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REVIEW

The Impact of 7-valent Pneumococcal Conjugate Vaccine on Invasive Pneumococcal Disease: A Literature Review

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ABSTRACT

Introduction: *Streptococcus pneumoniae* can cause invasive pneumococcal diseases (IPD), such as bacteremic pneumonia, bacteremia, meningitis, and sepsis, and non-IPDs, such as otitis media, nonbacteremic pneumonia, and upper respiratory tract infections. It was estimated in 2000 that, worldwide, *S. pneumoniae* was responsible for 826,000 deaths annually in children aged between 1 month and 5 years. A 7-valent pneumococcal conjugate vaccine (PCV7) was licensed in 2000 in the USA and in 2001 in Europe.

Methods: A literature search was performed in PubMed to identify studies assessing the impact of routine childhood PCV7 vaccination on pneumococcal morbidity and mortality. Here, the impact on IPD is reported.

Results: A total of 37 articles reporting impact data on IPD were included in this review: four from Australia, 17 from western Europe, and 16 from North America. In vaccine-eligible children in the postvaccination period, a reduction ranging from 39.9% in Spain to 99.1% in the USA in vaccine-type (VT) IPD incidence, compared with the prevaccination period, was reported in 18 studies. All but one of the 30 studies assessing the impact of PCV7 on all-type IPD reported a reduction ranging from 1.7% in Spain to 76.3% in Australia. In addition, the majority of studies reported reductions in VT and all-type IPD incidence in age groups that were not vaccine eligible.

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Conclusions: The results from this review illustrate that PCV7 has had a significant impact on IPD across all ages through its use in pediatric immunization programs. With the introduction of 13-valent pneumococcal conjugate vaccine (PCV13) further reductions in the incidence of IPD due to the six additional serotypes included, as well as continued protection against IPD due to PCV7 serotypes may be expected. Robust surveillance systems are essential for the evaluation of the impact of PCV13 on all-type IPD and for monitoring the evolution of non-VT IPD.

Keywords: Direct vaccine impact; Immunology; Indirect vaccine impact; Infectious diseases; Invasive pneumococcal disease; *Streptococcus pneumoniae*; Vaccine impact; 7-valent pneumococcal conjugate vaccine

INTRODUCTION

Streptococcus pneumoniae is a Gram-positive diplococci surrounded by a polysaccharide capsule that protects it from the human immune system. More than 90 serotypes have been identified, with a serotype distribution that varies geographically. However, only a limited number of serotypes cause invasive pneumococcal disease (IPD) throughout the world [1]. *S. pneumoniae* causes invasive diseases, such as bacteremic pneumonia, bacteremia, meningitis, and sepsis, and non-IPDs, such as otitis media and upper respiratory tract infections [2]. It was estimated in 2000 that, worldwide, *S. pneumoniae* was responsible for 826,000 deaths annually in children aged between 1 month and 5 years [3]. In 2005, over a 12-month period, 23,470 cases of IPD were reported in 18 European countries, with the incidence varying from 0.4 in Italy to 20.2 and 20.3 per 100,000 general population in Finland and Denmark, respectively [4]. In 1998–1999 in eight geographical areas in the USA, the incidence of IPD ranged from 19.0 to 29.9 per 100,000 general population [5]. However, the surveillance systems, case definitions, and diagnostic standards for IPD in Europe are very heterogeneous making direct comparisons difficult.

A 7-valent pneumococcal conjugate vaccine (PCV7) was licensed in 2001 in Europe and introduced into the national immunization programs (NIPs) as a universal childhood vaccine in around 2006–2008. Its introduction into the NIPs in different countries varied, with some countries initially only recommending vaccination for high-risk children before generalizing to all children (e.g., UK, Germany, and France). PCV7 was licensed and introduced into the NIP in 2000 in the USA. In Australia, it was licensed in 2002 and was initially recommended for high-risk children, but in 2005 PCV7 was introduced into the NIP for all children.

PCV7 has now been in use for over 10 years and many studies have reported its effectiveness and impact [6–9]. PCV7 has been replaced by 13-valent pneumococcal conjugate vaccine (PCV13) in many countries, and a 10-valent conjugate pneumococcal vaccine is also available. These higher-valent conjugate vaccines include some of the important emerging serotypes, while continuing to protect against the serotypes in PCV7. In this review, the wealth of data available on the impact of routine childhood PCV7 in reducing all-type and vaccine-type (VT) IPD, in vaccine-eligible (direct effect) and nonvaccine-eligible populations (indirect effect) in North America, western Europe, and Australia is summarized.

MATERIALS AND METHODS

The data presented are part of a larger global literature review that assessed the impact of PCV7 in different pneumococcal disease areas.

The PubMed search was performed using the following terms: (pneumonia OR "invasive pneumococcal disease" OR IPD OR "otitis media" OR death) AND ([pneumococcal AND conjugate AND vaccin*] OR PCV).

In this paper, the data on the impact of PCV7 vaccination in infants on the incidence of IPD (VT and all type) in the general population is summarized, in vaccine-eligible children (direct effect) and in nonvaccine-eligible age groups (indirect effect). Studies that were published between January 2000 and March 2011, and performed in western Europe, North America, and Australia were included. Before/after studies were included if the impact data (percentage change in crude or adjusted incidence rates) were provided or could be calculated. The calculation used was ([incidence prevaccination – incidence postvaccination]/ incidence prevaccination)* 100.

Publications that reported efficacy (i.e., randomized clinical trials), modeling or health economics studies, studies on specific populations (e.g., those with comorbidities, such as HIV positive, patients with sickle cell disease), and studies in specific locations with unknown denominators were excluded.

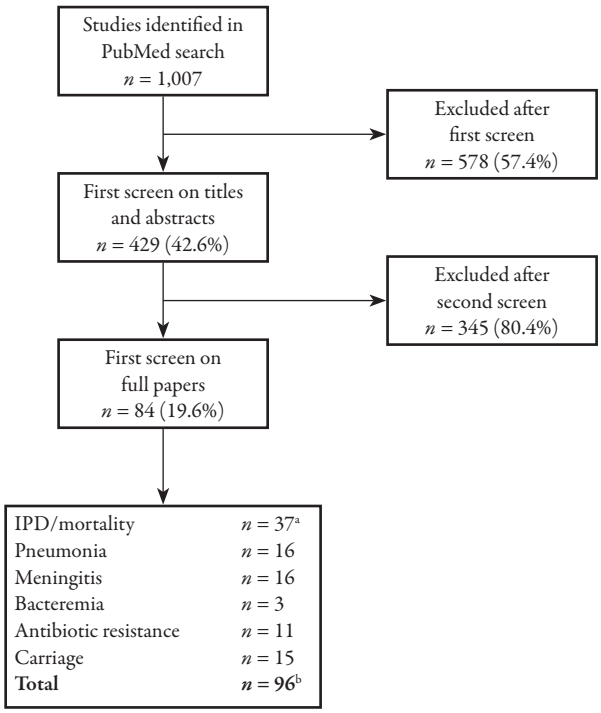

Fig. 1 Flow diagram describing the literature search in PubMed and screening process. [a]Analyzed in this paper. [b]Some papers contributed more than one topic. *IPD* invasive pneumococcal disease

