Impact factor 5·7

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 21 | Weekly issue 14 | 07 April 2016

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Influenza vaccine effectiveness in adults 65 years and older, Denmark, 2015/16 – a rapid epidemiological and virological assessment

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Citation style for this article:
Emborg H, Krause TG, Nielsen L, Thomsen MK, Christiansen CB, Skov MN, Nielsen XC, Weinreich LS, Fischer TK, Rønn J, Trebbien R. Influenza vaccine effectiveness in adults 65 years and older, Denmark, 2015/16 – a rapid epidemiological and virological assessment. Euro Surveill. 2016;21(14):pii=30189. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.14.30189

Article submitted on 16 March 2016 / accepted on 07 April 2016 / published on 07 April 2016

In Denmark, both influenza A(H1N1)pdm09 and influenza B co-circulated in the 2015/16 season. We estimated the vaccine effectiveness (VE) of the trivalent influenza vaccine in patients 65 years and older using the test-negative case–control design. The adjusted VE against influenza A(H1N1)pdm09 was 35.0% (95% confidence interval (CI): 11.1–52.4) and against influenza B 4.1% (95% CI: –22.0 to 24.7). The majority of influenza A(H1N1)pdm09 circulating in 2015/16 belonged to the new genetic subgroup subclade 6B.1.

In Denmark, both influenza A(H1N1)pdm09 and influenza B co-circulated in the 2015/16 season. The trivalent influenza vaccine (TIV) did not include the circulating influenza B Victoria lineage and there is evidence in Europe for genetic evolution of the circulating influenza A(H1N1)pdm09 virus [1]. We estimated the influenza vaccine effectiveness (VE) in people aged 65 years and older. In addition, we describe the genetic and antigenic characteristics of the influenza A(H1N1) pdm09 variant and the influenza B strain circulating in Denmark.

Data for vaccine effectiveness estimation

In the Danish Microbiology Database, all patients swabbed at the general practitioner's (GP) or at hospital and tested for influenza A and B viruses by PCR are registered in real time [2]. During the influenza season, national guidelines recommend that patients belonging to risk groups, including the elderly who present with influenza symptoms at GPs and hospitals are swabbed and tested for influenza. At hospitals, all patients with lower respiratory infections are also recommended to be swabbed. All diagnostic influenza tests from patients aged 65 years and older were included in this study.

Influenza symptoms were defined as sudden onset of fever, muscle ache and upper airway symptoms. The trivalent influenza vaccine (TIV) is offered free of charge to Danish citizens 65 and older between week 40 and week 53, and date of vaccination is registered in the Danish Vaccination Register [3]. In The Danish National Hospital Register, data on all hospital admissions are collected [4]. Comorbidities that can lead to severe influenza disease and were diagnosed between October 2010 and October 2015 were extracted from the Danish National Hospital Register.

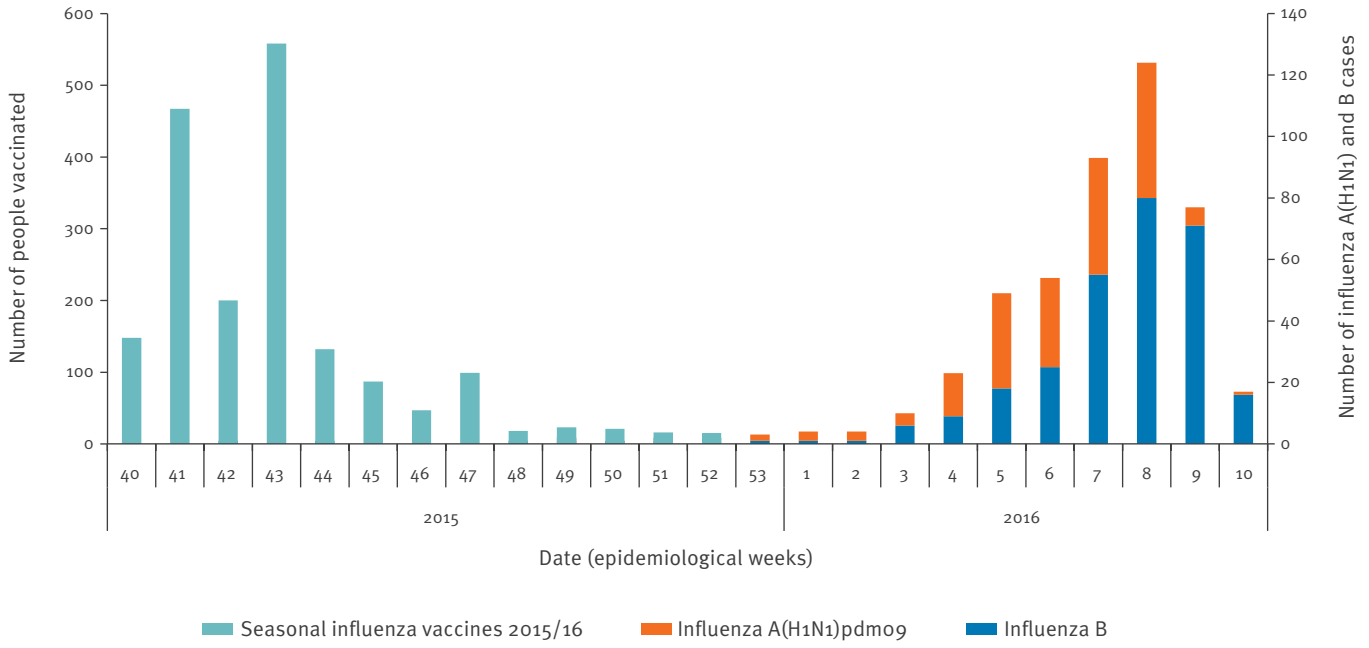
Data from the Danish Microbiology Database, the Danish Vaccination Register and the Danish National Hospital Register were linked using unique identifiers.

Case definitions and statistical analysis

Cases were defined as patients who tested positive for influenza A(H1N1)pdm09 or influenza B, and a patient was only included the first time a test was positive for either type. Controls were patients who tested negative for both influenza A and B. Patients were considered vaccinated if they had received the TIV at least two weeks before the sample was taken. A logistic regression model was used to estimate VE against influenza A(H1N1)pdm09 and influenza B using the test-negative case–control design (1-OR) × 100%. The

Figure 1

Trivalent influenza vaccines received (n = 1,831) and laboratory-confirmed influenza A(H1N1)pdm09 and B cases among tested patients ≥ 65 years (n = 468), Denmark, 28 September 2015–9 March 2016



Influenza vaccines are given free of charge to the elderly 65 years and older from 1 October to 31 December. Due to delay in registration of vaccinations, data from week 53 were not available at the time this analysis was performed.

In weeks 40 to 53, between 0 and two influenza A(H1N1) and B cases were registered per week (not visible at presented range of the y-axis).

estimates were adjusted for sex and co-morbidities diagnosed within a five-year period before the 2015/16 influenza season. Among 195 subtyped influenza A isolates from patients aged 65 years and older, less than 10% (n = 18) were A(H3N2) and VE against this subtype was not estimated.

The statistical programme SAS version 9.4 was used for the descriptive and statistical analyses (SAS Institute, Cary, United States).

Influenza virus characterisation

All influenza samples received at The National Influenza Center in Denmark (NIC) were screened for influenza virus by an in-house multiplex real-time reverse-transcriptase PCR (qRT-PCR), with primers and probes detecting influenza A and B virus as well as subtypes of H3 haemagglutinin (HA) and N1pdm09 neuraminidase. Subtyping of influenza B virus is also performed by an in-house duplex qRT-PCR which differentiates between the Yamagata and Victoria lineage on a fragment of the HA gene.

Sequencing of the HA gene of influenza A(H1N1)pdm09 and influenza B viruses was performed on extracted viral RNA from 62 and 20 samples, respectively. Total nucleic acid was extracted using 200 µl of sample material and the MagNA Pure LC Total Nucleic Acid Isolation Kit on the MagNa Pure 96/32 (Roche). RT-PCR of the complete HA gene was performed using in-house primers and an in-house one-step RT-PCR programme on a TRIO cycler (Biometra). Sequencing was performed by using Big Dye chemistry on an ABI3500 capillary sequencer (Thermo Fisher). Assembly of contigs was done in Bionumerics version 6.6 (Applied maths) and alignment and phylogenetic analysis were conducted with MEGA version 6 [5]. For alignment, the Muscle algorithm was used and phylogenetic trees were created by the maximum likelihood method using 1,000 bootstrap replicates. Sequences were also analysed by BLAST at NCBI GenBank, the Global Initiative on Sharing All Influenza Data (GISAID) and at the FLUSERVER [6]. The authors gratefully acknowledge the 59 originating and submitting laboratories who contributed sequences used in the phylogenetic analysis to GISAID (www.gisaid.org).

