months of age had not received any doses, 37% had received only one dose of pertussis vaccination, and 12% had received 2 or more doses. The majority of cases (75%) reported were from the South and South-East of the country, in states representing around 45% of the population. As the most recent hospitalization data available are from 2007, confirmation of this increase in reported cases through hospitalizations rates in infants under 1 is not possible. Within the Brazilian national notifiable diseases information system (SINAN), 25% of the notified hospitalized cases do not have any data on vaccination status. Of those hospitalized cases where information on the vaccination status is provided, approximately 50% have received a full primary series of pertussis vaccination. Generally outbreaks do not account for the majority of cases; the last outbreak reported in 2010 had fewer than 25 cases.

The accumulated number of deaths from 2000 to 2012 is reported by age-group. Of all deaths, 342 (97%) occurred in infants under 1 year. In older age groups, only 10 deaths are reported for this time period. Between 2008 and 2012, 185 pertussis-related deaths occurred in children less than 4 years of age: 125 had never been vaccinated, 20 had received one dose, 2 had received 2 doses, 1 case had received 3 doses, and 2 cases had received 3 doses plus the first booster. The immunization status was unknown for 35 of the deaths.

The increase in fatal cases among infants led the country to introduce aP in pregnant women and recommend a cocooning strategy. An increase in cases was observed in neighboring countries as well.

**Figure 5**: Pertussis cases by age group, Brazil, 2001 to 2012

Key conclusions:	• Data quality is reasonable but could be improved. Reporting and testing has been suboptimal.
	• Evidence to confirm pertussis resurgence is limited. A recurrence of the natural cycle might be responsible for the observed trends as hardly any cases after 5 years of age were seen. A drop in coverage might have led to an increase in cases. The increase in laboratory testing and increased sensitivity of surveillance might have magnified the increase in reported disease, supported by the fact that the increase is seen in infants and not in older age-groups.
	• There is no evidence for waning immunity as it is predominantly infants too young to be immunized that have been affected.

Canada (total population in 2012: 34.84 M)

Surveillance	Mandatory universal passive notification as a statutory requirement for laboratory and clinicians plus active surveillance system: the pediatric tertiary care hospital active system (IMPACT). Data on hospitalization and deaths are obtained through ICD10 or IMPACT.
Laboratory confirmation	In the past, laboratory confirmation was obtained using culture; in 2000 PCR was introduced and is currently being implemented nationwide (91% of cases).
Vaccination coverage	Coverage is 99% for DTP3 at 24 months, 98% for the first booster at 2 years of age, 67% for the 7 year booster, and around 90% for the adolescent booster dose (varies by province).
Current vaccine in use	aP
Vaccination recommendations	wP was used until 1997-1998. In 1997, aP was introduced. The current vaccination schedule includes primary vaccination at 2, 4, 6, and 18 months using DTaP-IPV-Hib or DTaP-IPV-Hib-HepB, a booster dose using DTaP-IPV or TdaP-IPV at 4-6 years, an adolescent booster at 12-16 years (depending on the province) and an adult booster, both with Tdap. The adolescent booster dose was introduced in 2003. Cocooning or post-partum vaccination is recommended in 4 provinces if no adult booster has been received.

Over the last 30 years disease cycles have recurred periodically every 4 years, with the largest peaks observed in 1990, 1994, and 1998. During the last 10 years, several cycles had been missed. In 2012, a slight increase in cases was observed in comparison to the preceding years (Figure 6). The resurgence observed in the 1990s was likely due to a combination of factors, including the low efficacy of the whole-cell vaccine introduced between 1981 and 1985[1-3], as well as increased physician awareness, improved diagnostics, and improved reporting of pertussis infection[4].

Figure 6: Incidence of pertussis in Canada by age group from 1980 to 2012
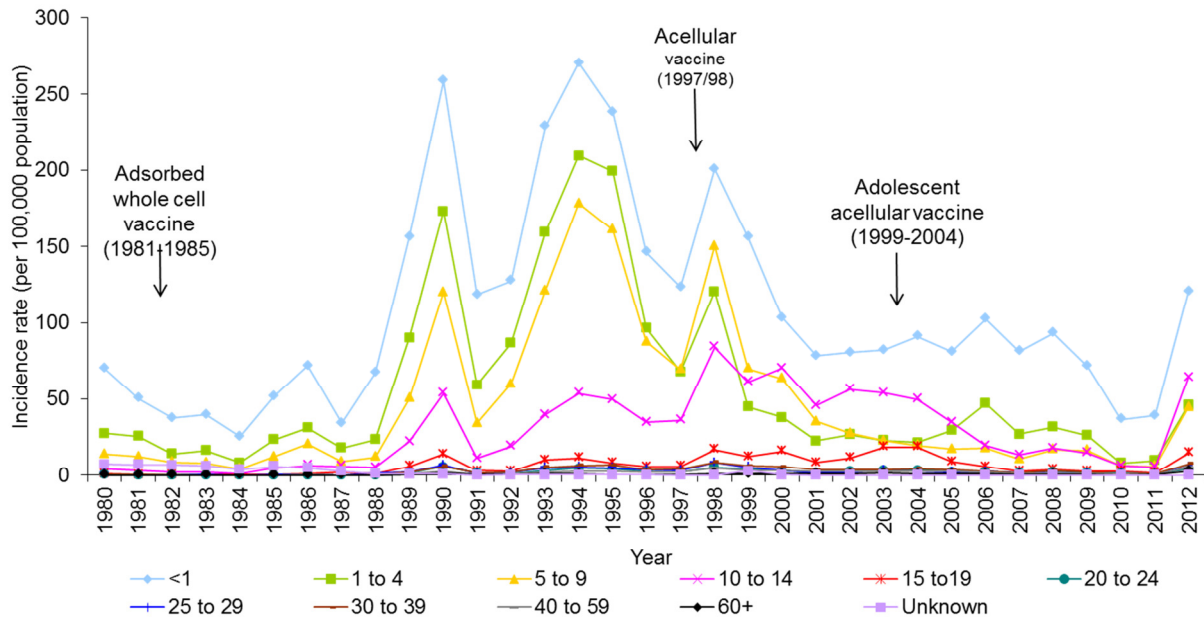
An increase in cases was generally limited to certain regions over discrete time periods. There were 3 outbreaks in the last few years, mainly related to religious or aboriginal communities with subsequent spread to neighboring provinces.

Hospitalization data from IMPACT sites suggest most admitted pediatric cases are restricted to infants less than 6 months of age (Figure 7).

Figure 7: Reported pertussis hospitalizations admitted to Canadian IMPACT sites by age group and year, 1990 to 2012
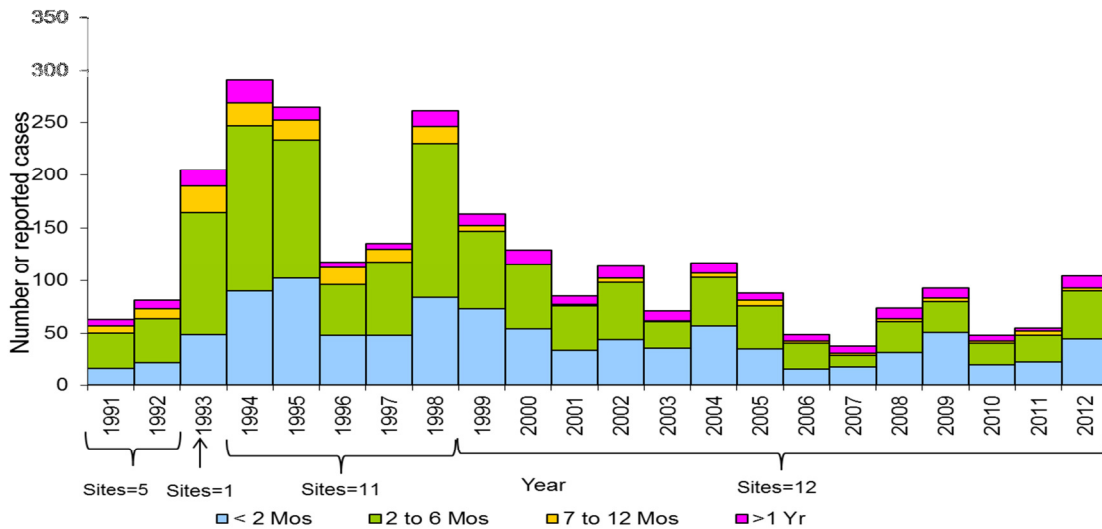
Annual death numbers are low; on average 1-4 cases occur per year with no change over time. In 2012, a total of 3 deaths were reported (7.9/1.000.000 births), all in infants less than 2 months of age.

Key conclusions:	• Data quality is good but there are reporting gaps.
	• No resurgence was observed, but the periodic cycle had a higher peak in 2012 than the 2 cycles before. An increase in cases was mostly limited to certain regions over discrete time periods.
	• In general, the situation in the country is very heterogeneous with multiple causes of increase (low coverage, waning immunity, earlier wP vaccine with low vaccine effectiveness), yet there is no evidence that aP has contributed to the most recent increase in cases.
	• Data suggest some aP-induced waning of immunity before adolescent booster; hence, it is concluded that the timing of adolescent booster is important with 14 to 16 years of age being too late for the 3rd booster.

Chile (total population in 2012: 17.46 M)

|	
Surveillance	Mandatory universal passive notification since 2000. A national system is in place to register hospitalization and death from pertussis.
Laboratory confirmation	Laboratory method used is direct immunofluorescence (DIF); PCR is not used in the whole country, only in 6 large hospitals. Only 0.5% of the cases were laboratory confirmed in 2012.
Vaccination coverage	In 2012, coverage was 92.8% (DPT3) for the full primary series at 24 months and 90.9% for the first booster dose. School entry coverage was 77.0% for the DTP pre-school booster at 4 years in 2011, and 57.9% for Tdap pre-school booster at 6 years in 2012.
Current vaccine in use	wP (multiple s used historically there have been several switches of vaccine, including those from Sanofi Pasteur, SII, GSK , Biosano, and Novartis products)
Vaccination recommendations	DTwP was used from 1952 to 1971 with a 3 dose primary schedule at 4, 6, and 18 months, and a pre-school booster at 4 years. From 1975-2011, DTwP was used with a 3 dose primary schedule at 2, 4, 6 months, a booster at 18 months, and a pre-school booster at 4 years. Since 2012, Tdap as a 3/5 component vaccine has been recommended, the pre-school booster was moved from 4 to 6 years, and cocooning was recommended for adults. In 2013, the pre-school booster was dropped and an adolescent booster (Adacel) at 13 years was introduced.

In 2011, an ongoing significant increase in notified cases over all age groups was observed. Children <6 months and <1 year of age were particularly affected (Figure 8). Vaccination coverage (full primary schedule) was 61.4% among the reported cases in 6-11 month old children.
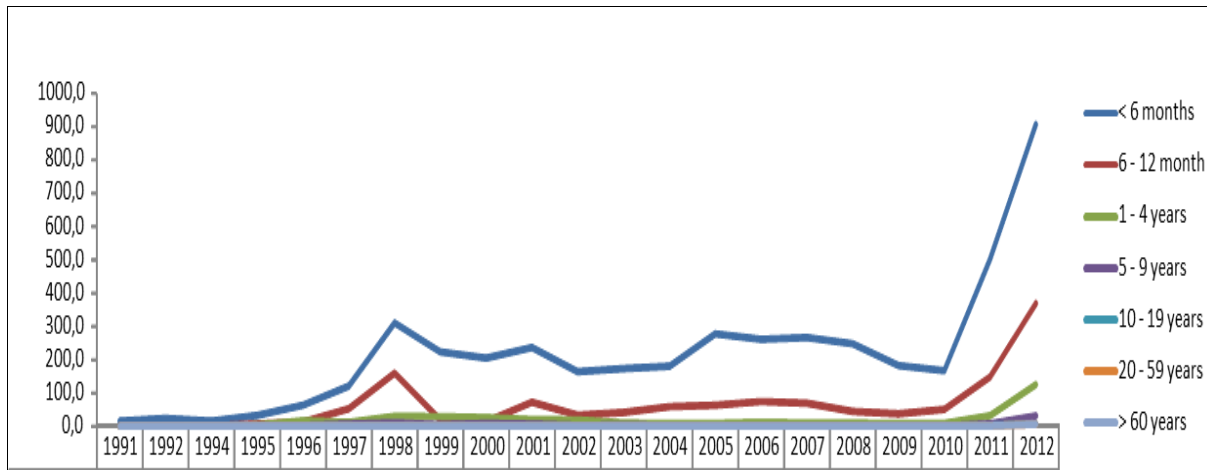
Vaccination coverage in recent years has substantially declined and could potentially be related to the current increase in pertussis cases (Table 1). This decline followed the health reform in 2005. The recent further drop in coverage in 2002 is probably related to a new monitoring system. The activity of anti-vaccination movements has also increased. Cohorts born around 2004 with lower coverage might have led to an increase in disease circulation, increasing the risk of transmission to infants too young to be vaccinated.

Table 1: Vaccination coverage with 2nd booster does estimated at school entry in Chile

Vaccine	Age	2005	2006	2007	2008	2009	2010	2011	2012
		Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)	Coverage (%)
DTwP	4 years	91.3	81.3	81.1	85.1	81.8	78.1	77.0	58.1
dtap	6 years								57.9

Hospitalizations and deaths have also increased, mainly in infants in <1 year. A substantial number of deaths were seen over a decade in young infants. The crude number of deaths in 2011 and 2012 was 16 and 13 respectively; 7 deaths occurred in each of 2010 and 2009. Mortality was highest in 2-3 month old infants in 2011 and 2012 (47.6 per 1, 000, 000 births in 2012). After a cocooning strategy was implemented in 2012, reported infant mortality has decreased.

Information on fatalities are obtained from the reporting system, hospital discharge data, and national death statistics; neither autopsy nor PCR confirmation are done. The actual increase in mortality may be overestimated as direct immunofluorescence (DIF) test is known to result in more false positives than PCR. As well, the potential overlap of respiratory syncytial virus (RSV) and pertussis cases might lead to false positive cases. There has also been some reluctance by physicians to report cases. The system captures severe hospitalized cases in infants, but a low proportion have mild symptoms, which might indicate low system sensitivity. Nevertheless the system has the capacity to detect outbreaks.

A hexavalent aP-containing vaccine is used in the private market but accounts for only 3.9% of the population. The overall quality of the wP vaccine used was good.
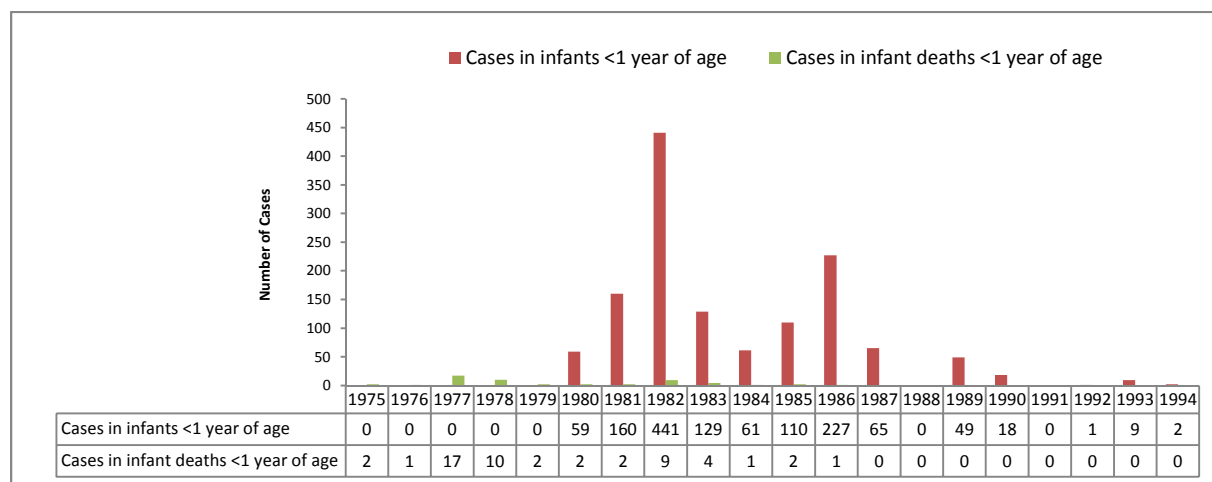
Key conclusions:	• Data quality greatly improved in 2012. Before 2012, the laboratory methods used were not ideal. Sensitivity and specificity of the laboratory methods may not be satisfactory (DIF related false-positive cases reported). • The resurgence of pertussis observed in 2011 and 2012 was preceded by a sustained drop in vaccine coverage and so might in part be linked with this drop in coverage.

Cuba (total population in 2012: 11.27 M)

Surveillance	Mandatory universal notification of clinical cases (all age groups). There is a sentinel surveillance system at the level of polyclinics notifying "Pertussis syndromes".
Laboratory confirmation	None since 1990
Vaccination coverage	Vaccination coverage of 100% of DTP3
Current vaccine in use	wP (Cuban manufacturers)
Vaccination recommendations	From 1962 to 1979, DTwP was recommended at 1, 2, and 3 months, along with a DTwP booster at 15months. In 2005, a tetravalent vaccine (DTwP--HepB) was introduced at 2, 4 and 6 months, moving the booster to 18 months. In 2006, the currently used pentavalent wP vaccine (DTwP-HepB-Hib) was introduced, using the pre-existing schedule.

Vaccination coverage is generally high for DTP3 at 12 months as well as for DTP3 plus the booster dose, with the exception of 2004 and 2007 (59% and 57%). Pertussis has been notifiable since 1962. From 198019 to 1990, laboratory culture was used in the country, but from 1990 to present, no laboratory confirmation is carried out. The last confirmed case of pertussis was reported in 1994 (Figure 9).

Figure 9: Infant (<1 year of age) pertussis cases and infant deaths by year, 1975-1994

	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
Cases in infants <1 year of age	0	0	0	0	0	59	160	441	129	61	110	227	65	0	49	18	0	1	9	2
Cases in infant deaths <1 year of age	2	1	17	10	2	2	2	9	4	1	2	1	0	0	0	0	0	0	0	0

No studies on vaccine effectiveness from Cuba are available. Data from the clinical reporting system has indicated an increase in cases for the last 5 years. It is unclear if this reflects a true increase in pertussis or related to the development of this surveillance system.

Key conclusions:	• Notification based on clinical definition only, no laboratory confirmation. Low sensitivity of surveillance system.
	• The working group concluded the data from Cuba are not comparable with data from other countries because of the lack of laboratory confirmation, limiting their utility.

Denmark (total population in 2012: 5.60 M)

Surveillance	Mandatory universal passive notification of cases by clinicians in children less than 2 years since 1994. Since 2007, all laboratory confirmed cases regardless of age are statutory notifiable by the diagnosing laboratory to the national reference laboratory. A national system is in place to register hospitalization and death from pertussis.
Laboratory confirmation	Historically, culture has been used for laboratory confirmation. In 1998, PCR was introduced. In 2012, about 73% of the cases were PCR confirmed. Serology has been used since 2010 (25% in 2012). In children <8 years and infants, PCR is commonly used (>95%), with the remaining cases confirmed by culture.
Vaccination coverage	Vaccination coverage in 2012 was 91% for the full primary schedule at 24 months. Since 2003, vaccination coverage with booster doses (DTP4) ranges from 81 to 84%.
Current vaccine in use	aP (monocomponent)
Vaccination recommendations	The vaccination schedule from 1961 to 1969 consisted of 5, 6, 7 and 15 month doses of a combined DTwP-IPV vaccine. From 1969 to 1997 wP was used as a single vaccine at 5 weeks, 9 weeks and 10 months of age. From 1997 onwards, monocomponent aP was used at 3, 5, and 12 months of age. In 2003, a pre-school booster dose was introduced at 5 years of age. Rational for the booster was to extend immunity as well as to provide indirect protection to infants.

Historically, pertussis incidence has been low. An outbreak-related increase in cases was observed in 2002 and again in 2004. In 2012, an increase in cases was reported, in part caused by increased use of serology (Figure 10). This trend was not sustained in 2013 and declined to pre-2012 levels.

Figure 10: Incidence of reported pertussis cases in infants under 1 year of age in Denmark, 1995 to 2012
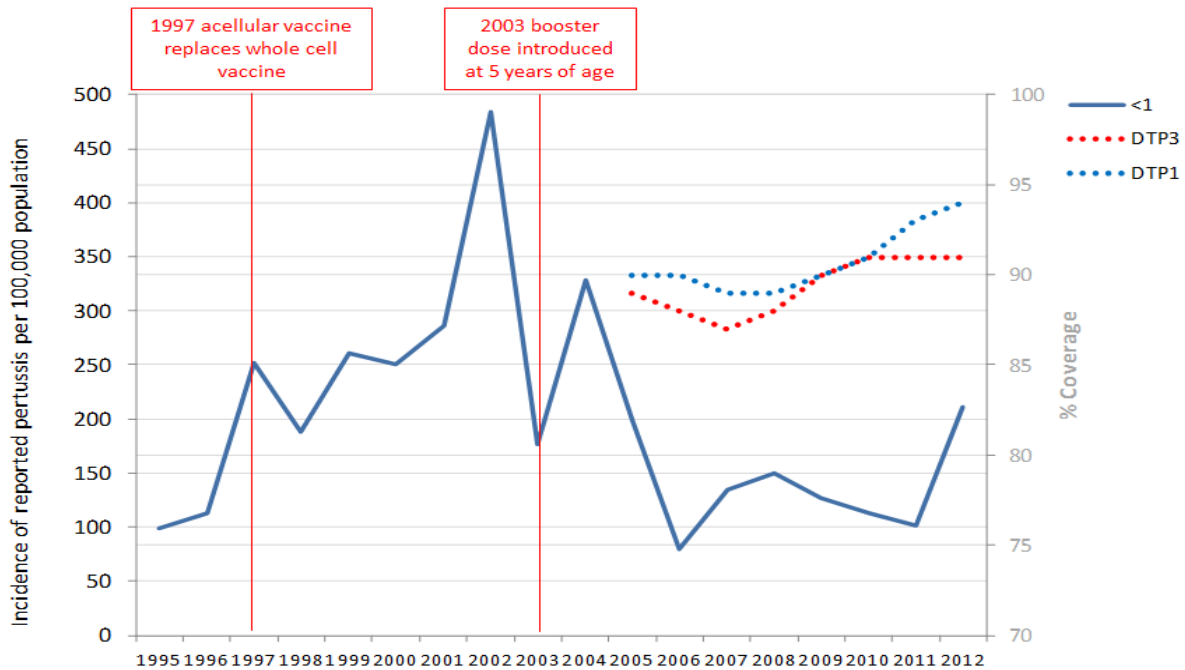
Hospitalizations are reported for notified cases aged 2 years and under only. Deaths are reported through the disease reporting system. In general, deaths are rare with an average one fatality every 2 to 3 years, with the last fatal case being reported in 2010.

| Key conclusions:	• Historically data quality was already good but is still improving. • No resurgence of pertussis. The situation in Denmark is stable, with an observed increase in cases occurring due to naturally recurrent cycles and an increased use of serology. • Denmark uses a monovalent PT vaccine and a unique schedule with the start of the primary immunization at age 3 months. Since 2004, the total number of reported cases has remained relatively stable since aP vaccine introduction. This is contrary to what has been reported from other countries with long-standing use of aP vaccines. Notably, Denmark stands out as the only country with exclusive use of monovalent PT vaccine, delivered according to the 3,5,12 month "Scandinavian" schedule of primary doses.