RESULTS

A total of 1,007 publications were identified from the global search, and after two rounds of screening 84 were selected for inclusion in the global literature review (Fig. 1). The main reasons for exclusion were: cohort study with no comparative group (epidemiology data); modeling or cost-effectiveness studies; only specific patient subgroups; review articles; and no incidence data or data sufficient for calculating incidence (mainly missing data on denominator). From these, all 37 articles reporting data on the impact of routine childhood IPD vaccination were analyzed: four from Australia, 17 from western Europe, and 16 from North America [10–46]. The characteristics of these studies are summarized in Table 1 [10–46]. Eight of the European studies were from Spain, two each from Norway and the UK, and one each from Austria, Belgium, Denmark, Germany, and the Netherlands [10–26]. Five of the North American studies used data from the active bacterial core surveillance (ABCs) database; they used the same pre pneumococcal conjugate vaccine (PCV) vaccination period (1998–1999) but analyzed different post-PCV vaccination periods and populations [29–33]. Two other studies from North America used the same database from Alaska; they used the same pre-PCV vaccination period (1995–2000)

Table 1 Summary of characteristics of included studies *(continued on next page)*

Study ID [ref], country (specific area)	Data sources	PCV vaccination policy/schedule	Prevaccination/ postvaccination time periods	Age groups analyzed	Outcomes analyzed
Rendi-Wagner 2009 [10], Austria	National active hospital and laboratory surveillance database	PCV7 in NIP in 2004 (reimbursed for at-risk children)/2 + 1	2001–2004/ 2004–2007	<2 years 2–5 years	All-type IPD; VT IPD; non-VT IPD; VRT IPD
Hanquet 2011 [11], Belgium	Laboratory surveillance data (62% of hospitals)	PCV7 in NIP in 2004 – partially reimbursed; in Jan 2007 free for <2 years with catch-up for 2 years/3 + 1	2002–2003/ 2007, 2008	<5 years	All-type IPD; VT IPD; non-VT IPD
Harboe 2010 [12], Denmark	National laboratory surveillance system	PCV7 in NIP in 2007 with two-dose catch-up for 12–17 months/ 2 + 1	2000–2007/2008	<2 years 2–4 years 5–17 years 18–49 years 50–64 years ≥65 years Overall	All-type IPD
Rückinger 2009 [13], Germany	National hospital and laboratory surveillance systems	PCV7 in 2006, with catch-up <2 years (<5 years for identified risk groups)/3 + 1	1997–2003/ 2007–2008	<2 years 2–4 years 5–15 years 0–15 years	All-type IPD
Rodenburg 2010 [14], Netherlands (25% of population)	National Reference Laboratory	PCV7 in 2006/3 + 1	2004–2006 2006–2008	<2 years 2–4 years 5–49 years 50–64 years ≥65 years Overall	All-type IPD; VT IPD; non-VT IPD
Vestrheim 2008 [15], Norway	National Surveillance System for Communicable Diseases	PCV7 in NIP in 2006 with catch-up (for children 3–6 months)/ 2 + 1	2004–2005 2007	<1 year 1 year 2–4 years <5 years Overall	All-type IPD; VT IPD; non-VT IPD
Vestrheim 2010 [16], Norway	National Surveillance System for Communicable Diseases	PCV7 in NIP in 2006 with catch-up (for children 3–6 months)/ 2 + 1	2004–2005 2008	<5 years 5–19 years 20–39 years 40–64 years ≥65 years ≥5 years Overall	All-type IPD; VT IPD; non-VT IPD

Table 1 continued

Study ID [ref], country (specific area)	Data sources	PCV vaccination policy/schedule	Prevaccination/ postvaccination time periods	Age groups analyzed	Outcomes analyzed
Ardanuy 2009 [17], Spain (one hospital in Southern Barcelona)	Single hospital, prospective study from 1997 to 2007	PCV7 introduced in 2001, but in NIP only for high-risk children/3 + 1	1997–2001 2002–2004 2005–2006	18–64 years ≥65 years ≥18 years	All-type IPD; VT IPD; non-VT IPD
Aristegui 2007 [18], Spain (Basque Country and Navarre)	Retrospective and prospective data from nine hospitals	PCV7 introduced in 2001, but only private market/3 + 1	1998–2001 2002–2003	<1 year 1–2 years <2 years 2–5 years <5 years	All-type IPD; VT IPD; non-VT IPD
Barricate 2007 [19], Spain	Data from all laboratories in the region	PCV7 introduced in 2001, but only private market/3 + 1	2000–2002 2004–2005	<2 years <5 years	All-type IPD
Calbo 2006 [20], Spain (two hospitals in one health district in Barcelona region)	Data from two hospitals	PCV7 introduced in 2001, but only private market/3 + 1	1999–2001 2002–2004	≤5 years	All-type IPD
Fenoll 2009 [21], Spain	Data from National Reference Laboratory (from 190 hospitals in country)	PCV7 introduced in 2001, but only private market/3 + 1	1996–2001 2005–2006	Global (no age groups)	All-type IPD
Guevara 2009 [22], Spain (Navarre)	Active surveillance with participation of all six laboratories in the region	PCV7 introduced in 2001, but only private market/3 + 1	2001–2002 2003–2005 2006–2007	Global (no age groups)	All-type IPD; VT IPD; non-VT IPD
Munoz-Almagro 2008 [23], Spain (one hospital in Southern Barcelona)	Prospective study in one hospital	PCV7 introduced in 2001, but only private market/3 + 1	1997–2001 2002–2006	<2 years 2–4 years 5–17 years	All-type IPD; VT IPD; non-VT IPD
Perez-Trallero 2009 [24], Spain (Gipuzkoa province, Basque Country)	One hospital (referral hospital for whole region)	PCV7 introduced in 2001, but only private market/3 + 1	1996–2001 (pre for <5 years) 1998–2001 (pre for >64 years) 2002–2007 (for both)	<5 years >64 years	All-type IPD