Virus isolation was successful for 32 influenza A(H1N1) pdm09 and 13 influenza B samples by standard procedures in confluent monolayers of MDCK and/or MDCK-SIAT cells [7]. Several samples were shipped in E-swab medium which is cytotoxic and therefore is challenging for virus isolation [8]. Antigenic characterisation was performed by HA inhibition (HAI) test [7] using reference ferret antiserum against A/California/07/2009 (H1N1pdm09), B/Brisbane/60/2008 (Victoria lineage) and B/Phuket/3073/2013 (Yamagata lineage) provided

Figure 2

Phylogenetic tree of the haemagglutinin gene with reference viruses for the different phylogenetic clades of H1N1pdm09 influenza A viruses (n = 40)

The Danish viruses are indicated with a black circle. A subclade formed by viruses with the amino acid substitutions S101N, S179N and I233T, subclade 6B.1, is indicated as well as the subclade formed by viruses with the V169T, V190I, E508G and D518E substitutions, subclade 6B.2. The authors gratefully acknowledge the 59 originating and submitting laboratories who contributed sequences used in the phylogenetic analysis to GISAID (www.gisaid.org).

Table

Laboratory-confirmed influenza A(H1N1)pdm09 and B cases (n = 468) and influenza A and B test-negative controls (n = 3,363) aged ≥ 65 years by trivalent influenza vaccination status, age group and sex, and vaccination coverage among influenza cases and controls by age group and sex, Denmark, 28 September 2015–9 March 2016

Characteristic	Influenza A(H1N1)pdm09			Influenza B			Controls		
	Vaccinated (n)	Not vaccinated (n)	Vaccination coverage (%)	Vaccinated (n)	Not vaccinated (n)	Vaccination coverage (%)	Vaccinated (n)	Not vaccinated (n)	Vaccination coverage (%)
Age group									
65–69	16	42	27.6	37	42	46.8	337	488	40.8
70–74	20	29	40.8	37	41	47.4	385	458	45.7
75–79	18	22	45.0	27	34	44.3	363	323	52.9
≥ 80	13	17	43.3	34	39	46.6	544	466	53.9
Comorbidities									
No	15	34	30.6	36	66	35.3	347	480	42.0
Yes	52	76	40.6	99	90	52.4	1,282	1,255	50.5
Sex									
Female	28	45	38.4	70	79	50.0	780	865	47.4
Male	39	65	37.5	65	77	45.8	849	869	49.4
Total	67	110	37.8	135	156	46.4	1,629	1,734[a]	48.3

[a] Sex was not known for one person.

by the World Health Organization (WHO) Collaboration Centre, Mill Hill, London.

Vaccine effectiveness results

By 9 March 2016, 3,831 patients 65 years and older were tested for influenza A(H1N1)pdm09 and B, and 65% of them were swabbed at a hospital. In total, 177 patients were positive for influenza A(H1N1)pdm09 and 291 for influenza B. In total, 1,505 (82%) of 1,831 study participants had received the TIV before 2 November in 2015 (Figure 1).

Vaccine coverage in cases diagnosed with influenza A(H1N1)pdm09 was 37.8%, which is lower than the coverage in controls (48.3%), cases diagnosed with influenza B (46.4%) (Table) and the estimated national coverage of 44% (data not shown). The coverage, for both cases and controls, was higher among patients with comorbidities compared with patients without comorbidities (Table).

Adjusted interim VE among those aged 65 years and older against influenza A(H1N1)pdm09 was 35.0% (95% confidence interval (CI): 11.1–52.4) and against influenza B 4.1% (95% CI: –22.0 to 24.7).

Virus characterisation results

Full gene sequencing of the HA gene from 62 influenza A(H1N1)pdm09 samples revealed in 46 of them an amino acid substitution at position 179 (H1 complete open reading frame numbering) from serine to asparagine, which leads to a potential glycosylation site formed by positions 179–181 with the amino acid motif asparagine–glutamine–serine (NQS) (Table). Additional substitutions were revealed at amino acid position S101N and I233T in the 46 samples having the S179N. Two of the patient samples had an additional substitution at H155Y. Nine samples had a different amino acid motif with substitutions at positions V169T, V190I, E508G and D518E.

Phylogentic analysis revealed that all 62 sequenced HA genes of A(H1N1)pdm09 viruses belonged to genetic clade 6B (Figure 2), however, the 46 viruses with the S101N, S179N, and I233T substitutions formed their own subclade which now is categorised by the WHO as subclade 6B.1. In addition, the nine V169T, V190I, E508G and D518E viruses clustered together with the A/Minnesota/32/2015(H1N1pdm09) virus (Figure 2) and are now categorised as subclade 6B.2.

Of the 32 A(H1N1)pdm09 viruses isolated in cell culture, 25 belonged to subclade 6B.1, three belonged to subclade 6B.2, and four belonged to clade 6B. Antigenic characterisation showed all 32 virus isolates to be equally inhibited or inhibited to a lesser extent (two- to fourfold decrease in HAI titre), by ferret antiserum against A/California/07/2009 (H1N1pdm09) compared with the A/California/07/2009 (H1N1pdm09) reference virus HAI titres.

Of 447 influenza B virus samples from all age groups received for the national influenza surveillance programme at NIC Denmark by mid-March 2016, 350 were subtyped; 307 (88%) belonged to the B-Victoria lineage and 43 (12%) belonged to the B-Yamagata lineage. The HA genes of 15 B-Victoria viruses were sequenced and all belonged to clade 1A, corresponding to the

strain included in the quadrivalent vaccine but not included in the trivalent vaccine used in Denmark in the current season. Antigenic characterisation by HAI test of 13 virus isolates showed a two- to fourfold decrease in HAI-titre using the ferret antiserum against B/Brisbane/60/2008 compared with the vaccine reference virus B/Brisbane/60/2008. None of the B-Victoria viruses was inhibited by the B-Yamagata reference antiserum B/Phuket/3073/2013.

Discussion

Due to the late start of the influenza season in Europe only few interim VE estimates have been published [9,10] and in particular, little information is available on the VE in those aged 65 years and older, an important target group for influenza vaccination. Furthermore, a mismatch was observed between the circulating B-Victoria lineage and the B-Yamagata lineage included in the TIV for the northern hemisphere.

We found no effect of the TIV against influenza B 4.1% (95% CI: −22.0 to 24.7), which accounted for 62% of the influenza detections in patients aged 65 years and older in Denmark until 9 March 2016. This can be explained by the mismatch because 88% of the B infections were Victoria lineage. This is in line with findings from Hong Kong in 2011/12 where B-Victoria was included in the vaccine and VE against paediatric influenza B-Yamagata hospitalisation was estimated at 9.5% (95% CI: −240.4 to 76.0) [11]. However, in the same season, a study from the United States estimated a VE of 66% (95%CI: 38–81) against B-Yamagata although only the B-Victoria lineage was included in the vaccine [12], which could suggest cross-protection between lineages. Antigenic characterisation at the Danish NIC supports a lack of cross-reactivity between B-Yamagata and B-Victoria when using the current season's vaccine antiserum against B/Brisbane/60/2008 and B/Phuket/3073/2013 in the HAI test which is also reported in the study from Hong Kong [11]. Influenza B lineage-specific TIV VEs have earlier been estimated in seasons with both mismatch and/or cocirculation of two influenza B lineages. Some VE studies have suggested cross-protection between lineages and others not. The reasons for these differences are not known but may be explained by methodological issues or by differences in population immunity due to variations in vaccination strategies or differences in circulating lineages between regions [13].

It is likely that immunity against influenza B Victoria in the Danish population is low, as only few isolates from this lineage have been detected in Denmark since 2010/11 and have not been included in the vaccine since 2011/12. Influenza B-Victoria also dominates over B-Yamagata in the rest of Europe [14], and if the quadrivalent vaccine had been used instead of TIV during the current season morbidity due to influenza B might have been lower.

We found a moderate to low VE against influenza A(H1N1)pdm09 of 35.0% (95% CI: 11.1–52.4) in patients aged 65 years and older, although the majority of influenza A(H1N1)pdm09 circulating in Denmark in the 2015/16 season belonged to the new genetic subclade 6B.1. VE against influenza A(H1N1)pdm09 in the current season was similar to the VE against influenza A(H1N1)pdm09 in the 2014/15 season in Denmark of 31% (95% CI: −0.7 to 52.7) where 114 patients were positive for influenza A(H1N1)pdm09 and 3,351 patients tested negative (data not shown). This estimate also corresponds to the estimated VE of 22% (95% CI: −44.4 to 58.4) against influenza A(H1N1)pdm09 in the same age group in season 2014/15 reported by I-Move following a multicentre case–control study [15].