Finland (total population in 2012: 5.41 M)

Surveillance	Mandatory universal passive notification. Since 1995, only laboratory confirmed pertussis cases have been reported to the national infectious disease register.
Laboratory confirmation	Laboratory methods used in 2010 were PCR in 5% of cases, serology in 92% of cases, and culture in 3% of cases.
Vaccination coverage	Coverage before 2005 was 97% for the entire 3+1 schedule (3, 4 and 5 + booster at 20-24 months) based on 2003 birth cohort. Latest coverage for DTP3 was 99% based on 2007 birth cohort.
Current vaccine in use	aP (3 component)
Vaccination recommendations	The vaccine used from 1952 to 1957 was monovalent wP. From 1957 to 2004, DTwP-vaccine (National Public health Institute ((KTL)) was used. The 3+1 schedule, with 3, 4, 5 and 20-24 month doses, has been used since early in the beginning of the programme. Since 2005, new combination vaccines with an aP-component are being used: DTaP-IPV-Hib (Infanrix-Polio+Hib or Pentavac) is given at 3, 5 and 12 months, a booster DTaP-IPV (Tetravac or Infanrix-Polio) at 4 years, and a booster Tdap (Boostrix) for adolescents at 11-13 years (for those born before 1997) or 14-15 years (for those born 1997 or later).

Vaccination coverage data is based solely on a survey of 1000 children under 2 years of age which is conducted every second year. The results of the 2009 birth cohort coverage study are not available yet. Finland plans to establish a national immunization registry.

The incidence of pertussis increased from 1998 to 2000. Implementation of a booster with Tdap at 6 years of age in January 2003 was done to protect the children who were reaching the school age. The highest pertussis incidences were reported in 2003 and 2004. In 2005, the vaccines in the national program were changed to new combination vaccines containing aP-component; the vaccination schedule was changed at the same time and a Tdap booster for adolescents was added to prevent outbreaks of pertussis among school children. The aim of the changes was also to protect very young children. Another increase in incidence observed in 2011 and 2012 was mainly restricted to infants <1 year old, with older age-groups not greatly affected (Figure 11).
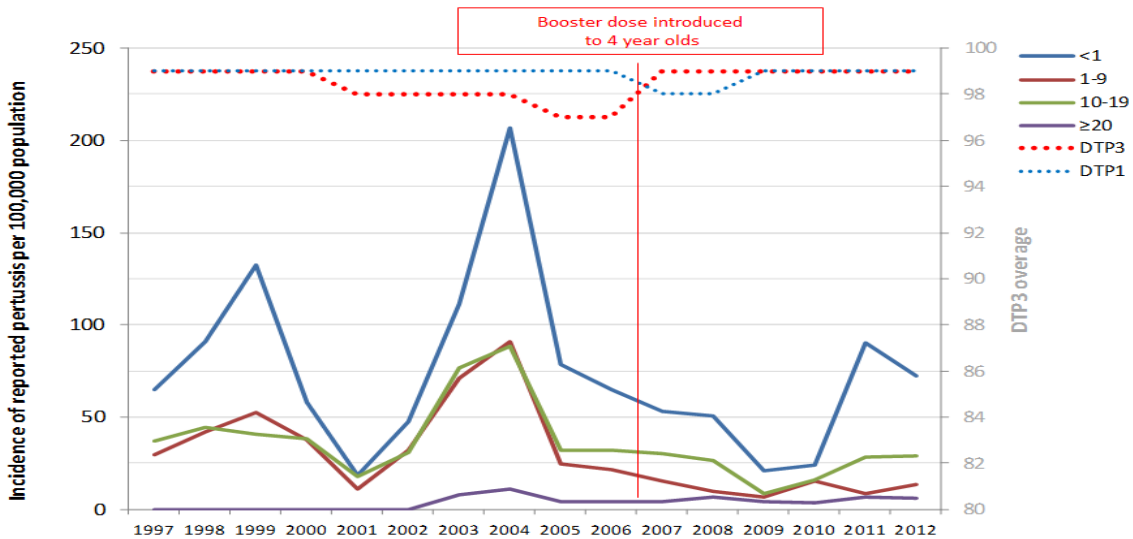
Data on hospitalization and death were not provided. Hospitalization data are not yet linked to the national surveillance system or discharge database using ICD codes, and data on pertussis related deaths are not routinely collected by the national surveillance system.

Key conclusions:	• Data quality is good but could be improved. • The observed epidemiology is explained by the naturally recurrent cycles. In general the situation is stable; no statistically significant change in trends is identified after 2003-2004. Overall vaccination coverage is high. • aP was introduced in 2005, resulting in less time to potentially result in resurgence due to aP related waning of immunity. • In the future, the "real time" vaccination registry will provide an easier way to follow the coverage and will enable will register linkage studies.

France (total population in 2012: 63.94 M)

Surveillance	Active voluntary hospital-based pediatric sentinel network of 42 hospitals has been in place since 1996, covering 30% of all pediatric admissions. Through this active surveillance (Renacoq), bacteriologists and pediatricians report cases in children. A detailed clinical form is filled in by pediatricians for cases in infants aged 0-5 months only. Information on pertussis deaths is obtained from national death certificates
Laboratory confirmation	PCR in 99% of cases. Only 1% of the cases are clinically confirmed.
Vaccination coverage	In 2011, 98.4 % for DTP3 at 24 months of age and 90.5% at the 18 month booster dose. Cocooning recommendations did not lead to high coverage among parents, with was estimated to be around 27% in mothers and 21% in fathers by a web-based survey.

Current vaccine in use	aP (3 components and 2 components for young children and adolescents ; 3 and 5 components for adults)
Vaccination recommendations	From 1990 to 2003, wP (DTwP-IPV-Hib) was used in a 2, 3, 4 and 18 months schedule. An additional booster at 11-13 years with aP containing vaccines was introduced in 1998. Progressive replacement of wP by aP (DTaP-IPV-Hib ± Hep B) took place in toddlers and infants from 1998 to 2003. After 2005, wP was no longer available. In 2004, aP vaccination was recommended for future parents along with a cocooning strategy for household members and health care workers (HCW) in charge of newborns and young infants. In 2008, an additional booster was added for adults at 26-28 years. In 2013, there was a change in the French immunization schedule to a slightly modified Scandinavian-like extended schedule with doses at 2, 4, and 11 months and the addition of a booster dose at 6 years.

Over the observation period from 1996 to 2012, a typical cyclic pattern of increases in pertussis incidence was observed every 3-4 years, with the most recent peak in 2012. The small peak observed in 2009 could also be due to the new PCR technique used (the end point PCR was replaced by RT-PCR which is 100 times more sensitive) (Figure 12).

Figure 12: Pertussis Incidence rate among infants aged 0-5 months and vaccine coverage against pertussis (3 doses at 24 months of age), 1996 to 2012
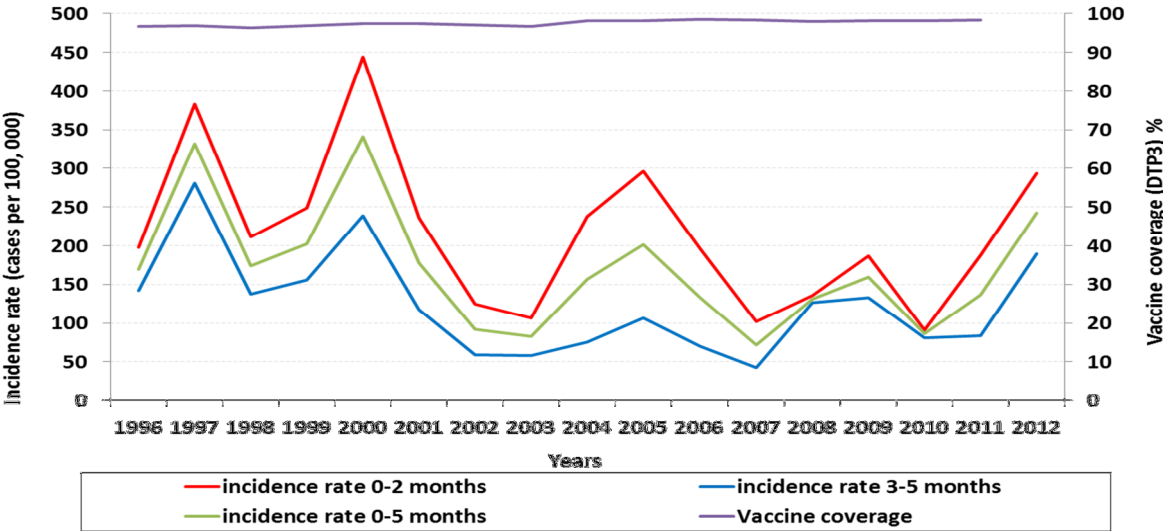
Pertussis incidence in France has always been highest for infants 0-2 months of age as compared to 3-5 months olds. The majority of reported cases (>90 %) under 3 months of age are unvaccinated. The crude number of deaths varies between 1-10 cases depending on the year of the cycle. There was only one fatal case in a vaccinated child during the last 15 years of surveillance (with 1 dose of vaccine), as high vaccination coverage has had a large impact on the prevention of infant deaths. Between 50 to 60 % of likely contaminators of hospitalized young infants are parents, with siblings identified as the likely source of infection in another 20 to 30 %.

Key conclusions:	• Data quality is good, yet limitations apply to the surveillance method used
	• No resurgence was observed, with only periodic increases in cases related to the natural recurrent cycle.
	• aP has been in use for 15 years and exclusively used for the last 10 years, with a highly effective wP program in place before that time. High population coverage was obtained.
	• Data suggest a recent increase in incidence in 5 to 10 years olds, which may reflect greater waning of protection in cohorts exclusively vaccinated with aP containing vaccines.
	• While other strategies such as the adult booster and cocooning have not had a big impact, their level of implementation remains low.

Germany (total population in 2012: 82.80 M)

Surveillance	Universal passive notification was only mandatory in 5 federal states of the former East Germany (FEW) during the period of 1991-2013. From 2013 onwards notification has been mandatory in all federal states, though data are not yet available.
Laboratory confirmation	The laboratory methods and frequency of testing including serology, PCR, and culture vary from states to states.
Vaccination coverage	Historically lower in former West Germany (FEW) (2-60% dependent on region. Mandatory vaccination in FEW (>95%). In 2011, vaccination coverage was 95.1% at school entry.
Current vaccine in use	aP (3/5 component)
Vaccination recommendations	wP was used from 1991-1997 with a 4 dose schedule (2, 3, 4 and 11-14 months). DTaP was used exclusively from 1997 onwards. A DTaP booster dose at 9-17 years was introduced in 2000. In addition, cocooning was recommended for child care and health care workers (2003), and for care-givers of infants (2004). From 2006 onwards, a pre-school booster was introduced at 5-6 years. From 2010, one dose of Tdap for universal adult vaccination was recommended.

The historical split in East Germany and West Germany resulted in differences in vaccination use, notification, and coverage until the time of unification. Vaccination was mandatory in the Former East Germany (FEG) but not recommended in the Former West Germany (FWG), hence vaccination coverage was high in FEG and low in FWG.

Incidence rates can only be assessed for FEG, as these are the only states requiring notification for notification for pertussis prior to 2013. Hospitalization data are available from all parts of Germany, with the highest rates among those <1 year of age (Figure 13). Incidence was highest in 2005/2006 and 2011 (Figure 14).

Figure 13: Incidence of notified pertussis disease and hospitalizations in Germany, 1947 to 2007[5]

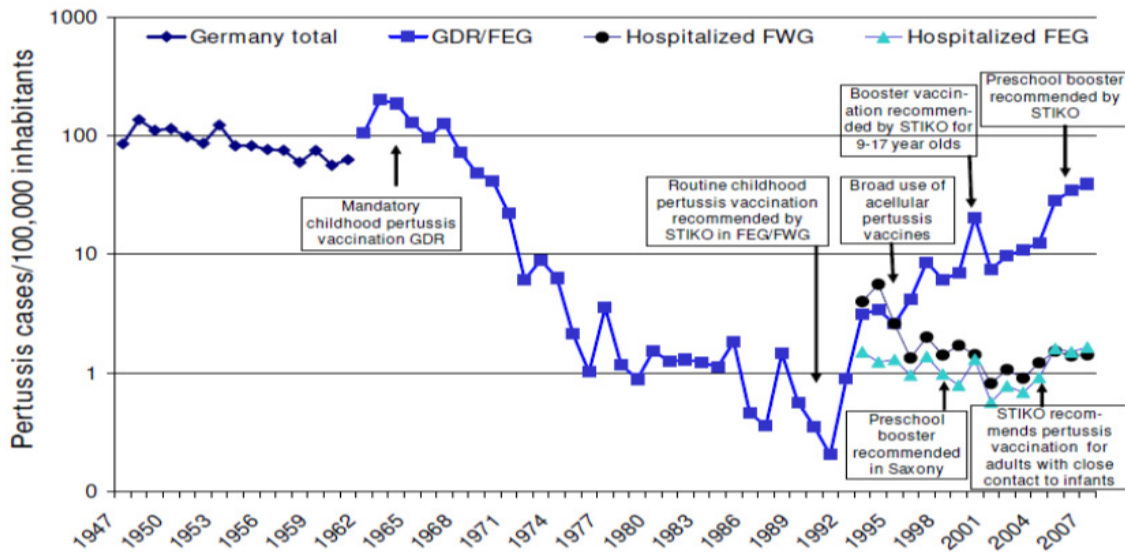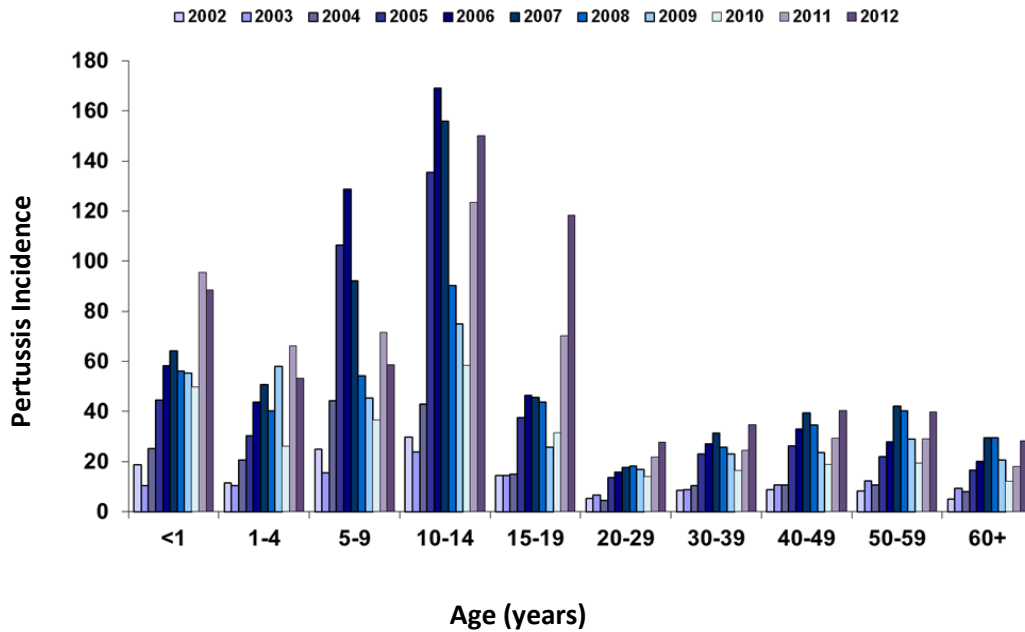**Figure 14**: Age-specific pertussis incidence of pertussis in the FEG, 2002 to 2012

Only 2 deaths were reported from 1998-2011 based on notification data from Federal Statistics. However, based on death notifications from hospital statistics, 11 deaths were reported over the same time period. This discrepancy and possible underestimation will be assessed in a surveillance survey covering >90% of all pediatric hospitals.

Key conclusions:	• Data quality is good, but has been regionally limited to FEG.
	• The presented data do not suggest a resurgence of pertussis in Germany. An overall low incidence (70/100,000 in infants <1year) and low number of hospitalizations are observed despite recurrent peak years. A magnification of the peaks may be due to an increase in serology testing in adolescents. A recent increase was observed in the last 2 years, yet in 2013 this number has already decreased significantly.

Israel (total population in 2012: 7.64 M)

Surveillance	Mandatory passive universal notification has been in place since 1950.
Laboratory confirmation	90% serology, followed by PCR with a small proportion of laboratory confirmation done using culture.
Vaccination coverage	Vaccination coverage was 94% for the complete primary series (DTP3) in 2012 at 24 months and 95% for the booster dose given at 7 years of age.
Current vaccine in use	aP (3/5 component)
Vaccination recommendations	wP was used as DTwP from 1957 to 2004 in a 2, 4, 6, 12 month schedule. Since 2005, aP (Infanrix-iPV+Hib (GSK) and Pediacel (Sanofi PasteurSP)) has been used, with 2 additional boosters doses recommended at 7 years (Tdap+IPV; Boostrix-Polio or Adacel Polio) and 13 years (Tdap; Boostrix or Adacel).

Review of the incidence suggests an increase in cases over the last few years. Historically, infants have had the highest incidence of any age group, although in 2007, the 10-14 year-old age group had a higher incidence. A sharp rise in the incidence rate among infants was observed between 2010 and 2012 that was not reflected in a parallel increase of adult cases (Figure 15).

Figure 15: Incidence of reported pertussis cases per 100,000 in Israel, 1995-2012
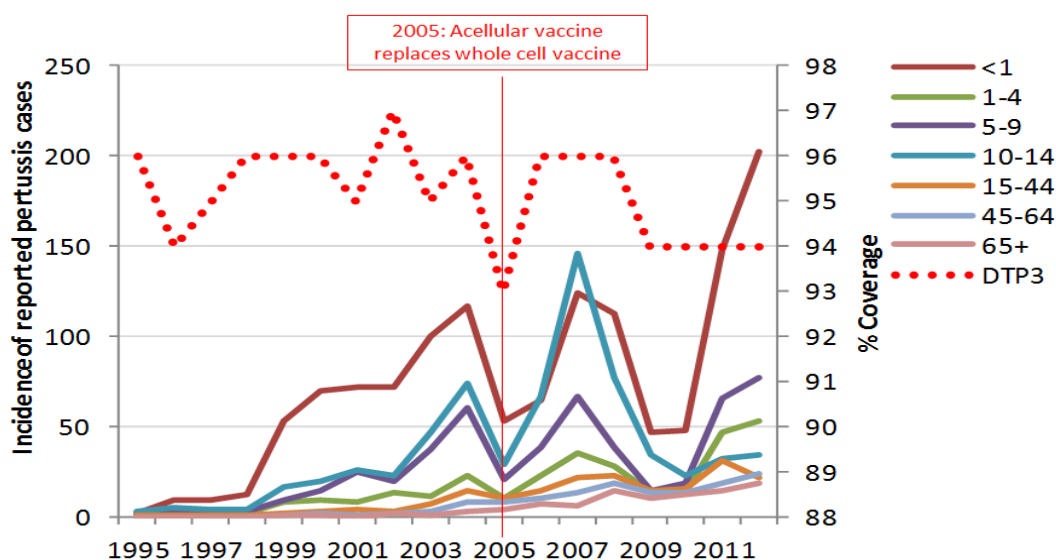
Hospitalization data are available from 2005 to 2011 through the national surveillance system. 80% of hospitalized pertussis cases during this period were <1 year of age. Information on deaths is derived from the national surveillance and not from death registries. For the period from 2005 to 2012, there were 9 deaths due to pertussis identified among infants (age <1). There were no deaths recorded in the other age groups.

Key conclusions:	• Data quality is satisfactory with room for improvement. • Available data does not provide clear evidence about resurgence. No definite conclusion can be drawn on actual resurgence vs. an increase in cases related to the natural recurrent cycle. • Possible explanations for the increase in infant cases include a greater awareness of pertussis and the availability of better laboratory tests... • Overall vaccination coverage is high with aP (3/5 component), despite this vaccine having only be in use for 7 years.

Japan (total population in 2012: 127.25 M)

Surveillance	Universal passive sentinel-site notification by pediatricians
Laboratory confirmation	Laboratory tests used for case confirmation are PCR or culture; laboratory testing is done mainly during outbreaks
Vaccination coverage	Administrative data overestimates true vaccination coverage which is reported to be 101.8% for DTP3+ booster at 24 months. One study provided coverage estimates of 96.6% and 67.9% for the booster.
Current vaccine in use	aP (different vaccines from different manufacturers have been used with different purification processes and number of components)
Vaccination recommendations	Historically, the vaccination schedule was 3/5 component aP vaccine (DTaP) at 3, 4 and, 6 months plus a booster at 12-18 months. Since 2012, DTaP-IPV has been used with recommendation for pre-school booster pending.