Table 1 continued

Study ID [ref], country (specific area)	Data sources	PCV vaccination policy/schedule	Prevaccination/ postvaccination time periods	Age groups analyzed	Outcomes analyzed
Foster 2011 [25], UK (Oxfordshire)	Ongoing surveillance system	PCV7 introduced in 2006/2 + 1	1995–2006 and 2003–2006/2006–2009	<2 years ≥2 years All age	All-type IPD; VT IPD; VRT IPD; non-VT IPD
Miller 2011 [26], UK (England and Wales)	Laboratory reports given to the HPA and isolates sent to HPA reference lab for serotyping	PCV7 introduced in 2006/2 + 1	2000–2006/ 2009–2010	<2 years 2–4 years 5–14 years 15–44 years 45–64 years ≥65 years All ages	All-type IPD; VT IPD; non-VT IPD
Albrich 2007 [27], USA (Georgia)	Active laboratory and population-based surveillance systems from CDC-sponsored Georgia Emerging Infections Program	PCV7 introduced in 2000/3 + 1	1997–2000 (June)/2000 (July)–2004	≤4 years 5–17 years 18–39 years 40–64 years ≥65 years <18 years ≥18 years	All-type IPD
Black 2007 [28], USA (NCKP)	NCKP database	PCV7 introduced in 2000/3 + 1	1996–2000 (March)/2000 (April)–2005	<5 years <6 months 6–23 months 2–5 years	All-type IPD; VT IPD; non-VT IPD
Whitney 2003 [29], USA (ABCs in eight states)	Active surveillance system (ABCs)[a]	PCV7 introduced in 2000/3 + 1	1998–1999/2001	<1 year 1 year 2 years <2 years 5–19 years 20–39 years 40–64 years ≥65 years	All-type IPD; VT IPD; non-VT IPD; VRT IPD
Lexau 2005 [30], USA (ABCs in eight states)	Active surveillance system (ABCs)[a]	PCV7 introduced in 2000/3 + 1	1998–1999/ 2000–2001/ 2002–2003	50–64 years 65–74 years 75–84 years ≥85 years	All-type IPD; VT IPD; non-VT IPD; STs only in polysaccharide vaccine
Hicks 2007 [31], USA (ABCs in eight states)	Active surveillance system (ABCs)[a]	PCV7 introduced in 2000/3 + 1	1998–1999/2004	<5 years ≥65 years	All-type IPD; VT IPD; non-VT IPD

Table 1 continued

Study ID [ref], country (specific area)	Data sources	PCV vaccination policy/schedule	Prevaccination/ postvaccination time periods	Age groups analyzed	Outcomes analyzed
CDC 2008 [32], USA (ABCs in eight states)	Active surveillance system (ABCs)[a]	PCV7 introduced in 2000/3 + 1	1998–1999/2005	<1 year 1 year 2 years 3 years 4 years <5 years	All-type IPD; VT IPD; non-VT IPD
Pilishvili 2010 [33], USA (ABCs in eight states)	Active surveillance system (ABCs)[a]	PCV7 introduced in 2000/3 + 1	1998–1999/2007	<5 years 5–17 years 18–49 years 50–64 years ≥65 years	All-type IPD; VT IPD; non-VT IPD; 19A IPD; VRT IPD
Hennessy 2005 [34], USA (Alaska)	Active surveillance system in Alaska, run by CDC	PCV7 introduced in 2000/3 + 1	1995–2000/ 2001–2003	<2 years 2–4 years 5–17 years 18–44 years ≥45 years	All-type IPD; VT IPD; non-VT IPD
Singleton 2007 [35], USA (Alaska)	Active surveillance system in Alaska, run by CDC	PCV7 introduced in 2000/3 + 1	1995–2000/ 2001–2003/ 2004–2006	<2 years 2–4 years 5–17 years 18–44 years ≥45 years Global	All-type IPD; VT IPD; non-VT IPD
Hsu 2005 [36], USA (Massachusetts)	Passive laboratory surveillance with calls to primary care provider or parents	PCV7 introduced in 2000/3 + 1	1990–1991/ 2001–2003	<5 years	All-type IPD; VT IPD; non-VT IPD
McBean 2005 [37], USA (Medicare)	Medicare analysis and review files	PCV7 introduced in 2002/3 + 1	1996–2000/ 2000–2001/ 2001–2002/ 2002–2003	65–74 years 75–84 years ≥85 years	All-type IPD (ICD-9-CM codes)
Pulido 2010 [38], USA (national)	National Center for Health Statistics data files on cause of death (ICD-9 and ICD-10 codes)	PCV7 introduced in 2002/3 + 1	1990–1998/ 2001–2005	<2 years 2–4 years 5–14 years 15–24 years 25–34 years 35–44 years 45–54 years 55–64 years 65–74 years 75–84 years ≥85 years	IPD mortality (all type)

Table 1 continued

Study ID [ref], country (specific area)	Data sources	PCV vaccination policy/schedule	Prevaccination/ postvaccination time periods	Age groups analyzed	Outcomes analyzed
Simonsen 2011 [39], USA (10 states)	Health Care Utilization Project State Inpatient Databases with ICD-9 codes	PCV7 introduced in 2002/3 + 1	1996–1997/ 2005–2006	<2 years 2–4 years 5–17 years 18–39 years 40–64 years ≥65 years	All-type IPD; all-type IPD mortality
Tsigrelis 2008 [40], USA (Minnesota)	Two laboratory databases	PCV7 introduced in 2002/3 + 1	1995–1999/ 2001–2007	<5 years 5–19 years 20–39 years 40–64 years ≥65 years	All-type IPD mortality
Tyrrell 2009 [41], Canada (Alberta)	National Center for Streptococcus database	PCV7 introduced in 2002/2 + 1	2000/2006	<2 years 2–4 years 5–19 years 20–39 years 40–64 years ≥65 years	All-type IPD; VT IPD; non-VT IPD
Kellner 2009 [42], Canada (Calgary)	Prospective, population-based surveillance system	PCV7 introduced in 2002/2 + 1	1998–2001/ 2003–2007	0–6 months 6–23 months 2–4 years 5–15 years 16–64 years 65–84 years ≥85 years	All-type IPD; VT IPD; non-VT IPD
Hanna 2010 [43], Australia (North Queensland)	Prospective surveillance system (obligatory notification)	PCV7 (and PPV23) introduced universally in 2005/2 + 1	2001–2004/ 2006–2009	<5 years 5–14 years 15–64 years All ages	All-type IPD; VT IPD; for ≥15 years: ST common to both and only in PPV23
Lehmann 2010 [44], Australia (Western Australia)	Prospective surveillance system (obligatory notification)	PCV7 (and PPV23) introduced universally in 2005/2 + 1 (in 1999 and 2001, respectively, for aboriginals)	1997–2001/ 2002–2004/ 2005–2007	<2 years 2–4 years 5–14 years 15–29 years 30–49 years 50–64 years ≥65 years	All-type IPD; VT IPD; non-VT IPD

Table 1 continued

Study ID [ref], country (specific area)	Data sources	PCV vaccination policy/schedule	Prevaccination/ postvaccination time periods	Age groups analyzed	Outcomes analyzed
Roche 2008 [45], Australia (national)	Prospective surveillance system (obligatory notification) in National Notifiable Diseases Surveillance System	PCV7 (and PPV23) introduced universally in 2005/2 + 1 (in 1999 and 2001, respectively, for aboriginals)	—	<2 years 2–14 years 15–49 years 50–64 years ≥65 years	All-type IPD; VT IPD; non-VT IPD; IPD mortality
Williams 2011 [46], Australia (national)	Prospective surveillance system (obligatory notification) in National Notifiable Diseases Surveillance System	PCV7 (and PPV23) introduced universally in 2005/2 + 1 (in 1999 and 2001, respectively, for aboriginals)	2002–2004/ 2006/2007	<2 years	All-type IPD; VT IPD; non-VT IPD

ABCs active bacterial core surveillance, *CDC* Centers for Disease Control and Prevention, *HPA* Health Protection Agency, *ICD-9-CM* International Statistical Classification of Diseases and Health-related Problems, 9th Revision clinically modified, *ICD-10-CM* International Statistical Classification of Diseases and Health-related Problems, 10th Revision clinically modified, *IPD* invasive pneumococcal disease, *NCKP* North Carolina Kaiser Permanente, *NIP* national immunization program, *non-VT IPD* nonvaccine-type IPD, *PCV* pneumococcal conjugate vaccine, *PPV23* 23-valent pneumococcal polysaccharide vaccine, *ST* subtype, *VT IPD* vaccine-type IPD, *VRT IPD* vaccine-related-type IPD

[a]ABCs is run by the CDC and covers a population of 29,757,552 persons in California (San Francisco County and children <5 years in Alameda and Contra Costa counties); Colorado (five county Denver area); Connecticut; Georgia (20 county Atlanta area); Maryland (six county Baltimore area); Minnesota; New Mexico; New York (15 county Rochester and Albany areas and children <5 years in Erie county); Oregon (three county Portland area); Tennessee (20 counties)

but analyzed different post-PCV vaccination periods [34, 35]. Two of the North American studies were from Canada [41, 42]. Four studies were from Australia [43–46].