Conclusion

We estimated similar VE against influenza A(H1N1)pdm09 in season 2014/15 and 2015/16 in those aged 65 years and older in spite of the occurrence of the new subclade 6B.1. This is reassuring as the WHO recommendations for the influenza A(H1N1)pdm09 component in the 2016/17 vaccine for the northern hemisphere remained the same as in previous years, while the influenza B component changed from Yamagata to Victoria [16].

Acknowledgement

Test results for influenza virus were obtained from the Danish Microbiology Database (MiBa, http://miba.ssi.dk), which contains all electronic reports from departments of clinical microbiology in Denmark since 2010, and we acknowledge the collaboration with the MiBa Board of Representatives.

The authors gratefully acknowledge the 59 originating and submitting laboratories who contributed sequences used in the phylogenetic analysis to GISAID (www.gisaid.org).

We also acknowledge for the laboratory work, Dennis Jelsbak Schmidt and Bente Andersen, National Influenza Center Denmark, Statens Serum Institut, Copenhagen, Denmark.

Statens Serum Institut would also like to acknowledge the participation in the I-MOVE+ (Integrated Monitoring of Vaccines in Europe) project that has received funding from the European Union´s Horizon 2020 research and innovation programme under grant agreement Nº 634446.

Conflict of interest

None declared.

Authors' contributions

Hanne-Dorthe Emborg led the writing of the paper. Ramona Trebbien was responsible for the virological characterization and Jesper Rønn for the laboratory work. Lene Nielsen, Marianne Kragh Thomsen, Claus Bohn Christiansen, Marianne Nielsine Skov, Xiaohui Chen Nielsen and Lenette Sandborg Weinreich performed the initial diagnostics of influenza positive samples. Tyra Grove Krause and Thea Kølsen Fischer conceptualised the study together with Hanne-Dorthe Emborg and Ramona Trebbien and discussed

the data and perspectives. All authors provided contributions to the paper and approved the final version.

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Research article

Adverse events following school-based vaccination of girls with quadrivalent human papillomavirus vaccine in Slovenia, 2009 to 2013

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Citation style for this article:
Šubelj M, Učakar V, Kraigher A, Klavs I. Adverse events following school-based vaccination of girls with quadrivalent human papillomavirus vaccine in Slovenia, 2009 to 2013. Euro Surveill. 2016;21(14):pii=30187. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.14.30187

Article submitted on 04 April 2015 / accepted on 04 August 2015 / published on 07 April 2016

Adverse events following immunisation (AEFIs) with qHPV reported to the Slovenian AEFI Registry for the first four school years of the vaccination programme were analysed. We calculated annual reporting rates for 11–14 year-old vaccinees with AEFIs, using the number of qHPV doses distributed within the school-based vaccination programme as the denominator. Between September 2009 and August 2013, 211 AEFIs that occurred in 89 vaccinees were reported, a rate of 149.5 vaccinees with AEFI per 100,000 qHPV doses distributed. For five vaccinees, serious AEFIs (8.4 per 100,000 doses distributed) were reported. The highest reporting rates were for fatigue, headache, and fever (≥ 38.0°) (53.8, 40.3, and 35.3 per 100,000 qHPV doses distributed, respectively). As no AEFI resulted in permanent sequelae and they all were categorised as serious only due to the criterion of a minimum of one day of hospitalisation, this provides reassurance for the safety of our school-based HPV vaccination programme. Further AEFI surveillance is warranted to provide data for HPV vaccination programme monitoring and evaluation of its safety.

Introduction

Two vaccines against human papillomavirus (HPV) infection are currently licensed in Europe. In September 2006: the quadrivalent HPV vaccine (qHPV) (Silgard/Gardasil), containing virus-like particles (VLPs) of the recombinant major capsid L1 protein of HPV types 6, 11, 16 and 18, was licensed for the prevention of cervical, vaginal, and vulvar precancerous lesions, cervical cancer and genital warts (condyloma acuminata). The bivalent vaccine (Cervarix), containing VLP antigens for HPV types 16 and 18, was licensed for preventing precancerous cervical lesions and cervical cancer [1,2] in September 2007. In February 2015, the nine-valent HPV vaccine (Gardasil 9), containing four HPV VLPs that are in the qHPV (6, 11, 16, and 18) plus five additional HPV VLP types (31, 33, 45, 52, and 58), was recommended for approval in Europe for use in the prevention of cervical, vulvar, vaginal, and anal cancer, genital warts and precancerous lesions of the cervix, vulva, vagina, and anus [3]. Neither of the vaccines protect against HPV types for which the individual is already seropositive at the time of vaccination [4]. HPV vaccination programmes in 25 European countries are currently being conducted for adolescent girls with full or partial funding [5].

Within the Slovenian national immunisation programme, a three-dose intramuscular vaccination with single qHPV vaccine vials at 0, 2, and 6 months interval has been subsidised for adolescent girls aged 11–12 years since September 2009. The qHPV vaccination, financed through mandatory health insurance, was offered via the school-based vaccination programme, performed by school physicians. Vaccination coverage, measured as the ratio between the number of girls aged 11–12 years in the 6th grade who received all three doses of qHPV and the number of eligible girls in the 6th grade (birth cohort of ca 10,000 girls) as reported by school physicians, was 48.7% and 55.2% in school years 2009/10 and 2010/11, respectively. In order to increase the vaccination coverage, in September 2011, vaccination with qHPV has been offered also to girls aged 13–14 years, if they have not been vaccinated previously.

Pre-licensure clinical trials of qHPV showed that most adverse events following immunisation (AEFIs) with qHPV have been temporary and mild or moderate in intensity [6,7]. The most common AEFI was injection-related local reaction [8,9]. Fever, nausea, vomiting, dizziness, myalgia and diarrhoea were the most commonly reported systemic symptoms [8,10,11]. Severe

Table 1

Reporting rates of vaccinees with adverse events following immunisation, overall and serious, according to school year, school-based vaccination of girls aged 11–14 years with quadrivalent human papillomavirus vaccine, Slovenia, 1 September 2009 to 31 August 2013

School year	Number of qHPV doses distributed	All AEFI reports		AEFI reports with serious AEFI	
		Number[a]	Rate per 100,000 qHPV doses	Number[a]	Rate per 100,000 qHPV doses distributed
2009/10	14,601	20	137.0	1	6.8
2010/11	14,640	22	150.3	2	13.7
2011/12	15,945	19	119.2	0	0.0
2012/13	14,334	28	195.3	2	14.0

AEFI: adverse events following immunisation; qHPV: quadrivalent human papillomavirus vaccine.

[a] An individual with a single AEFI report may have more than one adverse event.

AEFIs, such as severe headache with hypertension and bronchospasm were described in 0.5% [8]. Pooled analyses of clinical trials involving almost 12,000 participants exposed to the qHPV vaccine did not identify an increased risk of chronic or autoimmune diseases overall [12]. However, these studies were not large enough to study individual conditions and that is why post-licensure monitoring of AEFIs using large population-based cohorts is necessary to develop evidence for overall safety assessment of any vaccine in order to ensure the safety of the vaccination programme and to maintain public confidence in the vaccine and its uptake [13-15].

In Slovenia, physicians are obliged to report all recognised AEFIs according to the Law governing the infectious diseases to the AEFI Registry at the National Institute of Public Health (NIPH).

Our objective was to summarise AEFIs with qHPV passive surveillance data for the first four years of the school–based vaccination programme targeting girls aged 11–14 years in order to evaluate the safety of our vaccination programme.

Methods

Design and study population

We conducted a retrospective observational study of all AEFIs reported to the AEFI Registry at the NIPH from September 2009 to August 2013 that were associated with qHPV vaccination of all Slovenian adolescent girls aged 11–14 years. AEFI was regarded as any untoward medical event temporally associated with vaccination (vaccine itself, its handling or its administration) regardless of whether causal association was suspected or not [16].

Because the AEFI Registry at the NIPH is a legally mandated surveillance system, institutional review board approval and informed consent were not required.

Data collection

We collected individual level information, using AEFI reporting forms, on AEFI predefined signs and/or symptoms such as injection site pain, erythema, oedema, fever (≥ 38 °C), fatigue, nausea, diarrhoea, headache, sleep disorders, maculopapular rash, anaphylaxis, meningitis, and any other signs, symptoms or laboratory results the reporting physician may think relevant. The forms also include information on the date of vaccination, time of AEFI occurrence, AEFI start/end date, treatment, outcome and possible sequelae, vaccinee (name, age, sex, address), the vaccine (brand name, batch number, manufacturer), date of report, and the reporting physician's identity. One of the authors (MS) coded all reported AEFIs according to the system organ class, using the Medical Dictionary for Regulatory Activities (MedDRA) used by the European Medicines Agency (EMA) and assessed reported AEFIs for seriousness using the World Health Organization (WHO) surveillance definitions [16,17].