Incidence data are not available as the sentinel surveillance reports only crude number of cases from the sentinel sites. Reported cases were highest in 2000 for children under 6 years of age. The most recent data from 2010 show an increase in cases in 2009 and 2010 in adults >20 years. This increase was not reflected in infants and only a small increase could be observed among older children (Figure 16). No data could be obtained on pertussis-related hospitalizations and deaths in Japan.

Figure 16: Number of reported pertussis cases in Japan by year
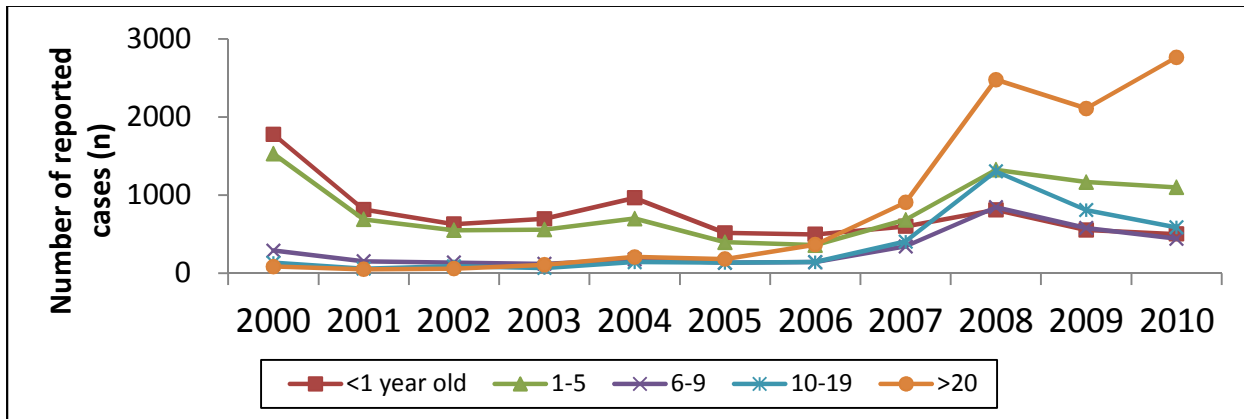
Key conclusions:	• Data quality could be better
	• No evidence for resurgence though data are limited.

Mexico (total population in 2012: 120.85 M)

Surveillance	Mandatory universal passive notification for all age-groups.
Laboratory confirmation	Culture only for 100% of probable cases. PCR has not been introduced systematically in the country but a pilot test has been conducted in 2011 with the support of the Centers for Disease Control and Prevention (CDC).
Vaccination coverage	National vaccination coverage in 2012 at 24 months with primary vaccination was 76.09%.
Current vaccine in use	aP (5 components)
Vaccination recommendations	From 1973-1997, Mexico used DTwP with a 3 dose primary schedule and 2 booster doses at 2 years and 4 years. From 1998-2006, DTwP was replaced by pentavalent whole-cell pertussis vaccine for the primary series, with retention of DTwP booster doses at 2 years and 4 years. Since 2007, Mexico has been using a primary schedule of 2, 4, 6, and 18 months doses with a pentavalent aP vaccine (Pentaxim) and a booster dose of DTP at 4 years of age

Vaccination coverage over the last 20 years ranged from 68% (1999) to 87% (2005). Yet a great variation between the different federal states was observed. 13 of 32 states have coverage below the national level and only 5 states have coverage levels above 90%.

An evaluation of the surveillance system (established in 1994) was conducted in 2010 with the help of a working group from the CDC. Strong surveillance infrastructure was in place but laboratory confirmation was only done by culture so there is limited sensitivity to recognize pertussis in children under 5 years of age. Further, sensitivity is further reduced due to inability of health care professionals to recognize cases. The overall number of reported cases since 1993 has varied substantially, with the vast majority of cases

being reported in infants (Figure 17). In 2012, an increase in total infant cases was observed, with 25.6% of these cases having received at least one vaccine dose.

This increase in identified cases was not associated with in an increase in infant mortality (Figure 18). No effectiveness studies are available from Mexico. The possibility was raised that ethnicity might explain the high mortality rate compared with that observed in other countries, considering US mortality rates are highest in Hispanic infants. It was also noted that mortality rates in Mexico tend to be higher in the first year of an epidemic cycle than in the second.

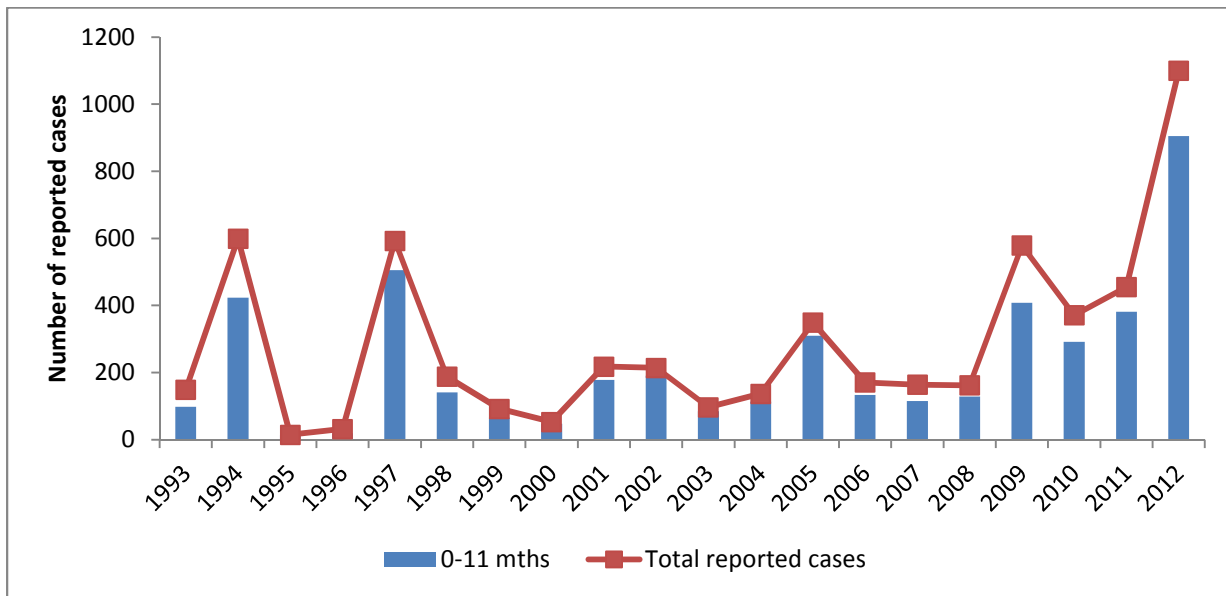**Figure 17**: Number of reported cases in infants and in the entire population in Mexico by year, 1993 to 2012

Figure 18: Number of infant deaths <12months in Mexico by year

Key conclusions:	• Data quality suffers from serious limitations and there surveillance system sensitivity is low. • Data are not suggestive of a real resurgence. • Increase in cases might be related to low and heterogeneous vaccination coverage. • The use of a more sensitive laboratory method (PCR) might explain the recent rise in cases, an idea supported by the dissociation between total infant cases and infant mortality in 2012.

Norway (total population in 2012: 4.99 M)

Surveillance	Mandatory universal passive notification by laboratories and clinicians.
Laboratory confirmation	Performed laboratory tests consist of PCR (60%), serology (40%) and culture (<1%) in 2012.
Vaccination coverage	In 2012, vaccination coverage was 100% with DTP 1 and 95% with DTP3 at 24 months and for the booster at 7-8 years of age (at 9 years).
Current vaccine in use	aP (3 component)
Vaccination recommendations	wP was used until 1998 and was then replaced by a primary 3 component aP series (Infanrix) at 3, 5 and 10 months. In 2001, the schedule changed to consist of 3, 5 and 12 months doses using Infanrix-Polio. In 2006, a pre-school booster (Tetravac) was introduced at 7-8 years. In 2012, a teenage booster at 15 years of age (Boostrix polio) was recommended for those born after 1998, with the maintenance of maintenance of adult booster every 10 years.

Pertussis incidence was highest for infants <1 year of age until 2001. From 2002, the highest incidence was reported in 10-19 year olds with a peak in 2005/2006. This led to the introduction of an adolescent booster dose. The incidence in the <1year olds (150/100,000) lies within global average (Figure 19).

Figure 19: Incidence of reported pertussis cases in Norway, 2003 to 2012

Hospitalization data are based on the number of cases reported as hospitalized to the national surveillance system for notifiable diseases. Data are not linked to hospital discharge database using ICD codes. Trends in hospitalization and notification of patterns for cases under 1 year of age are closely related. The highest incidence of hospitalized cases under 1 year was in 2004 with approximately 140/100,000 population. In total, 4 deaths have been reported since 1995, with the last death in 2004. No data on vaccination status are available for one fatal case in 1995, the other 3 deaths occurred in unvaccinated infants of 1 month of age.

Hypotheses concerning possible explications of the increase in infant cases include a greater awareness of pertussis, availability of better laboratory tests, and true increase in the incidence of pertussis resulting from reduced potency of pertussis vaccines, waning of vaccine-induced immunity, or genetic changes in *B. pertussis* strains.

Ongoing studies (unpublished data) in Norway suggest that a decreasing trend in disease-free duration in pertussis cases occurring after receiving 3 doses of vaccine seems to have stabilized in the past few years. In addition, the impact of the first booster dose at age 7-8 years (introduced in 2006) is currently being evaluated.

Key conclusions:	• Data quality is good.
	• Data do not support a resurgence as a stable cyclic situation for all age-groups was seen in the last several years. The exception is the ongoing increase in older age-group (10-19 years), which is higher than the 1-7 years prior to introduction of the booster at 7 years of age.
	• It is highlighted that Norway is a country which has been using an extended schedule over a long time. In regard to lab methods, application of serology might have magnified the effect of increased incidence.

Portugal (total population in 2012:10.60 M)

Surveillance	Mandatory universal passive notification by medical practitioners.
Laboratory confirmation	PCR and culture.
Vaccination coverage	National pertussis vaccination coverage for children aged 12 months of age with the third dose of pertussis-containing vaccine was estimated at 93%-98%. (1993 to 2012) For children aged 7 years, the vaccination coverage with the 5th dose of pertussis-containing vaccine was estimated at 89%-97% (2007-2012).
Current vaccine in use	aP (3/5 component)
Vaccination recommendations	wP vaccine was introduced in 1965 in the Portuguese immunisation schedule for children aged 3, 4, 5 months followed by a booster doses at 18 months and 5-7 years. Since the late 1980s, primary series doses were recommended to be given at 2, 4 and 6 months of age. The 4th dose was recommended for 18-24 months of age and the pre-school booster dose for 5-6 years of age. From 2000 onwards, the4th dose was recommended at 18 months of age. In 2006, acellular pertussis vaccine replaced the whole cell vaccine. In 2011-

	2013, Pentavac (Sanofi PasteurSP) was used for the primary series and Infanrix-Hib (GSK) was used for the 4th dose. For the 5th dose, Infanrix Tetra (GSK) was used in 2011 and subsequently changed to Tetravac (Sanofi Pasteur) from 2012 onwards.

Despite the long standing immunization programme for pertussis, and generally high vaccination coverage, a cyclical pattern of disease occurrence has emerged in the 2000s with peaks every 3-4 years. However, a sharp rise in incidence in 2012 deserves particular attention. In the period from 1993 through the first 6 months of 2013, 788 cases of pertussis have been recorded in Portugal. Since 2000, a cyclic pattern of disease occurrence became noticeable with peaks in 2005, 2008-2009, and 2012. Between January 2011 and June 2013, 338 cases of pertussis were reported: 32 in 2011, 237 in 2012 and 69 for the first 6 months of 2013 (Figure 20).

Overall, 76% (n=258) of cases were below 6 months of age. In 2011, the proportion of cases < 6 months was 94% (n=30) declining to 79% (n=187) in 2012 and 59% (n=41) in 2013. The proportion of cases aged 10 years and older increased from 3% (n=1) in 2011 to 7% (n=17) in 2012 to 23% (n=16) in 2013. Of the total cases, 39% (n=132) were infants that had not reached the recommended age of 2 months to receive the first dose of pertussis vaccine.

Figure 20: Incidence of reported pertussis cases in Portugal, 1993 to 2012
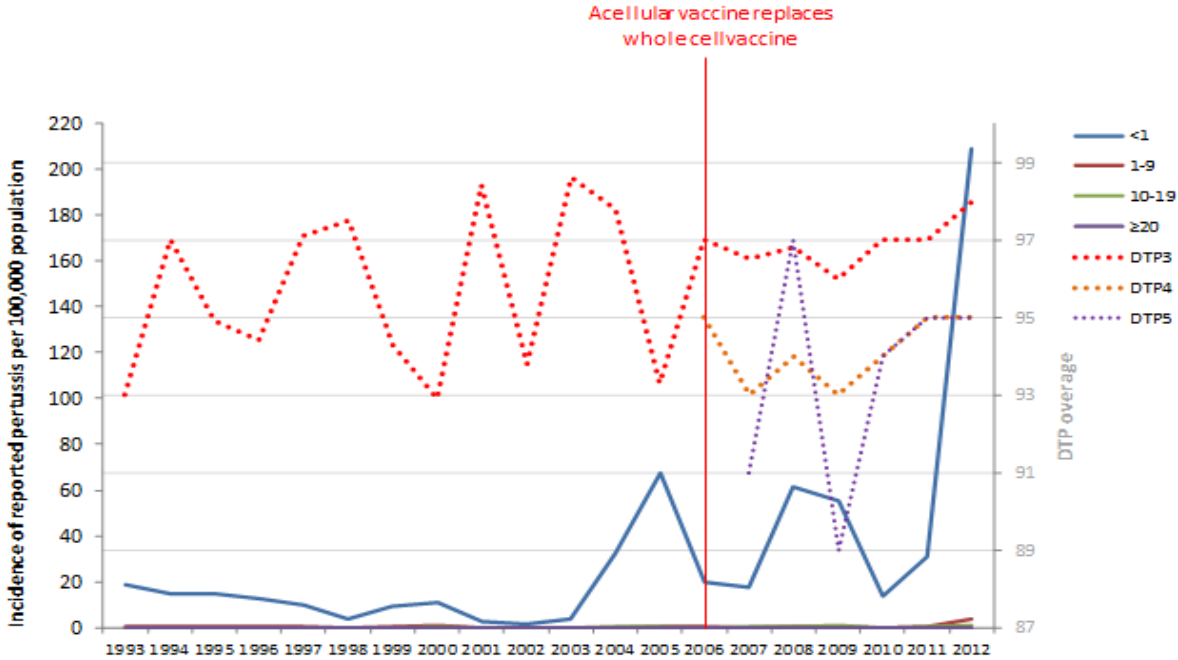
Of the 258 cases below 6 months of age, 108 (42%) were infants between the 2 months and 6 months old and therefore eligible for at least one dose of pertussis vaccine. Of these, 21 (19%) were unvaccinated, 73 (68%) had received one dose of pertussis vaccine, 11 (10%) had received 2 doses and in 3 cases the number of vaccine doses received was unknown. Of these 258 infants below 6 months of age, 247 (96%) were hospitalized.

Twelve pertussis-related deaths were reported for the period 2000-2013, with ages ranging from 2 to 57 weeks. With the exception of2 cases all were unvaccinated. The case fatality rate (CFR) varied between 1.4% in 2005 and 7.7% in 2000. For 2012 and the first 6 months of 2013, the CFR was 2.1% and 4.7%, respectively. The mortality rate per 1,000,000 infants (<1 year old) was highest in 2012 (45 per 1,000,000) relative to mortality rates in 2000, 2004, 2005 and 2008 (range 8-19 per 1,000,000).

Delayed vaccination may have contributed to a number of cases in infants and the high pertussis incidence observed. Similarly, 80% of the fatal infant cases from 2000-2012 had not received any observed (20% had received one dose).

Key conclusions:	• Data quality is acceptable. • In the 2012, a significant rise in incidence in infants <1 years of age was observed suggesting a true resurgence, though incidence may be magnified by increased PCR testing. Infant mortality was very high in 2012, while the mortality over period from 2000-2011 was similar to that in other countries. A possible underreporting in the older age groups is noted. • Whole cell vaccine was replaced by acellular vaccine in 2006.

Singapore (total population in 2012: 5.30 M)

Surveillance	Mandatory universal passive notification since 2008.
Laboratory confirmation	PCR from 2006 onwards, prior to which direct immunofluoresence and culture were used.
Vaccination coverage	98% for the first dose and 97% for full primary schedule (2012). In 2006, a serosurvey that found seroprevalence to be low in adolescents (~50%) and high in adults (~97%) was suggestive of natural infection of adults.
Current vaccine in use	aP (3 component)
Vaccination recommendations	wP (DTwP) in a 3, 4 and 5 months primary schedule, plus a wP booster at 18 months was recommended in 1982. In 2006, a switch to aP (DTaP-OPV) was recommended. In 2008, the 2nd Td booster dose at 6-7 years of age was moved to 10-11 years of age and switched to Tdap and the 3rd Td booster dose was discontinued. In June 2013, DTaP was replaced with DTaP-IPV-Hib. DTaP-IPV-Hib-HepB is also available through both public and private sector facilities. In 2010, an additional booster (Tdap) was recommended for HCWs.

The population size of Singapore greatly increased over the last several years but for the <1 year of age it remained stable. In the below cited surveys the demographics of the reported cases were in line with demographics of the general population.

From 2008-2012, reported pertussis cases occurring in vaccinated persons were generally low (1-3 cases) and predominantly in infants under one year having received only one dose of vaccine. In 2011 and 2012, a slight increase in disease activity was observed with 3 cases in 11-19 year olds and 6 (2011) and 8 (2012) cases in individuals over 20 years occurring after having received more than three doses of pertussis vaccination.

From 2008-2012, hospitalizations were reported mainly from infants under 1 year of age. There were 19 (2008), 5 (2009), 5 (2010),) 10 (2011), and 7 (2012) infant cases hospitalized. No pertussis related deaths have been reported.

A retrospective review of children diagnosed with pertussis from 2004 through 2007 in2 major hospitals (KK Women's and Children's Hospital (2006-2007) and Singapore General Hospital (2004-2006)) was performed.

An increase in incidence for infants <1 year of age was observed between 2007 and 2010. Incidence in 2006 rose from 4/100.000 to 75/100.000 (population) in 2007. Incidence decreased in 2010, but incidence increased again in 2011 to 59/100.000 population (Figure 21). Incidence was highest for infants under 6 months (Table 2).

Figure 21: Pertussis vaccine coverage and reported pertussis incidence
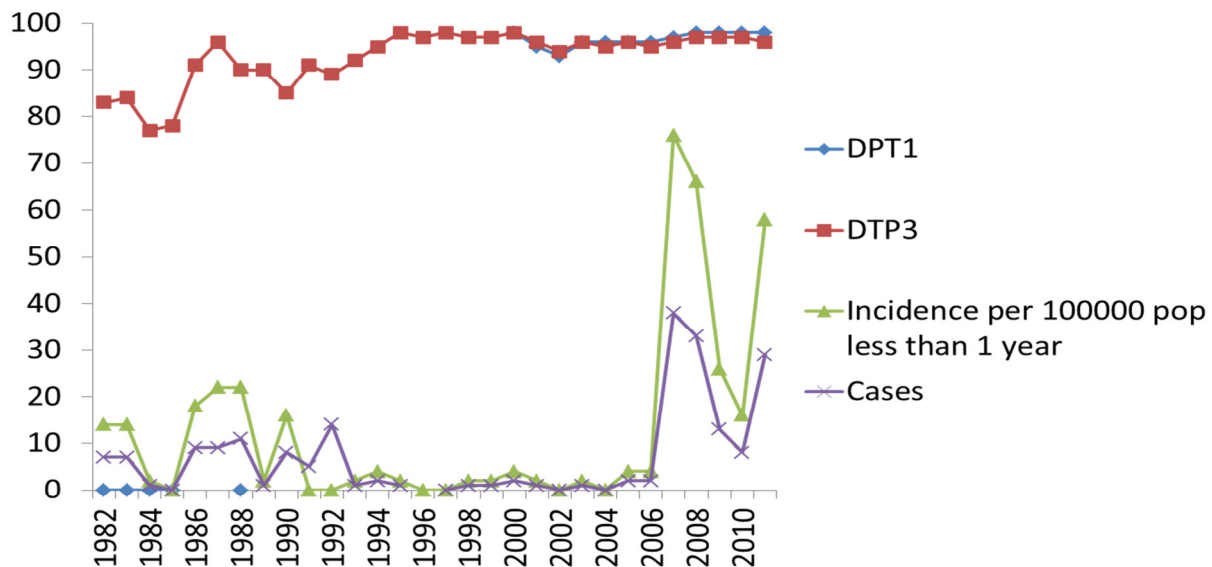
Table 2: Incidence of pertussis by year in infants <6 months and 6-12 months

Incidence of pertussis by year	2009	2010	2011	2012
Infants <6 months	52.1 /100.000	38.2 /100.000	88.2 /100.000	22.9 /100.000
Infants 6-12 months	5.2/100.000	0/100.000	5.5/100.000	0/100.000

In older age-groups over all years of reporting, incidence was ≤1/100,000 with the exception of 2012 where a slight increase in incidence could be observed in 10-14 year olds (1.4/100.000).

Since 1982, an average of 4 cases of pertussis per year have been reported among unimmunized or incompletely immunized children less <1 year. In 2007, a sharp increase in disease activity, with 38 reported cases, was observed.

There were 45 confirmed pertussis cases from 2004 through 2007. Most children (n=42) were <6 months with an age range from 13 days through 5.4 years, with mean age of 4.1 months. 77.8% of children were not vaccinated, 15.6% had received only one dose, 2.2% had received 2 doses, and 4.4% had received 3 doses.

