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Haemophilus influenzae type b conjugate vaccine: Review of observational data on long term vaccine impact to inform recommendations for vaccine schedules

James P. Watt, MD, MPH
Johns Hopkins Bloomberg School of Public Health

Sheena Chen, MPH

Mathuram Santosham, MD, MPH
Johns Hopkins Bloomberg School of Public Health

Corresponding Author: James P. Watt, 510 Carmel Avenue, Albany, CA 94706 USA. Tel. +1 510 528 8640. jamespatrickwatt@yahoo.com.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

Objective

Our objective was to review data from observational studies and surveillance reports on Hib vaccine effectiveness. This review specifically seeks to assess which of the following factors influence invasive Hib disease occurrence at least five years following vaccine introduction:

1. Primary Hib vaccine schedule. Are there settings where early administration of the first dose is needed to prevent invasive Hib disease in infants?
2. Booster dose schedule. Is a booster dose needed for sustained reductions in Hib disease burden? Are there data available on the long term effectiveness of a booster dose given before the first birthday?
3. Vaccination coverage. How do vaccination coverage levels impact the effectiveness of different vaccination schedules?
4. Epidemiologic characteristics of the country. Do epidemiologic characteristics favoring early Hib transmission reduce the effectiveness of different vaccination schedules?

Methods

We reviewed data on invasive Hib disease at least 5 years following vaccine introduction. We limited our analysis to countries with at least 100,000 live births per year so that disease incidence estimates for young children would be stable. We used several approaches to identify data on either Hib disease incidence or number and characteristics of Hib disease cases.

1. We reviewed articles from a WHO sponsored systematic literature review carried out by Dr. Pippa Scott at the University of Bern in 2010. This literature review was designed to identify studies of Hib vaccine immunogenicity, clinical efficacy, and effectiveness. We reviewed article titles, abstracts, year of publication, and country represented to assess whether articles might contain relevant data.
2. We conducted literature searches targeted by country and year to identify data related to Hib disease published after the literature review was carried out.
3. We conducted Internet searches targeted by country to identify publicly available data outside of the scientific literature (e.g., surveillance reports).
4. We contacted investigators who had previously published Hib disease incidence data to identify more recent, unpublished information.

If relevant data were present, they were abstracted using a standardized form. We described and summarized disease incidence and characteristic data as reported in the original source. For some countries we estimated disease incidence using publicly available population data. Data on the national coverage with 3 doses of Hib conjugate vaccine by 1 year of age were obtained from WHO estimates.

Results

Data on Hib disease at least 5 years after vaccine introduction were available from 34 (68%) of 50 countries with at least 100,000 live births which had introduced Hib vaccine on or before January 1, 2006. Data on disease incidence was available from 21 countries. Data on case characteristics from sentinel sites was available from an additional 13 countries. In addition, we collected data from The Gambia (birth cohort 66,000 per year) because it was the first country in Africa to introduce Hib conjugate vaccine and several studies on Hib disease from The Gambia have been published.

Primary Hib vaccine schedule. Are there settings where early administration of the primary series is needed to prevent invasive Hib disease in infants?

Data on delayed administration of the primary series are limited. All countries recommend completion of the primary series by six months of age and all but two countries recommend the first two doses by four months of age. All countries continue to identify invasive Hib disease, albeit at low levels relative to the pre-vaccine era. In most countries, the highest incidence or proportion of cases continue to occur in children less than 1 year of age. In addition, a change to a delayed primary series in Alaska was associated with an increase in Hib disease. These findings suggest that current vaccines and vaccination strategies have not eliminated Hib transmission and that unvaccinated children remain at risk of disease.

Booster dose schedule. Is a booster dose needed for sustained reductions in Hib disease burden? Are there data available on the long term effectiveness of a booster dose is given before the first birthday?

Limited data are available on the use of a schedule without a booster dose in industrialized countries. The one large industrialized country to implement a schedule without a booster dose, the United Kingdom, experienced a resurgence of Hib disease approximately 6 years after vaccine introduction. While multiple factors likely contributed to this resurgence, addition of a booster dose resulted in decreased disease incidence. However, in developing country settings that do not use a booster dose, reductions in Hib disease incidence have been sustained to date. An ecological study in four Latin American countries found no difference in vaccine impact in the two countries which use a booster dose (Argentina and Uruguay) compared with the two which do not (Chile and Colombia). With respect to the administration of a booster dose before the first birthday, only two countries recommend the booster dose at 11 months of age. The Netherlands, which uses a schedule of 2, 3, 4, and 11 months did experience a small increase in invasive Hib disease incidence. However, disease incidence declined without change in schedule. Italy, which recommends a booster dose at 11-12 months of age, has had sustained low incidence of Hib disease. There are no data available on the effectiveness of a schedule with a booster dose administered prior to 11 months of age.

Vaccination coverage. How do vaccination coverage levels impact the effectiveness of different vaccination schedules?

This question could not be addressed due to insufficient data.

Epidemiologic characteristics of the country. Do epidemiologic characteristics favoring early Hib transmission reduce the effectiveness of different vaccination schedules?

Hib conjugate vaccine schedules are highly correlated with development status and WHO region. Therefore, there are limited data available to assess the interaction of different epidemiologic settings and vaccination schedule. With a few exceptions, industrialized countries have implemented schedules that include a primary series and a booster dose. There is limited variability in the timing of the primary doses, the number of primary doses, and the timing of the booster dose. In general, schedules used in industrialized countries have been highly effective. In the United Kingdom, a primary series without a booster dose was associated with a resurgence in Hib disease. Multiple factors may have contributed to this disease resurgence, but addition of a booster dose was temporally associated with a decline in disease incidence. In Alaska, a setting with high transmission pressure, a change in vaccine type which effectively delayed the achievement of primary immunity was associated with a disease resurgence. Most developing countries have implemented a primary series only, with good effectiveness.

Conclusions

Observational studies in countries using Hib conjugate vaccine for at least five years suggest that current Hib vaccination schedules have been very effective. Because instances of diminished vaccine effectiveness are few, there are limited data available to assess the relationships between different epidemiologic settings, vaccination coverage levels, vaccination schedules and vaccine effectiveness. Because most vaccination schedules follow a few basic themes, there are limited empiric data on the effectiveness of significantly different approaches. Some conclusions can be drawn from the available observational data. First, Hib vaccination remains a highly effective public health intervention in all countries studied. Second, Hib conjugate vaccine does not appear to have eliminated invasive Hib disease in any country with at least 100,000 annual live births. Third, in most countries the incidence of Hib disease remains highest in the first year of life, even after many years of routine vaccination. This finding suggests that early primary vaccination with Hib conjugate is necessary to maximize individual level protection. The experience in Alaska supports the need for early primary vaccination in settings of high transmission. Fourth, a two dose primary schedule may be sufficient in some settings if a booster dose is used. Two industrialized countries, Italy and Sweden, have effectively used a two dose (three and five months) primary series in a schedule with a booster dose. Immunogenicity studies and vaccine trials support the use of a two dose primary schedule in different settings, at least in the short term. Fifth, available observational data do not support the need for a booster dose in developing country settings. The experience in the United Kingdom suggests that a booster dose may be important in some situations, but the specific factors that would indicate a booster dose are not clear. There are no data on the effectiveness of a booster dose prior to 11 months of age. Sixth, current Hib

vaccination schedules appear to be effective across the range of vaccination coverage levels seen in different countries.

BACKGROUND

Haemophilus influenza, type b (Hib) causes a variety of serious childhood illness, most notably meningitis and pneumonia. The World Health Organization (WHO) estimated that in 2000 Hib was responsible for more than 8 million episodes of serious illness and 371,000 deaths in children worldwide.(Watt 2009) Hib protein-polysaccharide conjugate vaccines are highly efficacious in preventing Hib disease after the completion of a primary vaccine series and WHO recommends that Hib conjugate vaccine be included in all routine infant immunization programs.(World Health Organization, 2006) In many countries, Hib disease has been effectively controlled by the routine use of conjugate vaccines. As of 2010, WHO reported that 169 (88%) of the 193 WHO member countries had included Hib conjugate vaccine in some part of their infant immunization program and that global coverage with 3 doses of Hib conjugate vaccine in the first year of life was 42%.(World Health Organization, 2011)

Invasive Hib disease is rare in the first two months of life, possibly due to maternal antibodies transferred to the infant either transplancetally or through breast milk. Prior to Hib vaccine introduction, the median age of invasive Hib disease onset varied amongst different countries.(Ferrecio, 1990; Peltola, 2001) In developing country settings and indigenous populations in the USA and Australia , invasive Hib disease generally occurred earlier than in industrialized settings. In some developing country settings, median age of Hib meningitis cases was less than 6 months of age. The causes of differences in age of onset are not definitively known, but may have been related to living conditions that favored early transmission of Hib such as larger family size, household crowding, poor household ventilation, and environmental smoke exposure.(Levine, 1998) Another important feature of invasive Hib disease is that the great majority of illness occurs in the first two years of life and it is very rare after the fifth birthday, even without vaccination. Presumably, repeated exposures to Hib (and possibly related bacteria) result in the development of protective immunity.

Two vaccines which contain the Hib capsular polysaccharide (polyribosylribitol phosphate, PRP) conjugated to different proteins are in current use. PRP conjugated to tetanus toxoid (PRP-T) and PRP conjugated to the outer membrane protein of *Neiseria meningitidis* (PRP-OMP) have different immunogenicity profiles that are important for vaccine scheduling. PRP-T induces a strong immune response after two primary doses. PRP-OMP induces a more robust response following a single dose.(Granoff, 1992) Consequently, only two doses of PRP-OMP are used for a primary schedule, while PRP-T is typically given as a three dose primary series although some countries use a two dose primary series of PRP-T. Studies in Africa have shown that PRP-T is highly efficacious following either 2 or 3 primary doses.(Gessner, 2009) Both vaccines produce a strong booster response when given in the second year of life. Interval between doses and age at dosing may be important for immunogenicity and vaccine effectiveness. Southern et al. found that the immune response to a booster dose of PRP-T in English children increased with increasing age. Children boosted at 6-11 months, 1-2 years and 2-4 years of age had geometric mean anti-PRP antibody titers of 1.30, 4.99 and 5.92 microgram/ml two years after the booster dose. Nevertheless, at two years following the booster dose 99% of children boosted at 6-11 months of age had anti-PRP titers of at least 0.15 microgram/ml while and 54% had anti-PRP levels of at least 1.0 microgram/ml.(Southern, 2007)

Hib conjugate vaccines also reduce nasopharyngeal carriage of Hib. Reduction of nasopharyngeal carriage helps to reduce transmission to others leading to a significant indirect protective effect.(Blanchard-Rohner, 2008) The epidemiology of invasive Hib disease following introduction of Hib conjugate vaccines depends on a number of factors including direct protection from the vaccine, indirect protection associated with reduced transmission of the organism, and natural boosting from exposure to Hib or cross-reactive organisms. All of these factors are partly determined by the vaccine and vaccination schedule used.(Barbour, 1995; Blanchard-Rohner, 2008; Jackson, 2012)

Hib conjugate vaccine schedules currently in use can be grouped into two broad categories—schedules with and without a booster dose in the second year of life.(Fitzwater, 2010) The purpose of including a booster dose is to elicit high antibody titers and long term protection against Hib disease. Schedules that use a booster dose are mainly used in industrialized countries. The primary series used in industrialized countries are quite similar. Most countries use 3 doses in the first six months of life. Two countries use a 2 dose primary series in the first 6 months of life. Similarly, there is limited variability in the booster dose schedule. Recommended administration is between 11-18 months of age. Schedules that do not use a booster dose are mainly used in developing country settings. These schedules have usually been based on the Expanded Program on Immunization (EPI) recommended infant immunization schedule of 3 doses at 6, 10 and 14 weeks of age. Some countries use alternative schedules, but all recommend completion of the primary series by 6 months of age. Ages at actual dosing may vary from country to country.

A small number of countries, most notably the United Kingdom, have reported increases in Hib disease incidence several years after introduction of Hib conjugate vaccine. In the United Kingdom, where a primary series without a booster dose was used, there was evidence of waning antibody concentrations several years after vaccination, temporally associated with an increase in disease incidence.(Heath, 2000; Trotter, 2003) Subsequent introduction of a booster dose has led to reductions in disease incidence.(Ladhani, 2008) The experience in the United Kingdom is discussed in more detail below. The need for a booster dose to sustain low levels of Hib disease in different epidemiologic settings is not clear.

If routine Hib vaccination is able to reduce Hib transmission to very low levels, it is possible that the timing or number of vaccination doses could be altered to reduce costs or better fit within a vaccination program. Information about cases of Hib disease that continue to occur in countries with long term use of Hib conjugate vaccine could inform recommendations for Hib vaccination schedules. The objective of this analysis was to gather and evaluate data from observational studies and surveillance reports on long term Hib vaccine effectiveness. Specifically, we sought to assess which of the following factors influence invasive Hib disease occurrence at least 5 years after vaccine introduction:

1. Primary Hib vaccine schedule. Are there settings where early administration of the first dose is needed to prevent invasive Hib disease in infants?

2. Booster dose schedule. Is a booster dose needed for sustained reductions in Hib disease burden? Are there data available on the long term effectiveness of a booster dose given before the first birthday?
3. Vaccination coverage. How do vaccination coverage levels impact the effectiveness of different vaccination schedules?
4. Epidemiologic characteristics of the country. Do epidemiologic characteristics favoring early Hib transmission reduce the effectiveness of different vaccination schedules?

METHODS

As our primary objective was to analyze the correlation between vaccination schedule and other factors on the long term impact of Hib conjugate vaccine, we reviewed data on Hib disease at least 5 years following vaccine introduction. This time range was selected based on the experience in the United Kingdom where disease resurgence was observed beginning 6 years after vaccine introduction. Five years was selected as the threshold to increase the amount of data for review. Data searches were carried out in in the second half of 2011 and 2010 was the last full year for which data might be available. Therefore, we limited our analysis to countries which had introduced the vaccine on or before January 1, 2006. Dates of vaccine introduction were provided by WHO. In addition, we limited our analysis to countries with at least 100,000 live births per year so that disease incidence estimates for young children would be stable and less impacted by random fluctuation. The number of live births by country was determined from WHO statistics in 2010.(World Health Organization, 2011b)

We used several approaches to identify data on either Hib disease incidence or number and characteristics of Hib disease cases at least five years after vaccine introduction. First, we reviewed a list of articles from a WHO sponsored systematic literature review carried out by Dr. Pippa Scott at the University of Bern in 2010. This literature review was designed to identify studies of Hib vaccine immunogenicity, clinical efficacy, and effectiveness. We reviewed article titles, abstracts, year of publication, and country represented to assess whether articles might contain relevant data. Based on this review, articles that might have had relevant data were obtained and reviewed. If data on Hib disease incidence or case characteristics were present from at least five years following vaccine introduction, those data were abstracted using a standardized form. Second, we conducted targeted literature and Internet searches to identify data published after the literature review was carried out and to find publicly available surveillance reports. Third, we contacted investigators who had previously published Hib disease incidence data to identify more recent, unpublished information.

We present disease incidence and characteristic data as reported in the original source. In some cases, disease incidence was estimated using publicly available population data. Data on the national coverage with three doses of Hib conjugate vaccine by one year of age were obtained from WHO estimates (World Health Organization, 2011c).

RESULTS

One hundred two countries introduced Hib conjugate vaccine into their routine infant immunization schedule on or before January 1, 2006. Of these, 50 (49%) had at least 100,000 live births in 2010. Data on Hib disease at least 5 years after vaccine introduction were available from 34 (68%) of these 50 countries. By WHO region, data were available from 4 countries in the African region, 18 countries in the Americas, 11 in the European region, and 1 in the Western Pacific region. Data on disease incidence at least 5 years after vaccine introduction was available from 21 countries. Data on case characteristics from sentinel sites was available from an additional 13 countries. In addition, we collected data from The Gambia (birth cohort 66,000 per year) because it was the first country in Africa to introduce Hib conjugate vaccine and several studies on Hib disease from The Gambia have been published, including a report of possible disease resurgence.(Howie, 2007) In total, we included data from 35 countries (Table 1).

Table 1. Countries included in analysis of long term Hib vaccine impact.

COUNTRY	WHO REGION	YEAR OF VACCINE INTRODUCTION COUNTRYWIDE	VACCINE PRESENTATION	PRIMARY VACCINATION SCHEDULE	BOOSTER DOSE SCHEDULE	DATA TYPE AVAILABLE
The Gambia	AFRO	1997	DTP/HepB/Hib	2, 3, 4 months	None	Incidence
South Africa	AFRO	1999	DTP/Hib until 2008. DTaP/Hib/IPV from 2009 onward.	6, 10, 14 weeks	N/A Booster dose introduced in 2010.	Incidence
Kenya	AFRO	2001	DTP/HepB/Hib	6,10,14 weeks	None	Incidence
Malawi	AFRO	2002	DTP/HepB/Hib	6,10,14 weeks	None	Case
Uganda	AFRO	2002	DTP/HepB/Hib	6,10,14 weeks	None	Case
Canada	AMRO	1986	DTaP/Hib/IPV	2, 4, 6, months	18 months	Incidence
United States of America	AMRO	1991	Various	2, 4, 6, months	12-15 months	Incidence
Uruguay	AMRO	1994	DTP/HepB/Hib	2, 4, 6, months	12 months	Incidence
Chile	AMRO	1996	Hib until 2006. DTP/HepB/Hib from 2007 onward.	2, 4, 6, months	None	Incidence
Argentina	AMRO	1997	DTP/Hib	2, 4, 6, months	18 months	Incidence
Colombia	AMRO	1998	Hib until 2002. DTP/HepB/Hib from 2003 onward.	2, 4, 6, months	None	Incidence
Brazil	AMRO	1999	Hib until 2002. DTP/Hib from 2003 onward.	2, 4, 6, months	None	Incidence
Cuba	AMRO	1999	Hib until 2002. DTP/Hib in 2005. DTP/HepB/Hib from 2006 onward.	2, 4, 6, months	18 months	Case
Honduras	AMRO	1999	Hib in 1999. DTP/HepB/Hib from 2000 onward.	2, 4, 6, months	None	Case
Nicaragua	AMRO	1999	DTP/HepB/Hib	2, 4, 6, months	None	Case

Bolivia	AMRO	2000	DTP/HepB/Hib	2, 4, 6, months	None	Case
Venezuela	AMRO	2000	Hib until 2003. DTP/HepB/Hib from 2004 onward.	2, 4, 6, months	18 months	Case
Dominican Republic	AMRO	2002	DTP/HepB/Hib	2, 4, 6, months	None	Case
El Salvador	AMRO	2002	DTP/HepB/Hib	2, 4, 6, months	15-18 months	Case
Paraguay	AMRO	2002	DTP/HepB/Hib	2, 4, 6, months	None	Case
Ecuador	AMRO	2003	DTP/HepB/Hib	2, 4, 6, months	None	Case
Guatemala	AMRO	2005	DTP/HepB/Hib	2, 4, 6, months	None	Case
Peru	AMRO	2005	DTP/HepB/Hib	2, 4, 6, months	None	Case
Germany	EURO	1990	Various	2, 4, 6, months	11-14 months	Incidence
France	EURO	1992	DTaP/HepB/Hib/ IPV	2, 3, 4 months	16-18 months	Incidence
Sweden	EURO	1992	Various	3, 5 months	12 months	Incidence
United Kingdom	EURO	1992	DTP/Hib until 1999. DTaP/Hib combinations from 1999 onward.	2, 3, 4 months	12 months Added in 2003.	Incidence
Belgium	EURO	1993	DTaP/Hib/HepB/IPV	2, 3, 4 months	15 months	Incidence
Netherlands	EURO	1993	Hib monovalent until 2002. Switched to DTP/Hib/IPV in 2003. Switched to DTaP/Hib/IPV or DTaP/Hib/HepB/IPV in 2005	2, 3, 4 months	11 months	Incidence
Israel	EURO	1994	DTP/Hib/IPV until 2001. DTaP/Hib/IPV from 2002 onwards.	2, 4, 6 months	12 months	Incidence
Spain	EURO	1998	DTaP/HiB/IPV and DTaP/Hib/Hep/IPV	2, 4, 6, months	15-18 months	Incidence
Italy	EURO	1999	Various DTaP/Hib combinations	3, 5 months	11-12 months	Incidence
Greece	EURO	2000	Various including DTaP/Hib combinations	2, 4, 6 months	12-15 months	Incidence
Czech Republic	EURO	2001	Hib monovalent until 2006.	9, 13, 17	18 months	Incidence