Outcome definitions and ascertainment

Serious AEFI was defined as any untoward event that resulted in death, was life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or required intervention to prevent permanent impairment or damage. The single case causality assessment of all serious AEFIs was performed according to the new criteria published by WHO in 2013. Causality was categorised as consistent, indeterminate, inconsistent, and unclassifiable [16]. For causality assessment, additional clinical information was obtained on vaccination history (previous vaccination, prior AEFI), relevant medical and treatment history (e.g. underlying disease, known allergies, concomitant medication), and associated event(s) (e.g. exposure to environmental toxins). The timing of the onset of symptoms, consistency or plausibility of symptoms with the known pharmacology and toxicology of the qHPV, and whether or not an alternative trigger was present were all considered [18-20]. Finally, all serious AEFIs were

Table 2

Adverse effects following immunisation (symptoms and/or signs), school-based vaccination of girls aged 11–14 years with quadrivalent human papillomavirus vaccine, Slovenia, 1 September 2009 to 31 August 2013

AEFIs Symptoms and/or signs	Number	% of all AEFIs reported	Rate per 100,000 qHPV doses distributed
Malaise	32	15.2	53.8
Headache	24	11.4	40.3
Fever	21	10.0	35.3
Injection site pain	21	10.0	35.3
Injection site swelling	12	5.7	20.2
Injection site erythema	12	5.7	20.2
Fatigue	12	5.7	20.2
Sleep disorder	10	4.7	16.8
Dizziness	10	4.7	16.8
Syncope	8	3.8	13.4
Nausea	6	2.8	10.1
Rash	6	2.8	10.1
Abdominal pain	5	2.4	8.4
Pruritus	3	1.4	5.0
Face erythema	3	1.4	5.0
Pallor	2	0.9	3.4
Thrombocytopenia	2	0.9	3.4
Vomiting	2	0.9	3.4
Seizures	2	0.9	3.4
Diarrhoea	2	0.9	3.4
Cough	1	0.5	1.7
Facial contusion	1	0.5	1.7
Gilbert's syndrome worsening	1	0.5	1.7
Anaemia	1	0.5	1.7
Myalgia	1	0.5	1.7
Conjunctivitis	1	0.5	1.7
Chest discomfort	1	0.5	1.7
Tachycardia	1	0.5	1.7
Tremor	1	0.5	1.7
Migraine episode	1	0.5	1.7
Palm oedema	1	0.5	1.7
Injection site induration	1	0.5	1.7
Tonsillitis	1	0.5	1.7
Herpes zoster	1	0.5	1.7
Otitis externa	1	0.5	1.7
Ear pain	1	0.5	1.7
Total	**211**	**100.0**	**354.5**

AEFI: adverse effects following immunisation; qHPV: quadrivalent human papillomavirus vaccine.

assessed for unexpectedness. An unexpected /unusual AEFI was defined as any event that in its nature, severity, outcome, or frequency was not consistent with the AEFIs pre-specified in the summary of product characteristics for qHPV [16]. Reporting rates of vaccinees with AEFI (AEFI reports), using as the denominator the number of qHPV doses distributed to the school physicians conducting the vaccination programme for eligible girls provided by the vaccine supply division at the NIPH were calculated for the first four school–years after the qHPV vaccine was marketed.

Results

Between September 2009 and August 2013, the AEFI Registry at the NIPH received 89 reports of AEFIs with qHPV within vaccination programme, with a total of 211 AEFIs that occurred in girls aged 11–14 years. Overall, 59,520 qHPV doses were distributed. The overall reporting rate was 149.5 AEFI reports per 100,000 qHPV doses distributed and varied from the lowest 119.2 per 100,000 in the school year 2011/12 to the highest 195.3 per 100,000 in the school year 2012/13 (Table 1).

More than half of AEFIs (51.1%) occurred after the administration of the first qHPV dose, 27.3% after the second, and 21.6% after the third qHPV dose.

On average there were two adverse events per one AEFI report (range 1–5). Among all AEFI reports, 6.8% included only injection site reactions, 61.4% only systemic AEFIs, and 31.8% a combination of local and systemic AEFIs. Of the 211 AEFIs reported, all were completely resolved.

The most frequently reported AEFIs among 165 (78.2%) systemic events were malaise (15.2% of all AEFIs reported), followed by headache (11.4%) and fever (10.0%). Among 46 (21.8%) local events, injection site pain (10.0%) and swelling (5.7%) were the most frequently reported AEFIs (Table 2). Post-vaccination syncope, and seizures (associated with syncope), were reported in eight (9.1%) and two (2.3%) vaccinees, respectively.

According to system organ class classification of AEFIs with qHPV, general disorders and injection site reactions were the most frequent (68.7%), followed by nervous system disorders (10.4%) and gastrointestinal disorders (7.1%).

Five vaccinees had a serious adverse event, corresponding to the overall reporting rate of 8.4 per 100,000 qHPV doses distributed. Annual reporting rates of serious adverse events varied from 0 to 14.0 per 100,000 qHPV doses distributed (Table 3). All vaccinees with serious AEFI were hospitalised for 1–3 days, and all of them stayed in hospital only for observation, thus fulfilling one of the criteria for serious AEFIs (Table 3). One of the serious AEFIs, a severe headache preceded by blurred vision that was diagnosed as migraine episode by the attending physician,

Table 3

Serious adverse events following immunisation, school-based vaccination of 11–14 year-old girls with quadrivalent human papillomavirus vaccine, Slovenia, 1 September 2009 to 31 August 2013 (n=5)

School year	Age (years)	AEFI following dose number [a]	Time to onset of AEFI after vaccination	AEFI symptoms and/or signs	Hospitalisation (days)	Expected AEFI	Causality assessment [b]
2009/10	11	2	0 min	Seizures, syncope	1	Yes	Consistent
2010/11	11	1	Several minutes	Nausea, fatigue, headache, pallor, palm oedema, tonsillitis[c]	1	Yes	Consistent
2010/11	11	3	Several hours	Migraine episode	3	No	Indeterminate
2012/13	11	1	45 min	Nausea, fatigue, somnolence, dizziness	1	Yes	Consistent
2012/14	11	1	5 min	Syncope	1	Yes	Consistent

AEFI: adverse effects following immunisation; min: minutes; qHPV: quadrivalent human papillomavirus vaccine.

[a] Recommended schedule is a three 0.5 mL dose series with second and third doses administered 2 and 6 months after the first dose.

[b] The single-case causality assessment according to the World Health Organization criteria (consistent, indeterminate, inconsistent, and unclassifiable).

[c] Tonsillitis was also reported but with no temporal relation to a vaccination (onset 3 days before vaccination).

was classified as unexpected/unusual, since migraine is not listed among expected AEFIs with qHPV. This AEFI was classified as adverse event with indeterminate causal relation with qHPV. In the remaining four vaccinees, serious adverse events were classified as expected and to be consistently causally related to vaccination with qHPV.

Discussion

In the first four school years after the school-based qHPV vaccination of 11–14 year-old girls in Slovenia, nearly 57,000 qHPV doses were distributed. Although the observed overall reporting rate of AEFIs with qHPV was relatively high, the proportion of reported serious AEFIs was similar to those from other passive AEFI surveillance systems. All AEFIs categorised as serious (only due to the criterion of hospitalisation for at least one day) were transient and resolved completely 1–3 days after receiving a vaccine. No cases of anaphylaxis and autoimmune disorders were reported. Among the reported AEFIs, we observed few cases of syncope that were occasionally accompanied by a brief seizure-like event, relatively frequent headaches and fever, in contrast to relatively few injection-site conditions. A migraine episode was recorded, an unexpected AEFI with qHPV.

The relatively high overall reporting rate of individuals with AEFIs (149.5 per 100,000 qHPV doses distributed) during the first four years of the Slovenian school–based vaccination programme in comparison to overall reporting rates published by the Vaccine Adverse Event Reporting System (VAERS) in the United States of America (US), from June 2006 to December 2008; Ontario's female school-based HPV programme, Canada, from September 2007 to December 2011; and the Pharmacovigilance Centre in the Valencian Community, Spain, from September 2007 to December 2011 of 53.9 per 100,000, 19.2 per 100,000, and 103 per 100,000, respectively, might at least in part be explained by the fact that in Slovenia, AEFIs are mandatorily reportable by all physicians, while in the above-mentioned countries the reporting of AEFIs is voluntary [20-22].

The reporting rate of serious AEFIs per 100,000 doses distributed in Slovenia was higher in comparison to the reporting rates from the US and Canada (8.4 vs 3.3 and 1.5, respectively) [20,21]. The lack of serious reports with sequelae, which are usually very rare, may simply be related to the relatively low absolute exposure.

Syncope, which may be considered a procedure- or anxiety-related AEFI, was reported at similar reporting rates of ca 8–10 per 100,000 vaccine doses distributed as reported from the US, and Australia, but at a somewhat lower rate in comparison to the reporting rate from Spain (13.4 vs 17 per 100,000 qHPV doses distributed) [22-26].