Impact on VT IPD in Vaccine-Eligible Children

The impact of PCV7 on VT IPD in vaccine-eligible children (<2 or <5 years old, depending on the study) was evaluated in 18 studies (Table 2). A reduction in VT IPD incidence was reported in all the studies, ranging from 39.9% in Spain [23] to 99.1% in the USA [32]; the median rate reduction was 90.1%.

Vaccine Impact on All-Type IPD in Vaccine-Eligible Children

The impact of PCV7 on all-type IPD in vaccine-eligible children (<2 years or <5 years depending on the study) was evaluated in 30 studies (three from Australia, 15 from Europe, and 12 from North America) (Table 3). All but one of the studies reported a reduction

Table 2 Impact on VT IPD in vaccine-eligible populations

Study (year of PCV7 implementation) [ref]	Study population	Prevaccination		Postvaccination		% change
		Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Australia (January 2005 for all <2 years)						
Lehmann 2010 [44]	Nonaboriginal, <2 years (PCV7 and PPV23)	1997–2001	61.2	2005–2007	6.6	−89.2
Roche 2008 [45]	Nonindigenous <2 years	2004	73.4	2006	6.7	−90.9
Williams 2011 [46]	<2 years	2002–2004	60.9	2007	2.1	−96.6
Europe						
Foster 2010, UK (September 2006) [25]	<2 years	2003–2005	26.4	2006–2009	5.5	−79.2
Miller 2011, UK (September 2006) [26]	<2 years	2000–2006	40.8	2009–2010	0.9	−97.8
Vestrheim 2008, Norway (2006) [15]	<1 year	2004–2005	40.5	2007	3.4	−91.6
	1 year		53.7		24.3	−54.7
Hanquet 2011, Belgium (January 2007) [11]	<2 years	2002–2003	92.9	2008	4.0	−95.7
Harboe 2010, Denmark (2007) [12]	<2 years	2000–2007	36.7	2008	7.7	−79.0
Munoz-Almagro 2008, Spain (2001) [23]	<2 years	1997–2001	26.8	2002–2006	16.1	−39.9
Barricarte 2007, Spain (2001) [19]	<2 years	2000–2002	56.0	2004–2005	16.0	−71.4
Rodenburg 2010, Netherlands (June 2006) [14]	<2 years	2004–2006	24.3	2006–2008	8.0	−67.1
North America (2001 in USA and 2002 in Alberta, Canada)						
Hennessy 2005 [34]	Nonnative <2 years	1995–2000	101.3	2001–2003	20.0	−80.3
Singleton 2007 [35]	Nonnative <2 years	1995–2000	101.3	2004–2006	2.3	−97.7
Whitney 2003 [29]	<2 years	1998–1999	156.1	2001	33.6	−78.5
CDC 2008 [32]	1 year	1998–1999	177.3	2005	1.6	−99.1
	<1 year		144.0		2.7	−98.1
Pilishvili 2010 [33]	<5 years	1998–1999	81.9	2007	0.4	−99.5
Tyrrell 2009 [41]	<2 years	2000	86.3	2006	4.7	−94.6
Kellner 2009 [42]	<2 years	1998–2001	66.4	2003–2007	9.0	−86.4

CDC Centers for Disease Control and Prevention, *PCV7* 7-valent pneumococcal conjugate vaccine, *PPV23* 23-valent pneumococcal polysaccharides vaccine, *VT IPD* vaccine-type invasive pneumococcal disease

Table 3 Impact on all-type IPD reduction in vaccine eligible population *(continued on next page)*

Study (year of PCV7 implementation) [ref]	Study population	Prevaccination		Postvaccination		% change
		Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Australia (January 2005 for all)						
Lehmann 2010 [44]	Nonaboriginal <2 years	1997–2001	73.8	2005–2007	24.2	–67.2
Roche 2006 [45]	General population <2 years	2002	93.0	2006	22.0	–76.3
Williams 2011 [46]	<2 years	2002	98.1	2007	25.1	–74.4
Europe						
Verstrheim 2008, Norway (2006) [15]	<2 years	2004–2005	67.7	2007	32.6	–51.8
	<5 years		36.0		19.7	–45.3
Vestrheim 2010, Norway (2006) [16]	<5 years	2004–2005	35.9	2008	9.9	–72.4
Harboe 2010, Denmark (2007) [12]	<2 years	2000–2007	54.8	2008	23.8	–56.6
Foster 2010, UK (September 2006) [25]	<2 years	1995–2005	43.3	2006–2009	22.4	–48.3
		2003–2005	35.9	2006–2009	22.4	–37.6
Miller 2011, UK (September 2006) [26]	<2 years	2000–2006	54.2	2009–2010	23.6	–56.5
Rückinger 2009, Germany (July 2006) [13]	<2 years (capture-recapture)	1997–2003	20.0	2007–2008	11.0	–45.0
Hanquet 2011, Belgium (January 2007) [11]	<2 years	2002–2003	129.7	2008	82.4	–36.5
Rodenburg 2010, Netherlands (June 2006) [14]	<2 years	2004–2006	34.5	2006–2008	22.5	–34.8
Rendi-Wagner 2009, Austria (2003) [10]	<2 years	2001–2004	12.2	2004–2007	8.7	–28.7
Aristegui 2007, Spain (2001 – private) [18]	<2 years	1998–2001	93.5	2003	56.3	–39.8
Calbo 2006, Spain (2001) [20]	<5 years	1999–2001	96.9	2002–2004	90.6	–6.5
Munoz-Almagro 2008 (2001 not national, or reimbursed) [23]	<2 years	1997–2001	32.4	2002–2006	51.3	+58.3
Perez-Trallero 2009 (late 2001, not reimbursed) [24]	<5 years	1996–2001	50.0	2002–2007	39.6	–20.8