			DTaP/Hib/HepB/IPV from 2007 onward	weeks		
Australia	WPRO	1993	DTaP/Hib/HepB/IPV Hib/HepB (PRP-OMP, indigenous children)	2, 4, 6 months 2, 4 months	12 months	Incidence

EUROPE, NORTH AMERICA AND OTHER INDUSTRIALIZED COUNTRIES

The United Kingdom

The United Kingdom implemented a 3 dose primary Hib vaccine schedule at 2, 3 and 4 months of age without a booster dose in 1993. The primary Hib vaccine was changed to a combination vaccine including an acellular pertussis component in 1999. Following vaccine introduction and an initial catch up campaign there was a dramatic decline in Hib disease in both vaccinated and unvaccinated age groups. However, there was an increase in invasive Hib disease several years after vaccine introduction (See UK Figure, Appendix 1). Invasive Hib disease incidence remained far below pre-vaccination levels, but increases were seen across all ages.(Ladhani, 2008) Several factors, including the change to combination vaccines with an acellular pertussis component and waning immunity from the primary series may have contributed to this experience. In 2003, following the increase in Hib cases, a booster dose in the second year of life was added to the vaccination schedule with a subsequent decline in cases across all age groups, including unvaccinated adults, indicating that the booster dose had resulted in reductions in disease transmission. A similar pattern was seen in Ireland, although the number of cases is smaller and the epidemiology less well characterized.(Fitzgerald, 2005)

The Netherlands

The Netherlands introduced Hib vaccine in 1993 as a 3 dose primary series at ages 3, 4 and 5 months with a booster dose at 11 months of age. This schedule was changed to dosing at 2, 3, 4 and 11 months in 1999. Monovalent Hib vaccine or a combination vaccine with whole cell pertussis component was used until 2005 when an acellular pertussis combination vaccine was introduced.(Rijkers, 2003) In 2002, an increase in the incidence of invasive Hib disease in children less than 5 years of age was identified by the national surveillance system. The incidence peaked in 2005 at 2.7 cases per 100,000 (26 cases in children less than 5 years of age) compared with <1.0 cases per 100,000 seen in 1999-2001.(Rijkers, 2003; Spanjaard, 2005) In 2006, there was a decline in reported cases, and the incidence rate has returned to approximately 1.0 per 100,000 children less than 5 years of age (See Netherlands Figure, Appendix 1). The cause of the increase in incidence is not clear. There have been no changes in the surveillance system, and no geographic or demographic patterns among cases have been identified.(Mirjam Knol, personal communication)

Other European Countries

Surveillance data from 7 other eligible European countries are available through the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) and the European Centre for Disease Prevention and Control (ECDC).(European Centre for Disease Prevention and Control, 2007; European Centre for Disease Prevention and Control, 2009; European Union Invasive Bacterial Infections Surveillance Network, 2005) For these countries, Hib conjugate vaccine was introduced in different years: Germany (1990); Sweden and France (1992); Spain (1998); Italy (1999); Greece (2000); and the Czech Republic (2001). All seven countries use a primary series followed by a booster dose. There is a pattern of consistently low disease incidence following vaccine introduction across these countries (see Appendix 1).

Canada

Following implementation of Hib conjugate vaccine for children in the second year of life in 1988, Canada introduced Hib conjugate vaccination of infants in 1992. Currently, Canada uses an acellular pertussis combination vaccine with doses at 2, 4, 6 and 18 months of age. Disease incidence has remained low (see Canada Figure, Appendix 1).

United States

In the United States prior to Hib vaccine introduction, the annual incidence of *H. influenzae* meningitis was approximately 50-60/100,000, 25-35/100,000 and 5/100,000 for children <1 year of age, 1 year of age and 2-4 years of age, respectively.(Adams, 1993) Hib conjugate vaccine was introduced as a single dose at 18 months of age in 1987. Following vaccine introduction, there were declines in the incidence of Hib disease in vaccinated age groups. Incidence also declined in infants who were too young to be vaccinated, reflecting an indirect impact of the vaccine.(Adams, 1993) Infant vaccination was introduced in 1990. In the United States, a number of different vaccines and combinations and schedules have been used. However, since 1990, the basic approach to scheduling has been to use a primary series with a booster dose in the second year of life. Disease incidence has remained low (see U.S. Figure, Appendix 1).

Of note, there was a resurgence of invasive Hib disease among Alaska Native children reported in 1996 associated with a change in Hib conjugate vaccine. Prior to vaccine introduction, Alaska Native children had among the highest rates of invasive Hib disease reported worldwide. Use of PRP-OMP vaccine, which is more immunogenic after a single dose than other Hib conjugate vaccines, resulted in a large decline in disease incidence. However, disease incidence increased after a switch to PRP-CRM197 vaccine, which is less immunogenic until the third dose of the primary series. The resurgence of Hib disease in Alaska Native children was associated with ongoing circulation of the organism in pre-school and school aged children, despite several years of routine vaccination.(Galil, 1999; Singleton, 2000) Disease incidence declined following reinstitution of a PRP-OMP based schedule.

Australia

Australia introduced Hib conjugate vaccine in 1993. Currently, an acellular pertussis PRP-T combination vaccine is used with a schedule of 2, 4, 6 and 12 months for non-indigenous children. Indigenous children

receive PRP-OMP vaccine at 2, 4, and 12 months of age. Horby et al. reported national surveillance data showing that invasive Hib disease incidence fell sharply following vaccine introduction and remained low (<2/100,000 children less than 5) from mid-1996 through mid-2000.(Horby, 2003) Australia also participated in the EU-IBIS surveillance system from 1999-2006. Between these years, reported Hib disease incidence in children less than 5 years of age remained low, ranging from 0.5-1.6 cases per 100,000 (see Australia Figure, Appendix 1). Of note, incidence rates in indigenous populations living in Northern Australia who had very high levels of disease in the pre-vaccine era have fallen considerably, but remain higher than in non-indigenous persons.(Menzies, 2008)

Israel

Israel introduced Hib conjugate vaccine in 1991 and began implementing universal Hib conjugate vaccination in January 1994. Currently, an acellular pertussis combination vaccine with PRP-T is used at 2, 4, 6 and 12 months of age. Data from Israel are available from the EU-IBIS surveillance system from 1999-2006.(EU-IBIS, 2005) In addition, unpublished data have been provided by Dr. Noga Givon-Lavi for the years 2007-2011 (see Israel Figure, Appendix 1). From 1999-2011, there were from 4-14 cases of invasive Hib disease in children less than 5 years of age. This corresponds to incidence rates ranging from 0.6-1.9 cases/100,000 children per year. During this time, 81% of cases were less than one year of age.

Summary of Results from Industrialized Countries

Primary Hib vaccine schedule. Are there settings where early administration of the first dose is needed to prevent invasive Hib disease in infants?

There are limited data from industrialized countries to address this question. The experience in Alaska suggests that in settings conducive to transmission of Hib, early primary dosing is needed to reduce disease in young infants. In more representative industrialized country settings, Hib disease also persists, albeit at low levels relative to the pre-vaccine era. Among industrialized countries reviewed in this analysis, all but Italy and the Czech Republic reported higher disease incidence among children less than one year of age compared with children 1-4 years of age (Table 2). This finding indicates that indirect protection does not completely protect infants in these countries, despite use of a booster dose and high vaccination coverage levels. While early primary dosing appears to maximize individual protection in industrialized countries settings, the added benefit of early primary dosing is not known. Of note, two industrialized countries have successfully used a two dose primary series at three and five months of age using PRP-T and a schedule with a booster dose.

Table 2. Age Specific Hib Disease Incidence Rates for Industrialized Countries.**

Country	Most Recent 3 Years for which Age Specific Hib Disease Incidence Data Are	Average Incidence Rate for Children less than 1 Year of Age	Average Incidence Rate for Children 1-4 Years of Age	Most Recent 3 years for which Hib Disease Incidence Data Are Available for Children <5 Years	Average Incidence Rate for Children less than 5 Year of Age

	Available*			of Age*	
Czech Republic	2007-2008	0	0.41	2007-2009	0.29
France	2002-2004	0.50	0.19	2006-2008	0.05
Germany	2003, 2004, 2007	0.74	0.12	2007-2009	0.32
Greece	2003, 2004, 2007	3.9	0.25	2007-2009	0.20
Italy	2004, 2007, 2008	0	0.03	2007-2009	0.04
Netherlands	2008-2010	2.2	0.67	2008-2010	0.96
Spain	2007-2008	0.23	0	2007-2009	0.05
Sweden	2006-2008	0.68	0	2006-2008	0.14
United Kingdom	2006-2008	1.4	0.52	2006-2008	0.71
Australia	2002-2004	1.3	0.55	2004-2006	0.58
United States	2008-2010	0.25	0.10	2008-2010	0.19
Canada	2002-2004	1.8	0.39	Not Available	
Israel	2009-2011	4.7	0.4	2009-2011	1.3

*Only data at least 5 years following vaccine introduction is considered.
**Data sources and Hib disease type as indicated in Appendix 1.

Booster dose schedule. Is a booster dose needed for sustained reductions in Hib disease burden? Are there data available on the long term effectiveness of a booster dose is given before the first birthday?
The experience in the United Kingdome suggests that there are settings where a booster dose is needed for sustained reductions in Hib disease burden. However, the circumstances in the United Kingdom were unique, and there are insufficient data to identify the factors that would indicate the use of a booster dose. All other industrialized countries studied have used a booster dose, so no additional information is available from this group to assess the need for a booster dose. The Netherlands and Italy have used a booster dose at 11-12 months of age. The Netherlands did experience a small increase in Hib disease incidence for a few years. It is unclear whether the early booster dose contributed to the disease increase. Disease incidence in Italy has remained low.

Vaccination coverage. How do vaccination coverage levels impact the effectiveness of different vaccination schedules?

Vaccination coverage levels are generally high in industrialized countries. Therefore there are no data to address this question.

Epidemiologic characteristics of the country. Do epidemiologic characteristics favoring early Hib transmission reduce the effectiveness of different vaccination schedules?

The experience in Alaska supports the hypothesis that epidemiologic characteristics favoring early Hib transmission might reduce the effectiveness of a schedule with delayed primary dosing. Other industrialized country settings generally have epidemiologic characteristics that do not favor early Hib transmission. However, even in industrialized countries with high vaccination coverage and schedules that include a booster dose, Hib continues to circulate.

LATIN AMERICAN COUNTRIES

A variety of data on Hib disease are available from Latin America. Published incidence data are available from Argentina, Brazil, Chile, Colombia and Uruguay. Also, the Pan American Health Organization has created a sentinel surveillance network known as the Sistema Regional de Vacunas (SIREVA). Data from the SIREVA system are available for 13 other Latin American countries that met criteria for inclusion in this review.

Brazil

Brazil introduced Hib conjugate vaccine in 1999 as a primary series without a booster dose. Zanella et al. reported surveillance data from Sao Paulo state on Hib meningitis from 1990-2008.(Zanella, 2011) In the years 2000-2002, the annual incidences of Hib meningitis in children aged <1 year and 1-4 years were 1.26 and 0.38 cases/100,000 children, respectively. In the years 2006-2008, the corresponding rates were 0.26 and 0.17. Thus, there was no evidence of increasing incidence over time. Ribiero et al. reported data from active surveillance for meningitis in metropolitan Salvador. The incidence of Hib meningitis in children less than 5 years of age fell from between 23-28 cases/100,000 in the pre-vaccine era to <1 case/100,000 in 2004.(Ribeiro, 2007) Unpublished data from the same group shows continuing low incidence rates through mid-2007.(see Brazil Figure, Appendix 1)

Argentina, Chile, Colombia, and Uruguay

These four countries carried out a project specifically designed to assess the need for a booster dose of Hib conjugate vaccine in Latin America. Chile and Colombia introduced Hib conjugate vaccine as a 3 dose primary series without a booster dose in 1996 and 1998, respectively. Argentina and Uruguay introduced Hib conjugate vaccine as a 3 dose primary series with a booster dose at 12 months (Uruguay) and 18 months (Argentina) in 1997 and 1994, respectively. Selected sites in these 4 countries carried out population-based surveillance for Hib meningitis for at least 7 years after vaccine introduction. In all sites, Hib meningitis

incidence remained low following vaccine introduction. Disease incidence was higher among children less than 1 year of age compared with children 1-4 years of age (see Figures in Appendix 1).(Garcia, 2012)

SIREVA

Data from SIREVA are shown in Appendix 2.(Pan American Health Organization, 2012) In general, these data do not suggest increases in Hib disease in participating countries except for Argentina where a substantial increase was reported in 2010. After reporting 3-9 cases per year of invasive Hib disease in children less than 2 years of age from 2000 to 2009, Argentina reported 27 cases in 2010. In 2010, there were changes in the surveillance system in Argentina with increased efforts to identify meningococcal meningitis. Of note, in 2010 there was also an increase in the cases of pneumococcal meningitis identified. From 2000-2009 115-233 cases per year were ideintified while in 2010, 355 were found. Ongoing monitoring is needed to determine whether the increase in Hib meningitis reported in Argentina represents a trend. Conclusions about patterns of disease burden are difficult to make from a single year and from sentinel surveillance data, especially when surveillance activities are changing. Hib disease continues to be identified in all SIREVA participating countries with at least 100,000 births per year. SIREVA sites report Hib disease cases stratified into less than 2 years of age and 2-14 years of age. For most countries, the number of cases in the less than 2 year age group exceeds that of the 2-14 year age group suggesting that disease remains most common in very young children (See Appendix 2).

Table 2. Cases of Hib Disease in Children less than Two Years of Age Reported by SIREVA, 2000-2010*

Year	Argentina	Bolivia	Brazil	Chile	Colombia	Costa Rica	Cuba	Ecuador	El Salvador
2000	9	6	83	12	23	9	23	5	0
2001	9	2	42	22	11	7	11	9	22
2002	5	3	26	10	16	0	12	21	10
2003	5	8	19	16	7	1	8	9	3
2004	4	5	12	14	5	2	5	5	2
2005	5	7	9	11	3	0	2	5	0
2006	6		15	6	6	0		3	2
2007	3		14	8	0			2	0
2008	7	7	7	5	3	0		9	1
2009	5	0	9	6	3	0	2	4	1
2010	27	2	12	5	3	0	8	8	2

*Disease syndrome under surveillance varies by country and is indicated in Appendix 2.

Summary of Results from Latin American Countries

Primary Hib vaccine schedule. Are there settings where early administration of the first dose is needed to prevent invasive Hib disease in infants?

There are limited data from Latin American countries to address this question. Hib disease persists, albeit at low levels, in Latin American countries, with disease incidence highest in the first year of life.
Early primary dosing may maximize individual protection, but there no empiric data to assess the added benefit of early primary dosing at the population level.

Booster dose schedule. Is a booster dose needed for sustained reductions in Hib disease burden? Are there data available on the long term effectiveness of a booster dose is given before the first birthday?
In Latin America, the available data do not suggest that a booster dose is needed for sustained reductions in Hib disease burden. Countries using not using a booster dose have had similar experiences to countries using a booster dose. No countries are using a booster dose before the first birthday.

Vaccination coverage. How do vaccination coverage levels impact the effectiveness of different vaccination schedules?
Vaccination coverage levels are generally high in Latin American countries and there are no data to address this question.

Epidemiologic characteristics of the country. Do epidemiologic characteristics favoring early Hib transmission reduce the effectiveness of different vaccination schedules?
We did not identify data from Latin America to address this question.

AFRICAN COUNTRIES

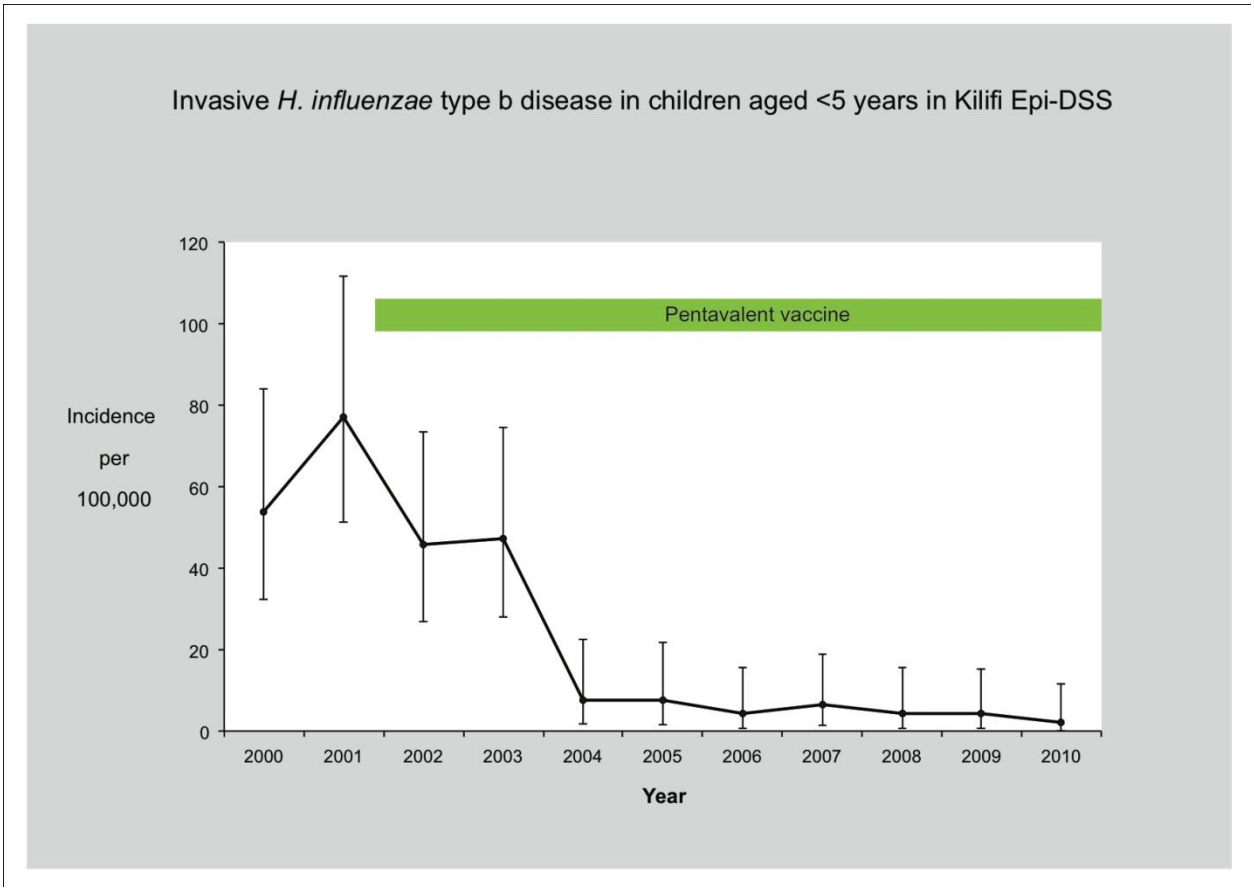
In general, Hib conjugate vaccine was introduced later in Africa than in industrialized countries and Latin America. Nevertheless, data on long-term Hib conjugate vaccine impact is available from several African countries. Unless otherwise indicated, all of these countries use a whole cell pertussis PRP-T combination vaccine as a three dose primary series without a booster dose. In general, these countries use a primary series of three doses in the first four months of life (Table 1), although actual age at vaccine administration varies.