Brief seizure-like events that can accompany syncopal episodes, secondary to transient hypoxia, with stiffening (tonic) movements and autonomic instability after vaccination with qHPV have been reported previously through VAERS and described in international case reports [25,27]. Reporting rate of seizures accompanying syncope after vaccination with qHPV in Slovenia was similar to the rates reported from Spain and Australia (3.4 vs 3.2 and 2.6 per 100,000 qHPV doses distributed, respectively) [22,25]. However, monitoring of qHPV occurred between 2006 and 2009, during which a total of 600,558 doses were administered in the Vaccine Safety Database (VSD) population, and no association between qHPV and seizures, whether recurrent or new onset was observed [14].

A relatively higher reporting rate of headache was reported in Slovenia in comparison to the US and Spain (40.3 per 100,000 qHPV doses distributed vs 4.1 and 23.5, respectively), and relatively higher reporting rate of fever in comparison to the US (35.3 vs 0.4 per 100,000 qHPV doses distributed) [20,22,27]. In contrast, although local reactions are usually frequently reported AEFIs with qHPV that are generally of short duration and resolve spontaneously, in our analyses only one fifth of reports with AEFIs with qHPV involved local reactions, mainly pain and swelling [28]. Varying frequencies may be due to a presumably much lower probability that a vaccinee with mild AEFIs seeks medical care and the fact that in Slovenia AEFIs are reportable only by physicians.

With respect to the unexpected/unusual AEFI after the vaccination with qHPV, a migraine episode possibly related to qHPV, migraine has, to the best of our knowledge, been so far reported as a possible AEFI only after the vaccination with the Ann Arbor strain live–attenuated influenza vaccine [29]. Moreover, it is well recognised that reporting of neuropathic pain syndromes such as migraine headaches as an AEFI with its uncertain aetiology and/or pathogenesis can be expected when a new vaccine is introduced into a population [28,30].

The major limitation of our passive surveillance system is that it can only identify early warning signals, and can neither estimate the risk relative to an unexposed population nor exclude risks with certainty [13]. Since the vast majority of vaccinees with mild AEFIs are not likely to seek medical care and AEFIs are reportable only by physicians, under-reporting of non-serious adverse events is expected [31]. The under-reporting of certain AEFIs in our surveillance system in comparison to the results from clinical trials is to be expected, as in our system only AEFIs presented to physicians are reported, in comparison to the clinical trials which report on the entire study population. The frequencies observed in the clinical trial programme of qHPV were highest for injection-related local reactions, but the systemic AEFIs, such as headache, were observed in only 0.5% in comparison to our results, where the most commonly reported AEFIs were systemic (malaise and headache) [8,9].

Generally, AEFI rates calculated using as the denominator the number of qHPV doses distributed to the school physicians conducting the vaccination programme for grade 6 and grade 8 girls need to be interpreted with caution, since vaccine distribution data do not provide accurate information about the numbers of vaccine doses actually administered [21]. However, we believe that the qHPV distribution data are a fairly good approximation of the number of qHPV doses actually administered, since the Unit for vaccine distribution at the NIPH issues qHPV vaccine to the school physicians in response to actual usage. Because only serious AEFIs were reported to the EudraVigilance database by EMA and due to resource constraints in Slovenia, causality assessment was performed only for serious AEFIs. Moreover, we have applied no specific case definitions for AEFIs. In parts of the US there is also the Vaccine Safety Datalink project, where vaccine registers are linked with data from, for example, VAERS and evaluations of safety concerns are made [31]. Data on notification rates for other vaccines for which there are solid estimates of rates of AEFIs in the literature allow us to be reassured about the satisfactory level of exhaustiveness of our passive vaccine-vigilance surveillance. Thus, in the period 2005–2014, the reporting rate of vaccine-related thrombocytopenia after the administration of measles-mumps-rubella (MMR) vaccine reported to our surveillance system was 2.5 per 100,000 doses of MMR vaccine distributed. Our findings correspond with the results from the study done in the US where MMR vaccine caused 2.5 cases of immune thrombocytopenia per 100,000 doses distributed [32]. However, linkage of hospital data to vaccine data is not possible in Slovenia as there is no vaccination registry. A capture–recapture study is also not possible as there is no alternative system for recording AEFIs. However, our passive AEFI surveillance system has the important strength of being universal and covers the whole target population [31].

Conclusions

Although our reporting rate of serious AEFIs was relatively high, none of the serious AEFIs resulted in any residual disability or incapacity. In fact, all serious AEFIs were categorised as such only due to the criterion of hospitalisation for at least one day, were transient and resolved 1–3 days after exposure to qHPV vaccine. Further post-licensure AEFI surveillance is necessary for continuous provision of reassurance for qHPV safety and to maintain confidence in the HPV vaccination programme.

Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

All authors made contributions to conception and design of the manuscript. MS contributed to acquisition of data and their analysis and interpretation. All authors participated in drafting the article and revising it critically for intellectual content, and gave final approval of the version to be submitted.

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Research article

Direct, indirect and total effects of 13-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in children in Navarra, Spain, 2001 to 2014: cohort and case–control study

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Citation style for this article:
Guevara M, Barricarte A, Torroba L, Herranz M, Gil-Setas A, Gil F, Bernaola E, Ezpeleta C, Castilla J, Working Group for Surveillance of the Pneumococcal Invasive Disease in Navarra. Direct, indirect and total effects of 13-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in children in Navarra, Spain, 2001 to 2014: cohort and case–control study. Euro Surveill. 2016;21(14):pii=30186. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.14.30186

Article submitted on 11 March 2015 / accepted on 07 October 2015 / published on 07 April 2016

We estimated the direct, indirect and total effects of the 13-valent pneumococcal conjugate vaccine (PCV13) on invasive pneumococcal disease (IPD) in children. A population-based cohort study followed children aged between 2.5 and 59 months between 2001 and 2014 in Navarra, Spain. IPD incidence was compared by PCV status and period. All cases diagnosed from July 2010 to December 2014 and eight matched controls per case were analysed to estimate the adjusted direct effect of PCV13. A total of 120,980 children were followed and 206 IPD cases were detected. Compared with unvaccinated children in the baseline period (2001–2004), overall IPD incidence in 2011–2014 (76% average PCV coverage) declined equally in vaccinated (total effect: 76%; hazard ratio (HR): 0.24; 95% confidence interval (CI): 0.14–0.40) and unvaccinated children (indirect effect: 78%; HR: 0.22; 95% CI: 0.09–0.55). IPD incidence from non-PCV13 serotypes increased among vaccinated children (HR: 2.84; 95% CI: 1.02–7.88). The direct effect of one or more doses of PCV13 against vaccine serotypes was 95% (odds ratio: 0.05; 95% CI: 0.01–0.55). PCV13 was highly effective in preventing vaccine-serotype IPD. The results suggest substantial and similar population-level vaccine benefits in vaccinated and unvaccinated children through strong total and indirect effects.

Introduction

The 7-valent pneumococcal conjugate vaccine (PCV7) has proved highly effective in preventing invasive pneumococcal disease (IPD) caused by the serotypes included in its formulation [1,2]. However, its impact has varied across countries due to factors that may include differences in serotype distribution, vaccination coverage and characteristics of vaccination programmes [3,4]. New, higher valency pneumococcal conjugate vaccines (PCVs) containing 10 (PCV10) and 13 (PCV13) serotypes were licensed on the basis of non-inferiority of immunogenicity compared with PCV7 [5]; thus, post-licensure studies are required to assess their effects under real-life conditions.