Key conclusions:	• Data quality is good.
	• No evidence for a resurgence of pertussis.
	• Data do not allow for any clear conclusions regarding the sudden increase of pertussis among unimmunized or incompletely immunized in 2007, which may been due to the introduction of PCR, or was a real increase with a doubling of cases in 2007. It is recognized that despite the2 peaks in 2007 and 2011, overall incidence was low.
	• The recent increase in pertussis started soon after the switch from wP to aP in 2006.

Sweden (total population in 2012: 9.51 M)

| Surveillance	Mandatory universal passive notification.
Laboratory confirmation	In 2012: PCR in 61%, serology in 32% and culture in 7% of cases over all age-groups. 97.4% of cases in infants of 0 to 12 weeks of age were PCR confirmed
Vaccination coverage	Vaccination coverage was 98.3% for the primary schedule (DTP3) at 24 months in 2012 and 96% for the booster doses.
Current vaccine in use	aP (2 or 3 component, except of Göteborg area using monocomponent vaccine from 1996-1999)
Vaccination recommendations	wP was withdrawn in 1979. Vaccination was reintroduced in 1996 at 3, 5 and 12 months without a later booster. Ten years later two booster doses were included to children born from 2002; the first at 5-6 years and the other at 14-16 years. Children born 1996-2001 received one single catch-up at the age of 10 years.

The number of reported cases was highest in 2004 and 2005 and has since declined. Incidence was highest among infants <1year of age in 2004, yet overall incidence of reported pertussis cases in Sweden decreased greatly in 1997-2011 in comparison with 1986-95. Hospitalization data are based on an enhanced national surveillance system for pertussis that actively collects hospitalization records. Hospitalization of children <1year of age was highest in 2004 (75/100,000 population) and has declined in parallel to notified cases (Figure 22).
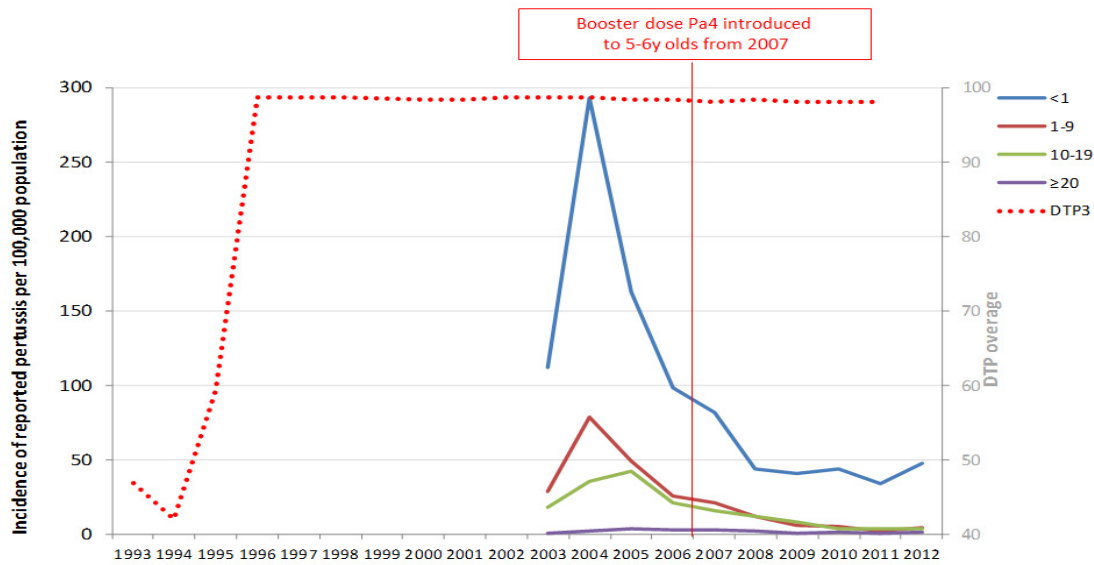
Ten pertussis-related deaths in children were reported from 1997 to 2009, whereof nine in unvaccinated infants and one case in a fully vaccinated 2-year old with severe underlying disease. No deaths have been reported since 2008. It is noted that the overall death rate is very low.

Hypotheses concerning low pertussis incidence include that the national vaccination program was initiated only 18 years ago in comparison to countries with programs ongoing since 40-50 years. It is possible that there still is a natural immunity in parts of the adult population due to previous pertussis disease. Other factors that may contribute to the low incidence is that the infant schedule includes an early booster (at 12 months), and coverage is very high both during infancy and at pre-school age. In addition, contact-tracing is mandatory and these secondary preventive measures reinforce the effect of the national primary prevention through vaccination. Post-exposure chemoprophylaxis are recommended to all infants.

| Key conclusions:	• Data quality is good. • No resurgence as yet and no major outbreaks since 2004. • A successive reduction in the overall pertussis incidence can be observed since the re-introduction of pertussis vaccine after a 17-year period without use of vaccine.

Thailand (total population in 2012: 66.79 M)

Surveillance	Mandatory universal passive notification
Laboratory confirmation	Infrequent use of PCR from 2005 onwards; culture was used previously.
Vaccination coverage	Vaccination coverage, derived from survey data, increased over time and reached 98% for complete primary series (DTP3) by 24 months in 2010.

Current vaccine in use	wP (before 2005, vaccine was locally produced; after 2005, use of DTwP produced by SII or Biofarma, and since 2008, DTPw-HB from GSK, SII or Biofarma. An exception was in 2009-2010, when the majority was produced by Shanta Biotech with local filling
Vaccination recommendations	wP vaccines have been used so far. From 1977 to 1981 at 2 and 4 months, vaccination was recommended for use in the Bangkok area only. From 1982 onwards, vaccination was recommended at 2, 4 and 6 months. In 1991, a booster dose was recommended at 18 months, and in 2000, an additional booster was recommended at 4 years of age.

No increase in cases has been observed in the recent years in infants <1year of age (Figure 23). Only 2 deaths were reported in the last 20 years in a 2 year old in 1999 and a less than 3 month old infant in 2003. In the last 10 years, only one outbreak was reported in a very remote area of the country (2006).

Figure 23: Pertussis incidence in Thailand by year, 1990 to 2012
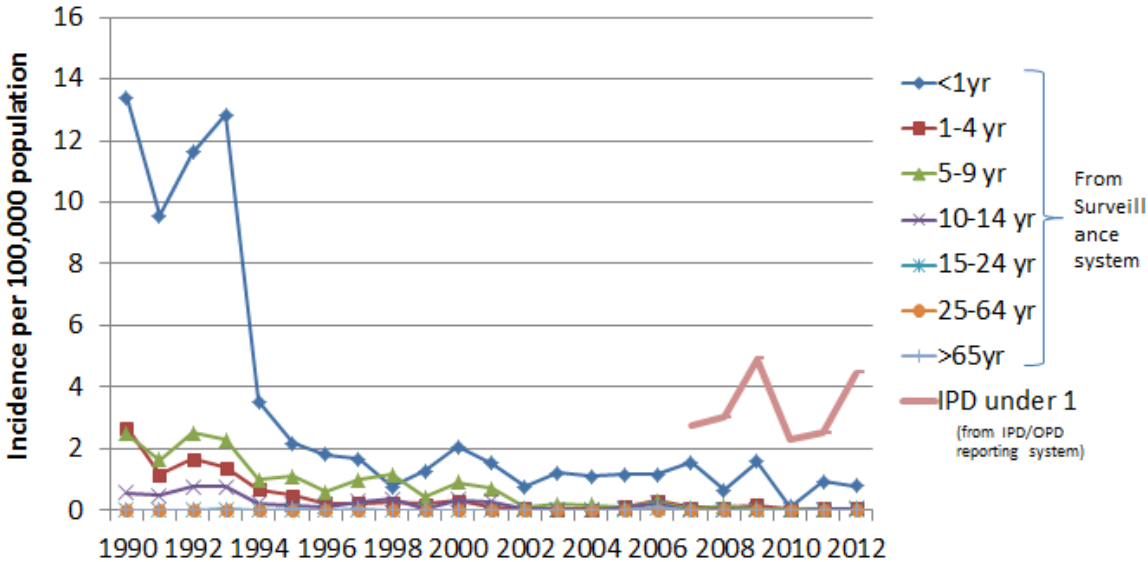
Two additional studies were highlighted: the first, a mathematical modeling study, suggests that there is no evidence for resurgence (Blackwood et al., 2013). The second, a study in a large children's hospital, recruited 96 patients aged up to 18 years of age with cough >7 days + additional symptoms. 92% had received DPT and 18.8% were PCR positive for pertussis, yet there were only 8 reports through national reporting system and hospital management information system, suggesting substantial underreporting. Yet the case definition varies between the reporting system and the study conducted in the children's hospital (cough for >14 days vs 7 days)[6]

Key conclusions:	• Data quality is limited • Underreporting of cases. Sensitivity of surveillance system is low. No change of surveillance system since its start. • No evidence of pertussis resurgence • Thailand has used only whole cell pertussis vaccination as stand-alone DTwP until 2008, after which DTwP-HepB has been used for the primary schedule.

UK (England & Wales) (total population in 2012: 56.57 M)[2]

Surveillance	In the UK there are three national surveillance systems in place based on laboratory confirmed cases, hospital admissions, and national notification.
Laboratory confirmation	PCR is mainly used in hospitalized infants <1 year but is currently being trialed across all age groups. Serology was introduced in 2001. Oral fluid collection, a new method of serologic testing assessing IgG levels, was introduced in January 2013 to test 8-16 year olds in an effort to further improve ascertainment in these age groups. This test has proven to be highly specific test, yet sensitivity is not optimal.
Vaccination coverage	Vaccination coverage is 96.4% at 12 months for the primary schedule (DTP3) and 89.2 % at 24 months with booster dose at 5 years of age.
Current vaccine in use	aP (5 component)
Vaccination recommendations	From 1957-1990, wP (DTwP) was used as primary immunization. From 1990 until today, the primary doses are given at 2, 3 and 4 months. In 2001, a TdaP preschool booster was introduced (Infanrix or Repevax). wP was used until 2004 after that only aP (DTaP5) has been used. In 2012, a single dose of TdaP (Repevax) was recommended for pregnant women.

In 2012 lab-confirmed pertussis incidence was highest among infants in the <3 months and 3--5 month age groups. From 2011, incidence increased predominantly in children 10-14 years and infants <1 year of age, but all age-groups, except children 1-9 years of age, were affected (Figure 24).

Figure 24: Incidence of laboratory confirmed pertussis by age group, 1998 to 2012
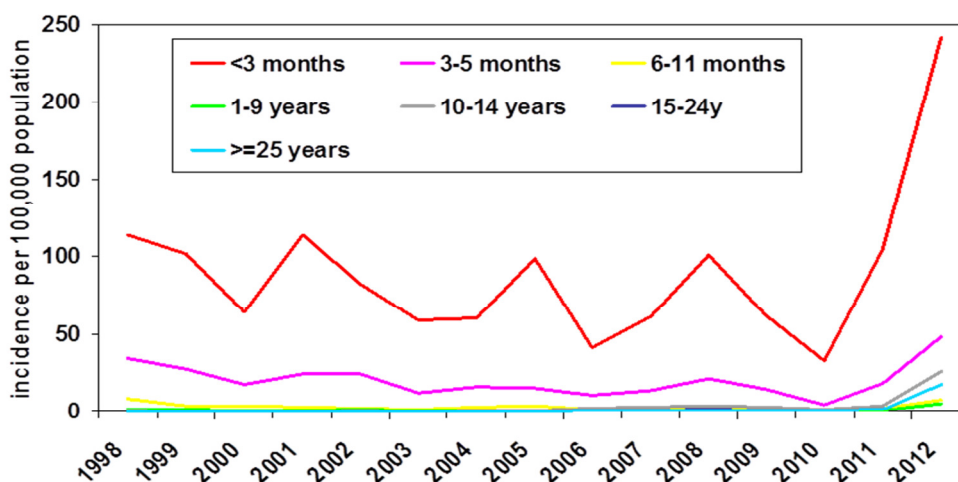
Hospitalization of infants <1 year increased in the last 2 years, particularly among infants <3 months of age. In 2012, 14 deaths from pertussis in infants <12 months were reported, with increasing mortality from an average of 4-5 per million per year to 19.7 per million per year.

It was hypothesized that the increase in pertussis cases was at least in part due to an aP induced waning of immunity and reduced acquisition of natural immunity, particularly in 10-14 year olds.

Key conclusions:	• Data quality is good. • Evidence suggests a resurgence of pertussis. • Although incidence has declined over the last 20 years, no interruption of natural 3-4 year epidemic cycle could be seen. A real increase over the natural cycle was observed in the infants <3 months in the years 2011 and 2012. An increase in notified cases, in hospitalization, and in the crude number of deaths could be observed. A real resurgence was registered 7 years after the introduction of aP vaccine, coinciding with the peak of the natural epidemic cycle.

USA (total population in 2012: 317.51 M)

Surveillance	Mandatory universal passive notification of pertussis disease. Hospitalization status is collected through national pertussis surveillance; however, ICD coded pertussis hospitalizations are also recorded through other hospital surveillance sources (National Immunization Survey (NIS), Kids' Inpatient Database (KID)). Death information is collected through national pertussis surveillance, and in addition, NCHS records pertussis deaths from death certificates.
Laboratory confirmation	Culture was historically used for lab confirmation, yet PCR is now widely used. 62% of the cases were confirmed by PCR in 2012.
Vaccination coverage	Vaccination coverage for completion of the primary schedule was 95.5% and was 84.6% for 4 or more doses.
Current vaccine in use	aP (3 and 5 component)
Vaccination recommendations	Early vaccination recommendations from 1992 included vaccination with wP primary schedule at 2, 4 and 6 months plus 2 aP (DTaP) booster doses at 15-18 months and 4-6 years. From 1997 onwards a switch to aP (DTaP) was recommended with no change in schedule. In 2005, additional booster doses were recommended at 11-12 years and in adults to replace the recommended dose of Td. In 2011, one dose was recommended for pregnant women; in 2012, this policy was extended to one dose recommended during each pregnancy.

In 2004, 2005, and 2012, an increase in cases was observed, mostly affecting infants <6 months and adolescents, but there was an increase in all age groups in 2011-2012 (Figure 25). This was reflected in an increase in hospitalizations, with the highest proportion of hospitalized cases in infants <3 months of age.

Reported pertussis incidence by age group: 1990-2012
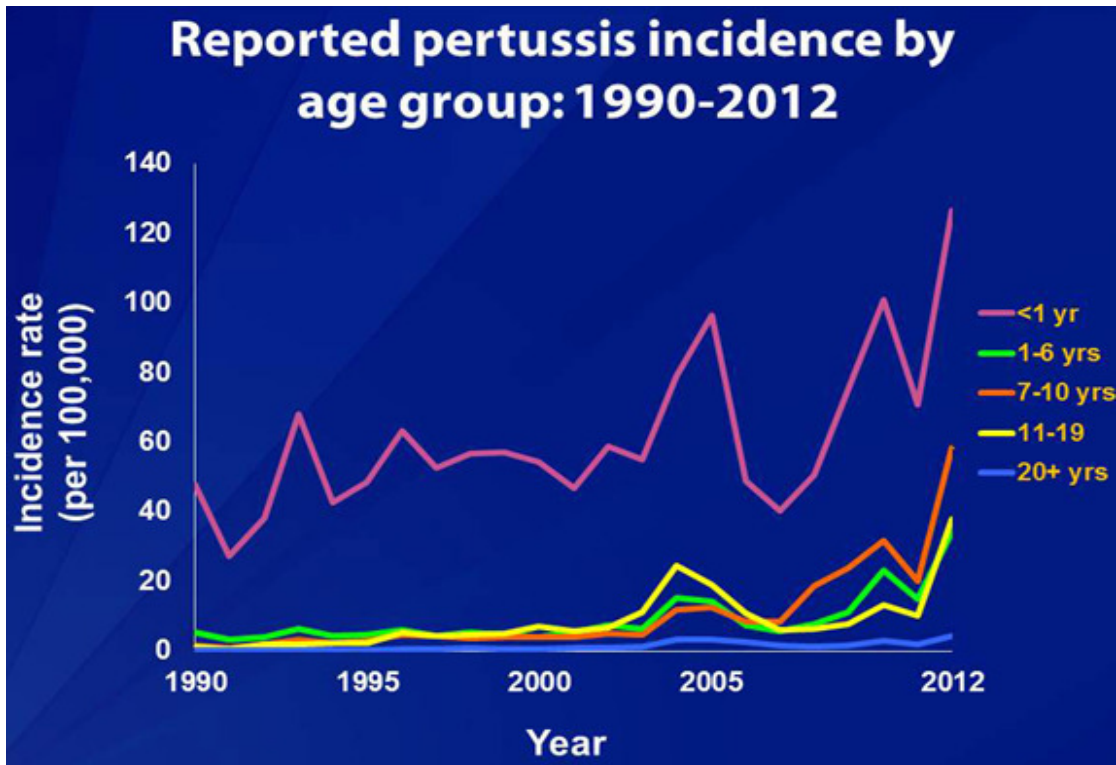
From 2003 to 2012, an average of 10 to 35 deaths were reported per year. In 2012, the death rate was 4.1/1,000,000 births in infants under 1 year of age. The majority of infant pertussis deaths occurred among unvaccinated individuals. From 2000 to 2012, only 7 of 231 total infant pertussis case-patients who died had received any documented doses of pertussis-containing vaccine prior to cough onset. 6 cases had received one dose of DTaP, and 1 case received 3 doses of DTaP. All of these deaths occurred among infants less than 6 months of age.

Regional differences of pertussis were noted, hospitalizations were lower in Washington compared to California, possibly related to ethnicity (Hispanic), as no differences in access or coverage of this population group could be observed, raising the point of genetic preposition or mixing patterns.

Key conclusions:	• Data quality is good. • Evidence suggests a resurgence of pertussis. • Since introduction of aP in 1997, despite stable coverage, an increase in incidence predominantly in older age-groups leading to high morbidity has been observed, suggesting a short protective effect of aP. Mortality and incidence under one has not (yet) been affected. • Ethnicity might have an influence on disease severity.

Conclusions and recommendations from country specific data

This review has several limitations. Assessment of the trends in the burden of pertussis is complex even at the country level, and especially so for between country and global comparisons. A number of factors relating to vaccines, populations in which they are used, and changes in surveillance over time, should be considered. With respect to vaccines, factors include the vaccine type in use (wP versus aP), differences in the composition and production of aP and wP vaccines, and differences in schedules over time, and duration of vaccine programs at various levels of coverage for the primary series and booster doses. With respect to populations, substantial changes may have occurred in age distribution (e.g. aging of populations and smaller ratio of birth cohort to the entire population) and mixing and transmission patterns over time. Finally, and most importantly, the nature and completeness of local surveillance is critical and highly variable. Changes in surveillance and diagnostic methods and performance (especially regarding laboratory confirmation of suspected cases) make it difficult, both within and especially between countries, to analyze and interpret epidemiological trends. However, the group concluded unanimously that this was nevertheless the best possible approach towards a greater understanding of pertussis epidemiology at the global level.

Figure 26: Incidence of infant (<1 year old) pertussis cases by year and country
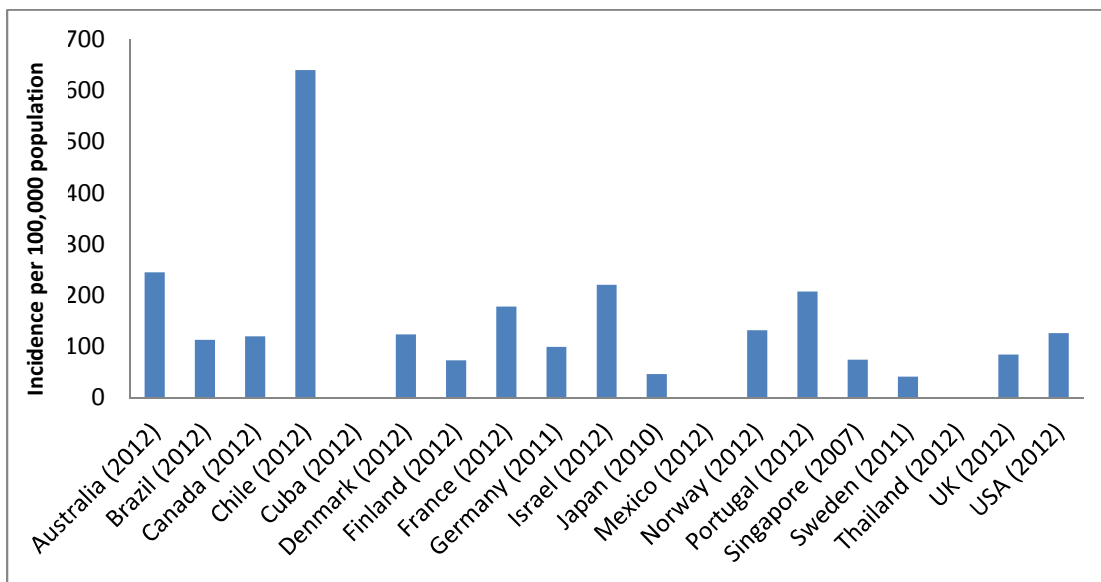
*Raw data available only from selected countries. Estimates stem from provided graphs (Finland, Thailand). Denominator data may deviate from nominator data (Japan). Incidence only provided for cases 0-5 months (France). Data provided only for Eastern Federal States (Germany). Data from JRF (Norway).