<u>South Africa</u>
South Africa introduced Hib conjugate vaccine in 1999 as a 3 dose primary series without a booster dose. The initial vaccine was a PRP-T combination vaccine with a whole cell pertussis component. In 2009, this vaccine was replaced with a combination vaccine containing an acellular pertussis component and inactivated polio vaccine (IPV).(Von Gottberg, 2012) Following vaccine introduction, there was a substantial decrease in the number of Hib cases identified by the national surveillance system.(Von Gottberg, 2006) However, from 2003-2009 the annual incidence (cases/100,000) of invasive Hib disease in children less than 5 years of age increased from 0.7 to 1.3.(Von Gottberg 2012) While this level of Hib disease was very low compared with the pre-vaccine era, it does suggest possible resurgence of Hib disease. A high level of HIV infection in young children and an early schedule for the primary series may have contributed to ongoing disease transmission. South Africa introduced a booster dose of the combination vaccine containing Hib in 2010. The purpose of the booster dose was for polio prevention since IPV was being used and not a response to change in Hib disease incidence.

Kenya

Kenya introduced Hib conjugate vaccine in 2001. The incidence of invasive Hib disease has been monitored prospectively in Kilifi District. Figure 1 shows the incidence of invasive Hib disease in children less than 5 years of age. There has been no evident increase in Hib disease up to 9 years following vaccine introduction.

Figure 1. Incidence (cases/100,000) of invasive Hib disease in children < 5 years of age, Kilifi District, Kenya, 2000-2010.



Source: Anthony Scott, personal communication.

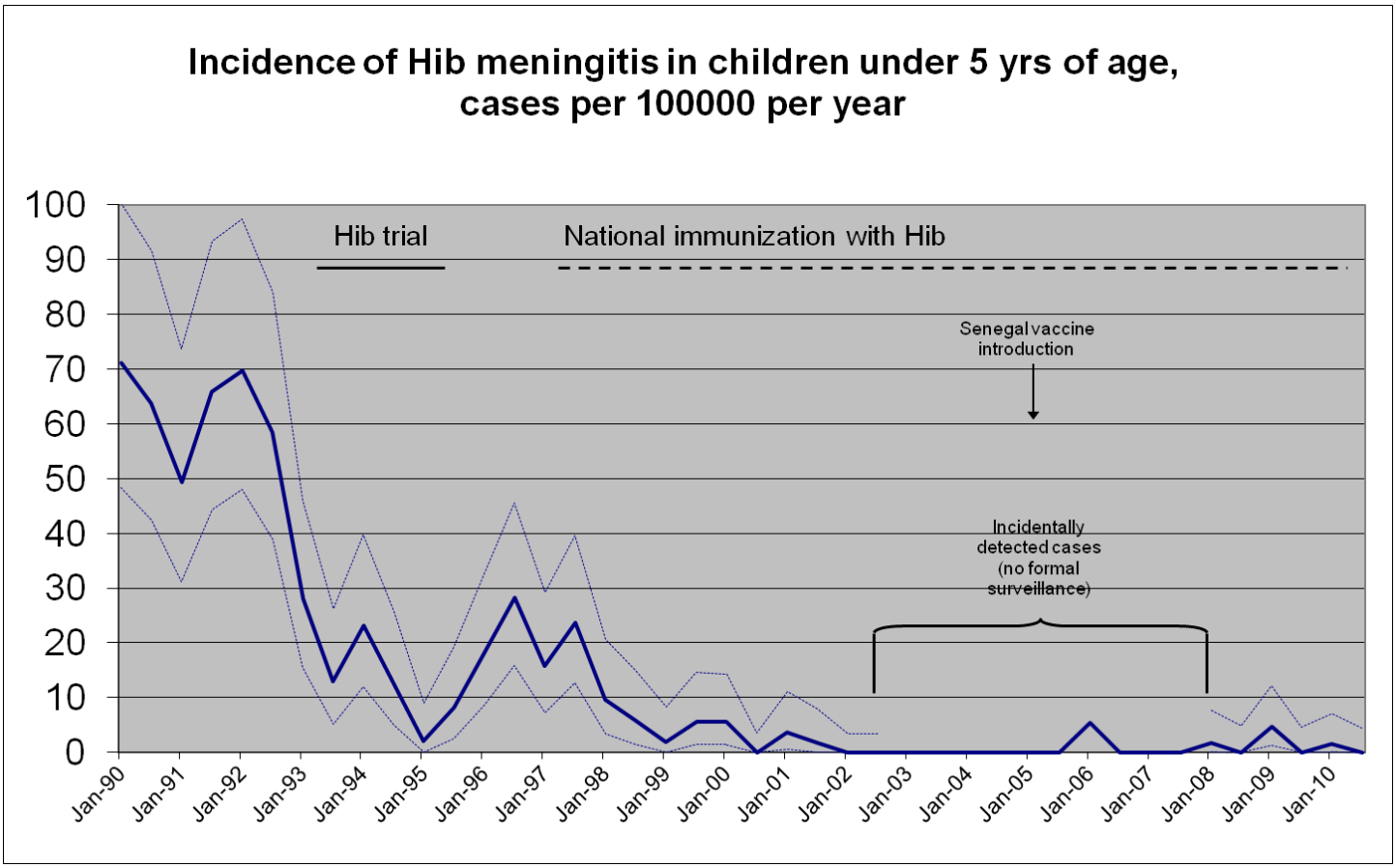
Malawi

Malawi introduced Hib conjugate vaccine in 2002. Data on cases of meningitis in children 15 years of age and younger were retrospectively reviewed at Queen Elizabeth Central Hospital, a large referral hospital in the capital, Blantyre. There was a substantial and sustained decrease in the number of Hib meningitis cases identified, falling from an average of 53 cases per year in the pre-vaccine era (1997-2002) to 5 cases in 2009. There was no change in the number of meningitis cases due to S. pneumoniae during the study period suggesting that the decline in observed Hib cases was not due to changes in surveillance, health care utilization or other non-vaccine factors.(McCormick, 2011)

The Gambia

The birth cohort in The Gambia is less than 100,000 per year so disease incidence estimates are somewhat labile due to a small sample size. Nevertheless, we included The Gambia because it was one of the first countries in Africa to introduce Hib conjugate vaccines in 1997 and there have been several reports on Hib disease in The Gambia published. Following vaccine introduction, there were rapid declines in Hib disease and no cases were identified in 2002. In that year, formal surveillance was stopped. In 2007, Howie et al. reported 5 cases of invasive Hib disease that were identified non-systematically. The cases raised the possibility of re-emergence of Hib disease.(Howie, 2007) From 2008-2010, surveillance in the Western Gambia was reestablished using the same methods as in 1997-2002. The population under surveillance was small (approximately 128,000 children under 5 years of age). In the 3 years from 2008-2010, 9 cases of invasive Hib disease were identified at 3 surveillance hospitals, including 5 cases of Hib meningitis. Surveillance from 2008-2010 has shown a continued low incidence of Hib meningitis in the Western Gambia 13 years following vaccine introduction (Figure 2). In 2008-2010, 8 of 9 cases identified were less than one year of age and the ninth case was 13 months of age.

Figure 2. Incidence of Hib meningitis (cases/100,000) in children < 5 years of age, Western Gambia, 1997-2010.



Source: Unpublished data provided by S. Howie.

Uganda

Uganda introduced Hib conjugate vaccine in 2002. Sentinel surveillance for pediatric bacterial meningitis at four large hospitals has been carried out to monitor vaccine impact. There has been a sustained decrease in the number of cases identified. At the one largest hospital in the year prior to vaccine introduction there were 69 cases of Hib meningitis identified.(Lewis, 2008) By comparison, for the period July 2009-June 2010 there were only 4 cases in this hospital and the three other sentinel hospitals combined.(Caroline Mate, personal communication)

Summary of Results from African Countries

Primary Hib vaccine schedule. Are there settings where early administration of the first dose is needed to prevent invasive Hib disease in infants?

There are limited data from African countries to address this question. All African countries use an early 3 dose primary series.

Booster dose schedule. Is a booster dose needed for sustained reductions in Hib disease burden? Are there data available on the long term effectiveness of a booster dose is given before the first birthday?

No African country had introduced a booster dose during the study period. Despite the absence of a booster dose, Hib disease incidence rates have remained low.

Vaccination coverage. How do vaccination coverage levels impact the effectiveness of different vaccination schedules?

Vaccination coverage levels are variable in African countries. Hib vaccination appears to be effective across the range of coverage levels seen in the countries for which data are available.

Epidemiologic characteristics of the country. Do epidemiologic characteristics favoring early Hib transmission reduce the effectiveness of different vaccination schedules?

The vaccination schedules used in the African countries with available data are very similar. Therefore, there is no way to assess the performance of different schedules in these countries.

DISCUSSION

We identified data on the long term impact of Hib conjugate vaccine from 35 countries. A few major insights can be drawn from the available data. First, Hib conjugate vaccination remains an extremely successful public health intervention resulting in substantial declines in disease incidence in all countries where long term data are available.

Second, Hib conjugate vaccine does not appear to have eliminated invasive Hib disease in any country with at least 100,000 annual live births. All countries with available data have reported low levels of ongoing Hib disease.

Third, in most countries the incidence of Hib disease remains highest in the first year of life, even after many years of routine vaccination. This finding suggests that early primary vaccination with Hib conjugate is necessary to maximize individual level protection. The experience in Alaska supports the need for early primary vaccination in settings of high transmission.

Fourth, a two dose primary schedule with a booster dose appears to be effective in some settings. Two industrialized countries, Italy and Sweden, have effectively used a two dose primary series with a booster dose. Immunogenicity studies and vaccine trials support the use of a two dose primary schedule in developing country settings, at least in the short term.

Fifth, available observational data do not support the need for a booster dose in developing country settings when a three dose primary series is used. The experience in the United Kingdom suggests that a booster dose may be important in some situations, but the specific factors that would indicate a booster dose are not clear. There are no data on the effectiveness of a booster dose prior to 11 months of age.

Sixth, current Hib vaccination schedules appear to be effective across the range of vaccination coverage levels seen in different countries.

The available data do not allow for definitive answers to the questions we set out to address. However, some insights are possible.

Primary Hib vaccine schedule. Are there settings where early administration of the first dose is needed to prevent invasive Hib disease in infants?
The most direct evidence to address this question comes from Alaska. In that setting with conditions conducive to transmission of Hib, early primary dosing appeared to be necessary to reduce disease in young infants. In addition, Hib disease persists across all countries studied, and disease incidence was generally highest in the first year of life. Early primary dosing may maximize individual protection, particularly in settings with greater transmission of Hib. However, from a population perspective, the added value of early primary dosing is not clear.

Booster dose schedule. Is a booster dose needed for sustained reductions in Hib disease burden? Are there data available on the long term effectiveness of a booster dose is given before the first birthday?
The experience in the United Kingdome suggests that there are settings where a booster dose is needed for sustained reductions in Hib disease burden. However, the circumstances in the United Kingdome were unique, and there are insufficient data to identify the factors that would indicate the use of a booster dose. The Netherlands reported a transient increase in disease incidence despite the use of a booster dose. In Latin American countries, the experience in countries using a booster dose has been similar to that of countries which have not used a booster dose. In Africa, schedules without a booster dose have been effective. South Africa did report an increase in incidence over several years, although this increase was small and disease incidence remained within the range reported from other countries.(Von Gottberg 2012) The number of

countries reporting disease increases has been too small to conclusively determine the conditions associated with such increases.

Vaccination coverage. How do vaccination coverage levels impact the effectiveness of different vaccination schedules?
We found insufficient data to address this question. Too few countries have experienced apparent reductions in vaccine effectiveness to permit an assessment of the relationship to vaccination coverage.

Epidemiologic characteristics of the country. Do epidemiologic characteristics favoring early Hib transmission reduce the effectiveness of different vaccination schedules?
The experience in Alaska supports the hypothesis that epidemiologic characteristics favoring early Hib transmission might reduce the effectiveness of a schedule with delayed primary dosing. Other industrialized country settings generally have epidemiologic characteristics that do not favor early Hib transmission. However, even in industrialized countries with high vaccination coverage and schedules that include a booster dose, Hib continues to circulate.

A few countries have experienced small increases in invasive Hib disease incidence in the long term following vaccine introduction. The most thoroughly evaluated increase was seen in the United Kingdom where an accelerated primary series containing acellular pertussis vaccine component was used without a booster dose. Implementation of a booster dose was associated with a subsequent decline in cases.(Ladhani 2008) Small increases were also reported in the Netherlands which uses a booster dose. However, these increases were not sustained and declined without changes in vaccination schedule. In Alaska, a setting with epidemiologic features supportive of high Hib transmission, a schedule change that effectively delayed primary immunity was associated with an increase in disease. Disease levels decreased with a return to an accelerated primary series. Finally, South Africa reported an increase in incidence over several years, although this increase was small and disease incidence remained within the range reported from other countries.(Von Gottberg 2012) The number of countries reporting disease increases has been too small to conclusively determine the conditions associated with such increases. Factors suggested in published reports include several things associated with decreased long term immune response to Hib conjugate vaccines: use of acellular pertussis containing combination vaccines; use of a vaccination schedule without a booster dose in the second year of life; short intervals between primary doses; and high levels of HIV prevalence.

In African and Latin American countries, use of a three dose primary schedule of PRP-T vaccine in combination with whole cell pertussis vaccine has not been associated with large or sustained Hib disease resurgence. Thus, currently available data do not support a change in vaccination recommendations for countries using this regimen. Ongoing surveillance is needed to determine whether the incidence of Hib disease will rise as more countries have longer experience with the three dose primary vaccination regimen. Countries which implement Hib conjugate vaccine in combination with acellular pertussis vaccine should closely monitor disease incidence if a booster dose is not used.

Several alternative vaccination strategies have been proposed to reduce the cost of Hib vaccination programs or to prevent increases in disease incidence over time. These include the use of a two dose primary series with a booster dose, addition of a booster dose to a 3 dose primary series, and use of a single dose in the second year of life.(Campagne, 1998; Fitzwater, 2010; Jackson, 2012; Levine, 1998) Two industrialized countries have successfully used a two dose primary series with PRP-T followed by a booster dose, with both doses administered before 6 months of age. A two dose primary series with PRP-OMP is also used in some industrialized countries, and has been effective in sub-populations with high transmission pressure. However, long term effectiveness has only been demonstrated in schedules that include a booster dose in the second year of life. Immunogenicity and vaccine trial data also suggest that a two dose primary series would be effective in the short term in developing country settings. However, there are no data on the long term effectiveness of a two dose primary series without a booster dose. As most developing countries use combination vaccines that include Hib as well as other components, a two dose primary series with a booster would likely require changes in Hib vaccine formulations. Nonetheless, available data suggest that such a schedule could be effective. Indeed, delaying administration of the third dose until the nine month vaccination visit used in many countries could result in improved effectiveness. Long term surveillance should be carried out if such a schedule is implemented in a developing country setting, especially if the booster dose is given before the first birthday.

Addition of a booster dose to a three dose primary series could require countries to use multiple Hib vaccine preparations and would likely present significant operational challenges. Further, developing countries do not typically have a scheduled vaccination point in the second year of life. No data exist on the added value of a booster dose at 9 months, which is the last scheduled vaccination point currently used in most developing countries. Addition of a booster dose could also increase the cost of the Hib vaccination program. Available data suggest that a three dose primary schedule without a booster dose is effective in developing country settings and the added value of a booster dose would be limited. Our review has not found sufficient data to change the previous WHO recommendation that the need for a booster dose in developing countries has not yet been defined.

The United State initially introduced Hib conjugate vaccine as a single dose in the second year of life. This schedule resulted in significant declines in disease incidence in vaccinated and unvaccinated children. However, a primary series in infancy was added after 3 years. There are no empirical data on the long term effectiveness of a single dose schedule. Because Hib continues to circulate in almost all populations despite long term vaccine use, there is an ongoing risk of Hib disease in unvaccinated infants. A single dose schedule should therefore be used with caution and careful monitoring.