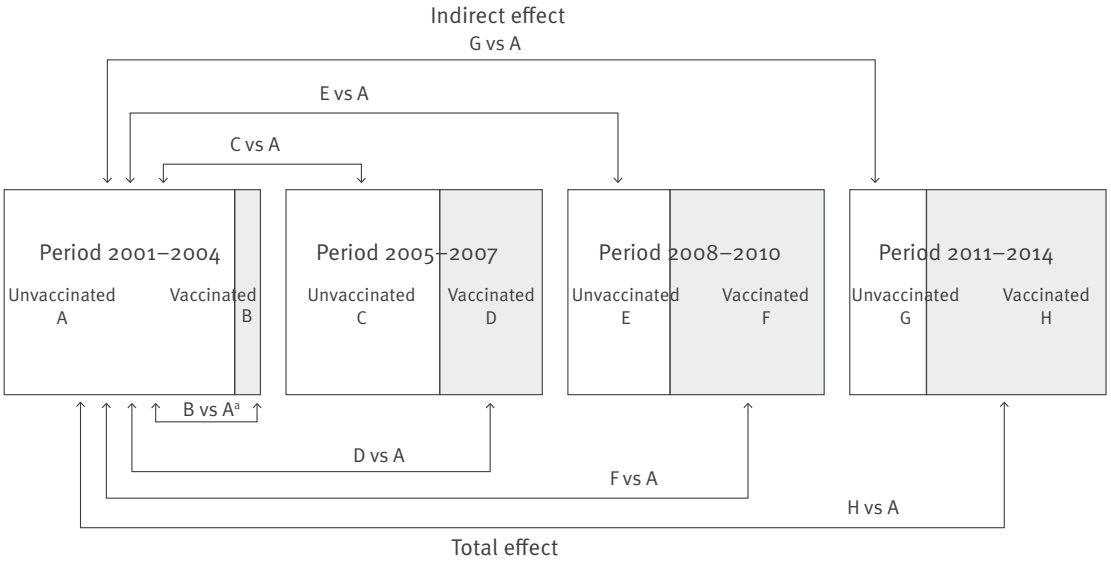
To date (June 2015), there are few studies published on the direct effect of PCV13 against IPD, and all except one have used the indirect cohort method and have hence been limited to evaluating it against vaccine serotypes rather than total IPD [6-8]. PCVs can also reduce IPD incidence among unvaccinated individuals as a result of reduced transmission. This indirect or 'herd' effect has been studied in unvaccinated age groups [9-12], but not in children targeted for vaccination. The total effect accounts for both the direct and indirect effects on vaccinated individuals [13,14].

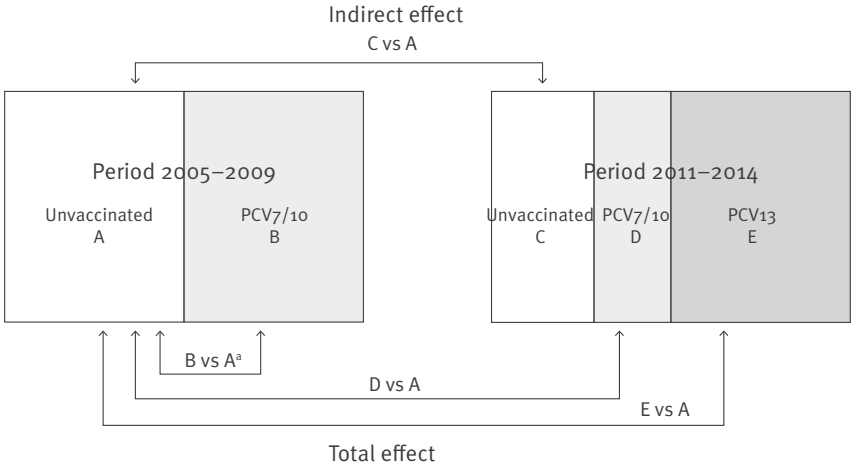
In Navarra, Spain, PCVs became available for private purchase in June 2001 (PCV7), November 2009 (PCV10) and June 2010 (PCV13), and are publicly funded only for children with selected IPD risk factors, including cardiovascular, respiratory, neurological, renal or hepatic disease, diabetes, cancer, immunosuppression, HIV infection, haemoglobinopathy, and cerebrospinal fluid leak [15]. The Spanish Association of Paediatrics recommends PCV for all children younger than 5 years [16], and coverage has increased progressively through

Figure

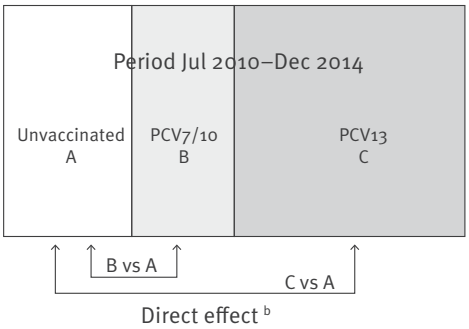
Scheme of the main study groups and the comparisons made, cohort and case–control study, effects of pneumococcal conjugate vaccination on invasive pneumococcal disease in children, Navarra, Spain, 2001–2014

Cohort study





Case–control study



PCV: pneumococcal conjugate vaccine.

a B vs A in the cohort study is the direct effect in the baseline period.

b The direct effect in the case–control study is estimated by the odds ratio of vaccination vs non-vaccination in cases compared with controls.

Table 1

Incidence of invasive pneumococcal disease in children younger than 5 years and younger than 2 years by conjugate pneumococcal vaccine status and period, Navarra, Spain, 2001–2014

Age	Period	Unvaccinated with PCV			Vaccinated with PCV			Total		
		Number of cases	PY	Incidence rate per 100,000 PY	Number of cases	PY	Incidence rate per 100,000 PY	Number of cases	PY	Incidence rate per 100,000 PY
75 days to 59 months	2001–2004	77	102,845	75	10	13,162	76	87	116,007	75
	2005–2007	27	47,597	57	33	43,232	76	60	90,829	66
	2008–2010	13	32,025	41	23	61,310	38	36	93,335	39
	2011–2014	5	30,482	16	18	94,454	19	23	124,937	18
75 days to 23 months	2001–2004	51	34,626	147	9	7,014	128	60	41,640	144
	2005–2007	18	14,331	126	18	17,805	101	36	32,136	112
	2008–2010	8	10,700	75	11	22,697	48	19	33,397	57
	2011–2014	3	9,872	30	13	34,731	37	16	44,603	36

PCV: pneumococcal conjugate vaccine; PY: person-years.
Culture-negative cases were excluded (n = 0, 2, 6 and 5 in each period, respectively).

the private market, reaching 78% in children up to 23 months of age in 2013 [17]. Most of the vaccinated children have received a complete 3+1 schedule, with doses at 2, 4 and 6 months plus a booster dose at 12–15 months. Since 2010, PCV13 has been the predominant PCV in use. After the change from PCV7 to PCV13, IPD incidence from all serotypes decreased by 69%, from 60.7 to 18.7 cases/100,000 inhabitants, in children younger than 5 years [17], in line with what has been observed in other countries [10,11,18-21].

The aim of this study was to estimate the effect of PCV13 on IPD incidence in vaccinated (direct and total effects) and unvaccinated (indirect effect) children younger than 5 years.

Methods

Study design

A population-based cohort study with follow-up during 2001–2014, and a nested case–control study from July 2010 to December 2014 were conducted in Navarra, a region with ca 640,000 inhabitants, including ca 34,700 aged less than 5 years, in 2014 [22]. The Navarra Ethical Committee for Medical Research approved the study protocol.

Sources of information and variables

The Navarra Health Service provides healthcare, free at point of service, to 97% of the inhabitants of the region. Clinical records have been computerised since 2000 and include reports from primary care, hospital admissions, the regional vaccination register, and laboratory test results.

Vaccination history was obtained from the regional vaccination register [23], which includes all doses received by children, including those acquired in the private market. Vaccine doses were counted starting 15 days after their administration and the 14 days after receiving the first dose were not considered for the analysis. Cases of IPD were identified through the active laboratory-based surveillance. IPD was defined as isolation, PCR or antigen detection of *Streptococcus pneumoniae* from a normally sterile body site. Pneumococcal isolates were serotyped at the national reference laboratory (Instituto de Salud Carlos III, Madrid) by the Quellung reaction or dot-blot assay, and were classified as PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F), additional PCV13 serotypes (1, 3, 5, 6A, 7F, 19A), or non-PCV13 serotypes.

Cohort study to evaluate the indirect and total vaccine effects

The cohort included children covered by the Navarra Health Service from birth to their fifth birthday, the end of the follow-up on 31 December 2014 or date of death, whichever occurred first. Cox regression was performed to obtain hazard ratios (HR) with their 95% confidence intervals (CI). Age in days was used as the underlying time scale, with entry time defined as age at 1 January 2001 or 75 days of age if it was later, and exit time as 59 months of age, age at IPD diagnosis or death, or at 31 December 2014, whichever occurred first. Calendar periods and PCV status were defined as time-dependent variables. Person-years (PY) at risk were used as the denominators of the IPD incidence rates. Since a culture was taken from all suspected cases and PCR and antigen detection were progressively introduced as complementary tests, culture-negative cases (n = 13) were excluded to maintain comparability between the periods.