Table 3 continued

Study (year of PCV7 implementation) [ref]	Study population	Prevaccination		Postvaccination		% change
		Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Barricarte 2007, Spain (2001) [19]	<2 years	2000–2002	117	2004–2005	115	–1.7
Guevara 2009, Spain (June 2001) [22]	<5 years	2001–2002	82.5	2006–2007	72.4	–12.2
North America (2001 in USA and 2002 in Canada)						
Albrich 2007 [27]	≤4 years	1997–2000	139.7	2000–2004	44.1	–68.4
Black 2007 [28]	<5 years	1996–2000	62.5	2000–2005	15.3	–75.5
Whitney 2003 [29]	<2 years	1998–1999	188.0	2001	59.0	–68.6
Hsu 2005 [36]	<5 years	1990–1991	56.9	2001–2003	17.4	–69.4
Hicks 2007 [31]	<5 years	1998–1999	95.2	2004	22.6	–76.3
CDC 2008 [32]	1 year	1998–1999	213.6	2005	37.8	–82.3
	<1 year		170.5		40.0	–76.5
Pilishvili 2010 [33]	<5 years	1998–1999	98.7	2007	23.6	–76.1
Kellner 2009 [42]	6–23 months	1998–2001	77.7	2003–2007	18.0	–76.8
Tyrrell 2009 [41]	<2 years	2000	96.7	2006	25.8	–73.3
Hennessy 2005 [34]	Nonnatives <2 years	1995–2000	131.1	2001–2003	51.0	–61.1
Singleton 2007 [35]	Nonnatives <2 years	1995–2000	135.5	2004–2006	43.6	–67.8
Simonsen 2011 [39]	<2 years	1996–1999	27.8	2005–2006	5.5	–80.2
	2–4 years		5.4		2.0	–63.0

CDC Centers for Disease Control and Prevention, *IPD* invasive pneumococcal disease, *PCV7* 7-valent pneumococcal conjugate vaccine

in all-type IPD incidence ranging from 1.7% (in Spain) [19] to 80.2% in the USA [32], with a median rate reduction of 45.0%. The highest rate reductions were reported generally in North America, Australia, and Norway, and the lowest was in Spain; the only study that did not report a reduction was performed in a single hospital in Barcelona, Spain, which reported 198 episodes of IPD in 194 children, with an increase of 58.3% between 1997–2001 and 2002–2006 [23].

Impact on VT IPD in All Ages

The impact of PCV7 on VT IPD in all ages was evaluated in nine studies that all reported a reduction ranging from 1.4% in the Netherlands [14] to 93.5% in the USA [33] with a median reduction rate of 65.5% (Table 4). In the study in the Netherlands, the periods compared were 2004–2006 and 2006–2008, so the postvaccination period was soon after the introduction of PCV7 into the NIP in 2006.

Table 4 Impact on VT IPD reduction in all ages

Study (year of PCV7 implementation) [ref]	Study population	Prevaccination		Postvaccination		% change
		Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Australia (January 2005 for all)						
Lehmann 2010 [44]	Nonaboriginal, all ages (PCV7 & PPV23)	1997–2001	5.3	2005–2007	2.2	–58.5
Hanna 2010 [43]	Nonindigenous people, all ages	2001–2004	6.1	2006–2009	1.4	–77.0
Europe						
Foster 2010, UK (September 2006) [25]	All ages	2003–2005	4.3	2006–2009	2.2	–48.8
Miller 2011 (September 2006) [26]	All ages	2000–2006	8.0	2009–2010	1.1	–86.3
Fenoll 2009, Spain (June 2001) [21]	<15 years	1996–2001	5.2	2005–2006	2.4	–53.8
Guevara 2010, Spain (June 2001) [22]	All ages	2001–2002	5.5	2006–2007	1.9	–65.5
Rodenburg 2010, Netherlands (June 2006) [14]	All ages	2004–2006	7.0	2006–2008	6.9	–1.4
North America (2001)						
Singleton 2007 [35]	All ages, nonnatives	1995–2000	8.9	2004–2006	1.3	–85.4
Pilishvili 2010 [33]	All ages	1998–1999	15.5	2007	1.0	–93.5

IPD invasive pneumococcal disease, *PCV7* 7-valent pneumococcal conjugate vaccine, *PPV23* 23-valent pneumococcal polysaccharides vaccine, *VT* vaccine type

Vaccine Impact on All-Type IPD in All Ages

Data were available from 10 articles from Australia (two), western Europe (six) and North America (two) (Table 5). The prevaccination rate of all-type IPD per 100,000 varied from 4.0 in Germany [13] to 24.4 in the USA [33]. The postvaccination rate per 100,000 varied from 3.2 in Germany [13] to 17.1 in Denmark [12]. Eight studies reported a reduction in IPD incidence ranging from 9.6% in England [25] to 44.7% in the USA [33]; the median rate of reduction was 26.8%. The highest impact was observed in the USA, Australia, and the UK. In the UK, a higher reduction rate was observed in the later post-PCV7 period (2009–2010 vs. 2003–2005). Two studies reported small, statistically nonsignificant increases; 3.2% in Spain [22] and 6.0% in the Netherlands [14].

Impact on VT IPD in Age Groups not Vaccine Eligible (Indirect Effect)

Seven of the eight studies reporting data for nonvaccine-eligible children under 17 years

of age showed a reduction in VT IPD ranging from 40.0% in children aged 5–17 years in Spain and Alaska, USA [23, 35] to 78.3% in children aged 5–14 years in Western Australia [44] (Appendix Table 1). One study reported an increase of 150.0% in children aged 5–17 years in a postvaccination period soon after the introduction of PCV7 [34]; in a later period, for the same population, a reduction of 40.0% was reported [35].

The impact on VT IPD in adults aged 15/17–64 years was reported in 12 studies for a total of 18 age groups. A reduction was reported in all studies except one; in the Netherlands an increase of 9.9% was reported in those aged 50–64 years [14]. The reductions reported ranged

Table 5 Impact on all-type IPD in all ages

Study (year of PCV7 implementation) [ref]	Study population	Prevaccination		Postvaccination		% change
		Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Australia (January 2005 for all)						
Lehmann 2010 [44]	All ages, nonaboriginal people (PCV7 & PPV23)	1997–2001	7.5	2005–2007	4.8	−36.0
Hanna 2010 [43]	All ages, nonaboriginal people	2001–2004	9.3	2006–2009	6.1	−34.4
Europe						
Foster 2011, UK (September 2006) [25]	All ages	2003–2005	8.3	2006–2009	7.5	−9.6
Miller 2011, UK (September 2006) [26]	All ages	2000–2006	16.1	2009–2010	10.6	−34.2
Rückinger 2009, Germany [13]	<16 years (capture-recapture)	1997–2003	4.0	2007–2008	3.2	−20.0
Harboe 2010, Denmark [12]	All ages	2000–2007	19.6	2008	17.1	−12.8
Guevara 2009, Spain (June 2001: limited) [22]	All ages	2001–2002	15.8	2006–2007	16.3	+3.2
Rodenburg 2010, Netherlands (June 2006) [14]	All ages	2004–2006	15.0	2006–2008	15.9	+6.0
North America						
Pilishvili 2010 (late 2000) [33]	All ages	1998–1999	24.4	2007	13.5	−44.7
Singleton 2007 (January 2001) [35]	All ages, nonnatives	1995–2000	16.7	2004–2006	11.1	−33.5

IPD invasive pneumococcal disease, *PCV7* 7-valent pneumococcal conjugate vaccine, *PPV23* 23-valent pneumococcal polysaccharides vaccine

from 7.1% in those aged 30–49 years in Western Australia [44] to 90.8% in those aged 18–49 years in the USA [33].