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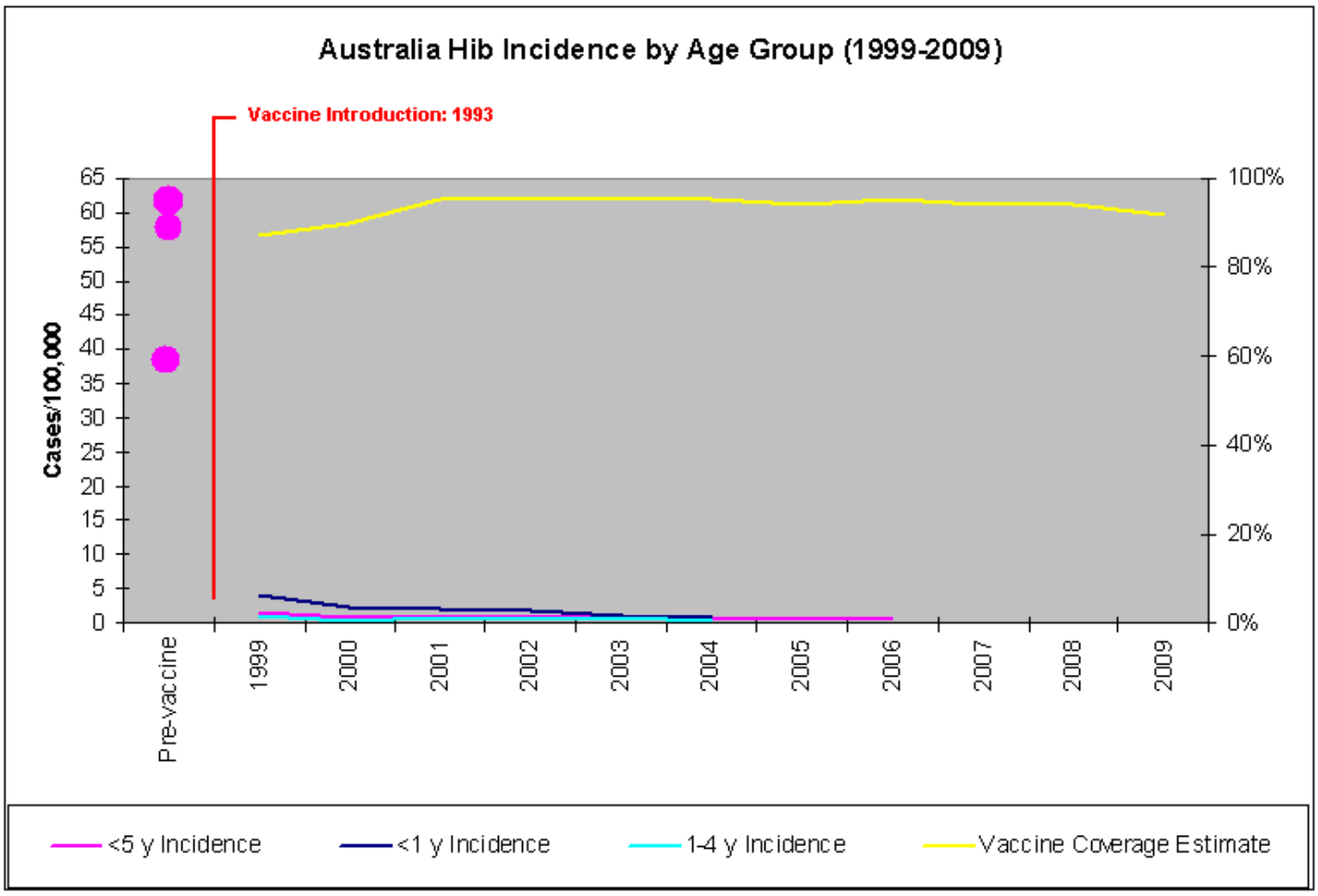
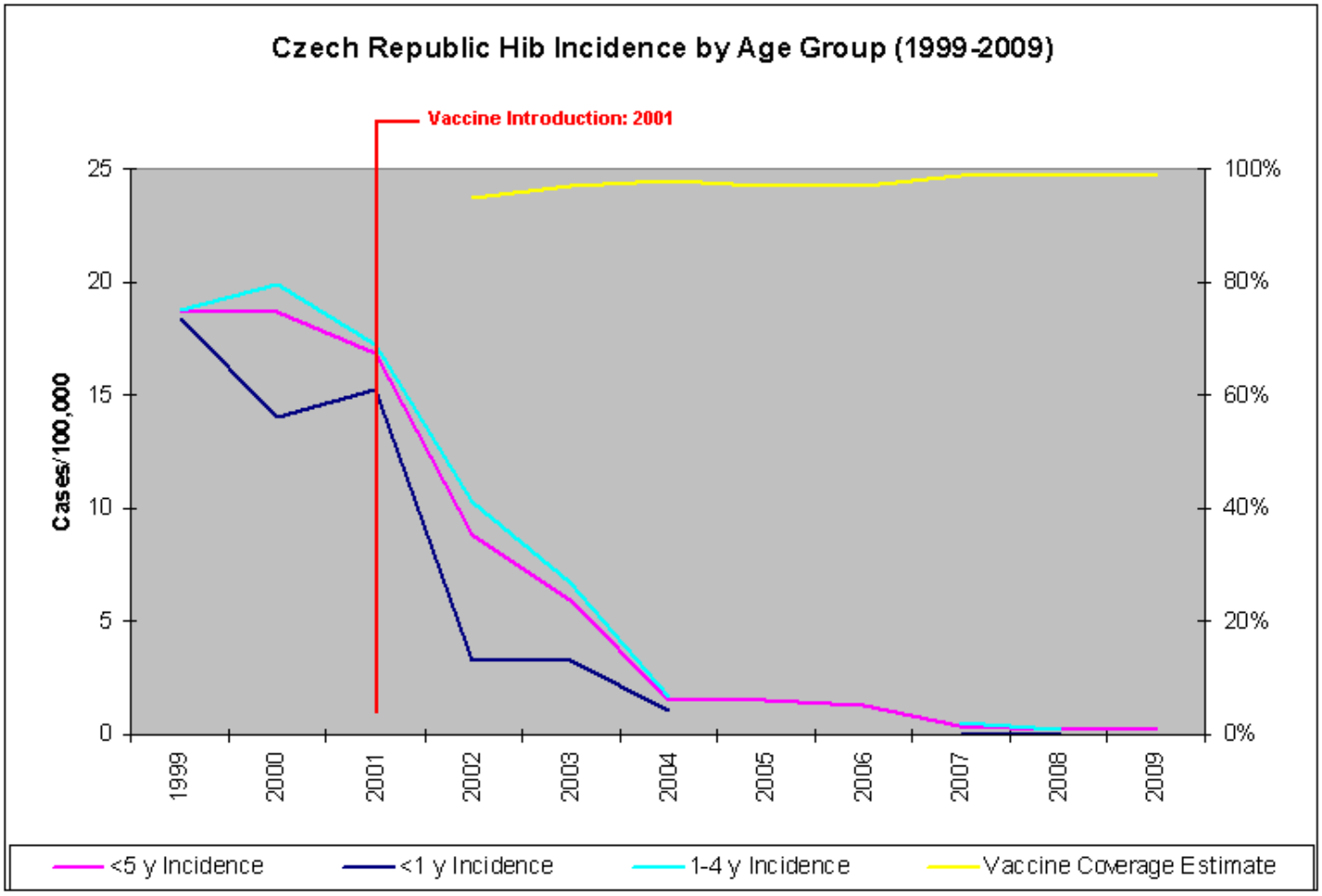


For all invasive Hib disease
Source of pre-vaccine incidence: Horby, 2000.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; and the 2007, 2008/9 ECDC publications.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9
Country total population for Australia from (2005-2009) and Spain from (2007-2009) were sourced from Google Public Database

<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



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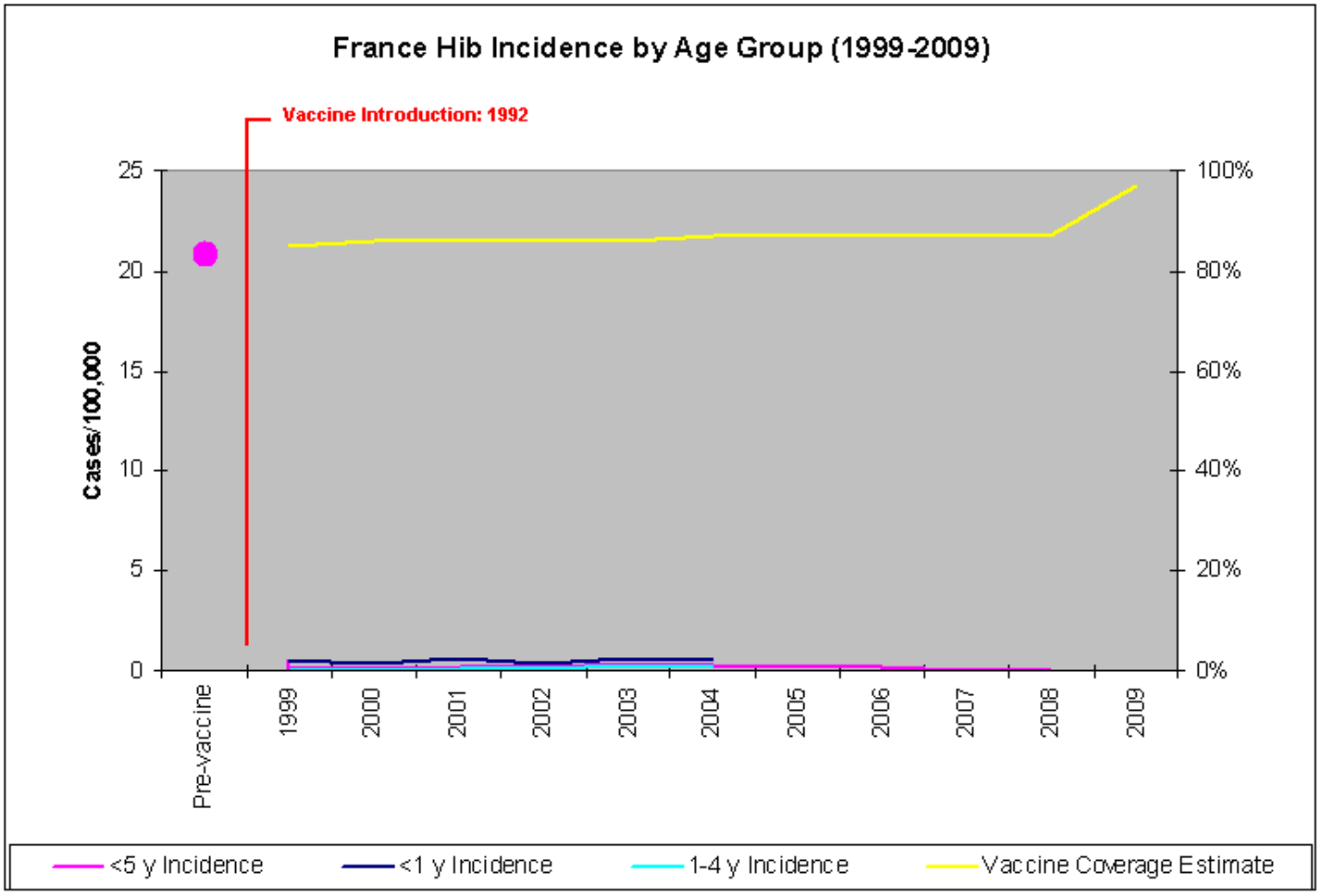
Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9

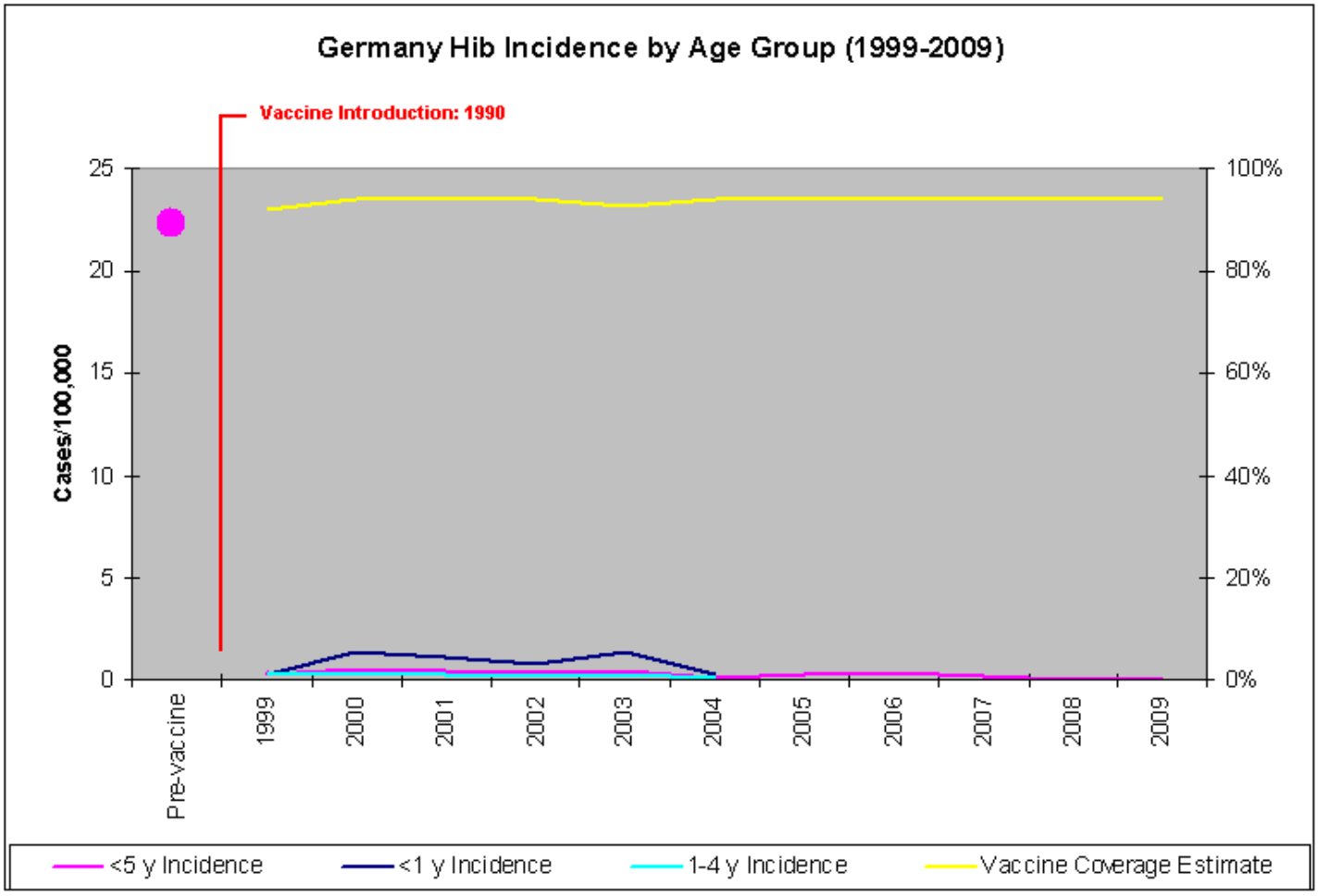
<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



For all invasive Hib disease
Pre-vaccine incidence estimate: 21/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; and the 2007, 2008/9 ECDC publications.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9

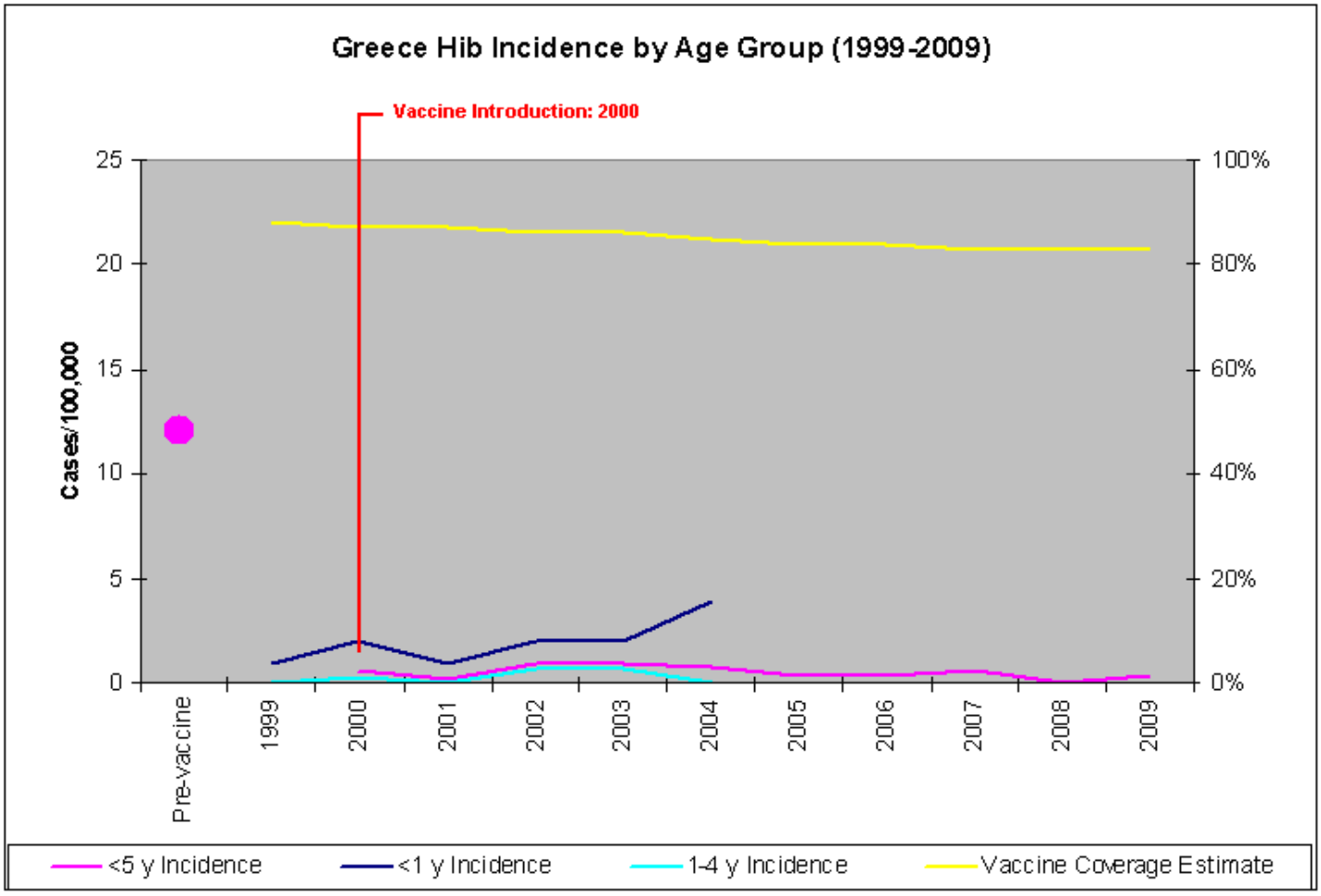
<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



For all invasive Hib disease
Pre-vaccine incidence estimate: 23/100,000
Note: Pre-vaccination Incidence estimate for H. influenzae meningitis, not all invasive disease
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; and the 2007, 2008/9 ECDC publications.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9
Country total population for Australia from (2005-2009) and Spain from (2007-2009) were sourced from Google Public Database

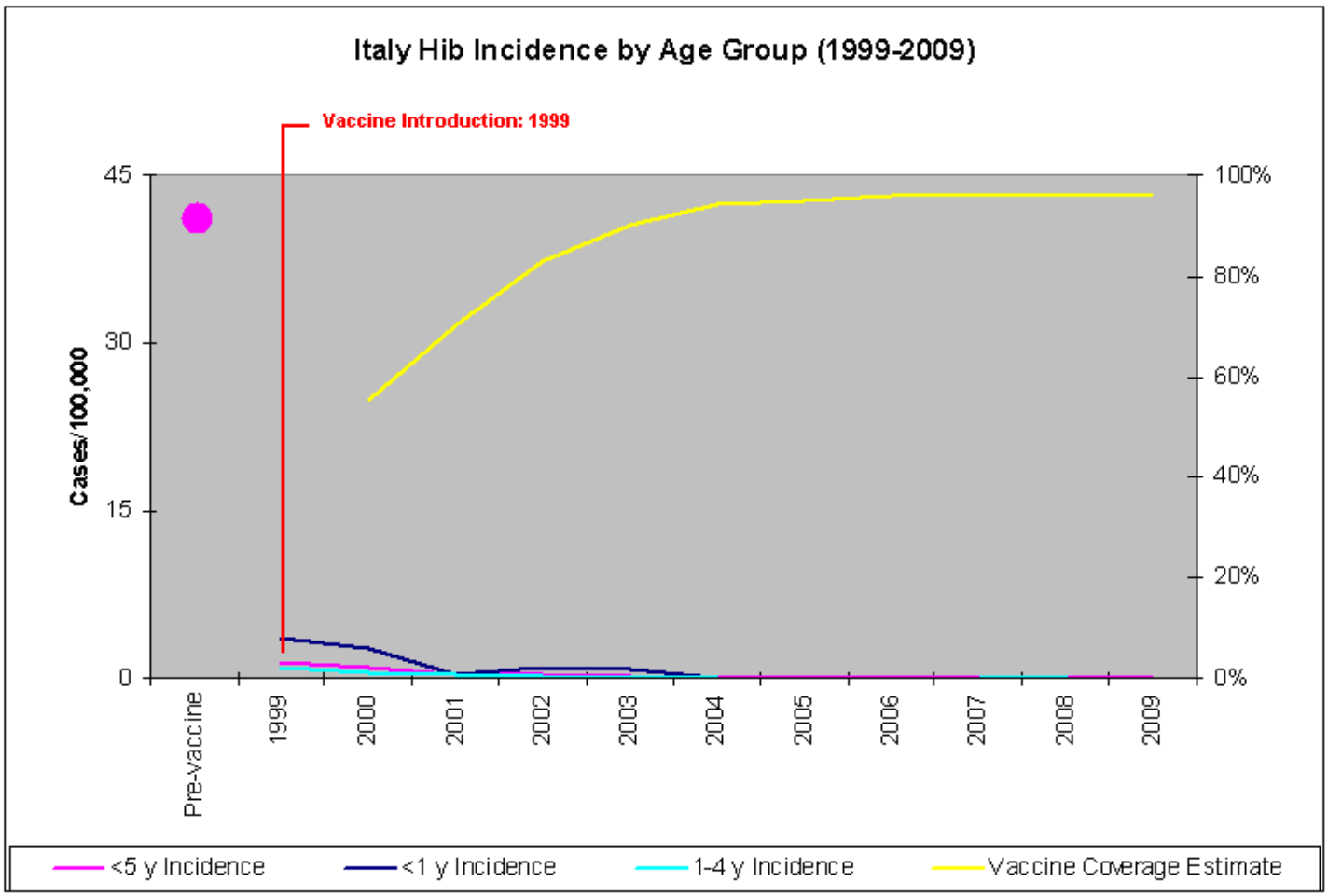
<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