To evaluate the indirect and total effects of the PCVs with respect to the pre-vaccine situation, we considered four periods according to PCV use and coverage in children younger than 5 years: the baseline period (2001–2004) during which PCV7 use was low; the

Table 2

Estimates of the indirect and total effects of the pneumococcal conjugate vaccines, with unvaccinated children younger than 5 years in the period with low use of pneumococcal conjugate vaccine (2001–2004) as reference category, Navarra, Spain, 2001–2014

Serotypes	Period	Unvaccinated with PCV (indirect effect)[a]			Vaccinated with PCV (total effect)[a]		
		Number of cases	Hazard ratio (95% CI)	p value	Number of cases	Hazard ratio (95% CI)	p value
All serotypes	2001–2004	77	Reference		10	0.77 (0.40–1.49)	0.430
	2005–2007	27	0.80 (0.52–1.30)	0.317	33	0.90 (0.60–1.35)	0.589
	2008–2010	13	0.55 (0.30–0.98)	0.044	23	0.47 (0.29–0.74)	0.001
	2011–2014	5	0.22 (0.09–0.55)	0.001	18	0.24 (0.14–0.40)	<0.001
PCV7 serotypes[b]	2001–2004	36	Reference		1	0.15 (0.02–1.08)	0.058
	2005–2007	4	0.26 (0.09–0.73)	0.011	0	0 (0.00–UD)	<0.001[c]
	2008–2010	1	0.09 (0.01–0.66)	0.018	0	0 (0.00–UD)	<0.001[c]
	2011–2014	1	0.10 (0.01–0.70)	0.021	0	0 (0.00–UD)	<0.001[c]
Additional PCV13 serotypes[b]	2001–2004	34	Reference		6	1.08 (0.45–2.57)	0.872
	2005–2007	15	1.00 (0.54–1.83)	0.987	22	1.37 (0.80–2.35)	0.251
	2008–2010	9	0.86 (0.41–1.79)	0.679	17	0.79 (0.44–1.41)	0.418
	2011–2014	4	0.40 (0.14–1.14)	0.085	3	0.09 (0.03–0.30)	<0.001
Non-PCV13 serotypes[b]	2001–2004	5	Reference		3	3.43 (0.82–14.42)	0.092
	2005–2007	4	1.85 (0.50–6.90)	0.358	9	3.66 (1.23–10.94)	0.020
	2008–2010	3	1.94 (0.46–8.10)	0.366	6	1.84 (0.56–6.04)	0.313
	2011–2014	0	0 (0.00– UD)	0.273[c]	14	2.84 (1.02–7.88)	0.045

CI: confidence interval; PCV: pneumococcal conjugate vaccine; UD: undefined.

[a] Cox regression adjusted for age as underlying time scale, sex and a variable that combines time periods and vaccination status.

[b] Non-typed cases were excluded from analyses by serotype group (n = 2, 6, 0 and 1 in each period, respectively).

[c] p value obtained by the two-tailed mid-p exact test without specific correction.

period of increased PCV7 coverage (2005–2007); the period of high PCV7 coverage and transition to higher valency PCVs (2008–2010); and the period of PCV13 use (2011–2014). Children were considered as vaccinated if they had received at least one dose of PCV. The cohort analysis used a variable that combines time periods and vaccination status, while also adjusting for sex.

In another cohort analysis we evaluated the specific effect of the change from PCV7 to PCV13, considering two periods: 2005–2009, or the period of PCV7 use; and 2011–2014, or the period of PCV13 use. Three exclusive categories of vaccination status were defined in the following order: at least one dose of PCV13, at least one dose of PCV7 or PCV10, and no dose of PCV. The year 2010 was excluded from this analysis because this was a transition year with appreciable use of PCV7, PCV10 and PCV13.

The incidence of IPD in unvaccinated children during the baseline period was used as the reference to estimate the indirect effect by comparison with the IPD incidence in unvaccinated children in each PCV period, and to estimate the total effect by comparison with the incidence in vaccinated children in each PCV period (Figure) [13,14]. Where zero cases were observed in one group, the p value was obtained by the two-tailed mid-p exact test.

Case–control study to evaluate the direct vaccine effect

A case–control study, nested within the cohort, included as case patients all children born since June 2008 (as they might have received at least one dose of PCV13) and who were diagnosed with IPD by culture, PCR or antigen detection between July 2010 and December 2014. For each case, eight controls were selected from children with no previous IPD, individually matched by

Table 3

Estimates of the indirect and total effects of the pneumococcal conjugate vaccines, with unvaccinated children in the period 2005–2009 (period of use of 7-valent pneumococcal conjugate vaccine) as reference category, Navarra, Spain, 2005–2014

	Number of cases	Person-years	Hazard ratio (95% CI)[a]	p value
All serotypes				
Period 2005–2009, unvaccinated	37	69,667	Reference	
Period 2005–2009, vaccinated with PCV7/10	52	82,667	1.03 (0.67–1.58)	0.889
Period 2011–2014, unvaccinated (indirect effect)	5	30,482	0.30 (0.12–0.77)	0.012
Period 2011–2014, vaccinated with PCV7/10 (total effect)	1	29,976	0.09 (0.01–0.65)	0.017
Period 2011–2014, vaccinated with PCV13 (total effect)	17	64,376	0.39 (0.22–0.70)	0.002
PCV13 serotypes[b]				
Period 2005–2009, unvaccinated	27	69,667	Reference	
Period 2005–2009, vaccinated with PCV7/10	36	82,667	0.92 (0.58–1.46)	0.714
Period 2011–2014, unvaccinated (indirect effect)	5	30,482	0.42 (0.16–1.08)	0.071
Period 2011–2014, vaccinated with PCV7/10 (total effect)	0	29,976	0 (0.00–UD)	<0.001[c]
Period 2011–2014, vaccinated with PCV13 (total effect)	3	64,376	0.10 (0.03–0.32)	<0.001
Non-PCV13 serotypes[b]				
Period 2005–2009, unvaccinated	6	69,667	Reference	
Period 2005–2009, vaccinated with PCV7/10	14	82,667	1.63 (0.62–4.24)	0.321
Period 2011–2014, unvaccinated (indirect effect)	0	30,482	0 (0.00–UD)	0.113[c]
Period 2011–2014, vaccinated with PCV7/10 (total effect)	1	29,976	0.69 (0.08–5.94)	0.737
Period 2011–2014, vaccinated with PCV13 (total effect)	13	64,376	1.67 (0.63–4.43)	0.305

CI: confidence interval; NA: not applicable; PCV: pneumococcal conjugate vaccine; UD: undefined.
[a] Cox regression adjusted for age as underlying time scale, sex and a variable that combines time periods and vaccination status.
[b] Non-typed cases were excluded from analyses by serotype group (n = 6 and 1 in each period, respectively).
[c] p value obtained by the two-tailed mid-p exact test without specific correction.

paediatric practice, district of residence and date of birth (±2 months). Of all the children who met these eligibility criteria, the eight with dates of birth closest to that of the case were selected. Previous inclusion of a twin was an exclusion criterion.

Healthcare computerised databases were used to obtain the sex, date of birth, paediatrician, district of residence, premature birth (<37 weeks' gestation), low birth weight (<2,500 g), major chronic illness (defined as cardiovascular, respiratory, neurological, renal or hepatic disease, diabetes, immunosuppression or cancer), primary care visits in the previous 12 months, other children younger than 5 years in the household, and parental income level (<EUR 18,000 and ≥EUR 18,000/year).

The reference date for cases was the date of symptom onset, and for controls, the date on which their age exactly matched the age in days of their corresponding case at the time of symptom onset. Different categorisations of PCV status were used to analyse the effect of either PCV13 including mixed schedules or PCV13-only schedules, with or without distinction of the number of doses received. Vaccination with PCV7 or PCV10 without PCV13, and non-PCV vaccination were assigned to two separate categories.

In different analyses we evaluated the effect of receiving PCV13 on the risk of IPD due to all serotypes, to PCV13 serotypes, to additional PCV13 serotypes and to non-PCV13 serotypes, using non-PCV vaccination as the reference. A sensitivity analysis was performed excluding children with any medical condition. Adjusted matched odds ratios (OR), with their 95% CI, were calculated using conditional logistic regression. We assessed for confounding by including additional variables one by one in the model. Covariates were removed if they did not change the OR by at least 15%. Vaccine effects were calculated as (1 – HR) x 100 or (1 – OR) x 100. Two-tailed p values<0.05 were considered to be statistically significant.