Figure 27: Incidence of infant pertussis hospitalizations by year and country
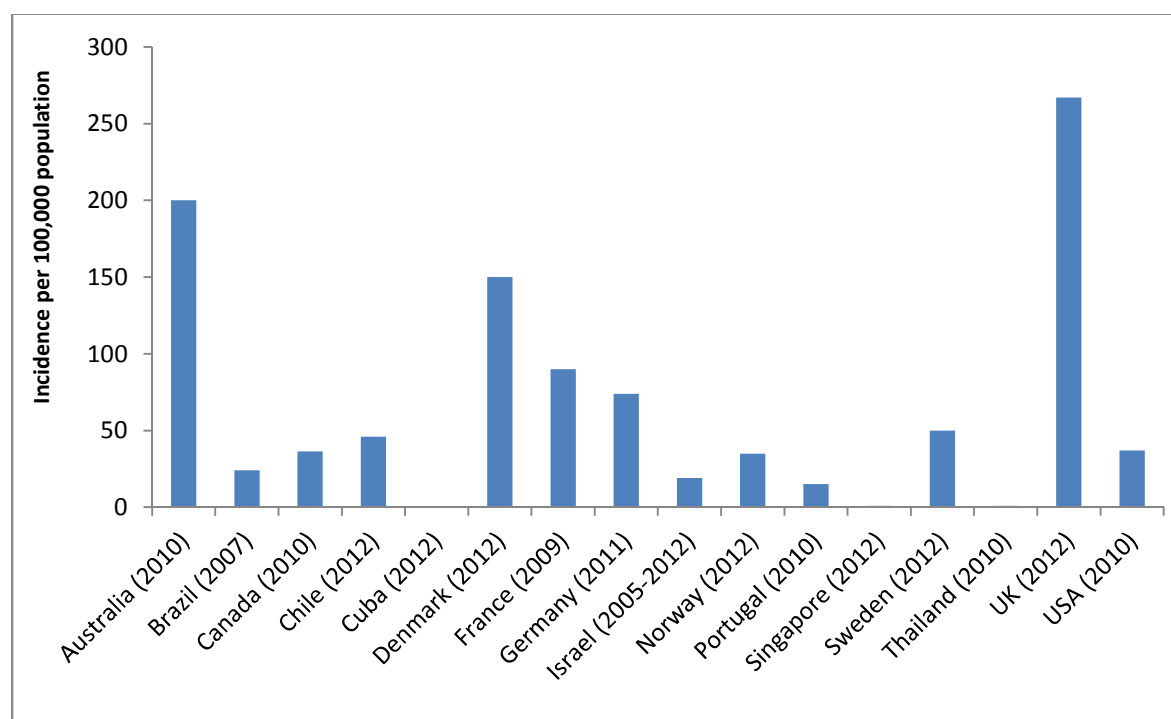
*No data available from Japan, Mexico and Finland. Brazil, data from 2007, denominator 2012. Crude data not available, estimate from graph (Denmark, Norway, Portugal, Sweden, Thailand). Data from 2009, denominator from 2012 (France). Average of Former Eastern and Western Federal states (Germany). Average from 2005-2012 (Israel). Two different incidence estimates: Incidence NNDSS: 36.92 in 2010, for NIS and KID: 79.37 (USA)

Table 3: Summary of a decade of pertussis deaths (age < 12 months)

Name of country	Total deaths 2003-2012	Birth cohort average 2003-2012	Peak deaths (year)	Birth cohort at peak year	Death rate per million		Death rate per million	
					per decade	(95% CI)	at peak year	(95% CI)
Australia	12	283684	3 (2001)	302189	4.2	(2.2, 7.4)	9.9	(2.0, 29.0)
Brazil*	342	3204365	83 (2012)	3008538	8.2	(7.4, 9.1)	27.6	(22.0, 34.2)
Canada	14	363659	3 (2012)	390900	3.8	(2.1, 6.5)	7.7	(1.6, 22.4)
Chile	94	246578	16 (2011)	245672	38.1	(30.8, 46.7)	65.1	(37.2,105.8)
Denmark*²	2	64174	1 (2010)	63852	3.9	(0.5,14.1)	15.7	(0.4, 87.3)
France*³	32	786394	10 (2005)	782481	4.1	(2.8, 5.7)	12.8	(6.1, 23.5)
Germany*³	2	706277	2 (2011)	697040	0.3	(0.1, 0.9)	2.9	(0.3, 10.4)
Israel*²	9	147086	4 (2007)	146563	7.6	(3.5,14.5)	27.3	(7.4, 69.9)
Mexico	192	2354798	38 (2012)	2268950	8.2	(7.0, 9.4)	16.7	(11.9, 23.0)
Norway	2	59654	1 (2012)	62109	3.4	(0.4, 12.1)	16.1	(0.4, 89.7)
Portugal	9	102846	4 (2012)	93814	8.8	(4.0, 16.6)	42.6	(11.6, 109.2)
Sweden	4	107293	2 (2004)	100232	3.7	(1.0, 9.5)	20.0	(2.4, 72.1)
Thailand	1	778790	1 (2003)	858079	0.1	(0.0, 0.7)	1.2	(0.0, 6.5)
England and Wales	50	676402	14 (2012)	731996	7.4	(5.5, 9.7)	19.1	(10.5, 32.1)
United States	178	4220322	35 (2005)	4212276	4.2	(3.6,4.9)	8.3	(5.8, 11.6)

* Brazil is included 13 years data from 2000 to 2012
*² Denmark, Israel are included 8 years data from 2005 to 2012
*³ Germany, France is included 10years data from 2002 to 2011
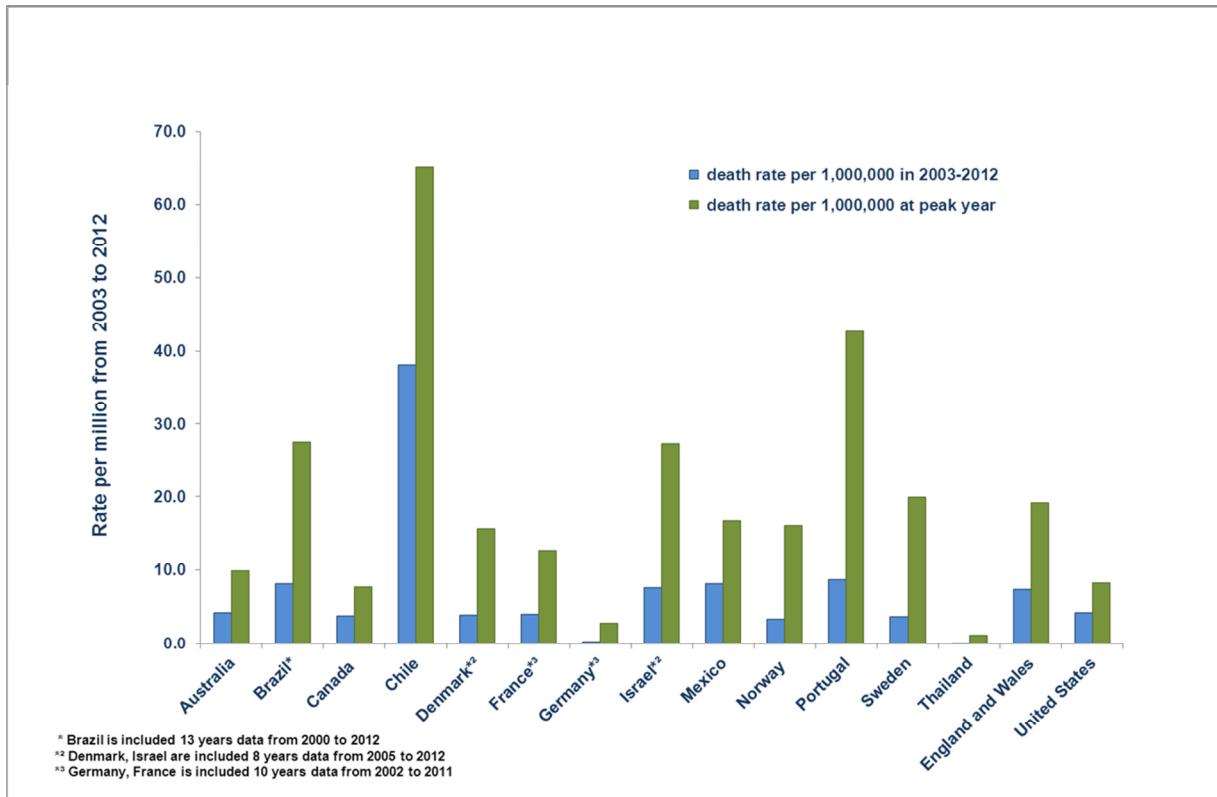
Country specific data from 19 countries provided no evidence of a broad resurgence of pertussis at the global level. The increase in pertussis cases was attributed to cyclic patterns in the majority of countries where the increase was noted over the recent years, likely amplified by increase in disease awareness, increase in overall laboratory testing, and the enhanced sensitivity of the PCR diagnostic methods being used more widely. Natural recurring cycles might be more noticeable in countries where surveillance is more sensitive and where the control of the disease in recent years has generally been good.

Data from only 5 out of 19 countries (Australia, Chile, Portugal, USA and UK) supported the presence of a true resurgence in pertussis related morbidity in recent years relative to prior comparison periods. For Israel, the situation was unclear and more information is needed on the use of new diagnostic methods and other factors, such as increased awareness that might have recently improved case ascertainment.

Only one country using whole cell pertussis vaccination, Chile, reported a resurgence. For now it seems that the increase in cases could be attributed to a sustained decrease of vaccine coverage, variable coverage at the district level, changes in surveillance practices as well as problems with the specificity of diagnostic tests. The increase in infant cases was notable and associated with increased mortality, but as this was based on fluorescent antibody test data alone (known to have problems with specificity), more data on the characteristics of laboratory confirmation and cases were needed. Although reported data suggested a major recent increase in pertussis in Brazil, another country still using wP, it seems that the appearance of the increase was exaggerated due to changes in the surveillance system and that the change in disease activity is not in excess from what would be normally expected in epidemic cycles.

Thus, pertussis resurgence is not observed to date in any country using whole cell pertussis vaccines.

Data from Australia suggest a major increase in morbidity in children less than 10 years of age, including hospitalizations in infants <1 year but without an increase in mortality in this age group. It was considered that the resurgence was most likely related to cessation of the early childhood booster dose and aP-related waning of immunity among children before the 4 year booster was due.

Data from Portugal suggest that although increased testing with PCR may have contributed to the observed increase in incidence, the high proportion of affected infants <1 year of age and the high mortality rate from pertussis in this age group suggest a true resurgence of the disease.

Data from the US suggest waning of immunity following aP, but no impact on infant mortality was observed. The US data also clearly point to the more limited duration of protection from adolescent booster vaccination in individuals primed with aP vaccines compared to those who had at least one dose of wP.

An increase in notified cases, in hospitalizations, and in deaths in young infants was observed in England and Wales in 2011. The cause of this resurgence is still unclear and is being investigated.

Limited evidence suggests that ethnicity may be a potential risk factor for fatal disease, but it should be further investigated. Specifically it was noted that Hispanic children in the US have a greater mortality rate. Whether this is genetic based or related to access to care remains to be determined.

Evidence is not sufficient to assess a significant difference in vaccine effectiveness using different component aP vaccines; there is no conclusive data yet establishing the superiority of one aP vaccine versus another.

Pertussis vaccination has had a great impact in reducing the overall burden of disease. Cyclic recurrent patterns of pertussis can still be observed, but there has been an overall reduction of pertussis incidence, and in particular, a reduction in infant mortality. Both wP and aP are effective in reducing infant mortality, yet data highlight the importance of timely vaccination and high coverage, and point to the presence of an aP-related waning of immunity.

3. Acellular pertussis vaccine immunogenicity and efficacy studies in infants

With the development and testing of new aP vaccines in the 1980s and 1990s, assays to measure the humoral immune responses to the new vaccines were established [7]. In addition, the NIH supported a large comparative safety and immunogenicity trial of 13 aP and2 wP vaccines, combined with diphtheria and tetanus toxoids, and administered to infants at 2, 4, and 6 months of age [8, 9]. The trial was termed the Multicenter Acellular Pertussis Trial (MAPT). Serum samples were taken prior to and 1 month after the third vaccination, and enzyme-linked immunosorbent assays (ELISA) were performed to measure humoral responses to pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbriae (FIM). As shown in Table 1, the antibody responses to the acellular vaccines and the whole cell vaccines were compared[10]. The PT response to the wP vaccine was noted to be in the middle of the responses, while the PT antibody responses to the aP vaccines generally were comparable or higher than those noted after the whole cell vaccine, but with substantial variability in responses. The antibody responses to the other pertussis antigens are also shown in Table 4.

Following MAPT, several randomized pertussis vaccine efficacy studies were conducted in Europe and Africa in the late 1980s and early 1990s to compare the safety and efficacy of the aP with the wP vaccines for the prevention of laboratory-confirmed pertussis disease in infants [11-14, 15-19]. Although they provided pivotal safety and efficacy data needed for the replacement of DTP vaccines by DTaP vaccines, important differences in the study design, such as the inclusion of different whole-cell vaccines as the comparator arms, the number of aP components included in the DTaP vaccines, and different case definitions, made comparisons of the many different studies problematic. A detailed summary of the data derived from these pivotal efficacy studies are presented in Table 4. As noted in the table, vaccine efficacy varied among the different acellular vaccines, among the different whole cell vaccines, and between different whole cell and acellular products. What was remarkable was that the Connaught whole cell vaccine that served as the control in the Swedish and the Italian trials was very poorly immunogenic, stimulating very little antibody to PT, FHA, and pertactin. The efficacy of the Connaught wP vaccine was also lower than the included aP vaccines, and lower than the efficacy of the wP vaccines used in the other trials.

Another efficacy study, not cited in the table, was a trial comparing the efficacy of the 2, 3, and 5 component aP vaccines against a UK whole cell vaccine in 82,892 infants randomized to receive the vaccines in2 different schedules; at ages 3, 5, and 12 months, or at ages 2, 4, and 6 months. The primary case definition was culture-confirmed *B. pertussis* with at least 21 consecutive days of paroxysmal cough (typical pertussis), and the secondary definition was any culture confirmed *B. pertussis* with or without cough (pertussis infection). Although no significant difference was found in the efficacy of the whole-cell and the 55-component aP vaccine, the 3-component aP vaccine was less effective than either whole cell or the 55-component vaccine against culture-confirmed pertussis [20]

Overall conclusions from these efficacy studies were that multi-component acellular vaccines, defined as vaccines containing three or more pertussis antigens, were effective in preventing confirmed pertussis

infections and were associated with fewer adverse events than whole cell pertussis vaccines for the primary series. Multi-component acellular vaccines were more effective than low-efficacy whole-cell vaccines, but less effective than the highest-efficacy whole-cell vaccines.

Table 4: Antibody levels one month following the third dose of vaccine: results from the multicenter acellular pertussis trial and a follow-up trial.

Manufacturer or Distributor	Vaccine†	Geometric Mean Antibody Level (95% CI) Following Immunization at 2, 4, and 6 Months			
		PT	FHA	PRN	FIM
Sanofi Pasteur (Canada)	Tripacel	36 (32–41)	37 (32–42)	114 (93–139)	240 (204–282)
Sanofi Pasteur (Canada)	CLL-3F₂	38 (33–44)	36 (31–41)	3.4 (3.1–3.6)	230 (183–290)
Sanofi Pasteur (France)	Triavax	68 (60–76)	143 (126–161)	3.3 (3.1–3.6)	1.9 (1.6–2.1)
Sanofi Pasteur (USA)	Tripedia	127 (111–144)	84 (73–95)	3.5 (3.2–3.9)	2.0 (1.7–2.3)
Baxter Laboratories	Certiva	54 (41–71)	1.1 (1.0–1.2)	n/a	n/a
Biocine Sclavo	BSc-1	180 (163–200)	1.2 (1.1–1.4)	3.4 (3.1–3.7)	1.8 (1.7–2.0)
Chiron Vaccines	Acelluvax	99 (87–113)	21 (18–25)	65 (53–79)	1.9 (1.7–2.1)
GlaxoSmithKline	Infanrix	54 (46–64)	103 (88–120)	185 (148–231)	1.9 (1.7–2.2)
Massachusetts Public Health Biologic Labs	SSVI-1	99 (87–111)	1.2 (1.1–1.3)	3.4 (3.1–3.6)	2.1 (1.8–2.4)
Michigan Department of Public Health	Mich-2	66 (59–75)	237 (213–265)	3.2 (3.0–3.4)	2.0 (1.8–2.3)
SmithKline Beecham Biologicals	SKB-2	104 (94–116)	110 (99–122)	3.3 (3.1–3.5)	1.9 (1.7–2.1)
Speywood (Porton) Pharmaceuticals	Por-3F₂	29 (25–33)	20 (17–23)	3.0 (3.0–3.1)	361 (303–430)
Wyeth Lederle Vaccines and Pediatrics	LPB-3P	39 (32–48)	144 (127–163)	128 (109–150)	19 (13–27)
Wyeth Pharmaceuticals	ACEL-IMUNE	14 (12–17)	49 (45–54)	54 (47–62)	51 (41–63)
Wyeth Lederle Vaccines and Pediatrics	Whole-cell	67 (54–83)	3.0 (2.7–3.4)	63 (54–74)	191 (161–227)

CI, confidence interval; FHA, filamentous hemagglutinin; FIM, fimbrial proteins; MAPT, Multicenter Acellular Pertussis Trial; n/a, not available; PRN, pertactin; PT, pertussis toxin.

Table 5: Pertussis vaccine efficacy trials

Study	Study Design	Vaccine(s)	Absolute Vaccine efficacy % (95CI)	Antigens	Whole cell vaccine	Case Definition
Stockholm-Sweden (1986)[21]	Randomized, double-blinded, placebo-controlled study	JNIH-6 JNIH-7	81 (61-90) 75 (53-87)	**PT, FHA** **PT**	None	≥ 21 days cough + ≥ 9 coughing spasms on at least 1 day + positive culture
Stockholm (1992)[18]	Randomized, fully blinded, placebo-controlled study	SKB-2 *Tripacel* **Connaught-DPT**	59 (51-66) 85 (81-89) 48 (37-58)	**PT, FHA, DT, TT** **PT, FHA, PRN, FIM 2, FIM3, DT, TT**	Connaught-DPT	≥ 21 days paroxysmal cough + either: positive culture, confirmed by serologic assay or PCR; 2-fold PT or FHA IgG rise; or epidemiological link to culture-positive case
Italy (1992)[16]	Randomized, double-blinded, controlled, comparative study	*Infanrix* *Acelluvax* **Connaught-DPT**	84 (76-89) 84 (76-90) 36 (14-52)	**PT[1], FHA, PRN, DT, TT** **PT[2], FHA, PRN, DT, TT**	Connaught-DPT	≥ 21 days paroxysmal cough + either: positive culture, confirmed by serologic assay or PCR;
Goteborg-Sweden (1991)[15]	Randomized, fully blinded, controlled study	*Certiva*	71 (63-78)	**PT, DT, TT**	None	≥ 21 days paroxysmal cough + either: positive culture confirmed by serologic assay or PCR; 3-fold PT or FHA IgG rise
Senegal (1990)[13]	Randomized, fully blinded, controlled study	*Triavax* **PMC-Fr DPT**	74 (51-86) 92 (81-97)	**PT, FHA, DT, TT**	PMC-Fr DPT	≥ 21 days paroxysmal cough + confirmation by culture, serology or epidemiological link
Erlangen-Germany (1991)[22]	Randomized, double-blinded, controlled study[3]	*ACEL-IMUNE* **Lederle DPT**	78 (60-88) 93 (83-97)	**PT, FHA, PRN, FIM 2, DT, TT**	Lederle DPT	≥ 21 days cough with paroxysm, whoop, or vomiting + confirmation
Mainz-Germany (1992)[23]	Passive monitoring for suspected household cases	*Infanrix* **Behring, SKB DPT**	89 (77-95) 98 (83-100)	**PT, FHA, PRN, DT, TT**	Behring, SKB DPT	≥ 21 days paroxysmal cough + either: positive culture, or serology in households
Munich (1993)[12]	Case-control study	*Tripedia* **Behring, DPT**	93 (63-99) 96 (71-100)	**PT, FHA, DT, TT**	Behring, DPT	≥ 21 days paroxysmal cough + either: positive culture or household contact with laboratory confirmation

Modified from Kathryn M. Edwards and Michael D. Decker. Pertussis vaccines. Vaccines. Plotkin and Orenstein. 4th ed.
CI, confidence interval; DTP, diphtheria and tetanus toxoids and whole-cell pertussis vaccine; FHA, filamentous hemagglutinin; FIM, fimbrial proteins; HCPDT, hybrid component pertussis-diphtheria-tetanus vaccine; PMC-Fr, Pasteur Merieux Connaught–France; PRN, pertactin; PT, pertussis toxin; SKB, SmithKline Beecham.
All results shown are for complete primary infant immunization series (3 doses, except Stockholm 1986, 2 doses); effects of booster dose not included.
[1] PT inactivated with formalin and glutaraldehyde.
[2] Genetically detoxified pertussis toxin.
[3] DTaP and DTP vaccines were administered in a double-blind, randomized design meanwhile DT vaccine was administered in an open arm of the study based on parental preference.

4. Baboon experimental model: comparison of aP and wP and proof of concept studies for neonatal and maternal vaccinations

Tod Merkel and his colleagues at the US Food and Drug Administration (FDA) in Bethesda, Maryland have developed a baboon model of pertussis that closely resembles human disease[24]. Recently they used that model to show that acellular pertussis vaccines protect against disease but are not fully effective in preventing infection and transmission of pertussis to other animals[25]. Their studies also show that the DTaP vaccines are much less effective at preventing infection than natural disease and are substantially less effective than DTwP vaccines[24]. Like for the nonhuman primates, asymptomatic transmission of *B. pertussis* to other humans may also occur in DTaP immunized humans and may drive pertussis outbreaks. The other notable finding in the baboon study is the role of both Th1 and Th17 cells in the immune response to natural infection and DTwP vaccine, but only Th2 immune responses after DTaP vaccines. It appears that both Th1 and Th17 memory responses are needed for sterilizing mucosal immunity. aP has therefore a reduced ability to prevent infection and reduce subsequent transmission relative to wP and natural infection.