For all invasive Hib disease
Pre-vaccine incidence estimate: 12/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; and the 2007, 2008/9 ECDC publications.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9

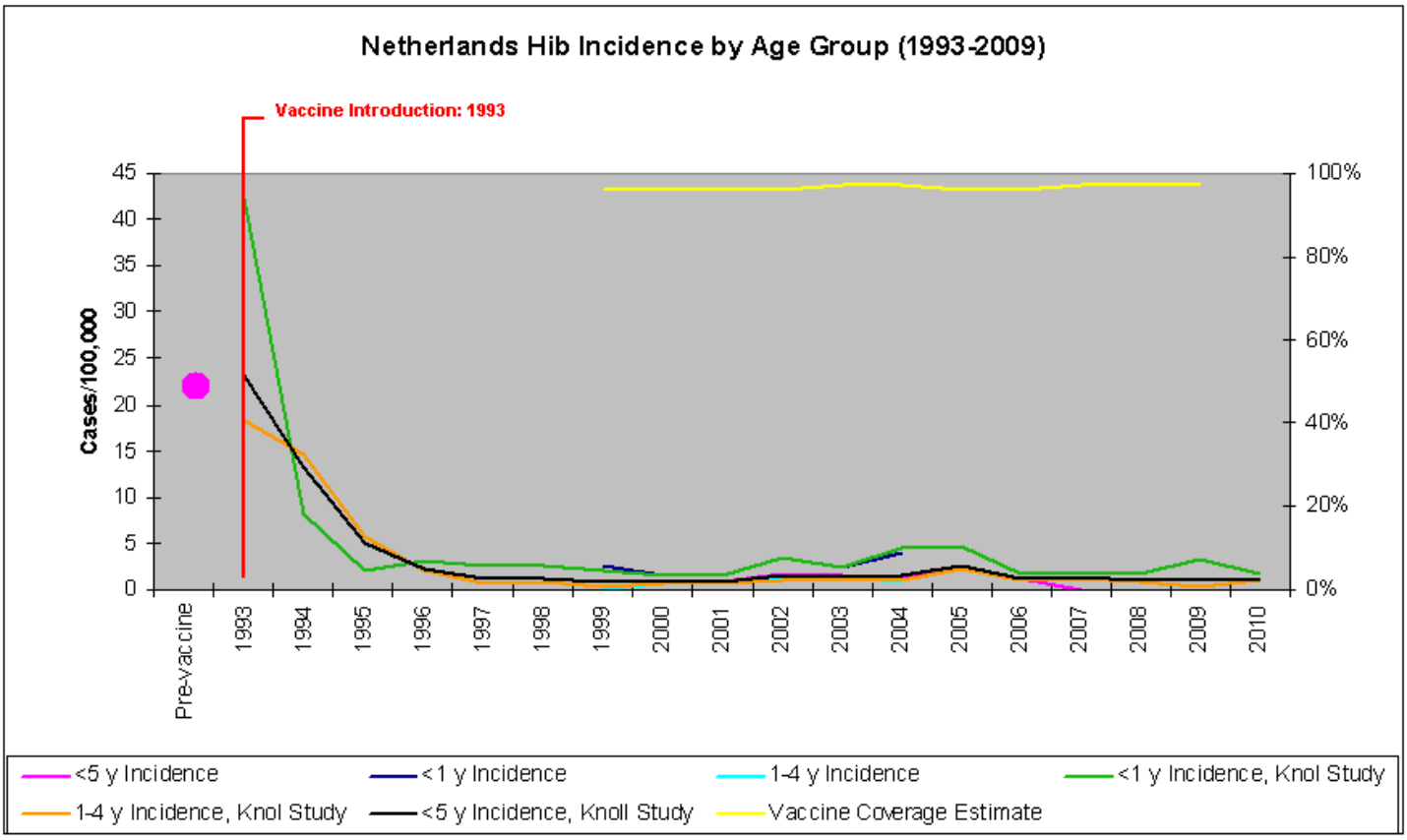
<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



For all invasive Hib disease
Pre-vaccine incidence estimate: 36.1 - 44.5/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; and the 2007, 2008/9 ECDC publications.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9
Country total population for Australia from (2005-2009) and Spain from (2007-2009) were sourced from Google Public Database

<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4

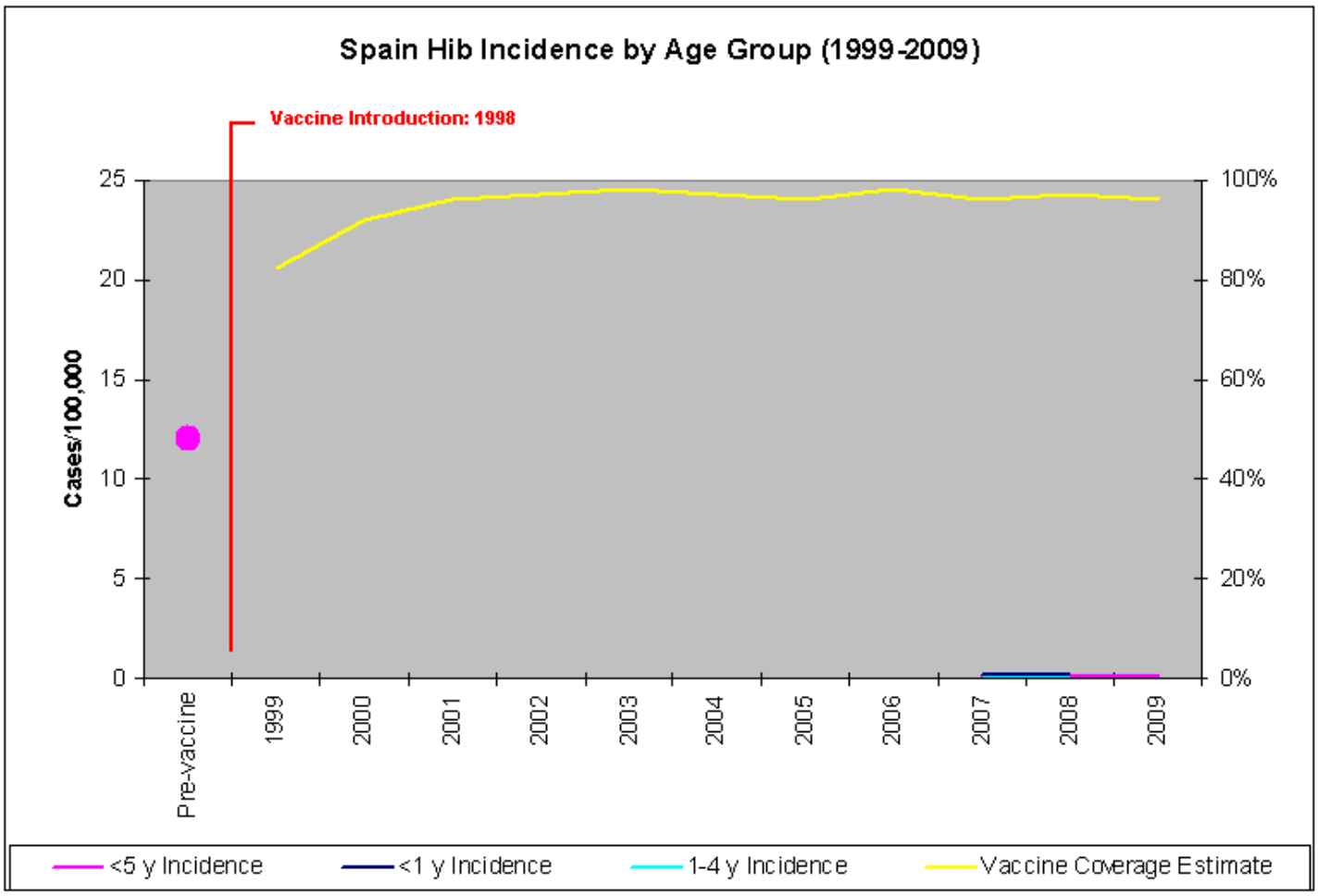


For all invasive Hib disease
Pre-vaccine incidence estimate: 22/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; and the 2007, 2008/9 ECDC publications.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9

<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4

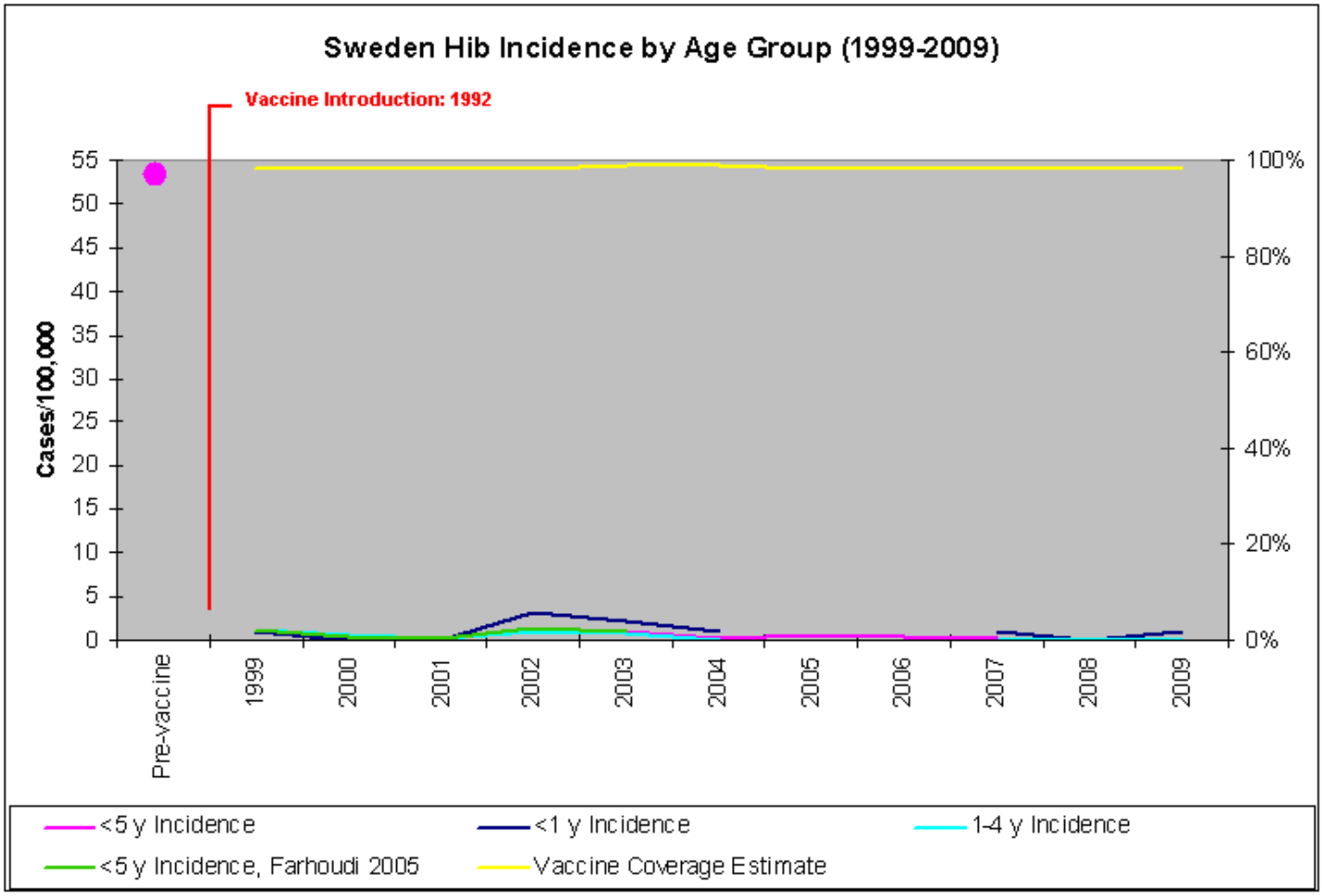
Separate post-vaccine incidence data provided by Mirjam Knol, National Institute for Public Health and the Environment (RIVM), The Netherlands.



For all invasive Hib disease
Pre-vaccine incidence estimate: 12.4/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; and the 2007, 2008/9 ECDC publications.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9
Country total population for Australia from (2005-2009) and Spain from (2007-2009) were sourced from Google Public Database

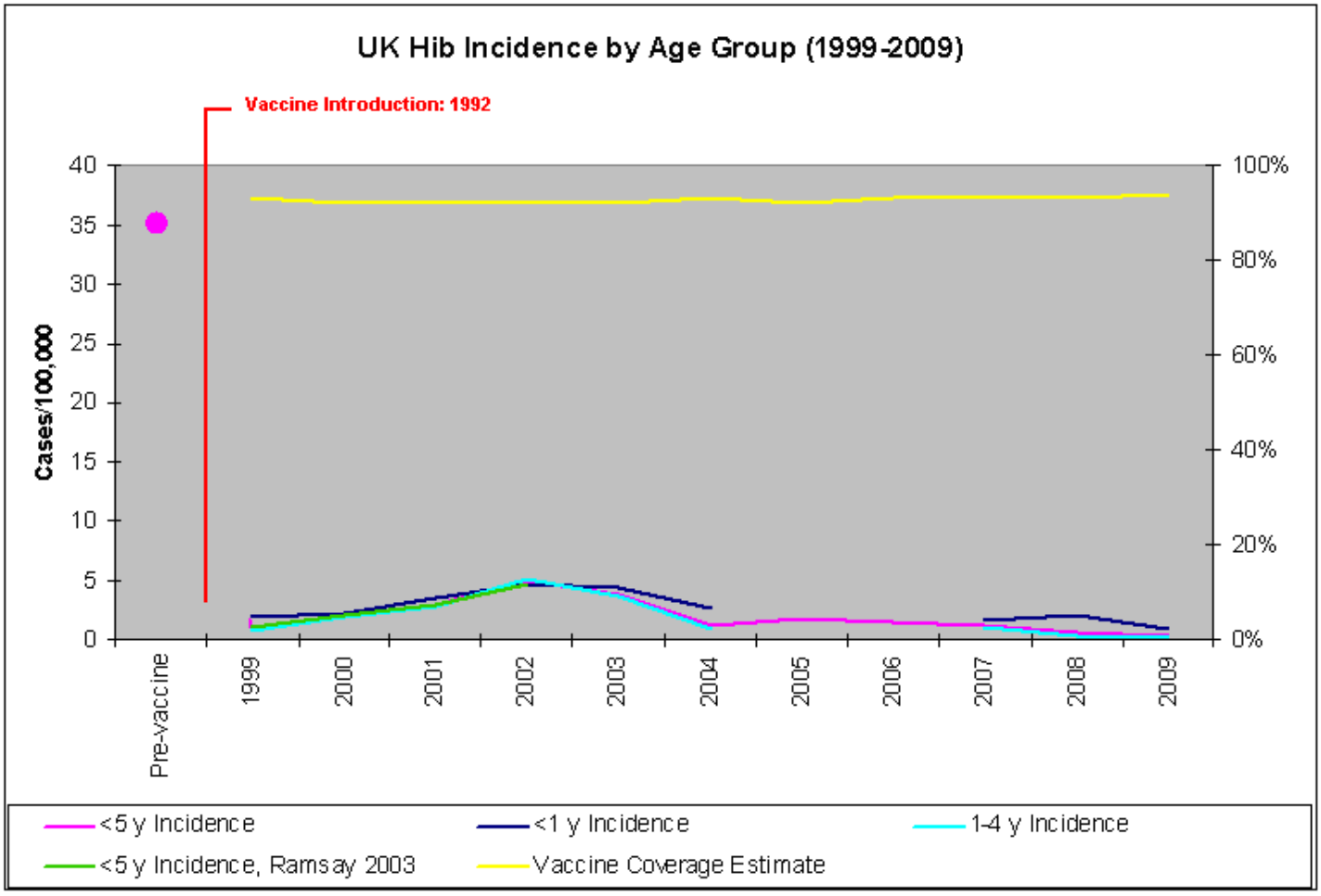
<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



For all invasive Hib disease
Pre-vaccine incidence estimate: 54/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; the 2007, 2008/9 ECDC publications; and Farhoudi, 2005.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9

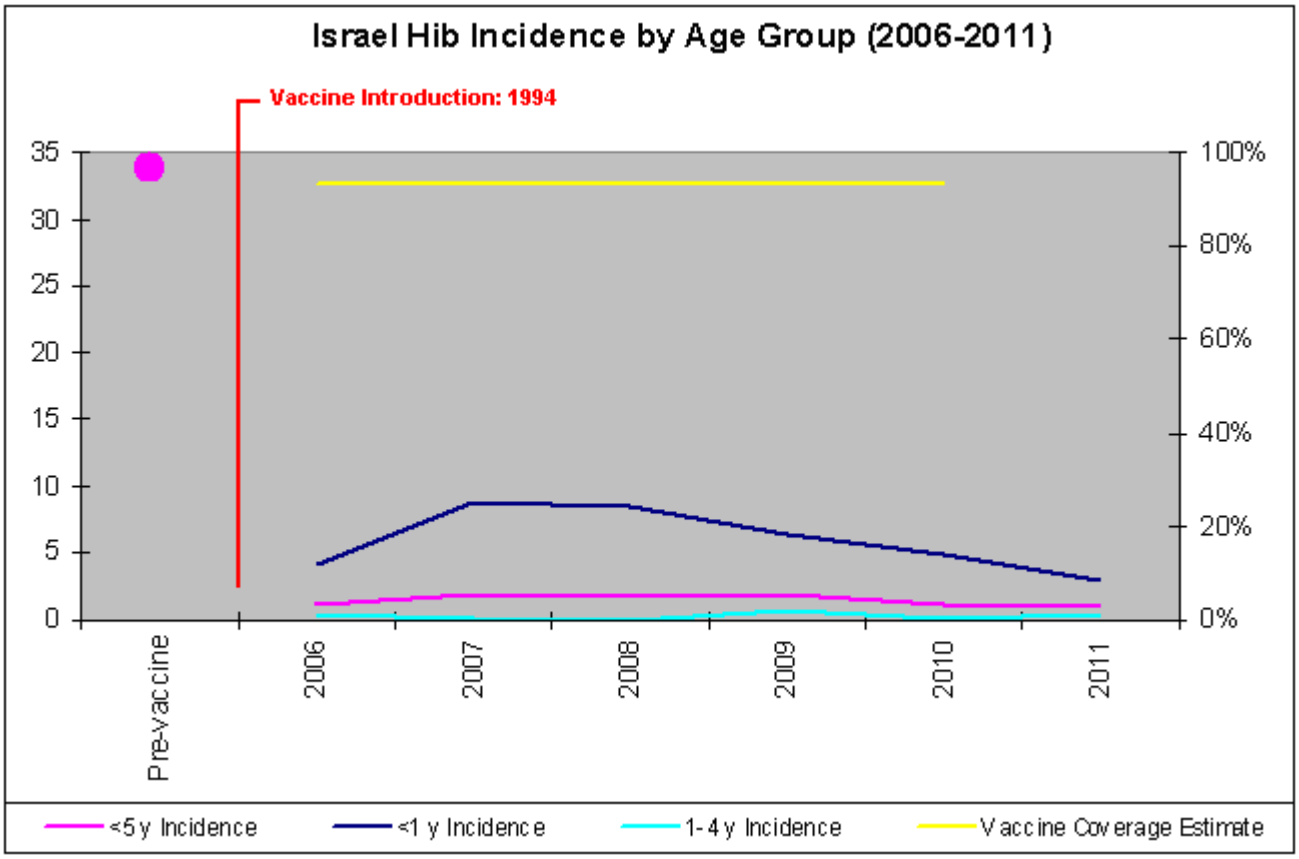
<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