All 13 studies reporting the impact for adults aged 65 years or older (with a total of 16 age groups) showed a reduction in the incidence of VT IPD ranging from 1.1% in the Netherlands [14] to 92.0% in the USA [33], with a median reduction of 53.8%.

Impact on All-Type IPD in Age Groups not Vaccine Eligible (Indirect Effect)

There was an overall decrease for 12 of the 16 studies that reported data for nonvaccine-eligible children aged from over 2 or over 5 years to less than 17 years; the rate reduction ranged from 6.6% for children aged 2 years or older in the UK [25] to 53.4% in children aged 2–4 years in Norway [15] (Appendix Table 2). In the five studies that reported an increase, the rate increase ranged from 9.1% in children aged 5–15 years in Germany [13] to 90.5% and 134.5% in children aged 5–17 years and 2–4 years, respectively, in one hospital in Barcelona, Spain [23].

Fourteen studies reported data in 25 adult age groups (from 15/17 to 64 years old). The rates reported for 19 of these age groups ranged from a reduction of 2.0% in 15–64 year-old nonnatives in north Queensland, Australia [43] to 48.9% in 18–44 year-old nonnatives in Alaska, USA [34]. In the six age groups in which an increased rate was reported, the increase ranged from 8.5% in nonnative 50–64 year olds in north Queensland, Australia [43] to 119.7% in 20–39 year olds in Alberta, Canada [41].

Seventeen studies reported data for those aged 65 years and over, with one study from Calgary, Canada reporting data for two age groups; 65–84 years and 85 years and over [42]. Reductions were reported in 12 of these studies, ranging from 7.1% in Denmark [12] to 44.1% in the USA [39]. In the remaining age groups, the increased rate reported ranged from 2.4% in the Netherlands [14] to 22.9% in Spain [17]. In one study from Canada, a reduction of 34.0% and an increase of 9.3% were reported for those aged 65–84 years and 85 year olds and older, respectively [42].

Impact on All-Type IPD and VT IPD Mortality

The impact of PCV7 vaccination on IPD mortality (both all-type [four studies] and VT [two studies]) was reported from North America only. One study reported reductions for VT IPD mortality across all age groups [33]. In another study, the reduction in VT IPD mortality in children less than 2 years observed was offset with an increase in non-VT IPD mortality resulting in no change [31]. Two studies reported reductions of 62.5% and 57.1% for all-type IPD in vaccine-eligible children [33, 38]. Two studies reported an overall reduction in all-type IPD mortality in all ages of 37.8% and 75.9% [38, 40]. There was a reduction in all-type IPD mortality for all the nonvaccine-eligible age groups reported ranging from 17.4% in those aged 50 years or older [30] to 50.0% in those aged 25–34 years [38].

DISCUSSION

The results from this review illustrate that PCV7 has had a significant impact on IPD across all ages through its use in pediatric immunization programs. PCV7 vaccination leads to a reduction in VT IPD in vaccine-eligible children and also to an overall reduction in all-type IPD in these children. PCV7 was also shown to have an indirect impact on VT and all-type IPD in the overall population, although this impact is

lower than that seen in vaccine-eligible children. Despite the increase in non-VT IPD that has been reported, it has been insufficient generally to offset the reduction of VT IPD resulting in an overall reduction of all-type IPD.

The extent of the impact varied across the studies; many factors (and probably a combination of factors) contribute to explain this heterogeneity.

One of these factors is the sero-epidemiology of *S. pneumoniae* before the introduction of PCV7 and the match with the serotypes in PCV7. In the USA, the serotypes included in PCV7 matched the most prevalent serotypes responsible for IPD, but in other countries and regions, the percentage of IPD due to these seven serotypes varied; thus partly explaining the different impact observed [25, 32].

The process for PCV7 introduction, its uptake, the recommended schedule, and the implementation of a catch-up program or not also varied between countries. In the USA, where the impact was the greatest, there was a rapid and high uptake after introduction into the NIP for universal vaccination of children less than 2 years old with a 3 + 1 schedule [47]. However, there was a vaccine shortage in the early stages after introduction into the NIP, so uptake of all four doses was low during this period [48]. In Australia, PCV7 was funded in mid-2001 for indigenous children less than 2 years of age, nonindigenous children living in central Australia, and for all children less than 5 years of age with predisposing medical conditions [44]. The recommended schedule was 3 + 0 (at 2, 4, and 6 months old) with no booster in the second year of life. Then in January 2005, PCV7 funding was extended to all children less than 2 years of age.

In Europe, although PCV7 received its licence in 2001, introduction into NIPs and funding varied widely. In some countries, such as the UK, following the introduction of PCV7 and reimbursement for all children under 2 years of age in 2006 with a 2 + 1 schedule, uptake was rapid and high, with an estimated uptake rate from 84.7% in 2007–2008 to 93% in 2009–2010 in the UK [49]. In other countries, such as France and Switzerland, PCV7 was introduced into the NIPs with a 3 + 1 schedule initially for at-risk children less than 2 years of age in France and under 5 years of age in Switzerland. In 2006, PCV7 was also recommended for all children under 2 years of age with a 2 + 1 schedule in France, and in Switzerland for healthy children under 2 years of age. In France, the incidence of all-type IPD in children less than 2 years was reduced by 30% between 2001–2002 and 2007 [50]. In Switzerland, the number of children under 2 years of age with all-type IPD was reduced from an average of 43 to 22 in 2009 (49% reduction) [51]. For the same periods, the reduction in VT IPD was 85% (from 27 to 4) while the number of non-VT IPD cases remained stable [51].

The periods chosen for prevaccination and postvaccination can also introduce variability in the estimated impact. It is difficult to differentiate changes that can occur independently of vaccination, such as natural evolution of circulating serotypes or antibiotic resistance, from changes due to vaccine-induced serotype replacement, and it is possible that several factors may be responsible for the changes. Data from the USA show an evolution of impact with a greater distance from PCV7 introduction for the postvaccination period. In Alaska, comparing the incidence of VT IPD in nonnative children under 2 years of age in 1995–2000 with that in 2001–2003 and 2004–2006 showed reductions of 80.3% and 97.7%, respectively (Table 2) [34, 35]. The same analysis for all-type IPD showed reductions of 61.7% and 67.8%, respectively. In another

USA dataset, the ABCs network, the analysis for 2001 just after the introduction of PCV7 showed a 78.5% reduction in the incidence of VT IPD in children lesst than 2 years of age compared with the analysis for 2005, which showed almost 100% reduction [29, 32].

The studies analyzed in this review used different surveillance systems and case definitions; in addition, it is possible that changes in diagnosis and reporting practices occurred after the introduction of PCV7. The studies also varied in their geographical coverage, with some able to claim regional or national representation, while some reported data from one or two hospitals, which was the case for four studies from Spain [17, 20, 23, 24]. In addition, different schedules (3 + 1 and 2 + 1) were used with differing rates of uptake; for example, in Norway and the UK, there was a rapid uptake after introduction into the NIPs with a 2 + 1 schedule, whereas in Spain there was a slow uptake after introduction through the private market with a 3 + 1 schedule.