Merkel et al. have also used the nonhuman primate model of pertussis to address the ability of neonatal and maternal vaccination to confer protection[26]. Neonate baboons were vaccinated with acellular pertussis (aP) vaccine at 2 days of age or at 2 and 28 days of age. To model maternal vaccination, adult female baboons that had been primed with aP vaccine were boosted at the beginning of their third trimester of pregnancy. Unvaccinated 5 week old baboons developed severe disease when challenged with *B. pertussis* at 5 weeks of age. Baboons receiving either 1 or2 doses of aP vaccine and infants born to mothers vaccinated at the beginning of their third trimester were protected. These studies clearly showed that neonatal and maternal vaccination confer protection in the baboon model and provide a proof-of-concept that supports further study of these strategies for protection of newborns from pertussis infection. The potential for evaluating alternative pertussis vaccine approaches in the nonhuman primate model is extremely attractive.

5. Pertussis modelling studies

Different country-specific mathematical pertussis models were presented from Australia, the UK and the US.

Australia

The existing 'Hethcote' model was adapted by Jodie McVernon et al. from the University of Melbourne and James Wood from the University of New South Wales to reflect Australian epidemiology. This new model allows incorporation of multiple national data resources, including recurrent national serosurveys of PT antibody distribution.

The research and policy questions driving this model were:

What are the relative contributions of natural and vaccine derived immunity on observed pertussis epidemiology?

How have the changes to the vaccine schedule and vaccine type influenced the patterns of disease and infection that we observe in Australia?

What are the likely public health impacts of suggested changes to the pertussis vaccine program in Australia?

Multiple data sources were consulted to inform the deterministic, age-structured, compartmental, dynamic model. Sub-categorization by immunologically naive and experienced (natural- or vaccine-acquired immunity) population was incorporated into the modelling. Assumptions were that all infections are infectious to some degree. Non-infectious boosting cycles were included in the model. Simulations were conducted for chosen parameters; the output was matched with key features of the Australian epidemiology. Alternative model assumptions were explicitly tested.

The key conclusion from the model was that natural immunity is the primary driver, with an influence over decades.

The model demonstrated a strong interaction between natural and vaccine immunity, and found that small changes in coverage could lead to loss of direct effects impacting on rates of pertussis infection decades later. The model explored the impact of different vaccination schedules and supports the assumption that additional doses are important for herd protection. The age at administration was less influential. Over the period of observation, aP inferred to have slightly shorter duration of protection than wP, but the period of observation for aP was much shorter and so may have under-estimated differences in duration of protection.

One potential role of the model is to explore long-term effects of vaccination and synthesize country-specific data. It models infection rather than disease, and suggests a role for serosurveillance in prediction, in that the Australian series of cross-sectional data over more than a decade found a low prevalence of elevated PT antibody titres prior to an epidemic year. The model predicts that small

changes in coverage or schedule can have a large subsequent impact on the resurgence of infection. In infants, unlike older age groups, infection would be expected to closely parallel disease. It was noted that the differences in model structures between groups can lead to differences in model outcomes.

The United States

Manoj Gambhir, currently at Monash University, Australia, described work he had done with collaborators while working at the US Centres for Disease Control and Prevention to construct a compartmental deterministic model simulating the natural history and population transmission of B. pertussis in the US. Infected individuals can be either primary infected or infected more than once. Several models were fitted to the available data with results based on the best-fitting model. Confidence intervals for model parameters had to be found. Ranges of plausible outcomes were chosen. Multiple data-sources fed into the model: Vaccination coverage obtained from National Immunization Surveys (NIS), U.S. demography, 'Polymod' age mixing matrix and National Notifiable Diseases Surveillance System (NNDSS) pertussis incidence counts.

Outputs of the model were the change in vaccine efficacy, the change in duration of protection, the infectiousness and susceptibility of secondary infections, the R0 and the reporting rate change. The known parameters are "fixed" and the unknowns vary. The results of the best-fitting model: The model demonstrates the shift of disease to adolescents over time (1994-2012). The best-fitting model incorporates a drop in vaccine efficacy and a rise in the waning rate of protection from the wP to aP. The duration of whole-cell vaccine protection corresponds with natural infection.

England and Wales

Yoon Choi et al. (Public Health England, London, UK) developed a realistic-age-structured, compartmental deterministic model to describe the pertussis transmission dynamics.

The main questions to the model were: Why did this resurgence occur and will it continue?

Is an adolescent booster programme enough to control this resurgence? What would have happened if wP vaccine was not replaced with aP vaccine in the primary schedule?

If there had been no dramatic decline in vaccine uptake in 1970s (associated with concerns about wP safety), would the continued use of wP still brought about the resurgence?

The model included 100 yearly age cohorts and a 52 weekly age structure in each annual age cohort. The model assumed the move to the compartment of non-susceptibility after natural infection. The model was parameterised using the pre-vaccination pertussis notification data and simulated with historical vaccine uptake and changes in vaccine programmes that occurred between 1956 and 2013 in England and Wales. The model was fitted to the 1956 age-stratified notification data as the pre-vaccine equilibrium year and simulated for 75 years between 1956 and 2030 with many transmission and vaccination scenarios to explore the uncertainty of model assumptions made. Comparing the simulation results with the annual notification data would inform us about plausible parameter scenarios to predict the impact of different intervention programmes. Yoon acknowledged that the mixing patterns have

changed over time. The parameters, duration of the natural immunity, reporting rate, mixing pattern, were varied in the simulations.

Simulation results showing the recent resurgence revealed that a shorter duration of aP than wP vaccine might be the cause of this resurgence. These scenarios predicted that elevated levels of pertussis would continue with the current vaccination programme and that while an adolescent booster programme could reduce the overall notifications marginally it would not prevent future resurgences as the highest future disease incidence was predicted to occur in individuals over 25 years of age.

Efficacious wP vaccines seem to induce a longer duration of protection than aP vaccines. Furthermore models with long durations of protection for aP [>10 years] did not fit the UK epidemiology; Protection afforded by aP against transmission was more difficult to assess given the short duration for which the vaccine had been used in the UK. Overall the model suggested that the drop of coverage in the 70s was not needed to generate the current resurgence, and that a resurgence may not have occurred with continued use of wP.

6. Prevention of early mortality

Review of effectiveness of 1 or 2 doses of pertussis vaccine against infant mortality

In 2009, SAGE addressed the protective effect of 1 or 2 doses of pertussis vaccine against death. At the time, the Working Group on Pertussis vaccines concluded that data were not sufficient to establish the existence or magnitude of a protective effect. In the context of the questionnaire distributed by the work group during 2013, countries were asked to provide data and results of observational studies on the effectiveness of 1 or 2 doses of pertussis containing vaccine. In view of limited specific effectiveness data against mortality, any pertussis disease, severe morbidity, and/or hospitalization, were also assessed. The data in the table were provided in responses to the surveys distributed to countries (Table 6). Further data might be added to the table, pending the results of the systematic review.

Table 6: Vaccine effectiveness against infant disease and hospitalization.

Country/ Vaccine	Single dose	Two doses	Full primary schedule
Australia[27] **aP**	VE hospitalization: 55% (95%CI: 43-65%)	VE hospitalization: 83% (95%CI: 70-90%)	VE hospitalization: 85% (95%CI: 75-91%)
England[28] **aP or wP**	VE against infant pertussis disease: 62% (95%CI: 53-69%)	VE against infant pertussis disease: 85% (95%CI: 77-91%)	VE against infant pertussis disease: 95% (95%CI: 86-99%)
France[29] **wP**	VE against infant pertussis disease: 58%[3]	VE against infant pertussis disease: 87%[4]	VE after 4 doses against infant pertussis disease: 84%- 100%
Germany[30] **aP**	VE hospitalization: 68.0% (95%CI: 45.6-81.1)	VE hospitalization: 91.8% (95%CI: 84.7-95.7)	
USA DTaP[31]**/ Tdap**[5]			VE after 5 doses of DTaP, approx. 98% in first year after vaccination but declining to approx. 75% >5years after vaccination. VE of Tdap: 75% in the first year declining to 40% after 2-4 years.
USA DTwP/DTaP[32]	VE against pertussis disease in ages 6-23mo: 50.5% (95% CI: -71.1-86.3)	VE in ages 6-23mo against pertussis disease: 80.1% (95% CI: 41.3-93.2)	

In general, incidence of pertussis peaks in the second month of life, prior to commencement of vaccination. Incidence declines rapidly as soon as 1 or 2 doses are received. This pattern was observed in data from the USA and Australia. For infants less than 1 year of age, disease is more likely to be severe than in older children, hence protection against any disease is expected to protect against severe

---

[3] Adjusted OR associated with risk of severe pertussis (ref: 0 dose) OR: 0.42 (95%CI: 0.19-0.91)

[4] Adjusted OR (2 or 3 doses) associated with risk of severe pertussis (ref: 0 dose) OR: 0.13(95%CI: 0.02-0.98)

[5] Unpublished data from CDC

outcomes including death and hospitalization. Further, observation of disease occurrence in the USA and Australia reveals a decline in hospitalization and deaths once the vaccination is initiated at age 2 months. Case-level data from Australia, France, the USA, and Canada indicate that hospitalizations and deaths predominate in the youngest ages (0-1 month), and that the majority of deaths occur in infants who received 0 or1 dose, while deaths are rare in those receiving2 or more doses.

Published and unpublished observational analyses of vaccine effectiveness were also reviewed. Australian data demonstrated that VE increases with the number of doses and age of the infant. VE for one dose is 55% (95% CI: 43-65%), 83% (95% CI: 70-90%) for 2 doses and is highest for a completed primary schedule (85% (95% CI: 75-91%) but rapid waning can be observed in the following three years. Effectiveness of pertussis vaccine against disease among infants aged 9 weeks to 6 months was assessed in England from 2002-2009. VE was 62% (95% CI: 53-69%) for one dose and 95% (95% CI: 86-99%) for three doses. Among infants aged 6-23 months, 11 and 2 2 dose VE were 50.5% (95% CI: -71.1-86.3) and 80.1% (95% CI: 41.3-93.2), respectively.

Among studies of hospitalization and severe disease, a Swedish study [33] suggests the risk of hospitalization decreases already after the first vaccine dose, and further after the second [[61% (no doses), 36% (single dose) to 2.7% (2 doses)]. A French study calculated the odds ratio for severe pertussis to be reduced to 0.42 after 1 dose and to 0.13 after 2 and 3 doses, with the number of doses received more predictive for disease than was age of the infant.

One unpublished analysis of US data using multivariable regression found that one dose of vaccine reduced the risk of fatal cases. From 1991 through 2008, pertussis-related deaths occurred among 258 (0.57%) of 45,404 reported cases. All deaths occurred before age 34 weeks at illness onset. Receiving >1 dose of pertussis vaccine was protective against death (adjusted odds ratio [aOR] = 0.29, 95% CI: 0.12–0.69), hospitalization (aOR=0.64, 95% CI: 0.58–0.71), and pneumonia (aOR= 0.78, 95% CI: 0.67–0.91).

There is increasing and consistent evidence both from observational and analytical studies from a number of industrialized countries using aP and wP to show that a single dose of either pertussis vaccine in infancy has around 50% effectiveness in preventing severe disease, hospitalization, and death and that 2 doses of either pertussis vaccine offers higher protection (83%-87%). Evidence is not sufficient to assess a significant difference in vaccine effectiveness using different component aP vaccines; there is no evidence pointing to the superiority of one aP vaccine over another. While the assessment of effectiveness is preliminary and may change upon completion of the systematic review of vaccination schedules, the data are consistent and convergent across multiple studies.

The group concluded that timely delivery of the first dose is critical, but the age at which the first dose is recommended should depend on the local epidemiology and vaccine delivery system. While on-time vaccination is crucial regardless of the schedule, the group reinforced that 1 or2 doses are not sufficient and that completion of the entire recommended number of doses is needed to protect older age groups, which might not be at risk of death but still at risk for increased morbidity and who may contribute to transmission of the disease to unvaccinated young infants.

Maternal immunization

In October 2012, in response to a national outbreak of pertussis in the UK with an increasing number of deaths and hospital admissions in very young infants, a temporary pertussis vaccination program for pregnant women was introduced. Antenatal women were offered a 5-component aP containing vaccine (dTaP/IPV) between 28 and 38 weeks of pregnancy. Analysis of laboratory confirmed pertussis (January 2008-September 2013) and hospital admissions (January 2011-September 2013) was undertaken to investigate the impact of the program on infant disease. Vaccine effectiveness was calculated using a screening method based on follow up of confirmed infant cases for vaccination status and estimates of vaccine coverage for the antenatal population. Vaccine safety was also assessed by identifying pregnant women with a record for a pertussis-containing vaccination from beginning October 2012 to end March 2013 in the Clinical Practice Research Datalink, a large computerized data base of health care consultations for over 12.5 million National Health Service (NHS) patients registered at a representative subset of general practices in the UK. Stillbirth rates following vaccination were compared to published national background data. A matched cohort study was also conducted using historical unvaccinated controls and examining a range of pre-defined pregnancy-related adverse events.

Uptake of vaccination by mothers was good, around 70% at the start of the programme and leveling out at around 60% in 2013. No deaths occurred in the infants of vaccinated mothers since the start of the programme in October 2012. Two deaths in the infants of unvaccinated mothers had occurred in 2013. In contrast to all other age groups, laboratory confirmed cases in < 3 month olds were lower in the first 9 months of 2013 than in the same period in 2011 (around 40% lower) compared with an overall increase in all age groups of 503%. Vaccine effectiveness (VE), based on 82 confirmed cases followed up by September 2013 in infants aged less than 3 months whose mothers were vaccinated at least 7 days before birth, was 91% (95% CI: 84%-95%), and 38%(-95% to 80%) for those vaccinated within 7 days before or 1-13 days after birth. These results are consistent with high vaccine effectiveness and likely to reflect protection of the infant by both passive antibody and reduced maternal exposure. The results of a second case control study were also reported and gave similar results. Of the 30 infants with confirmed pertussis at aged 8 weeks or less at onset in the study, 7 of the mothers had been vaccinated during pregnancy. In comparison, 39 mothers of the 55 controls had been vaccinated during pregnancy. The VE (after adjustment for sex and birth period) was 0.90 (95% CI: 0.67-0.97). In the safety evaluation, data were available for over 20,000 vaccinated pregnant women.

The safety study showed no evidence of an increased risk of stillbirth in the 14 days immediately following vaccination, or later in pregnancy, compared to that in unvaccinated women. There was no evidence that vaccination accelerated the time to delivery or caused an increased risk of maternal or neonatal death, (pre-) eclampsia, haemorrhage, foetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, or severe events that can occur naturally later in pregnancy. This large study provides the first controlled data on the safety profile of pertussis vaccination in pregnancy.

Interim results of an immunogenicity study in 129 infants of vaccinated mothers that subsequently received the routine vaccines in the UK schedule at 2, 3, 4 months of age were also reported. Compared with immunogenicity data from historical controls, infants' Hib and tetanus antibody levels post primary were enhanced. There was some reduction in infants' post primary antibody levels to pertussis antigens,

diphtheria, meningococcal C conjugate and some pneumococcal serotypes. The clinical significance of these reductions is uncertain but it is reassuring that national surveillance of pertussis, invasive pneumococcal disease and serogroup C disease in the cohort of infants whose mothers would have been eligible for vaccination in pregnancy has shown no evidence of an increase in those aged 3-11 months. For pertussis, the number of cases in 2013 in this age group was similar to that before the resurgence in 2011.

Data from unpublished immunogenicity studies in Canada and the US using a 2, 4, 6 month schedule also showed evidence of a reduction in pertussis specific antibody responses post primary immunisation in infants whose mothers were vaccinated in pregnancy.

Key conclusions:	UK experience indicates a high impact of vaccination of pregnant women against infant pertussis with an overall reduction in infant mortality. This impact is likely due to the direct protective effectiveness in the infant via the transfer of maternal antibodies, and via impact on risk of transmission through protection of the mother. The vaccine is safe and effective to use in pregnant women. There is some evidence of a reduction in antibody responses to pertussis antigens in infants of vaccinated mothers. The clinical significance of this is uncertain, but to date there is no evidence of an increased risk of pertussis in infants aged 3-11 months. The evidence reviewed relates only to the use of aP vaccine in pregnancy, and the immunogenicity data are confined to infants vaccinated with aP containing vaccines. Conclusions on maternal immunization cannot therefore be extrapolated to wP vaccines without additional immunogenicity and safety data.

Immunization of newborns

During the whole cell only era, research on neonatal immunization largely ceased after a published study claimed to demonstrated immune tolerance in neonates to pertussis vaccine, but this was based on very limited evidence [34]. There have now been 4 additional small studies evaluating neonatal use of acellular vaccines, 1 using DTPa [35] and3 using acellular pertussis (aP) without D and T [36-38].

As well as vaccine used (DTPa vs aP and antigen content), study methods varied by timing of dose, timing of serology and concomitant vaccine antigens administered. Primary response to vaccination was measured by IgG antibody to pertussis antigens (PT, PRN, FHA), and in some cases data on maternal antibody at the time of birth were also reported.

There were important differences between study outcomes. All 3 studies where aP was used showed an increase in IgG antibody to pertussis antigens in birth dose recipients, but the study using DTaP did not. Both the Halasa study using DTPa and the Belloni study using Chiron-manufactured aP showed lower antibody levels in birth dose recipients at 7 months of age following completion of the primary series. The 2 studies using GSK-manufactured aP vaccine did not show any reduction in antibody levels at 7 months in birth dose recipients. No safety issues were reported, but the combined sample size of all trials was only around 300 subjects. The limited available data suggest that neonatal immunization is safe and can achieve good antibody responses early if aP rather than DTaP is used. Several limitations are flagged, including overall sample size being small and the lack of currently commercially available monovalent aP. A larger trial of 440 infants randomised to aP and Hep B or Hep B vaccine alone within 5

days of birth followed by DTaP-HepB-Hib-IPV vaccine at 6 weeks (including ~100 infants born to mothers who had received dTap within the previous 5 years) was completed in Australia in 2012 and should have immunogenicity data at 2, 4, 7 months available in 2014. Monovalent aP to the newborn could be an option if the mother has not received immunization and there could be potential to combine aP with hep B vaccine, which is recommended for newborn immunization in many settings.

Key conclusions:	• The presented data suggests the efficacy of neonatal immunization though cannot be generally recommended (yet) due to limited data on impact and safety and lack of availability of an aP alone vaccine. However, data demonstrating protection against severe pertussis disease in human and baboon infants after a single dose support continued evaluation of neonatal pertussis strategies alongside maternal vaccination.

Cocooning strategies

Cocooning strategies from various countries were assessed, with particular focus on the implementation and analysis of a cocooning strategy in Chile.

Cocooning was defined as a strategy to protect young infants who are too young to be protected by the receipt of their DTaP series and who are at substantial risk of severe disease, hospitalization, or death by exposure to *B.pertussis* by inducing protection through vaccination of most likely sources of infection i.e. individuals in close contact to the infant. Infants <2 months are at highest risk as too young to be vaccinated with parents, grandparents and siblings being the main source of infection. Various possibilities to implement this strategy exist. In Chile vaccination is recommended for mothers and persons >12 years that live with the newborn, caregivers that stay during the day with the newborn, as well as pediatric healthcare personnel.

Vaccination of post-partum women, antibody response is highest by day 10 for serum IgG and peaked between days 10-14 for breast milk IgA. Maternal antibodies against pertussis in breast milk do not interfere with the infant immune response to vaccines.

A logistic regression model from Chile considering the potential impact of cocooning suggests 84% reduction of the probability of death for infants < 6 months where cocooning had been implemented in the household compared to infants where cocooning had not been implemented.

Experience in Chile, which implemented cocooning in 2011 in critical regions following an increase in infant deaths, was positive. Families, excluding the pregnant mother, were vaccinated 2 weeks before childbirth. The strategy was only implemented in regions with high infant morbidity and mortality. High coverage was reached in mothers (92% in 2012, 82% in 2013). Coverage among household contacts was 59% in 2012 and 55% in 2013. Multivariate analysis suggested a significant impact of cocooning with 84% reduction of infant mortality comparing cocooning against no measures (unpublished data). No impact was observed on the overall number cases, but a reduction in infant deaths in the first 6 months of age was seen. Yet more evidence is needed to confirm the impact of the cocooning strategy.

Data on the impact of cocooning strategies from further research studies and modeling were assessed. With respect to research, unpublished data from an Australian case control study to evaluate a funded

cocoon program with coverage of > 75% for adults in contact with infants under the age of one year in an epidemic between 2009 and 2011, suggested a significant decline in the risk of early onset pertussis if both parents had received a dose of dTap at least 4 weeks before disease onset. Most benefit appeared to accrue from maternal vaccination more than 4 weeks prior to disease onset, with relatively minor independent contribution from vaccination of the father. The findings highlighted the importance of timing of vaccination and suggested that a post natal vaccine dose delivered to the mother in the previous pregnancy may deliver persisting benefit in the next. This is an important consideration for future research as it has implications with respect to the risks and benefits of dTap in every pregnancy with respect to spacing of pregnancies.

Modeling suggests a 70% decrease in <3 months prevention if parents in the US (mothers and close household contacts before postpartum hospital discharge) are vaccinated. The number needed to treat is 605 adults to prevent one infant case [39]. Coudeville et al. 2008 found that in the US a combination of cocoon strategy (vaccination of adult household contacts) plus a single dose for all adults and a decennial routine adult vaccination (40% coverage) could highly effective in reducing pertussis in infants, adolescents and adults[40]. In the US across sectional study suggests difference in length of hospitalization and number of deaths due to post-partum vaccination of all care-givers[41]. Several studies were published to assess cost-effectiveness of the strategy. Westra et al. 2010 compared 3 different strategies (Immunization of infants at birth, cocooning, and maternal immunization). Findings suggest cocooning and maternal immunization to be cost-effective[42]. Scuffham et al. 2004 also compared three strategies (Immunization of infants at birth, at one month of age and parental immunization) of which parental vaccination at birth was the most cost-effective[43]. Coudeville et al. 2012 suggests an 80% incidence reduction through cocooning compared to childhood vaccination only[44]. Terranella et al. 2013 compared pregnancy vs post-partum vaccination. Pregnancy vaccination was superior over post-partum vaccination, even when post-partum vaccination was combined with additional cocooning doses[45].