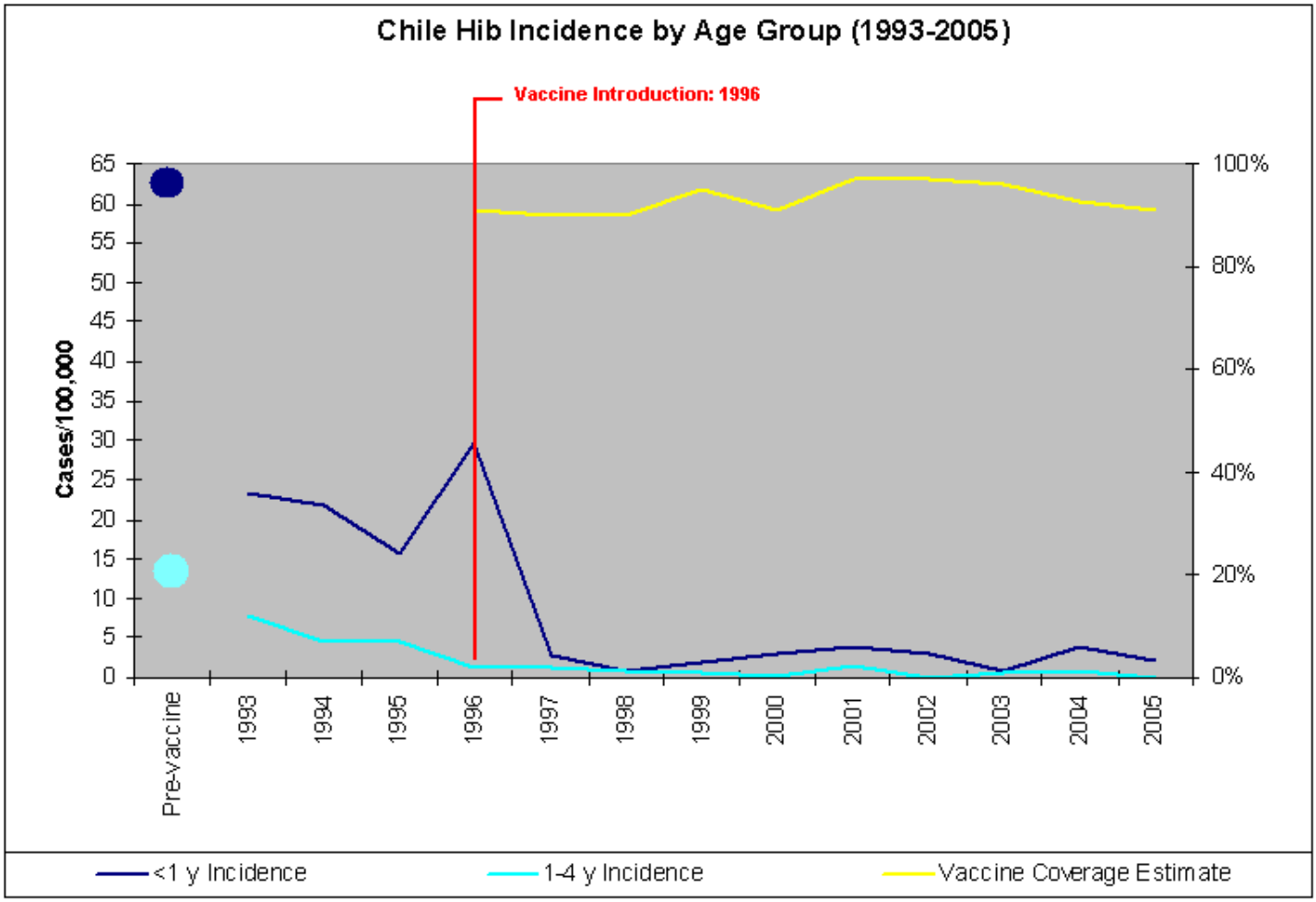
For all invasive Hib disease
Pre-vaccine incidence estimate: 35.5/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences were calculated from multiple sources. Population data, country age distribution, and Hib counts were all abstracted from the 2003/4, 2006 EU-IBIS; the 2007, 2008/9 ECDC publications; and Ramsay, 2003.

Country total population data:
(1999-2004) – EU-IBIS 2003/4
(2005-2007) – EU-IBIS 2007
(2008-2009) – EU-IBIS 2008/9

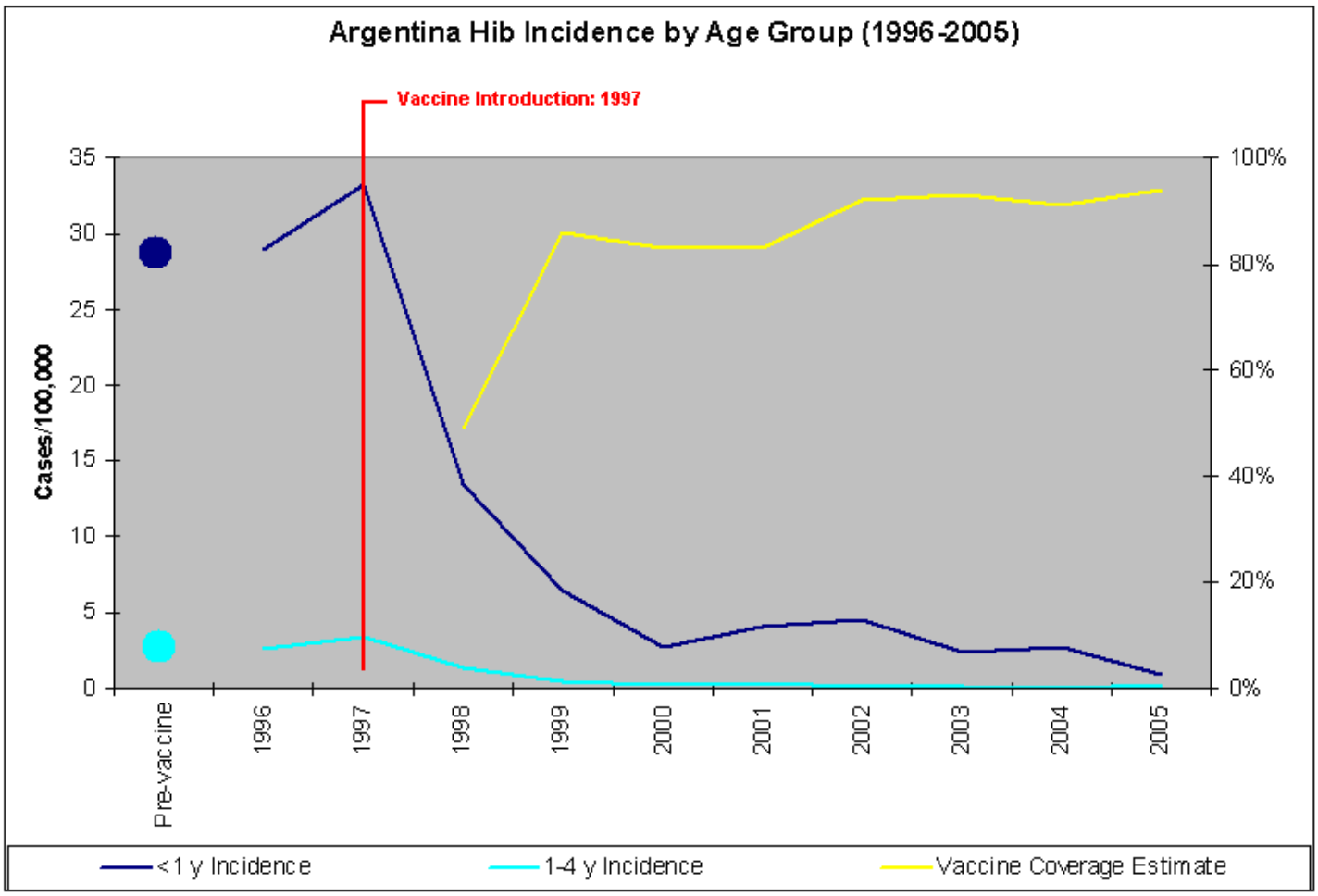
<5 y, <1 y, and 1-4 y country age distribution/breakdowns:
Calculated from a combined age distribution percentage provided by EU-IBIS 2003/4



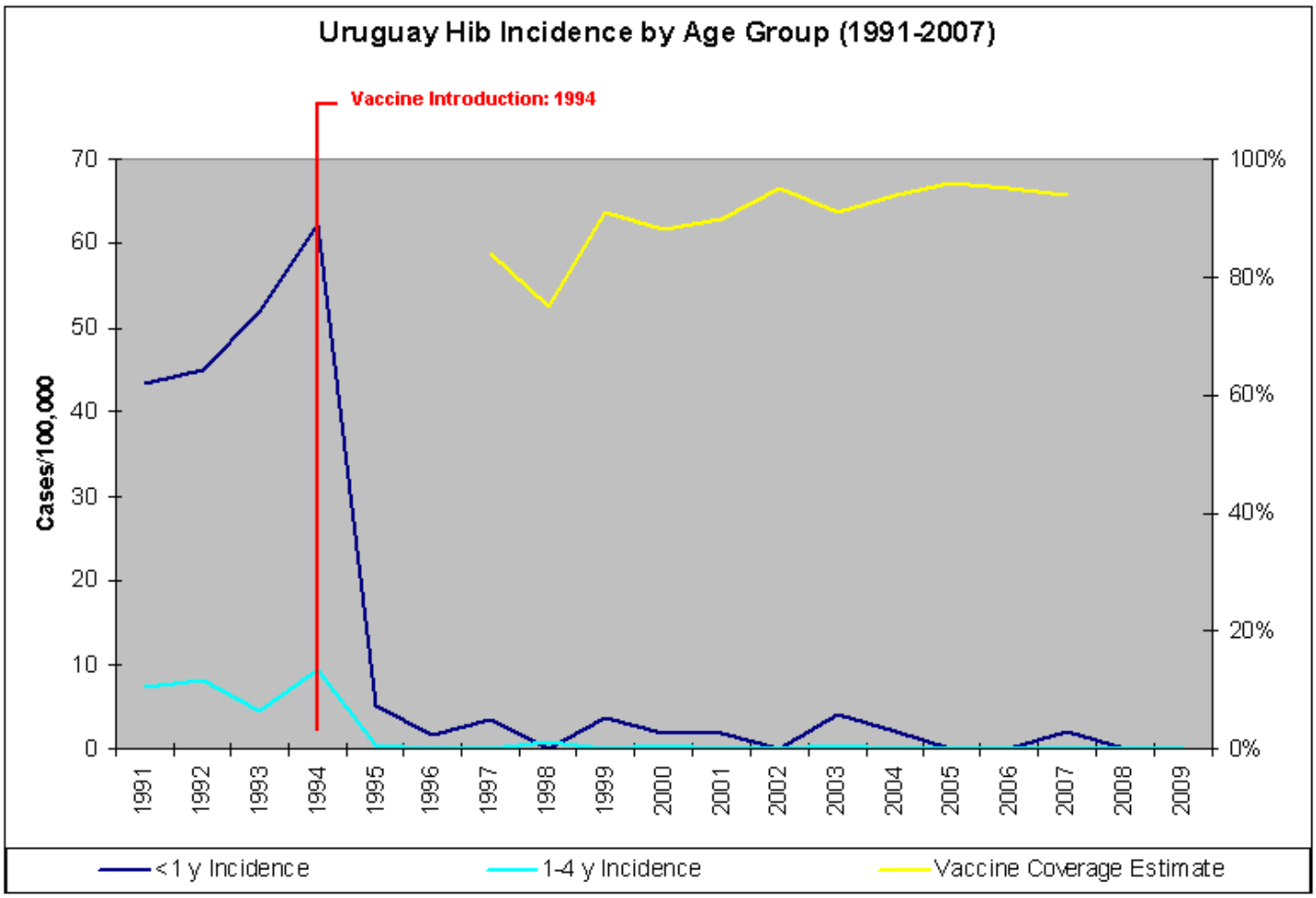
For all invasive Hib disease
Pre-vaccine era time frame: 1988-1990
Pre-vaccine incidence estimate: 34/100,000
Source of pre-vaccine incidence: Ramsay, 1999.
Post-vaccine incidences provided by Ron Dagan.



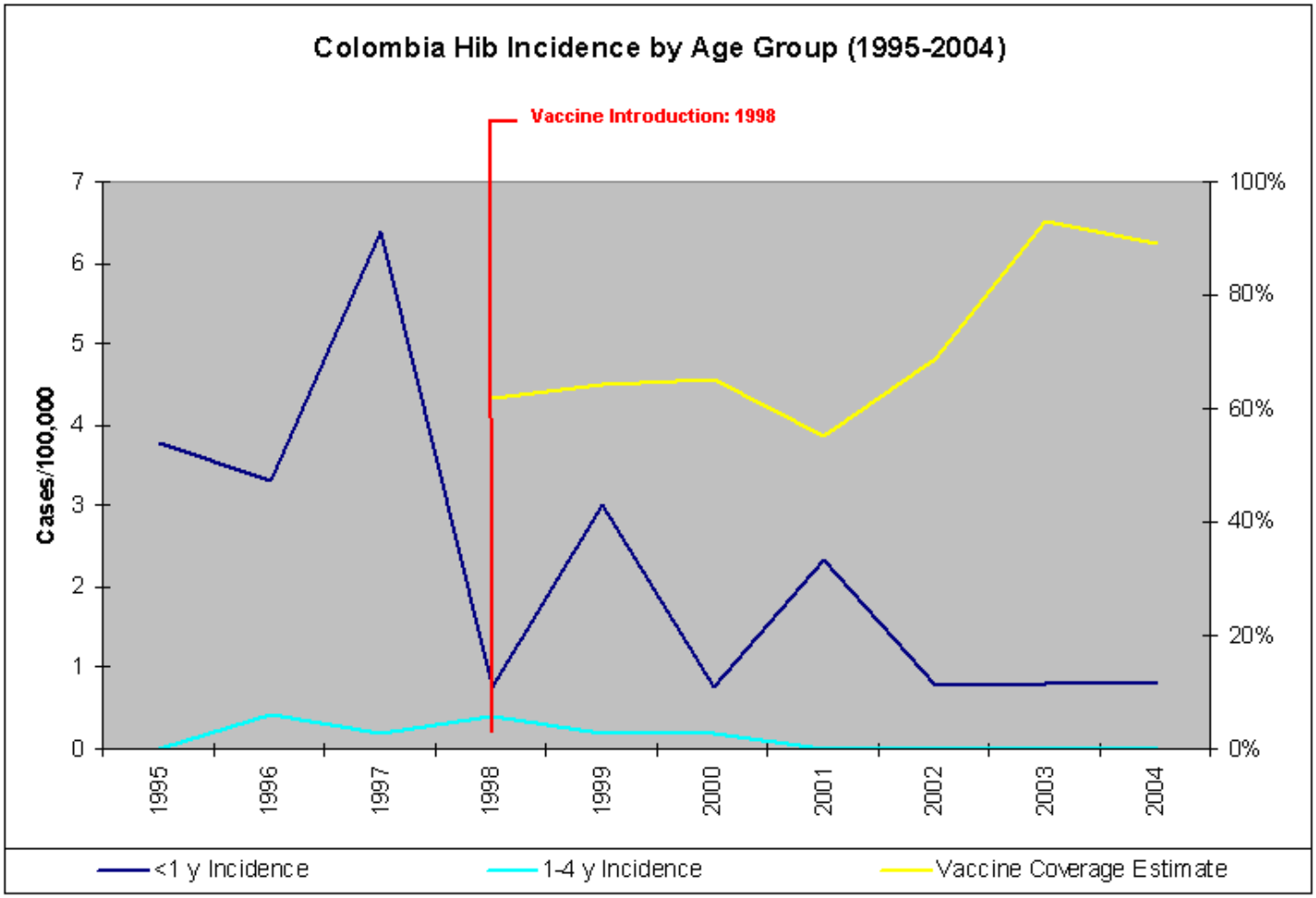
For all invasive Hib disease
Pre-vaccine era time frame: 1985-1987
Pre-vaccine incidence estimate: <1 y: 63.20; 1-4 y: 14.24
Source of pre-vaccine incidence : Ferreccio, 1990



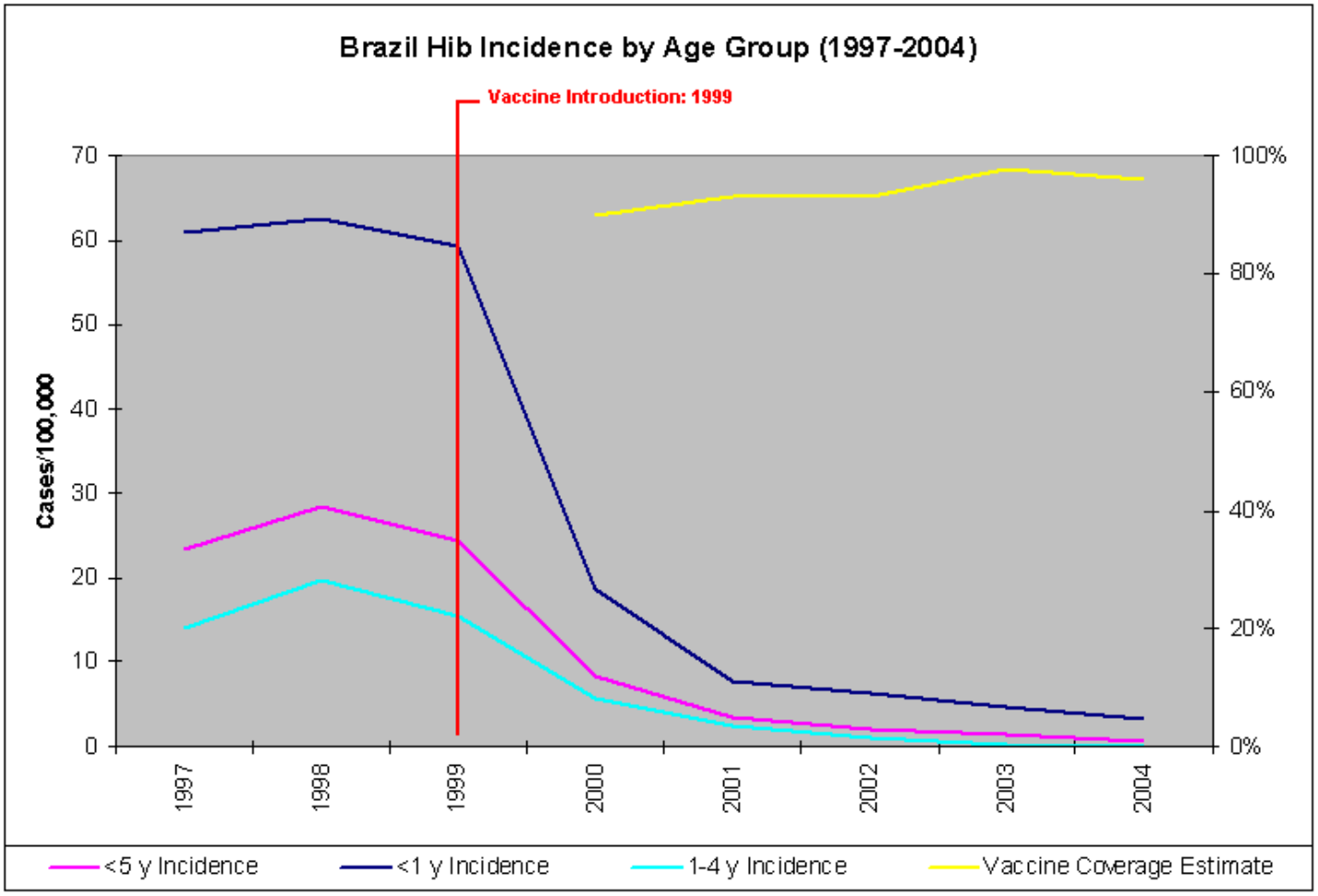
For Hib meningitis
Pre-vaccine incidence estimate: <1 y:29; 1-4 y: 2.6
Source of pre-vaccine incidence : Garcia, 2012.
Source of post-vaccine incidence: Garcia, 2012