Despite these limitations, this analysis generally confirms the impact of PCV7 on VT IPD and all-type IPD in vaccine-eligible children as well as an indirect impact on nonvaccine-eligible age groups. Since 2010 many countries have decided to replace PCV7 with PCV13. The vaccine includes the seven serotypes present in PCV7 (i.e., 14, 4, 9V, 19F, 18C, 6B, and 23F), and offers potential additional protection against serotypes 1, 5, 7F, 19A, 6A, and 3. PCV13 has been shown to be well tolerated and immunogenic for all 13 serotypes [52]. Although no PCV13 impact study results have been published yet, in the UK where PCV13 replaced PCV7 in April 2010, preliminary data suggest that, up to July 2011, IPD due to PCV13-only serotypes has been reduced by 50% in children under 2 years of age [53].

CONCLUSION

It is important not to lose sight of the significant impact that PCV7 has had on IPD, despite the increase in non-VT IPD, but we need to remain vigilant for serotype replacement. With the introduction of PCV13 we can expect to see a reduction in the incidence of IPD due to the six additional serotypes included, as well as continued protection against IPD due to PCV7 serotypes. Robust surveillance systems are essential for the evaluation of the impact of PCV13 on all-type IPD and for monitoring the evolution of non-VT IPD.

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Conflict of interest. Dr. Myint is employed by Pfizer, the manufacturer of Prevenar® and Prevenar 13®, Wyeth Pharmaceuticals Inc, marketed by Pfizer Inc, New York, USA. Dr. Madhava, Dr. Balmer, Dr. Christopoulou, Dr. Attal, Dr. Menegas, and Dr. Bonnet are all employed by Pfizer. Dr. Sprenger is employed by Pfizer at the time of submission.

APPENDIX

Table 1 Impact on VT IPD reduction in nonvaccine-eligible populations

	Study [ref]	Study population	Prevaccination		Postvaccination		% change
			Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Children <17 years not vaccine eligible	**Australia**						
	Hanna 2010 [43]	Nonaboriginal 5–14 years	2001–2004	1.2	2006–2009	0.6	–50.0
	Lehmann 2010 [44]	Nonaboriginal 2–4 years	1997–2001	17.9	2005–2007	4.2	–76.5
		Nonaboriginal 5–14 years		2.3		0.5	–78.3
	Europe						
	Miller 2011, UK [26]	5–14 years	2000–2006	2.2	2009–2010	0.5	–77.3
	Vestrheim 2008, Norway [15]	2–4 years	2004–2005	13.5	2007	7.5	–44.4
	Munoz-Almagro 2008, Spain [23]	2–4 years	1997–2001	6.8	2002–2006	9.2	+35.3
		5–17 years		0.5		0.3	–40.0
	North America						
	Hennessy 2005 [34]	Nonnative 2–4 years	1995–2000	13.6	2001–2003	7.5	–44.9
		Nonnative 5–17 years		1.0		2.5	+150.0
	Singleton 2007 [35]	Nonnative 2–4 years	1995–2000	13.6	2004–2006	0	–100.0
		Nonnative 5–17 years		1.0		0.6	–40.0
	Kellner 2009 [42]	2–4 years	1998–2001	17.9	2003–2007	7.3	–59.2
		5–15 years		2.5		1.3	–48.0
Adults 15/17–64 years	**Australia**						
	Hanna 2010 [43]	15–64 years	2001–2004	3.1	2006–2009	1.2	–61.3
	Lehmann 2010 [44]	Nonaboriginal 15–29 years	1997–2001	1.6	2005–2007	0.7	–56.3
		Nonaboriginal 30–49 years		1.4		1.3	–7.1
		Nonaboriginal 50–64 years		3.4		2.8	–17.7
	Europe						
	Miller 2011, UK [26]	15–44 years	2000–2006	3.3	2009–2010	0.4	–87.9
		45–64 years		7.7		1.1	–85.7
	Vestrheim 2010, Norway [16]	20–39 years	2004–2005	3.9	2008	3.1	–20.5
		40–64 years		12.2		4.9	–59.8
	Ardanuy 2009, Spain [17]	18–64 years	1997–2001	3.1	2005–2007	2.7	–12.9
	Rodenburg 2010, Netherlands [14]	50–64 years	2004–2006	7.5	2006–2008	8.2	+9.3

Table 1 continued

	Study [ref]	Study population	Prevaccination		Postvaccination		% change
			Years	Incidence/ 100,000	Years	Incidence/ 100,000	
	North America						
	Pilishvili 2010 [33]	18–49 years	1998–1999	7.6	2007	0.7	–90.8
		50–64 years		12.8		1.7	–86.7
	Hennessy 2005 [34]	Nonnatives 18–44 years	1995–2000	4.3	2001–2003	1.1	–74.8
	Singleton 2007 [35]	Nonnatives 18–44 years	1995–2000	4.1	2004–2006	0.8	–80.5
	Lexau 2005 [30]	50–64 years	1998–1999	12.9	2002–2003	6.9	–46.5
	Whitney 2003 [29]	20–39 years	1998–1999	6.6	2001	4.0	–39.4
		40–64 years		11.6		10.0	–13.8
	Kellner 2009 [42]	16–64 years	1998–2001	3.8	2003–2006	2.2	–42.1
Adults 65+ years	**Australia**						
	Hanna 2010 [43]	Nonaboriginal ≥65 years	2001–2004	12.5	2006–2009	2.8	–77.6
	Lehmann 2010 [44]	Nonaboriginal ≥65 years	1997–2001	12.6	2005–2007	6.5	–48.4
	Europe						
	Miller 2011, UK [26]	≥65 years	2000–2006	18.2	2009–2010	3.4	–81.3
	Guevara 2009, Spain [22]	≥65 years	2001–2002	11.8	2006–2007	3.7	–68.6
	Vestrheim 2010, Norway [16]	≥65 years	2004–2005	42.4	2008	24.0	–43.4
	Ardanuy 2009, Spain [17]	≥65 years	1997–2001	19.5	2005–2007	12.3	–36.9
	Perez-Trallero 2009, Spain [24]	>64 years	1996–2001	20.2	2002–2007	17.0	–15.8
	Rodenburg 2010, Netherlands [14]	≥65 years	2004–2006	28.2	2006–2008	27.9	–1.1
	North America						
	Pilishvili 2010 [33]	≥65 years	1998–1999	33.7	2007	2.7	–92.0
	Lexau 2005 [30]	65–74 years	1998–1999	21.6	2002–2003	10.2	–52.8
		75–84 years		41.0		15.4	–62.4
		≥85 years		69.2		31.3	–54.8
	Hicks 2007 [31]	≥65 years	1998–1999	34.5	2004	8.2	–76.2
	Whitney 2003 [29]	>64 years	1998–1999	33.4	2001	23.9	–28.5
	Kellner 2009 [42]	65–84 years	1998–2001	22.1	2003–2007	4.8	–72.3
		≥85 years		29.1		22.5	–22.7