Key conclusions:	• "Cocoon" doses may be able to reduce severe infant morbidity but timing is crucial and overall impact and cost-effectiveness might vary over countries and settings.
	• Advantages of cocooning are better acceptability of vaccination in the post-partum period than during pregnancy, the accessibility to the whole family and the opportunity to educate.
	• Disadvantages are the slow response to produce immunity to protect the newborn and the logistic and economic issues. In addition, challenges to implement cocooning strategies include parental refusal, low political commitment, logistical issues and cultural issues.
	• The cost-effectiveness of cocooning is likely to be substantially lower than maternal immunization, as the latter requires only one dose whereas cocooning requires doses for both parents at minimum.

Vaccination of health care workers

In many countries, vaccination with aP-containing vaccines of health care workers (HCW) is recommended. This may include either all HCWs or special groups of HCWs for whom a more intensive

contact to pregnant women, newborns and infants is assumed, such as pediatricians or obstetricians. No evidence for the effect of vaccination of HCWs in protecting transmission to newborns and/or infants has been documented; however, many case reports and outbreak reports have demonstrated the role of HCW in the transmission of nosocomial pertussis. Transmission has also been documented from HCWs with documented dTap in the previous 3 years, so it is an only partially effective preventive measure.

In many countries, vaccination of HCWs is also recommended to fulfil legal requirements for minimizing potential exposure of patients to infectious agents. As it is unclear to what extent aP vaccines protect against infection, the relative role of vaccination and antibiotic prophylaxis in minimizing pertussis transmission should be revisited.

In countries where vaccination of adults, either universal or for special groups, is recommended, HCW should be of highest priority to be vaccinated. In countries where no adult program exists, the implementation of such program would be logistically difficult.[46]

Summary of strategies aimed at the prevention of early mortality and key conclusions

When applied with high coverage, there is evidence of impact for cocooning strategies (Australia and Chile), but the degree of effect will vary depending on the setting and coverage rates and will likely require a substantial number of vaccinations per child protected.

Although the previous wisdom held that immunization at birth was detrimental as it was associated with immune tolerance, this point of view has been challenged by more recent data for aP vaccines and by data from infant baboon challenge studies. However, neonatal immunization cannot be recommended yet due to limited data on immune response and safety, especially over the longer term, and lack of availability of an aP alone vaccine. If data supporting immunogenicity, presumptive protection and safety become available, neonatal immunization could have a role in consort with other strategies.

The UK experience indicates a high impact of vaccination of pregnant women against infant pertussis with an overall reduction in infant mortality. This impact is due to the direct protective effectiveness in the infant via the transfer of maternal antibodies and via impact on risk of transmission through protection of the mother.

Evidence on the effectiveness of 1 or 2 doses of pertussis vaccine against mortality highlights the importance of timely vaccination and of starting DPT vaccination at 6 weeks where infant mortality remains a problem in the very young. Where vaccination of adults with TdaP is implemented, priority should be given to vaccination of health care workers to further reduce the risk of mortality/severe pertussis in infants.

7. Review of pertussis surveillance, vaccine quality, immunogenicity and strain selection

Surveillance

Variation in country-specific pertussis incidence raises the issue of discrepancies likely related to differences in surveillance. The question was raised whether countries like China and India, where a steep decline in reported cases is seen since the 1980s following implementation of the Expanded Program on Immunization (EPI), have had a true decrease or if there has been a fall in reporting of cases following introduction of pertussis vaccines into routine immunization. This was noted as key issue for low income countries, where clinically manifest pertussis, rather than laboratory positives, accounted for all reported cases.

DPT3 coverage differs over WHO regions (AFR 72%, AMR 92%, EMR 82%, EUR 95%, SEAR 72% and WPR 95%). The number and proportion of laboratory-confirmed cases differs widely between WHO regions (0 countries in AFR, 23 in EUR). In total, 43 (22%) countries reported lab-confirmed cases. Data on a pertussis outbreak in a remote Indian area with total susceptibility suggests high incidence and mortality, leading to the conclusion that the overall impact of pertussis vaccination on morbidity and mortality in unimmunized communities with poor access to health care was likely underestimated.

Development of laboratory capacity for pertussis surveillance may be financially challenging for countries, yet it was considered as crucial by the Working Group to enhance pertussis surveillance. First priority should be to better capitalize on existing sentinel networks e.g. potentially use existing influenza disease surveillance networks for pertussis surveillance, given that both are primarily respiratory diseases and both use PCR as one diagnostic tool. Further suggestions to enhance surveillance were to include pertussis surveillance in the invasive bacterial disease sentinel site network or the pneumonia and meningitis laboratory network. If financially feasible, hospital sentinel site surveillance should be established, with the aim of establishing sentinel sites in every region.

The WHO laboratory manual written in 2004, and modified in 2007, has been updated by the working group in 2014. This laboratory manual describes in details the "state of the art" assays which are requested for a proper pertussis biological diagnosis, as recommended after consensus meetings.

The document includes direct diagnosis, such as culture or RT-PCR on nasopharyngeal aspirates or swabs sampled during the3 first weeks when the subject is coughing. Culture, the golden standard method, is important in order to follow the evolution of the pathogen but also its antibiotic sensitivity. RT-PCR is more sensitive and faster than culture (1-12 days vs. 7 days). Culture is the diagnosis of choice, using infant's nasopharyngeal aspirates, in countries where reagents for RT-PCR cannot be obtained easily[47, 48]. Laboratories performing RT-PCR needs to perform EQA regularly.

The measurement of anti-*B. pertussis* antibodies using ELISA technique and purified pertussis toxin in the serum of a suspected case, coughing since more than3 weeks, is an indirect diagnosis useful, in particular for adults and adolescents coming late after the beginning of the cough[49,50].

Key conclusions:	• Despite the existence of various guidance documents and initiatives conducted in some regions and in particular in Europe and in the Americas, the current global surveillance and diagnostic capacity should be enhanced.
	• There is a need for improved epidemiological data. Surveillance of the disease in infants is crucial and an etiology should be sought on any infant that dies.
	• More solid laboratory data are needed. Laboratory methods should focus on enhanced specificity and cultures of the organisms should be retained so that there molecular characteristics can be assessed. Samples could be frozen to be sent for assessment in national or regional reference laboratories.
	• First priority should be to better capitalize on existing influenza sentinel networks which could be used for pertussis surveillance as both are primarily respiratory diseases and both use PCR as one diagnostic tool. Challenges include insufficient collaborations between virologists and bacteriologists and the nature of the samples collected by the various networks.
	• Hospital sentinel site surveillance may be an option with sentinel sites in every region.
	• Pertussis surveillance may be included in the invasive bacterial disease sentinel site network or the pneumonia and meningitis lab network.

Vaccine quality control and immunogenicity

An update on the formulation of whole cell pertussis vaccines and the antigens in acellular vaccines was provided. The whole cell pertussis vaccine is composed of formalin-inactivated whole cell *B. pertussis*. For the acellular pertussis vaccine, many types of antigens are used including pertussis toxoid (PT/PTxd) , filamentous hemagglutinin (FHA), fimbrial proteins, type 2 and 3 (Fim2, Fim3, Fim2-Fim3) and pertactin (PRN).From the experiences of vaccines registered in Thailand, the amount of bacterial content of whole cell pertussis component vaccines varied from 12 to 16 international units (IUI) per dose and there are 3 types of aP component vaccines with different components including 2 components (PT and FHA), 3 components (PT, FHA and PRN), and 5 components (PT, FHA, PRN, Fim2 and Fim3). The amount of each component varies from one vaccine to another, for example, one dose of 3 component-DTaP vaccine contains 25 µg of PT, 25 µg of FHA and 8µg of PRN whereas TdaP contains 8 µg of PT, 8 µg of FHA and 2.5µg of PRN. Moreover, one dose of 5 component-DTaP vaccine contains 20 µg of PT, 20 µg of FHA, 3µg of PRN, and 5 µg of Fim 2 & 3 and for TdaP are 2.5 µg of PT, 5 µg of FHA, 3µg of PRN, and 5 µg of Fim 2 & 3.

Quality control according to WHO recommendations includes a long list of control items such as identity, sterility, specific toxicity, innocuity test, adjuvant, and potency, among others, and final containers are inspected. The residual pertussis toxin activities, especially Histamine Sensitizing Factor (HSF), is determined[51, 52]

To estimate the potency of wP vaccines, the Kendrick test is used by vaccinating mice, and directly challenging the animals 14 days after with *B. pertussis.* ED50 of the vaccine sample is compared with

that of standard vaccine at day 28 and the potency is calculated in international units. According to WHO recommendations, the potency of wP should not be less than 4.0 IU/dose[52]

Two potency tests are used to evaluate aP vaccine. Most manufacturers use immunogenicity tests in mice (MIT) or Guinea-pigs to evaluate antibody responses, and the potency is justified by relative comparison between the immune response of the groups immunized by the vaccine sample to those of the group immunized by reference vaccine. Modified Intracerebral Mouse Protection Assay (MICA) is used by some manufacturers and the potency can be calculated in IU/dose[51]. P immunogenicity in clinical trials is tested using ELISA or agglutination test. The method to estimate aP immunogenicity in clinical trials is ELISA with cut-off values varying according to kit[53].

Several constraints were highlighted when comparing vaccine efficacy evaluations and immunogenicity evaluations. It was noted that different case definitions may lead to different outcome of efficacy evaluations. It is also hard to evaluate protective efficacy as there is low incidence rate of pertussis and it is not possible to compare the efficacy of aP to wP by using the immunogenicity evaluation because there is no standard methodology for determination of antibody titers. Protective antibody levels have not been defined and no immune response correlated with vaccine protective efficacy is defined.

WHO has developed a standard reagent for pertussis antiserum. Nevertheless there are still issues with standardization despite international standards. New vaccines are licensed on comparative immunogenicity levels and it is stressed that companies need to measure serological bridging. Good surveillance systems are necessary to evaluate efficacy, and at a later stage, effectiveness of the vaccine. Different regulatory systems in different countries complicate the situation.

Key conclusions:	• To date, there is not an adequate test correlate for vaccine effectiveness and duration of protection. Tests used for vaccine control only monitor consistency of production. As a result, in the systematic review of the various schedules, immunogenicity data may be of more limited value.

Variation of bacterial strains according to vaccination strategies: consequences for strain selection

Various methods for characterizing bacterial isolates can be used, generating different data sets very much depending on the primary question to be studied.

On a phenotypic level, these can be morphology (i.e., Gram stain), biochemical activity, and proteome analysis by MALDI-TOF, antibiotic sensitivity profiles, serotyping (i.e., fimbrial typing) or production of virulence factors measuring activity of these factors or using specific polyclonal antisera.

On the genomic level, methods can be distinguished whether they target the whole genome or limited parts of it. Genome-sequencing, SNP analysis or PFGE (Pulsed-field gel electrophoresis) are methods targeting the whole genome. It is also possible to target it by microarrays, whereas multi-locus sequence typing (MLST), PCR-based fingerprinting, and Multiple-Locus variable number tandem repeat analysis (MLVA) only study limited portions of the genome. The advantages and disadvantages of these methods may be summarized as follows (adapted from Huber et al. [54]). Genome sequencing produces accurate

and reproducible data with high discriminatory power, although bioinformatics expertise is needed. Phylogenetic relationship can be studied by SNP analysis, and these methods are cost-and labor-intensive. Microarrays can analyze the genomic content and also the gene expression; they can detect phylogenetic relationships, but are quite costly. PFGE has a high discriminatory power and it is cheap, but it is laborious and results are not readily comparable between laboratories. MLST produces stable and transferable data at high costs. PCR-based fingerprinting has limited discriminatory power. As an alternative, MLVA has rather high resolution power, it can detect phylogenetic relationships, but it is cost- and labor-intensive. Generally, it is important to realize that the genome of all bacteria adapts over time, whereby bacteria can acquire or lose genomic material, and can activate or inactivate genes. *B. pertussis* seems to be among the most monomorphic human pathogens. Phylogenetic analysis suggests that *B. pertussis* is a rather recently evolved human pathogen. Mainly due to its repetitive elements, the overall genomic structure of *B. pertussis* is rather fluid.

Concerning *B. pertussis* isolates, it is important to bear in mind that in most countries no standardized method of collection of isolates has been established. Thus, continuous data about isolate variability are available mainly from Europe, the US, Argentina, Australia, Russia (St Petersburg region) and Japan, whereas limited data can be obtained from other WHO regions. Furthermore, there may be a limited or skewed regional distribution of collected isolates in some countries. Available isolates often stem from young infants, although they are probably representative of circulating isolates. From children, adolescents and adults, isolates are collected more or less by chance.

On a phenotypic level, resistance to macrolides in *B. pertussis* so far is relatively rare but recent publications may indicate differences between countries (i.e. China) [55-58]. Macrolide resistance seems to depend on1 mutation until now, and these isolates have been circulating for at least 25 years[59]. Fimbrial typing can distinguish between types Fim 2 and/or Fim 3, and fimbrial subtypes, and for many years, a large variation in production and circulation of fimbrial types has been observed. However, no consensus exists about the role of fimbrial variation in regard to the vaccination coverage or the type of vaccine used[60] .

Concerning the production of other virulence factors, isolates have been collected that are deficient in vaccine antigens. So far, PT-negative and FHA-negative isolates rarely occur. PRN-negative isolates rarely occurred until 2007, but since then have been increasing in several countries[61-66] and making up a substantial proportion of all isolates. Concerning non-vaccine antigens, AC-Hly-negative isolates occur extremely rarely, if ever, and the structure of the LPS has not changed over time[67]. The prevalence of PRN-negative isolates varies according to region. In France, the prevalence reached 14% in 2012 and was still 14% in 2013, whereas it reached more than 60% in some North American countries using aP vaccines. However, none have been reported in the Saint Petersburg region (Russia) where aP vaccine is not used[68]. A preliminary study indicated that these isolates were as virulent in infants less than 6 months old and as transmissible as PRN-negative isolates[69].

It can be suggested that every epidemic cycle is characterized by the emergence of a change in the isolates. For example, during the 1996-1997 cycles, isolates producing prn 3 emerged and then disappeared[70, 71], and during the 2011-2012 cycle, PRN-negative isolates could increasingly be found[61]

but the increase of their prevalence seemed to have reached a maximum. "Directly linking epidemiology and strain typing is tempting but may lead to inaccurate conclusions with unwanted side-effects" [72], but the surveillance of the prevalence of these PRN-negative isolates needs to be pursued in different regions, which underlines the importance to continue culture as biological diagnosis and not rely only on the use of real time PCR. This surveillance is important since the circulation of such isolates can affect the duration of vaccine induced immunity. During the period of wP vaccines use in North America or Western Europe, change of the bacterial population was also observed, but vaccine effectiveness and duration of wP vaccine induced immunity remained unchanged [73].

Key conclusions:	- Data indicate that *B. pertussis* strains have evolved over time, with isolates differing in the pre- and post-vaccination era. Yet the evolution of the strains observed does not always correlate with changes in vaccine programme or epidemiology. - Nevertheless it remains important to continue collecting and analyzing isolates from many countries in order to follow future evolution of *B. pertussis* and to pursue the determination of aP-induced vaccine immunity. - There is no evidence to date for diminished effectiveness of vaccines against different allelic variants. In countries with a recently observed increase in cases, targeted vaccination intervention strategies were effective in providing additional evidence that the observed increase was not related to diminished effectiveness against currently circulating strains. - There is no evidence of emergence of *B. parapertussis* in aP or wP using countries.

8. Proposed recommendations

The main aim of pertussis vaccination is to reduce the risk of severe pertussis in infants. All children worldwide should be immunized against pertussis, and every country should seek to achieve early and timely vaccination (initiated no later than at 8 weeks of age) and maintain high levels of coverage (≥90%) with at least 3 doses of assured quality pertussis vaccine in infants. Evidence suggests that high coverage with highly efficacious vaccines leads to high levels of protection in children in the <5 year age group. In contrast, even minor reductions in overall coverage can lead to an increase in cases.

Consequently, all countries should consider starting their primary vaccination schedule as early as possible, ≥6 weeks of age. There is substantial and consistent evidence both from observational and analytical studies from a number of countries using aP and wP to show that a single dose of pertussis vaccine in infancy has significant effectiveness (around 50%) in preventing severe disease and that 2 doses of pertussis vaccination offers high protection (80% or more).
Choice of vaccines

Pertussis vaccination is highly effective in reducing disease from *B. pertussis*, with a drastic decline in overall global incidence and mortality seen compared with the pre-vaccination era. Protection against severe or fatal pertussis in infancy and early childhood can be obtained after a primary series of vaccination with either wP or aP vaccine.

Comparing the characteristics of aP and wP vaccines indicates that licensed aP vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission relative to currently internationally available wP vaccines. This is likely ascribed to the fact that aP vaccines induce a different type of immune response (higher Th2-promoting antibody responses but lower Th1 and Th17 responses), which is less effective at clearing mucosal infections.

When considering a switch from wP to aP vaccines, countries need to consider the overall goal of their immunization program;; disease-related mortality in the first year of life can be significantly reduced using a primary series of either wP or aP vaccination, whereas the protection of older children or adult requires repeat boosting with the less reactogenic acellular vaccines.

Countries where only a limited number of pertussis doses are used / affordable should use wP vaccines for primary pertussis early infant vaccination. Surveillance and modeling data suggests that the use of aP vaccines will result in a resurgence of pertussis after a number of years and this resurgence might also lead to an increased risk of death in those too young to be vaccinated. The magnitude and delay for this resurgence to occur are difficult to predict considering the many factors that intervene such as vaccine coverage, natural immunity, vaccine type, schedules, and so on. Thus, the use of aP vaccines should only be considered if large numbers of doses (including several boosters) may be included in the national immunization schedules, which has huge implications in terms of costs given the much higher cost of aP vaccines and higher number of doses required.

Supplemental strategies to reduce infant mortality

Vaccination of pregnant women and household contacts
Vaccination of pregnant women is likely to be the most cost-effective complementary strategy and appears to be more effective and favorable than cocooning and neonatal immunization. The working group recommends considering the immunization of pregnant women with TdaP (1 dose in the 2nd or 3rd trimester at least1 week prior to delivery) as an effective complementary strategy to routine primary infant pertussis vaccination in countries or settings with high infant mortality from pertussis. This will require surveillance studies assessing early infant disease burden in various country settings, as death from pertussis may easily be overlooked. The continued value of this strategy will need to be assessed in women that were primed with aP vaccines, as data from Germany suggests lower immune responses to Tdap in aP primed adolescents.

Boosters of pertussis vaccine in adolescents and adults
No evidence could be observed of an impact of a booster dose in adolescence or adulthood on infant disease, hence an adolescent booster is not generally recommended to control infant disease (although it has been shown to decrease disease in adolescents). If countries wish to introduce a an adolescent and/or adult boosters they should have carefully assessed local epidemiology, tried to estimate the contribution of adolescents as source of infections of young infants or selected adolescents and/or adults as a target groups for protection.

Vaccination of Health Care Workers
When a country has implemented a pertussis adult immunization programme, HCWs should be prioritized as a group to receive pertussis vaccine. There is some evidence of transmission in hospital settings, but no evidence yet on the effectiveness of vaccinating HCWs as a strategy to prevent the acquisition and transmission of pertussis. Nevertheless, vaccinating health-care workers may be used as a strategy to prevent nosocomial transmission to infants within health care settings if high coverage rates can be obtained. Selected groups with direct contact with pregnant mothers and infant patients, such as staff working in maternities or involved in neonatal and infant care, may be considered as priority groups for pertussis immunization. This recommendation will need to be revisited in the future to assess the impact in those primed with aP only.

Surveillance

Careful epidemiological surveillance of pertussis, particularly laboratory-confirmed disease, is to be encouraged worldwide to monitor the disease burden and the impact of immunization. Of particular interest are surveys comparing age-specific incidences of pertussis in countries with different policies on vaccine booster doses. In case of limited capacity or resources, the monitoring of pertussis incidence should focus on infants <1 year of age, possibly through hospital-based surveillance and with an evaluation of all deaths. Outbreak studies may also offer valuable information and should be encouraged.

More solid laboratory data are needed. Laboratory methods should focus on enhanced specificity, and cultures of the organisms should be retained so that there molecular characteristics can be assessed. Samples may be frozen to be sent for assessment in national or regional reference laboratories.

Research questions

The working group recommends the comparison of age-specific incidence rates of pertussis in countries with different policies on booster doses. There would be interest in applying the country data to the models in order to (a) validate the models and (b) evaluate strategies and understand the impact of specific programs.

The specific questions that could be explored with the models are:

1) What are the circumstances under which a resurgence should be expected?

2) What is the impact of different potential boosting strategies to avoid resurgence?

9. Reference List

1.   Bentsi-Enchill AD, Halperin SA, Scott J, MacIsaac K, Duclos P. Estimates of the effectiveness of a whole-cell pertussis vaccine from an outbreak in an immunized population. Vaccine 1997;15(3):301-306.

2.   De Serres G, Boulianne N, Duval B et al. Effectiveness of a whole cell pertussis vaccine in child-care centers and schools. Pediatr Infect Dis J 1996;15(6):519-524.

3.   Halperin SA, Bortolussi R, MacLean D, Chisholm N. Persistence of pertussis in an immunized population: results of the Nova Scotia Enhanced Pertussis Surveillance Program. J Pediatr 1989;115(5 Pt 1):686-693.

4.   Smith T, Rotondo J, Desai S, Deehan H. Pertussis surveillance in Canada: trends to 2012. Can Communic Dis Rep CCDR. 2014;40(3).

5.   Hellenbrand W, Beier D, Jensen E et al. The epidemiology of pertussis in Germany: past and present. BMC Infect Dis 2009;9:22.

6.   Suntarattiwong P. Revisit of pertussis in Thai children. Annual PIDST meeting: 2013.

7.   Meade BD, Deforest A, Edwards KM et al. Description and evaluation of serologic assays used in a multicenter trial of acellular pertussis vaccines. Pediatrics 1995;96(3 Pt 2):570-575.

8.   Edwards KM, Meade BD, Decker MD et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. Pediatrics 1995;96(3 Pt 2):548-557.