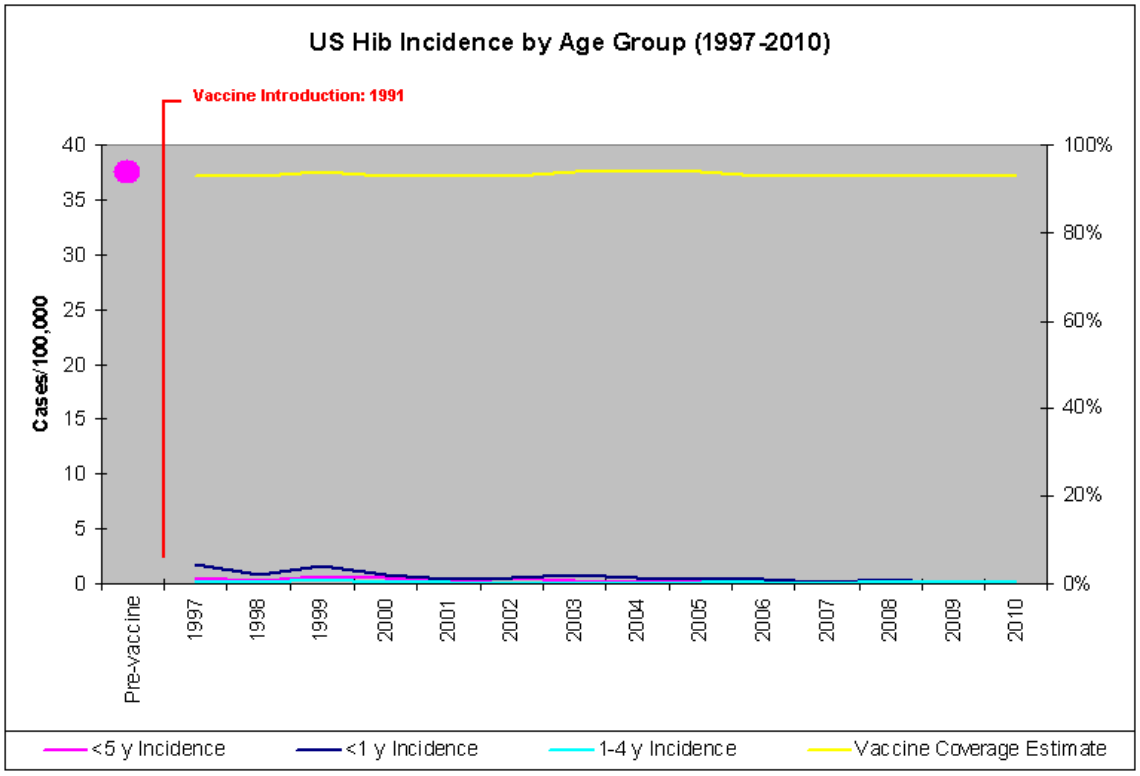
For Hib meningitis.
Pre-vaccine incidence estimate:
Source of pre-vaccine incidence : Garcia, 2012.
Source of post-vaccine incidence: Garcia, 2012



For Hib meningitis.
Pre-vaccine incidence estimate:
Source of pre-vaccine incidence : Garcia, 2012.
Source of post-vaccine incidence: Garcia, 2012



For Hib meningitis only.
Incidence rates provided by Ribeiro 2007 publication.



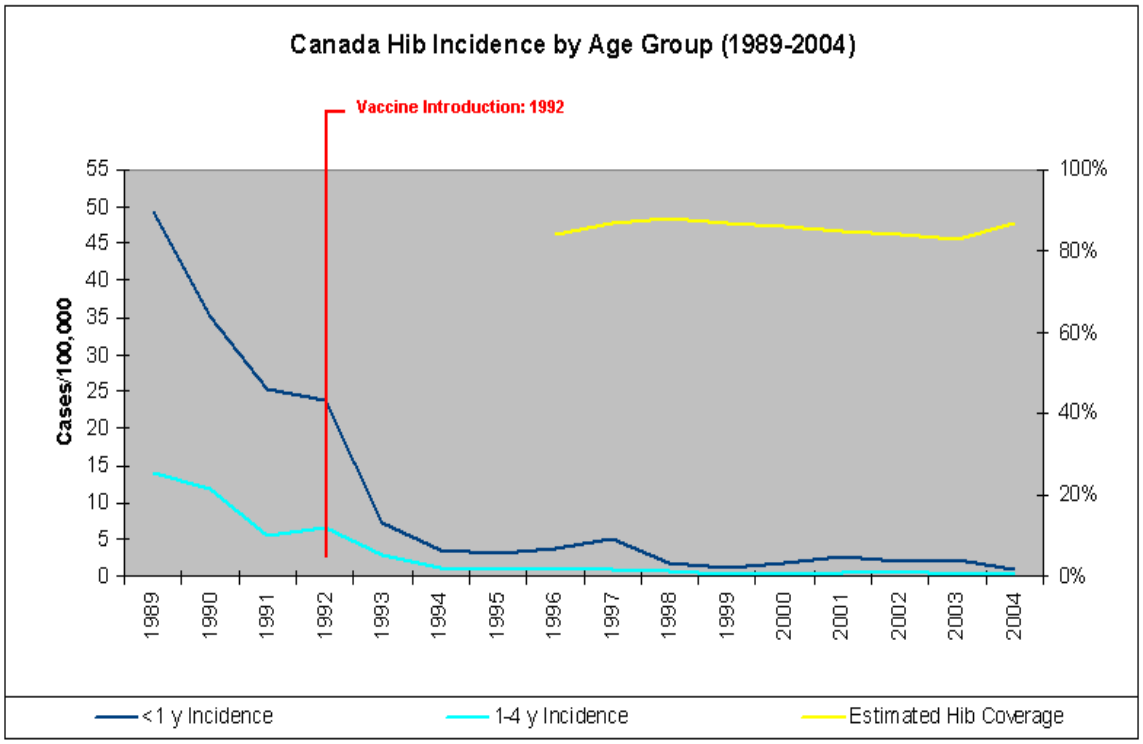
For bacterial meningitis Hib disease

Pre-vaccine era time frame: 1989

Pre-vaccine incidence estimate: 37/100,000

Source of pre-vaccine incidence: Adams, 1993.

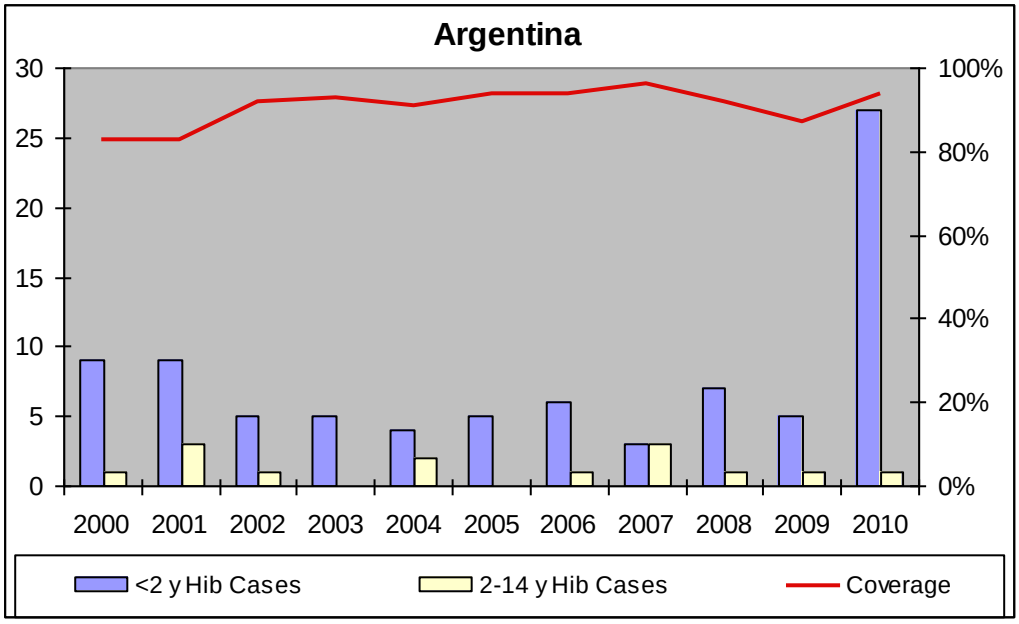
Post-vaccine incidences collected from Centers for Disease Control and Prevention, multiple years.



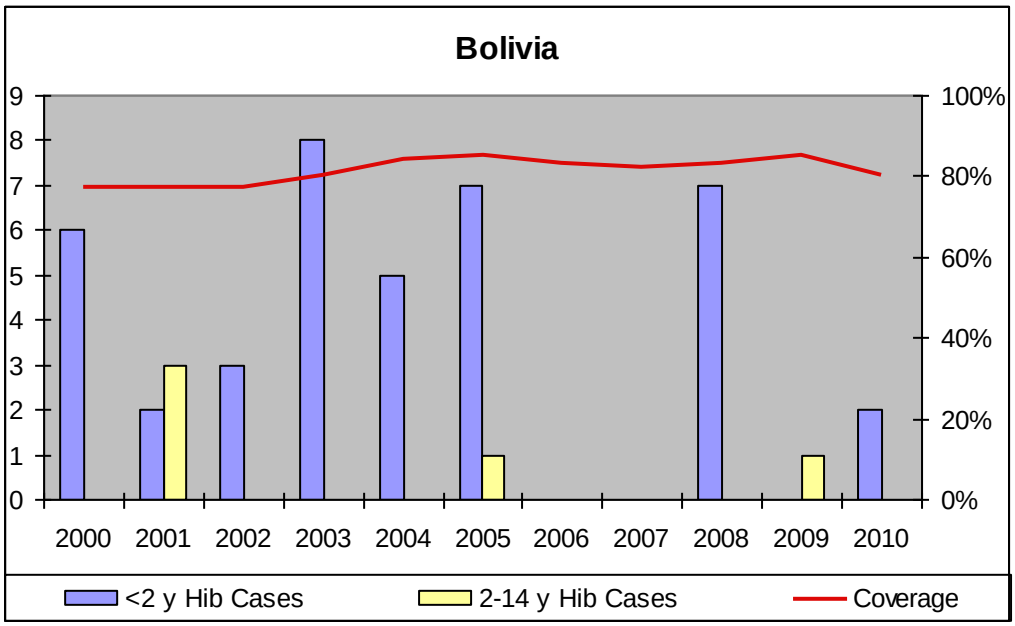
For all invasive Hib disease

Incidences collected from the Public Health Agency of Canada (http://www.phac-aspc.gc.ca/surveillance-eng.php)

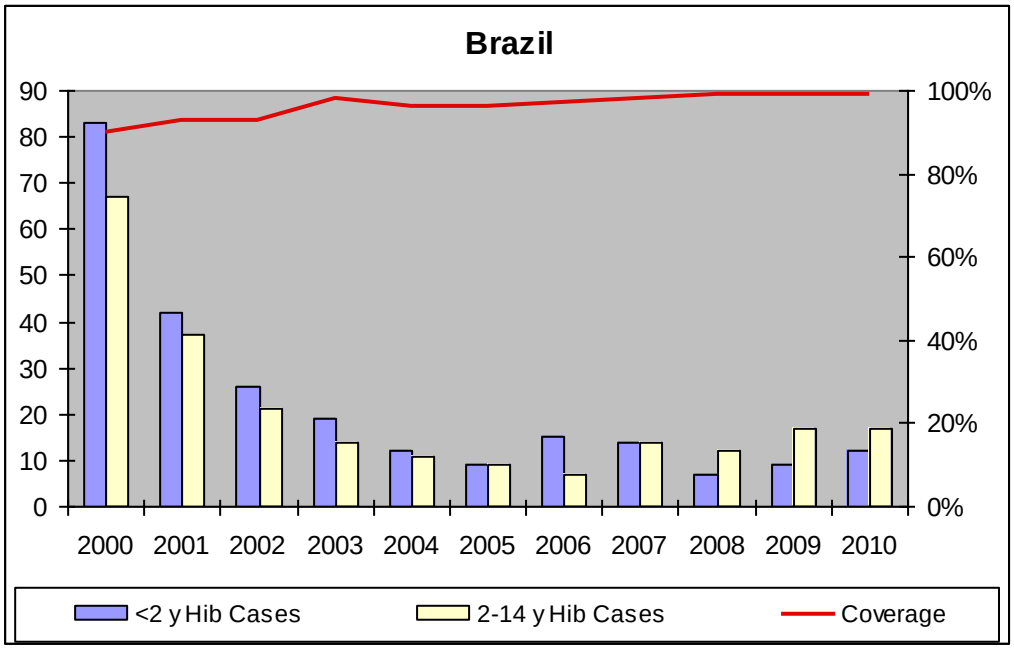
Appendix 2: SIREVA Data (2000-2010)