VT IPD vaccine-type invasive pneumococcal disease

Table 2 Impact on all-type IPD in nonvaccine-eligible populations

	Study [ref]	Study population	Prevaccination		Postvaccination		% change
			Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Children <17 years not vaccine eligible	**Australia**						
	Hanna 2010 [43]	Nonaboriginal 5–14 years	2001–2004	2.5	2006–2009	1.2	–52.0
	Lehmann 2010 [44]	Nonaboriginal 2–4 years	1997–2001	21.2	2005–2007	9.9	–53.3
		Nonaboriginal 5–14 years		2.8		1.7	–39.3
	Europe						
	Verstrheim 2008, Norway [15]	2–4 years	2004–2005	23.6	2007	11.0	–53.4
	Miller 2011, UK [26]	2–4 years	2000–2006	16.4	2009–2010	9.3	–43.3
		5–14 years		5.1		3.0	–41.2
	Aristegui 2007, Spain [18]	2–5 years	1998–2001	30.1	2002–2003	33.1	–10.0
	Foster 2011, UK [25]	≥2 years	2003–2005	7.6	2006–2009	7.1	–6.6
	Rückinger 2009, Germany [13]	5–15 years	1997–2003	1.1	2007–2008	1.2	+9.1
	Harboe 2010, Denmark [12]	2–4 years	2000–2007	8.5	2008	11.8	+38.8
		5–17 years		2.6		1.5	–42.3
	Munoz-Almagro 2008, Spain [23]	2–4 years	1997–2001	11.3	2002–2006	26.5	+134.5
		5–17 years		2.1		4.0	+90.5
	North America						
	Pilishvili 2010 [33]	5–17 years	1998–1999	4.2	2007	2.4	–42.9
	Hennessy 2005 [34]	Nonnatives 5–17 years	1995–2000	3.9	2004–2006	4.6	+17.9
	Singleton 2007 [35]	Nonnatives 5–17 years	1995–2000	3.8	2001–2003	2.8	–26.3
	Albrich 2007 [27]	5–17 years	1997–2000	3.9	2000–2004	3.3	–15.4
	Tyrrell 2009 [41]	5–19 years	2000	2.4	2006	4.0	+66.7
	Kellner 2009 [42]	2–4 years	1998–2001	22.7	2003–2007	12.6	–44.5
		5–15 years		3.3		2.4	–27.3
	Simonsen 2011 [39]	5–17 years	1996–1999	1.4	2005–2006	0.7	–50.0
Adults 15/17–64 years	**Australia**						
	Lehmann 2010 [44]	Nonaboriginal 15–29 years	1997–2001	2.4	2005–2007	1.5	–37.5
		Nonaboriginal 30–49 years		2.8		2.7	–3.6
	Hanna 2010 [43]	Nonaboriginal 50–64 years	2001–2004	4.7	2006–2009	5.1	+8.5
		Nonaboriginal 15–64 years		5.0		4.9	–2.0

Table 2 continued

	Study [ref]	Study population	Prevaccination		Postvaccination		% change
			Years	Incidence/ 100,000	Years	Incidence/ 100,000	
	Europe						
	Miller 2011, UK [26]	15–44 years	2000–2006	8.3	2009–2010	4.7	–43.4
		45–64 years		17.9		11.0	–38.5
	Harboe 2010, Denmark [12]	18–49 years	2000–2007	7.1	2008	5.8	–18.3
		50–64 years		23.5		19.6	–16.6
	Rodenburg 2010, Netherlands [14]	50–64 years	2004–2006	16.7	2006–2008	18.5	+10.8
	Ardanuy 2009, Spain [17]	18–64 years	1997–2001	8.4	2005–2007	12.5	+48.8
	North America						
	Hennessy 2005 [34]	Nonnative 18–44 years	1995–2000	9.2	2001–2003	4.7	–48.9
		Nonnative ≥45 years		23.5		16.9	–28.1
	Singleton 2007 [35]	Nonnative 18–44 years	1995–2000	9.1	2004–2006	6.2	–31.9
		Nonnative ≥45 years		24.3		18.4	–24.3
	Albrich 2007 [27]	18–39 years	1997–2000	11.7	2000–2004	6.9	–41.0
		40–64 years		23.0		17.2	–25.2
	Whitney 2003 [29]	20–39 years	1998–1999	11.2	2001	7.6	–32.1
		40–64 years		21.5		19.7	–8.4
	Tyrrell 2009 [41]	20–39 years	2000	6.1	2006	13.4	+119.7
		40–64 years		11.2		20.9	+86.6
	Pilishvili 2010 [33]	18–49 years	1998–1999	13.3	2007	8.0	–39.8
		50–64 years		24.0		19.8	–17.5
	Kellner 2009 [42]	16–64 years	1998–2001	7.1	2003–2007	12.3	+73.2
	Simonsen 2011 [39]	18–39 years	1996–1999	3.5	2005–2006	1.4	–60.0
		40–64 years		8.9		6.0	–32.6
Adults 65+ years	**Australia**						
	Hanna 2010 [43]	Nonaboriginal ≥65 years	2001–2004	23.0	2006–2009	14.1	–38.7
	Lehmann 2010 [44]	Nonaboriginal ≥65 years	1997–2001	19.9	2005–2007	13.0	–34.7
	Europe						
	Miller 2011, UK [26]	≥65 years	2000–2006	34.8	2009–2010	28.2	–19.0
	Harboe 2010, Denmark [12]	≥65 years	2000–2007	65.9	2008	61.2	–7.1
	Rodenburg 2010, Netherlands [14]	≥65 years	2004–2006	58.8	2006–2008	60.2	+2.4
	Guevara 2009, Spain [22]	≥65 years	2001–2002	32.4	2006–2007	33.7	+4.0

Table 2 continued

Study [ref]	Study population	Prevaccination		Postvaccination		% change
		Years	Incidence/ 100,000	Years	Incidence/ 100,000	
Perez-Trallero 2009, Spain [24]	>64 years	1996–2001	50.7	2002–2007	55.6	+9.7
Ardanuy 2009, Spain [17]	≥65 years	1997–2001	45.8	2005–2007	56.3	+22.9
North America						
McBean 2005 [37]	≥65 years	1996–2000	36.8	2002–2003	21.8	–40.8
Hicks 2007 [31]	≥65 years	1998–1999	61.5	2004	38.0	–38.2
Pilishvili 2010 [33]	≥65 years	1998–1999	60.1	2007	37.9	–36.9
Lexau 2005 [30]	≥50 years	1998–1999	40.8	2002–2003	29.4	–27.9
Albrich 2007 [27]	≥65 years	1997–2000	65.4	2000–2004	48.2	–26.3
Whitney 2003 [29]	≥65 years	1998–1999	60.1	2001	49.5	–17.6
Tyrrell 2009 [41]	≥65 years	2000	28.2	2006	23.0	–18.4
Kellner 2009 [42]	65–84 years	1998–2001	36.2	2003–2007	23.9	–34.0
	≥85 years		55.0		60.1	+9.3
Simonsen 2011 [39]	≥65 years	1996–1999	30.6	2005–2006	17.1	–44.1

IPD invasive pneumococcal disease

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