9.   Decker MD, Edwards KM, Steinhoff MC et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995;96(3 Pt 2):557-566.

10.   Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 6th ed. Philadelphia: Elsevier Incorporated, 2013:447-92. 2013.

11.   Schmitt HJ, Schuind A, Knuf M et al. Clinical experience of a tricomponent acellular pertussis vaccine combined with diphtheria and tetanus toxoids for primary vaccination in 22,505 infants. J Pediatr 1996;129(5):695-701.

12.   Liese JG, Meschievitz CK, Harzer E et al. Efficacy of a two-component acellular pertussis vaccine in infants. Pediatr Infect Dis J 1997;16(11):1038-1044.

13.   Simondon F, Preziosi MP, Yam A et al. A randomized double-blind trial comparing a two-component acellular to a whole-cell pertussis vaccine in Senegal. Vaccine 1997;15(15):1606-1612.

14.   Ad Hoc Group for the Study of Pertussis Vaccines. Placebo-controlled trial of two acellular pertussis vaccines in Sweden--protective efficacy and adverse events. Lancet, 1(8592), 955-960 (1988). Lancet 1988.

15.   Trollfors B, Taranger J, Lagergard T et al. A placebo-controlled trial of a pertussis-toxoid vaccine. N Engl J Med 1995;333(16):1045-1050.

16.   Greco D, Salmaso S, Mastrantonio P et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. N Engl J Med 1996;334(6):341-348.

17.   Blackwelder WC, Storsaeter J, Olin P, Hallander HO. Acellular pertussis vaccines. Efficacy and evaluation of clinical case definitions. Am J Dis Child 1991;145(11):1285-1289.

18.   Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996;334(6):349-355.

19.   Stehr K, Cherry JD, Heininger U et al. A comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. Pediatrics 1998;101(1 Pt 1):1-11.

20.   Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. Ad Hoc Group for the Study of Pertussis Vaccines. Lancet 1997;350(9091):1569-1577.

21.   Romanus V, Jonsell R, Bergquist SO. Pertussis in Sweden after the cessation of general immunization in 1979. Pediatr Infect Dis J 1987;6(4):364-371.

22.   Stehr K, Cherry JD. A comparative efficacy trial in Germany in which infants received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP (DTP) vaccine or DT vaccine. Dev Biol Stand 1997;89:58-62.

23.   Schmitt HJ, Von Konig CH, Neiss A et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. JAMA 1996;275(1):37-41.

24.   Warfel JM, Beren J, Kelly VK, Lee G, Merkel TJ. Nonhuman primate model of pertussis. Infect Immun 2012;80(4):1530-1536.

25.   Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. Proc Natl Acad Sci U S A 2014;111(2):787-792.

26.   Warfel JM, Papin JF, Wolf RF, Zimmerman LI, Merkel TJ. Maternal and Neonatal Vaccination Protects Newborn Baboons From Pertussis Infection. J Infect Dis 2014.

27.   Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. Pediatrics 2014;133(3):e513-e519.

28.	Campbell H, Amirthalingam G, Andrews N et al. Accelerating control of pertussis in England and Wales. Emerg Infect Dis 2012;18(1):38-47.

29.	Briand V, Bonmarin I, Levy-Bruhl D. Study of the risk factors for severe childhood pertussis based on hospital surveillance data. Vaccine 2007;25(41):7224-7232.

30.	Juretzko P, von KR, Hermann M, Wirsing von Konig CH, Weil J, Giani G. Effectiveness of acellular pertussis vaccine assessed by hospital-based active surveillance in Germany. Clin Infect Dis 2002;35(2):162-167.

31.	Misegades LK, Winter K, Harriman K et al. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA 2012;308(20):2126-2132.

32.	Bisgard KM, Rhodes P, Connelly BL et al. Pertussis vaccine effectiveness among children 6 to 59 months of age in the United States, 1998-2001. Pediatrics 2005;116(2):e285-e294.

33.	Nilsson L, Lepp T, von SK, Hallander H, Gustafsson L. Pertussis vaccination in infancy lowers the incidence of pertussis disease and the rate of hospitalisation after one and two doses: analyses of 10 years of pertussis surveillance. Vaccine 2012;30(21):3239-3247.

34.	Provenzano RW, Wetterlow LH, Sullivan CL. Immunization and antibody response in the newborn infant. I. Pertussis inoculation within twenty-four hours of birth. N Engl J Med 1965;273(18):959-965.

35.	Halasa NB, O'Shea A, Shi JR, LaFleur BJ, Edwards KM. Poor immune responses to a birth dose of diphtheria, tetanus, and acellular pertussis vaccine. J Pediatr 2008;153(3):327-332.

36.	Wood N, McIntyre P, Marshall H, Roberton D. Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age 4. Pediatr Infect Dis J 2010;29(3):209-215.

37.	Belloni C, De SA, Tinelli C et al. Immunogenicity of a three-component acellular pertussis vaccine administered at birth. Pediatrics 2003;111(5 Pt 1):1042-1045.

38.	Knuf M, Schmitt HJ, Wolter J et al. Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. J Pediatr 2008;152(5):655-60, 660.

39.	Van RA, Hethcote HW. Adolescent and adult pertussis vaccination: computer simulations of five new strategies. Vaccine 2004;22(23-24):3154-3165.

40.	Coudeville L, Van RA, Andre P. Adult pertussis vaccination strategies and their impact on pertussis in the United States: evaluation of routine and targeted (cocoon) strategies. Epidemiol Infect 2008;136(5):604-620.

41.   Castagnini LA, Healy CM, Rench MA, Wootton SH, Munoz FM, Baker CJ. Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection. Clin Infect Dis 2012;54(1):78-84.

42.   Westra TA, de VR, Tamminga JJ, Sauboin CJ, Postma MJ. Cost-effectiveness analysis of various pertussis vaccination strategies primarily aimed at protecting infants in the Netherlands. Clin Ther 2010;32(8):1479-1495.

43.   Scuffham PA, McIntyre PB. Pertussis vaccination strategies for neonates--an exploratory cost-effectiveness analysis. Vaccine 2004;22(21-22):2953-2964.

44.   Coudeville L, Van RA, Getsios D, Caro JJ, Crepey P, Nguyen VH. Adult vaccination strategies for the control of pertussis in the United States: an economic evaluation including the dynamic population effects. PLoS One 2009;4(7):e6284.

45.   Terranella A, Asay GR, Messonnier ML, Clark TA, Liang JL. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. Pediatrics 2013;131(6):e1748-e1756.

46.   Maltezou HC, Poland GA. Vaccination policies for healthcare workers in Europe. Vaccine 2013.

47.   Riffelmann M, Wirsing von Konig CH, Caro V, Guiso N. Nucleic Acid amplification tests for diagnosis of Bordetella infections. J Clin Microbiol 2005;43(10):4925-4929.

48.   Loeffelholz M. Towards improved accuracy of Bordetella pertussis nucleic acid amplification tests. J Clin Microbiol 2012;50(7):2186-2190.

49.   Riffelmann M, Thiel K, Schmetz J, Wirsing von Koenig CH. Performance of commercial enzyme-linked immunosorbent assays for detection of antibodies to Bordetella pertussis. J Clin Microbiol 2010;48(12):4459-4463.

50.   Guiso N, Liese J, Plotkin S. The Global Pertussis Initiative: meeting report from the fourth regional roundtable meeting, France, April 14-15, 2010. Hum Vaccin 2011;7(4):481-488.

51.   WHO Technical Report Series 979 Annex 4, 187-260. 2014.

52.   WHO Technical Report Series No 941, 2007, Annex 6, 301-333. 2014.

53.   WHO Laboratory manual for the diagnosis of whooping cough caused by *Bordetella pertussis-Bordetella parapertussis*. 2014.

54.   Huber CA, Foster NF, Riley TV, Paterson DL. Challenges for standardization of Clostridium difficile typing methods. J Clin Microbiol 2013;51(9):2810-2814.

55.   Zhang Q, Li M, Wang L, Xin T, He Q. High-resolution melting analysis for the detection of two erythromycin-resistant Bordetella pertussis strains carried by healthy schoolchildren in China. Clin Microbiol Infect 2013;19(6):E260-E262.

56.   Wang Z, Li Y, Hou T et al. Appearance of macrolide-resistant Bordetella pertussis strains in China. Antimicrob Agents Chemother 2013;57(10):5193-5194.

57.   Guillot S, Descours G, Gillet Y, Etienne J, Floret D, Guiso N. Macrolide-resistant Bordetella pertussis infection in newborn girl, France. Emerg Infect Dis 2012;18(6):966-968.

58.   Fry NK, Duncan J, Vaghji L, George RC, Harrison TG. Antimicrobial susceptibility testing of historical and recent clinical isolates of Bordetella pertussis in the United Kingdom using the Etest method. Eur J Clin Microbiol Infect Dis 2010;29(9):1183-1185.

59.   Bartkus JM, Juni BA, Ehresmann K et al. Identification of a mutation associated with erythromycin resistance in Bordetella pertussis: implications for surveillance of antimicrobial resistance. J Clin Microbiol 2003;41(3):1167-1172.

60.   Poolman JT, Hallander H, Halperin SA. Pertussis vaccines: where to now? Expert Rev Vaccines 2011;10(11):1497-1500.

61.   Hegerle N, Paris AS, Brun D et al. Evolution of French Bordetella pertussis and Bordetella parapertussis isolates: increase of Bordetellae not expressing pertactin. Clin Microbiol Infect 2012;18(9):E340-E346.

62.   Barkoff AM, Mertsola J, Guillot S, Guiso N, Berbers G, He Q. Appearance of Bordetella pertussis strains not expressing the vaccine antigen pertactin in Finland. Clin Vaccine Immunol 2012;19(10):1703-1704.

63.   Otsuka N, Han HJ, Toyoizumi-Ajisaka H et al. Prevalence and genetic characterization of pertactin-deficient Bordetella pertussis in Japan. PLoS One 2012;7(2):e31985.

64.   Queenan AM, Cassiday PK, Evangelista A. Pertactin-negative variants of Bordetella pertussis in the United States. N Engl J Med 2013;368(6):583-584.

65.   Pawloski LC, Queenan AM, Cassiday PK et al. Prevalence and Molecular Characterization of Pertactin-Deficient Bordetella pertussis in the United States. Clin Vaccine Immunol 2014;21(2):119-125.

66.   Quinlan T, Musser KA, Currenti SA, Zansky SM, Halse TA. Pertactin-negative variants of Bordetella pertussis in New York State: A retrospective analysis, 2004-2013. Mol Cell Probes 2013.

67.   Hegerle N, Guiso N. Epidemiology of whooping cough & typing of Bordetella pertussis. Future Microbiol 2013;8(11):1391-1403.

68.   Kurova N, Njamkepo E, Brun D, Tseneva G, Guiso N. Monitoring of Bordetella isolates circulating in Saint Petersburg, Russia between 2001 and 2009. Res Microbiol 2010;161(10):810-815.

69.   Bodilis H, Guiso N. Virulence of pertactin-negative Bordetella pertussis isolates from infants, France. Emerg Infect Dis 2013;19(3):471-474.

70.   van Amersfoorth SC, Schouls LM, van der Heide HG et al. Analysis of Bordetella pertussis populations in European countries with different vaccination policies. J Clin Microbiol 2005;43(6):2837-2843.

71.   Weber DJ, Rutala WA. Pertussis: a continuing hazard for healthcare facilities. Infect Control Hosp Epidemiol 2001;22(12):736-740.

72.   Hegerle N, Guiso N. Epidemiology of whooping cough & typing of Bordetella pertussis. Future Microbiol 2013;8(11):1391-1403.

73.   Guiso N. Bordetella pertussis and pertussis vaccines. Clin Infect Dis 2009;49(10):1565-1569.

10. Annex

Annex 1: List of figures and tables

Figures

Tables

Annex 2: Questionnaire

SAGE pertussis working group

Collection of country specific experience

The objectives of this questionnaire and related survey conducted in about 20 countries is to understand the causes of pertussis resurgence or lack of in countries with good pertussis vaccine coverage. The overall focus is on the prevention of severe morbidity and mortality in children populations.

Please complete each item below. If the item does not apply, please write "NA" [Not Applicable]. If you do not have the information, please write "No Information." If the answer is zero, please write "0". Do not delete items and do not leave items empty. For YES-NO Questions please put a check mark for the appropriate answer .

Please kindly make an effort to gather the requested information if potentially available from other sources within your country.

If you would like to add more information to this report, please include it as an annex or email electronic files in the format in which they are available.

This information will be shared with the Strategic Advisory Group of Experts on immunization and members of its pertussis Working Group. Following review and discussion by the working group we may have to request additional clarification.

It is hoped that the general analysis of data submitted by all countries surveyed may be consolidated and submitted for publication in a peer review journal. You would then hopefully accept co-authorship on this publication.

For the following questions please consider if there are different practices in different jurisdictions (provinces,…) of the country and indicate those differences and, if available and important, please provide the information by jurisdictions. Attached for your convenience is the information concerning your country that was already made available to WHO through the WHO/UNICEF Joint Reporting Form or through the European Center for Disease Control .

Information on responder

Name, affiliation and contact details (address, email and telephone numbers) of main person providing the information

_____
_____
_____

Vaccination schedules

 1. What is the current pertussis vaccination schedule (primary series and booster dose(s) if any) and since when has this been in place?

_____
_____

_____
_____

2. Please describe the successive vaccination schedules that were implemented in your country over the past 20 years, including primary series, number and timing of booster doses (type of vaccine, vaccine combination, recommended age for each dose).

_____
_____
_____
_____
_____
_____

3. Were any specific strategies adopted in the past 20 years to prevent mortality in the young infants, e.g. cocooning vaccination of newborns or pregnant women?

Yes _____   No_____   If Yes, please give further details?

_____

4. When was(were) this(these) strategy(ies) instituted_____

Coverage data

5. What is the latest estimated countrywide vaccination coverage of infants with a full primary series (DPT3) by 12 months of age?(if the third primary dose is administered at 12 months or after, please provide the estimated coverage by 24 months of age) _____

6. Kindly indicate if the data is representative of the true coverage or if it is an over or

75

underestimate and what approach is used to measure this coverage (administrative data, survey,…) _____

7. If you have this information by month of age, kindly provide.

_____

8. Please provide the historical vaccine coverage figures for the last 20 years(or as far backward as possible).

_____
_____
_____.

9. What is the estimated country-wide vaccination coverage of infants with the first dose of pertussis vaccine (DPT1)? _____

10. If one or several booster dose(s) is/are recommended, is there an estimation of the vaccine coverage with this (these) booster dose(s), and if so, for which booster(s) and what is the historical trend of this vaccine coverage?

_____

*11. What is the **actual** average age of children when receiving each dose in the primary series and first and second boosters if applicable? Please provide historical data if possible.*
DPT1_____
DPT2_____
DPT3_____
First booster_____
Second booster_____

_____
_____
_____

12. If a specific vaccination strategy was implemented to prevent infant mortality, what was the coverage (please provide information for the different strategies that were implemented? -

_____

13. Indicate if vaccination coverage is homogeneous throughout the country or if there are any identified discrepancies at sub-national level (regions/districts) and or in specific sub-groups -------
----
-- _____

Type of vaccine(s) used

14. Please specify which pertussis vaccines are currently used in your country (aP or wP and in which combination form), for which part of the schedule and when switches of vaccines if any have occurred. Please also specify the manufacturer(s).

_____
_____
_____
_____

_____

15. Further, please specify if there are subgroups in your country (e.g. health care providers, persons served by the private sector,..) using a different vaccine than that in the national routine immunization scheme. Please specify the vaccines used and approximate % of population covered.

_____
_____
_____
_____
_____

16. Have there been any studies of vaccine effectiveness conducted in your country in the last 20 years and if so what were the results?   Kindly provide the references of any published studies (if possible attach the published or unpublished report).

_____
_____
_____
_____
_____

17. Do you have any additional data with bearing on the determination of comparative effectiveness and duration of protection between aP versus wP containing vaccines

Yes ____   No____   If Yes, please provide:

_____
_____
_____
_____
_____

Surveillance systems

18. Is pertussis a notifiable disease? Yes ____   No____

        In all or restricted age groups? Please specify _____
        Please specify what is reportable, clinical disease or laboratory confirmed cases only
        _____

19. If pertussis is not notifiable, what is the source of information for the number of cases reported to WHO? _____

20. Is there any alternative surveillance system (e.g. sentinel surveillance,..)

Yes ____   No____   If Yes, please specify its nature

_____

_____

21. Have there been any assessments of the sensitivity of the surveillance system? (please share any available reports from these assessments)

Yes _____   No_____   If Yes, please specify its nature

_____

_____

22. Estimated % of underreporting of pertussis cases through the surveillance system for cases occurring among infants, children, adolescents, and adults respectively?

In infants _____

In children _____

In adolescents _____

In adults _____

23.Changes in surveillance overtime such as when pertussis became notifiable, when was laboratory confirmation used.

24. Is there laboratory confirmation and what proportion of cases in the above mentioned age groups are sent to the lab (please provide your best guess if you do not have actual specific data).

In infants _____

In children _____

In adolescents _____

In adults _____

25. Please provide information on current diagnostic method (i.e. clinical versus laboratory confirmation) _____and specific method(s) used for laboratory diagnosis of cases (culture, direct fluorescent assay (DFA), serology, conventional polymerase chain reaction (PCR), real-time polymerase chain reaction (rPCR, other laboratory diagnostic) if any   _____

> *If using rPCR, please list the targets used to confirm cases during this outbreak:*
> *___IS481*
> *___PTxS1*
> *___pIS1001*
> *___hIS1001*
> *Other targets:_____*

26. Is there an external quality assurance is in place? *Yes _____   No____*

27. Indicate any significant change(s)in methods of diagnosis used over the past 20 years and the year of change.

_____

_____

28. What case definition is being used for reporting pertussis cases in your country?

SUSPECT (CLINICAL DESCRIPTION)	
CONFIRMED	
PROBABLE	
OTHER (if applicable)	

29. Were any of these definitions changed over the last 20 years?

Yes ____   No____   If yes, describe how and when

_____
_____
_____
_____

Pertussis cases

30. . Please provide the number of reported pertussis cases by year for the last 20 years (or as far backward as possible)with a breakdown of reported cases among infants (<12 months- and if at all possible for some years a breakdown of such cases by month of age), children (1 through 9 years of age), adolescents(10 through 19 years of age), and adults (20 years and over). Please also specify if these are laboratory confirmed or suspected cases.

Please attach separate pages as need or best provide this information in whatever electronic format would be easier for you.

_____
_____
_____

31. If you have more specific information by specific age groups and/or are unable to accommodate the breakdown by age as above, kindly provide the raw data you have in whatever most specific age grouping and we will regroup from our end.

_____
_____
_____

*32. What is the proportion of reported pertussis cases that are occurring in **vaccinated** individuals. Please provide the breakdown by age group and if possible for each year for the last 20 years.*

AGE GROUP	ZERO DOSES	ONE DOSE	TWO DOSES	THREE DOSES	MORE THAN THREE DOSES
< 6 months*					
6 to 11 months					
1 to 9 years					
11-19 years					
20 or more years					
TOTAL					

* if available by month of age for those less than 6 months, please provide the breakdown accordingly.

33. If available, please provide the annual number of ICD coded pertussis hospitalizations for the last 20 years and with a breakdown of reported cases among infants (<12 months and if possible with the breakdown of cases by month of age), children (1 through 9 years of age), adolescents (10 through 19 years of age), and adults (20 years and over).

_____
_____
_____

34. Please attach separate pages as needed or provide this information in whatever electronic format would be easier for you.

_____
_____
_____

35. If available, please provide the % of PCR positives among hospitalized infants tested for pertussis.

_____

36. *What is the number of reported pertussis- related deaths. Please provide the information by year for the last 20 years and if available the following age breakdown <12 months and if possible with the breakdown of cases by month of age, >= 12 months) and breakdown by number of vaccine doses received.*

_____
_____
_____.

37. *Have there been important outbreaks of pertussis reported over the last 20 years?*
Yes ___ No___

38. *Are there published reports of the outbreak investigations? Yes ___ No___*

If so, please share these reports.

If there are no published reports available:

39. *Please provide information on the case definitions and methods used for investigating the outbreak(s)_____*
_____
_____.

40. *Please provide information on age breakdown and vaccination status (with type of vaccines used) of cases in each outbreak investigated.*
_____
_____
_____.

41. *What is the most likely explanation for the occurrence of this (those) outbreaks.*

_____
_____
_____.

With many thanks for your contribution

Annex 3: Lexicon

DTaP - Tetanus, diphtheria, acellular pertussis vaccine (childhood formulation)
- Infanrix® - GlaxoSmithKline (3 component)
- Ditekik® - Staten Serum Insitut of Denmark (1 component)

TdaP - Tetanus, diphtheria, acellular pertussis vaccine (adolescent/adult formulation)
- Adacel® - Sanofi Pasteur (5 component)
- Boostrix® - GlaxoSmithKline (3 component)

DTaP-IPV – diphtheria, tetanus, acellular pertussis, inactivated polio vaccine
- Tetravac® - Sanofi Pasteur (2 component)

TdaP-IPV - tetanus, diphtheria, acellular pertussis, inactivated polio vaccine (adolescent/adult formulation)
- Adacel-Polio® - Sanofi Pasteur (5 component)
- Boostrix-IPV® - GlaxoSmithKline (3 component)

DTaP-IPV-Hib - diphtheria, tetanus, acellular pertussis, inactivated polio, *H. influenza* type B vaccine
- Pediacel® - Sanofi Pasteur (5 component)
- Pentavac® - Sanofi Pasteur (1 component)
- Pentaxim® - Sanofi Pasteur (2 component)
- Infanrix®-IPV/Hib – GlaxoSmithKline (3 component)

DTaP-IPV-HebB - diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B vaccine
- Pediarix® - GlaxoSmithKline (3 component)

DTaP-IPV-Hib-HepB - diphtheria, tetanus, acellular pertussis, inactivated polio, *H. influenza* type B, hepatitis B vaccine
- Infanrix hexa® - GlaxoSmithKline (3 component)