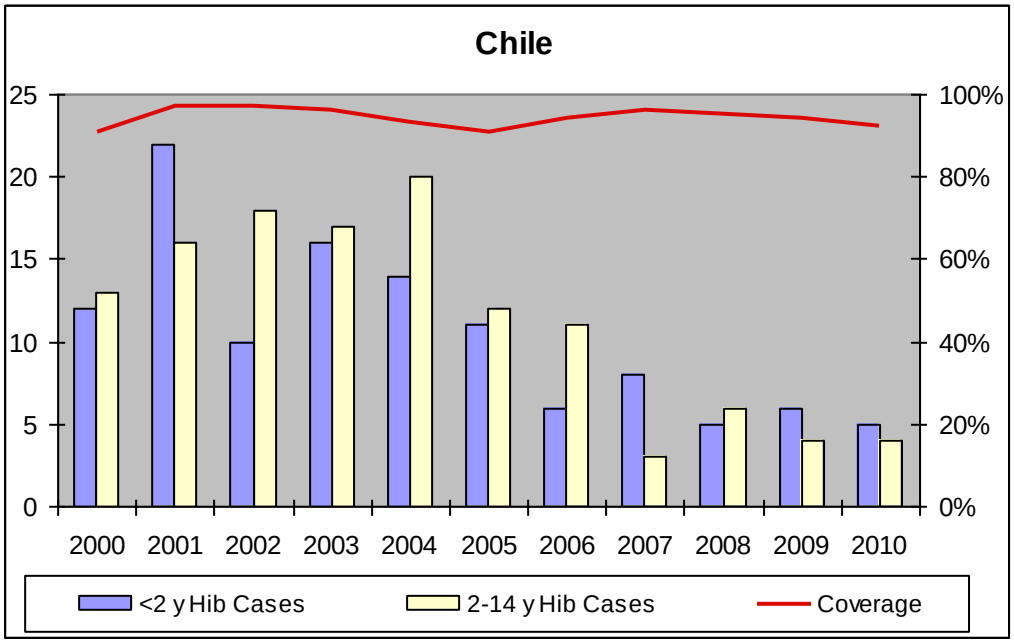
* all invasive Hib disease case count



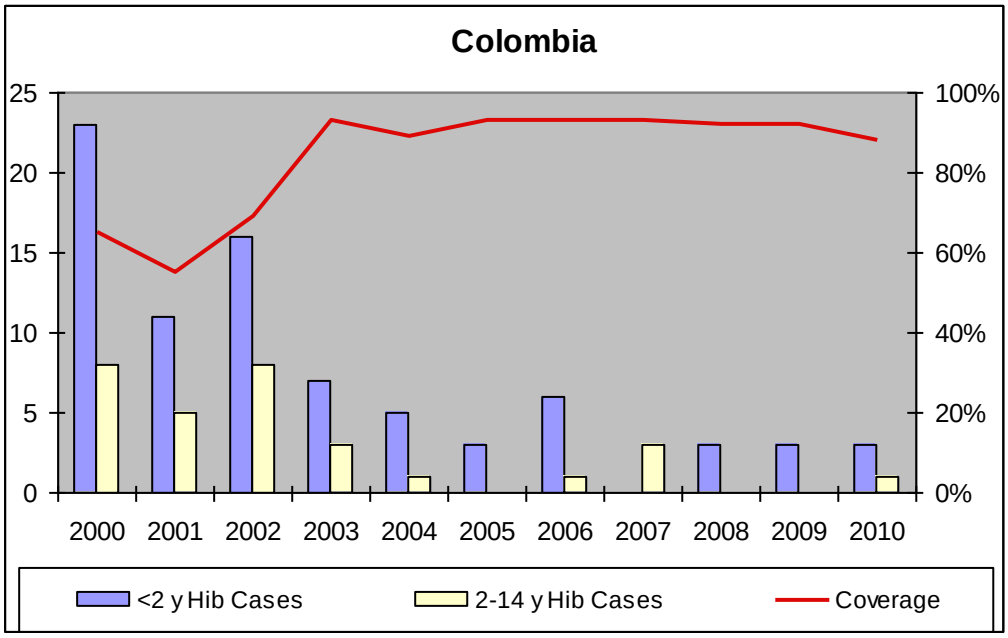
* all invasive Hib disease case count



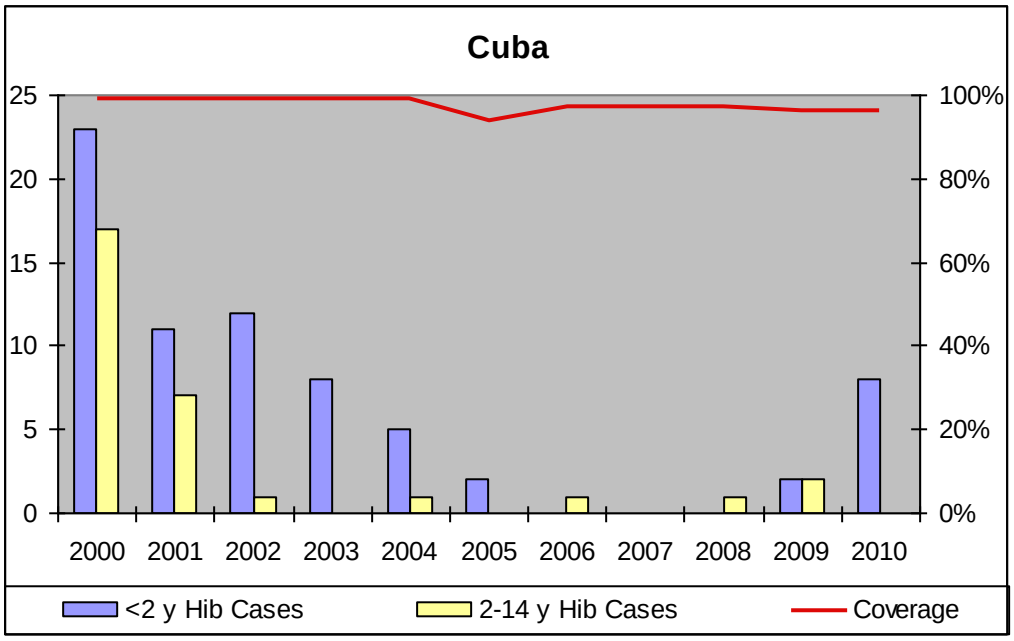
* all invasive Hib disease case count



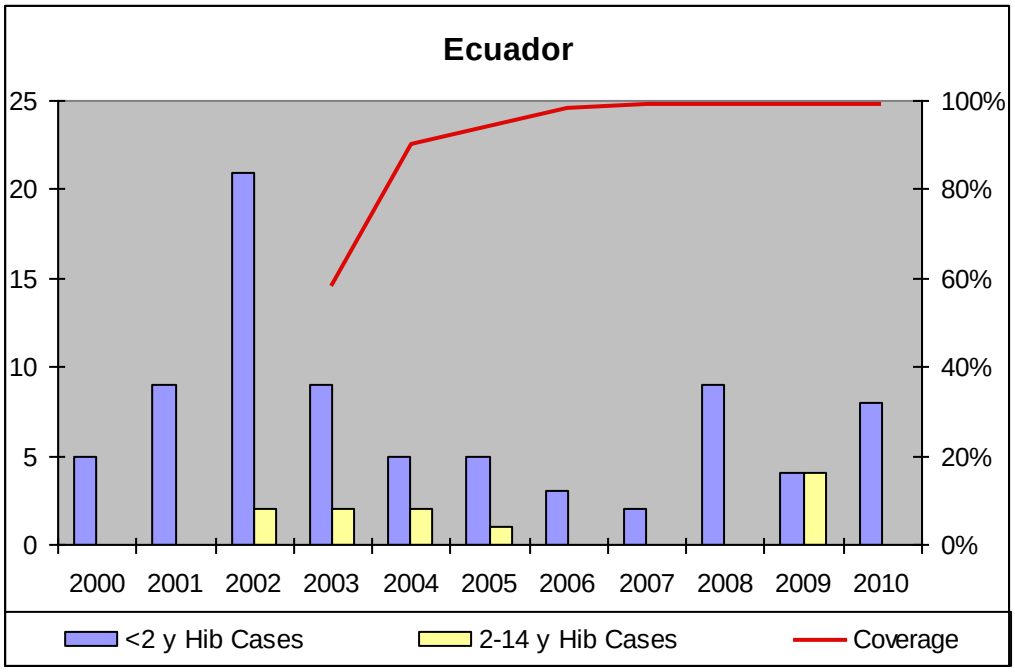
* all invasive Hib disease case count



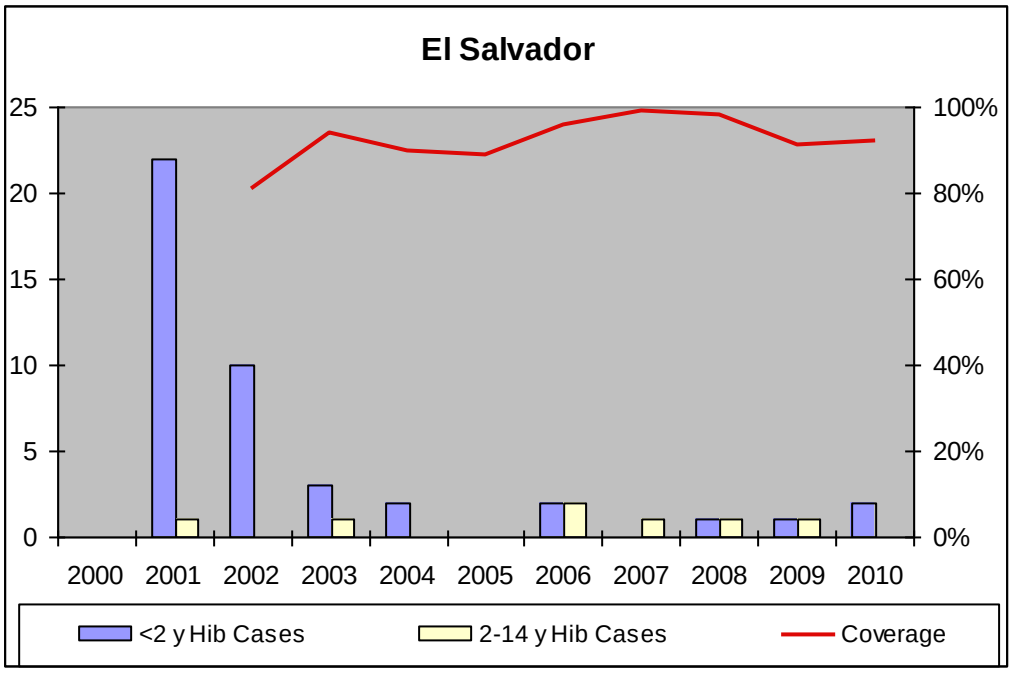
* all invasive Hib disease case count



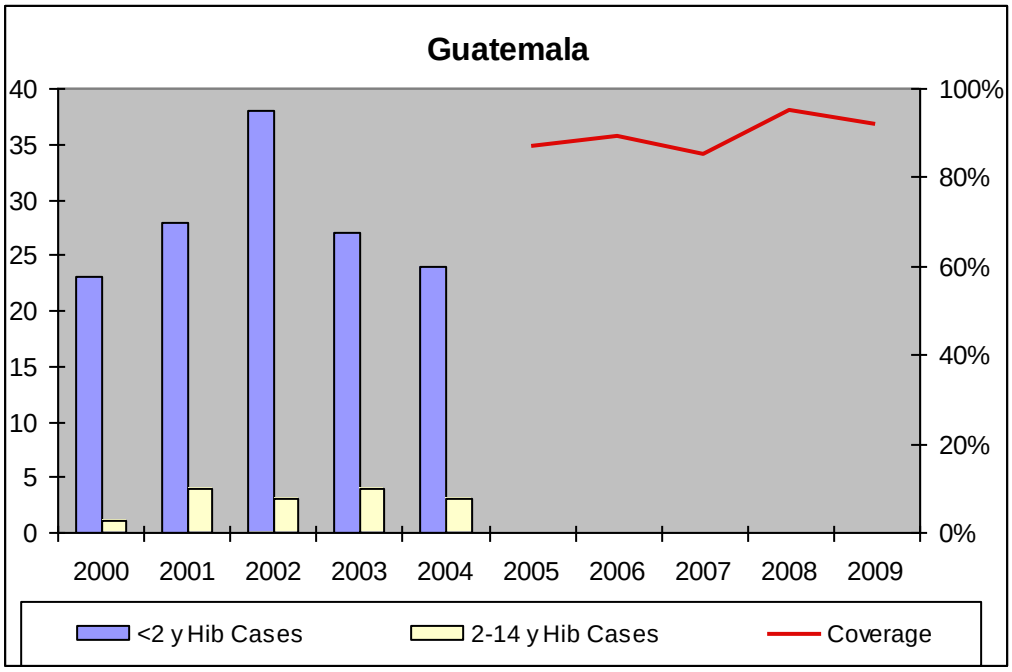
* all invasive Hib disease case count



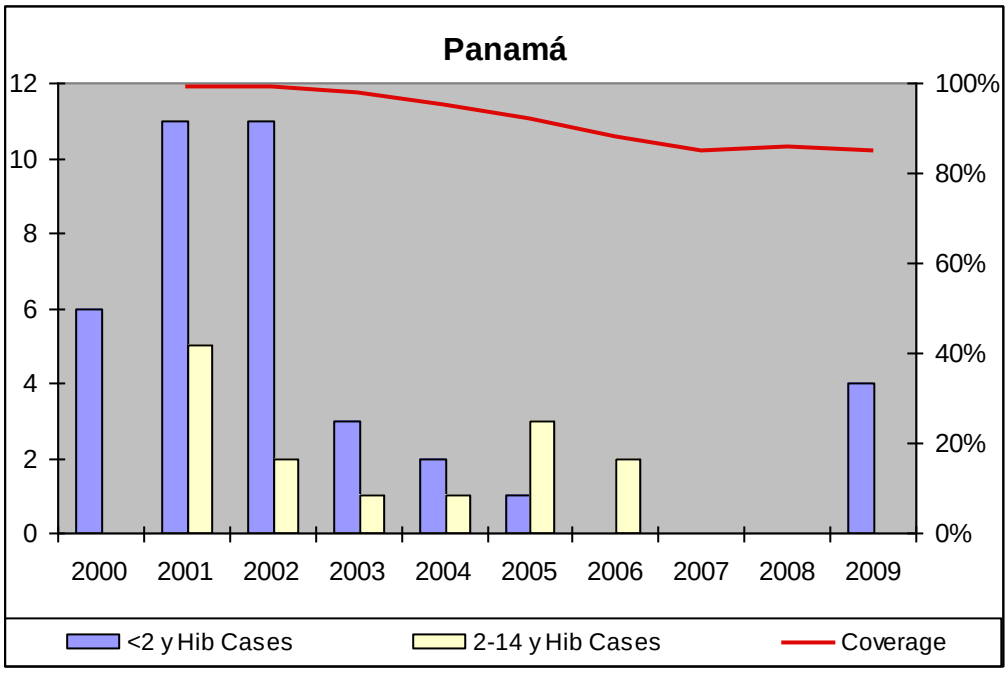
* all invasive Hib disease case count



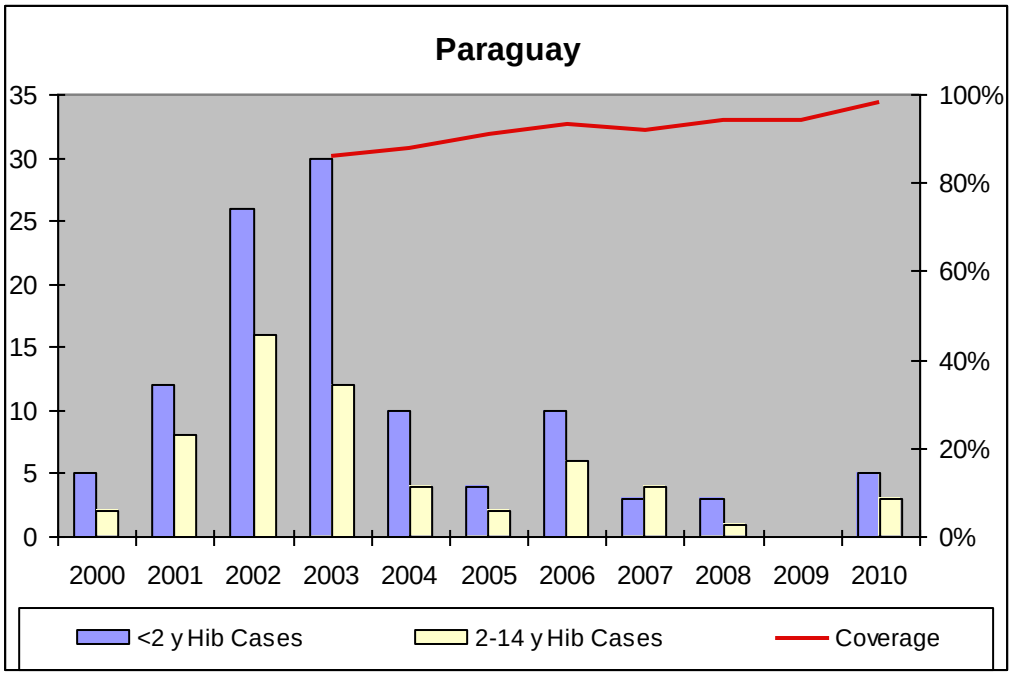
* all invasive Hib disease case count



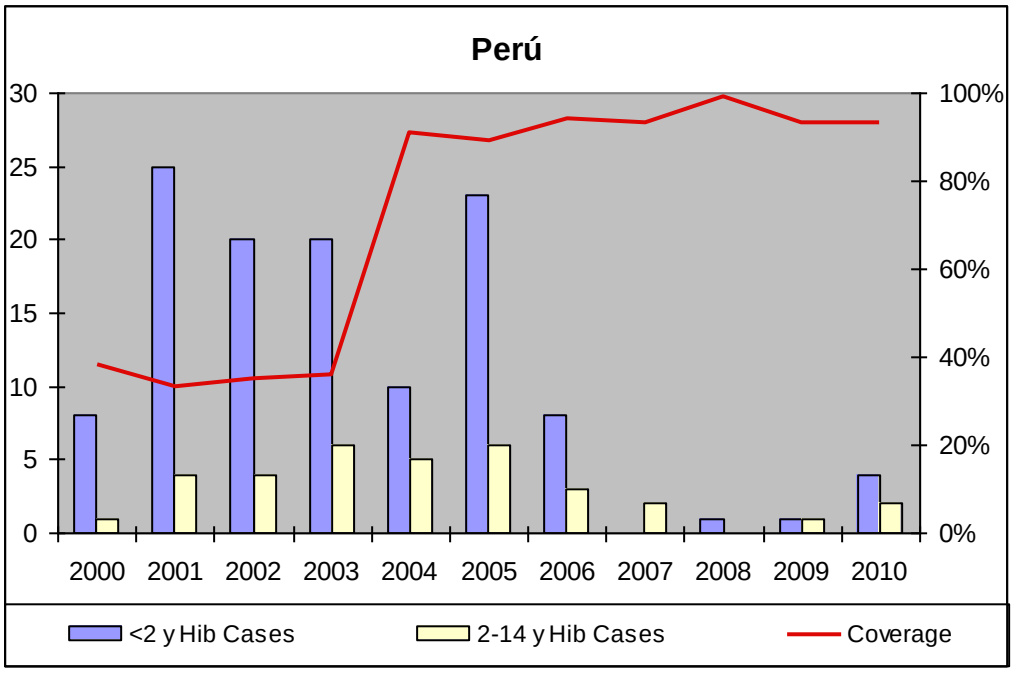
* all invasive Hib disease case count



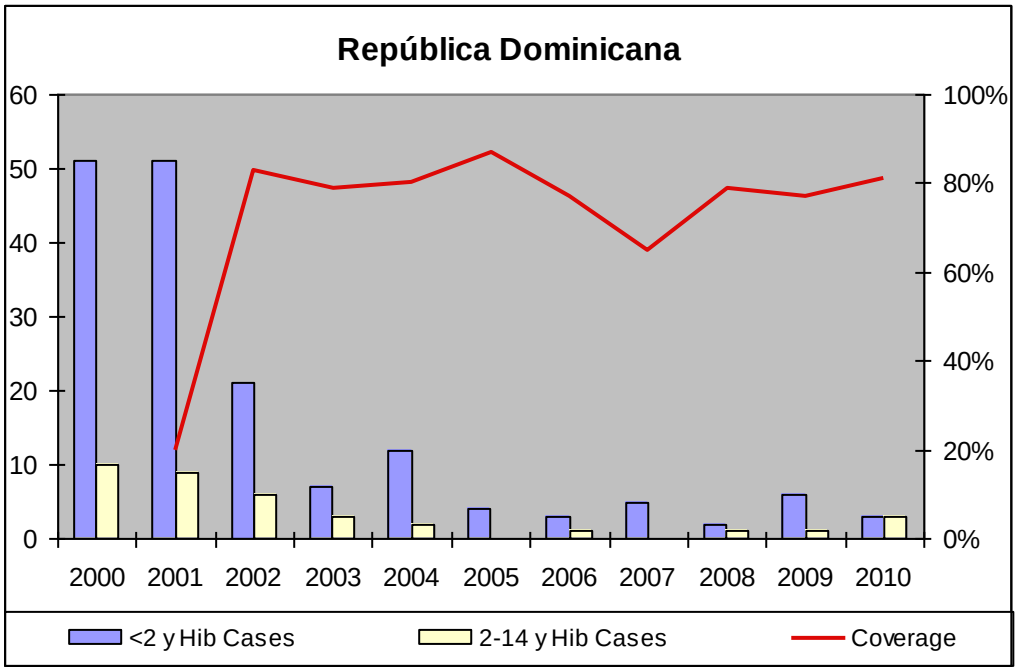
* all invasive Hib disease case count



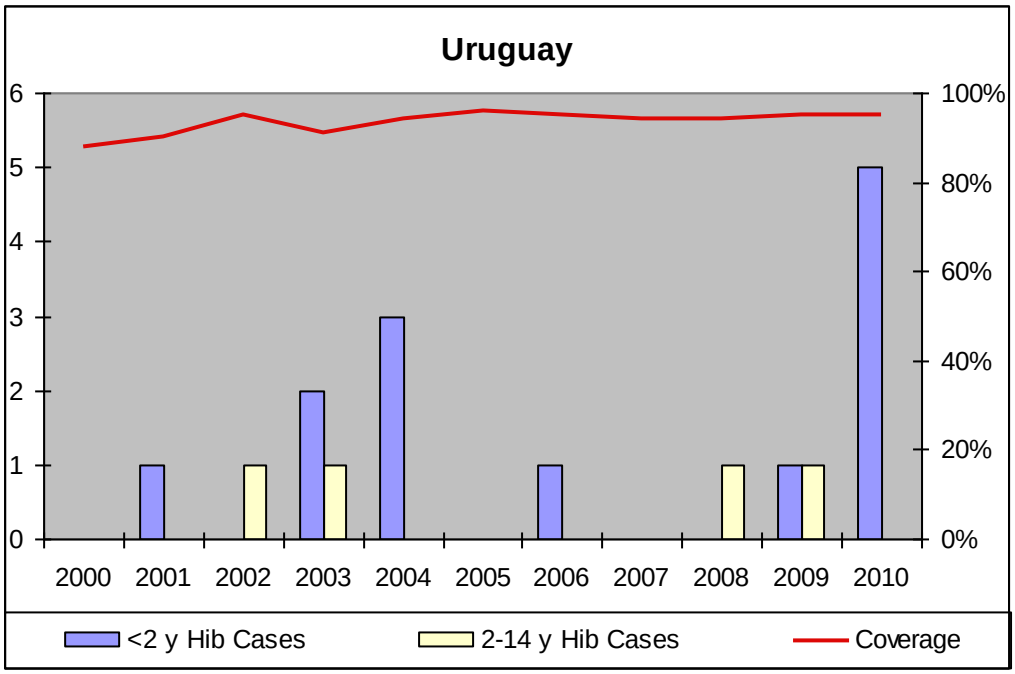
* all invasive Hib disease case count



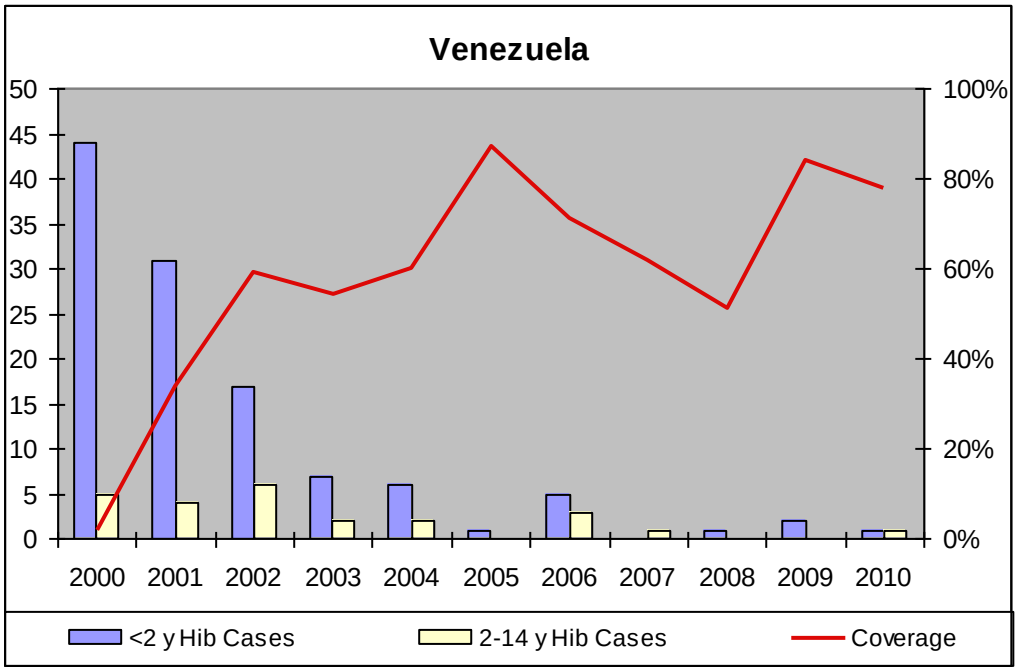
* all invasive Hib disease case count



* all invasive Hib disease case count



* all invasive Hib disease case count



* all invasive Hib disease case count