Results

Evaluation of the indirect and total vaccine effects

Between 2001 and 2014, 120,980 children were followed. In the periods 2001–2004, 2005–2007, 2008–2010 and 2011–2014, we registered 116,007 PY, 90,829 PY, 93,335 PY and 124,937 PY of follow-up, of which 11%, 48%, 66% and 76%, respectively, corresponded to children who had received at least one dose of PCV. Considering the PCV with the highest valency received, in the period 2011–2014, 52% of PY corresponded to children with at least one dose of PCV13, 6% of PCV10 and 18% of PCV7. During the follow-up, 206 cases of

Table 4

Characteristics of cases and controls included in the case–control study of the direct effect of pneumococcal conjugate vaccination on invasive pneumococcal disease in children, Navarra, Spain, July 2010–December 2014

	Cases n = 34	Controls n = 272	p value (matched)
Demographics			
Median age in months (range)	18.9 (3.4–57.7)	18.9 (3.4–57.7)	NA
Male sex	24 (71%)	139 (51%)	0.037
Resides in urban area	23 (68%)	184 (68%)	1.000
Number of other persons in household			
1–2	7 (21%)	73 (27%)	0.476
3	12 (35%)	107 (39%)	
≥4	15 (44%)	92 (34%)	
Other children younger than 5 years in household	16 (47%)	102 (38%)	0.282
Parental income level			
< EUR 18,000/year	19 (56%)	148 (54%)	0.868
≥ EUR 18,000/year	15 (44%)	124 (46%)	
Primary care visits in the previous year			
0–2	6 (18%)	58 (21%)	0.309
3–7	17 (50%)	100 (37%)	
≥8	11 (32%)	114 (42%)	
Medical conditions			
Major chronic illness [a]	1 (3%)	7 (3%)	0.899
Premature birth or low birth weight	2 (6%)	11 (4%)	0.626
Any underlying medical condition [b]	3 (9%)	15 (6%)	0.451
Vaccination history			
Meningococcal C conjugate vaccine	34 (100%)	272 (100%)	1.000
23-valent pneumococcal polysaccharide vaccine	0 (0%)	0 (0%)	1.000
At least one dose of any PCV	27 (79%)	217 (80%)	0.957
At least three doses of any PCV	19 (56%)	164 (60%)	0.552
Highest valency PCV received			
No PCV vaccination	7 (21%)	55 (20%)	0.955
PCV7	2 (6%)	12 (4%)	
PCV10	1 (3%)	7 (3%)	
PCV13	24 (71%)	198 (73%)	

PCV: pneumococcal conjugate vaccine; NA: not applicable.

[a] Defined as cardiovascular, respiratory, neurological, renal or hepatic disease, diabetes, immunosuppression or cancer.

[b] Defined as major chronic illness, premature birth (< 37 weeks' gestation), or low birthweight (< 2,500 g).

IPD were registered, 84 of them in children who had received at least one dose of PCV. The IPD incidence rates decreased over the four periods: from 75 to 66, 39 and 18 per 100,000 PY, respectively (Table 1).

In the reference group, unvaccinated children in the period 2001–2004, 48% (36/75) of the serotyped cases were due to PCV7 serotypes and 93% (70/75) to PCV13 serotypes. We observed an increasing indirect effect of the PCVs in preventing IPD from all serotypes in unvaccinated children, which reached 45% (HR: 0.55; 95% CI: 0.30–0.98) in 2008–2010 and 78% (HR: 0.22; 95% CI: 0.09–0.55) in 2011–2014. This indirect effect was similar to the total (direct and indirect) protective effect in vaccinated children, which reached 53% (HR: 0.47; 95% CI: 0.29–0.74) in 2008–2010 and 76% (HR: 0.24; 95% CI: 0.14–0.40) in 2011–2014 (Table 2).

The PCV effect in preventing IPD due to PCV7 serotypes was earlier and more pronounced in vaccinated than in unvaccinated children, with only one vaccine failure in the period 2001–2004, and 100% total effect from 2005 to 2014. Unvaccinated children showed an important indirect effect of 74% (HR: 0.26; 95% CI: 0.09–0.73) in the period 2005–2007 and 90% (HR: 0.10; 95% CI: 0.01–0.70) in 2011–2014. In the latter period the total effect against IPD due to additional PCV13 serotypes was 91% (HR: 0.09; 95% CI: 0.03–0.30). The incidence of IPD due to non-PCV13 serotypes in vaccinated children in the period 2011–2014 was higher than in the

Table 5

Estimates of the direct effect of the 13-valent pneumococcal conjugate vaccine and other pneumococcal conjugate vaccines in the case–control study, Navarra, Spain, July 2010–December 2014

Invasive pneumococcal disease serotypes	Cases	Controls	Crude effect[a]		Adjusted effect[b]	
	Vac./ Unvac.	Vac./ Unvac.	OR (95% CI)	p value	OR (95% CI)	p value
All serotypes						
≥1 dose PCV7/10, no PCV13	3/7	19/55	1.35 (0.28–6.42)	0.708	1.28 (0.25–6.52)	0.766
≥1 dose PCV13 (including mix)	24/7	198/55	0.90 (0.33–2.41)	0.828	0.91 (0.33–2.49)	0.848
≥1 dose PCV13 only	21/7	174/55	0.85 (0.29–2.50)	0.770	0.86 (0.29–2.56)	0.788
≥3 doses PCV13	14/7	123/55	0.75 (0.24–2.36)	0.622	0.75 (0.23–2.42)	0.629
≥1 dose PCV13, excluding children with any medical condition [c]	21/7	186/52	0.82 (0.31–2.21)	0.703	0.82 (0.30–2.24)	0.697
PCV13 serotypes						
≥1 dose PCV7/10, no PCV13	1/6	14/19	0.33 (0.03–3.27)	0.341	0.09 (0.01–1.66)	0.106
≥1 dose PCV13 (including mix)	3/6	47/19	0.15 (0.03–0.85)	0.032	0.05 (0.01–0.55)	0.014
≥1 dose PCV13 only	2/6	40/19	0.08 (0.01–0.76)	0.028	0.04 (0.00–0.57)	0.018
≥3 doses PCV13	2/6	35/19	0.10 (0.01–0.96)	0.046	0.04 (0.00–0.61)	0.021
≥1 dose PCV13, excluding children with any medical condition [c]	3/6	44/19	0.16 (0.03–0.90)	0.037	0.06 (0.01–0.58)	0.015
Additional PCV13 serotypes						
≥1 dose PCV7/10, no PCV13	1/5	11/14	0.41 (0.04–4.54)	0.466	0.13 (0.01–2.45)	0.174
≥1 dose PCV13 (including mix)	3/5	47/14	0.15 (0.03–0.86)	0.033	0.07 (0.01–0.70)	0.023
≥1 dose PCV13 only	2/5	40/14	0.08 (0.01–0.77)	0.029	0.05 (0.00–0.70)	0.027
≥3 doses PCV13	2/5	35/14	0.10 (0.01–0.97)	0.047	0.05 (0.00–0.76)	0.031
≥1 dose PCV13, excluding children with any medical condition [c]	3/5	44/14	0.16 (0.03–0.91)	0.039	0.08 (0.01–0.73)	0.026
Non-PCV13 serotypes						
≥1 dose PCV7/10, no PCV13	1/1	5/31	5.94 (0.32–111.11)	0.233	7.66 (0.38–154.19)	0.184
≥1 dose PCV13 (including mix)	18/1	124/31	5.44 (0.64–46.17)	0.121	6.75 (0.77–59.19)	0.085
≥1 dose PCV13 only	16/1	114/31	5.03 (0.50–50.33)	0.169	5.70 (0.59–55.23)	0.133
≥3 doses PCV13	9/1	69/31	4.48 (0.40–50.06)	0.223	5.08 (0.43–59.53)	0.196
≥1 dose PCV13, excluding children with any medical condition [c]	16/1	117/28	4.41 (0.52–37.18)	0.173	5.51 (0.64–47.19)	0.120

CI: confidence interval; Mix: schedules consisting of PCV13 and another PCV; OR: matched odds ratio with unvaccinated children as the reference group; PCV: pneumococcal conjugate vaccine; Unvac: unvaccinated (children with zero doses of any PCV); Vac: vaccinated.

[a] Conditional logistic regression.

[b] Conditional logistic regression adjusted for sex and parental income level.

[c] Any medical condition was defined as major chronic illness (cardiovascular, respiratory, neurological, renal or hepatic disease, diabetes, immunosuppression or cancer), premature birth (<37 weeks' gestation), or low birthweight (<2,500 g).

reference group (HR: 2.84; 95% CI: 1.02–7.88) (Table 2).

Taking the period of PCV7 use (2005–2009) as the reference, we evaluated the effect of PCV13 in 2011–2014, obtaining an estimate of the indirect protective effect in unvaccinated children of 70% (HR: 0.30; 95% CI: 0.12–0.77) and a total effect in children with PCV13 of 61% (HR: 0.39; 95% CI: 0.22–0.70) against all-serotype IPD. In a similar analysis limited to IPD cases from PCV13 serotypes, the total effect was 90% (HR: 0.10; 95% CI: 0.03–0.32) (Table 3).

Evaluation of the direct vaccine effect

Between July 2010 and December 2014, 34 cases of IPD were included in the case–control study. The median age was 18.9 months (range 3.4–57.7 months). Clinical presentations were bacteraemia (17 cases), pneumonia (14 cases) and meningitis (three cases). In 30 cases the serotype was available: 10 cases were caused by PCV13 serotypes and 20 cases by non-PCV13 serotypes. There were two vaccine failures due to serotype 3 in immunocompetent children who had received four doses of PCV13. Additionally, there was one case due to serotype 19A (a PCV13-only serotype) in a child who had received three doses of PCV10 and a booster dose of PCV13. All but one of the seven cases in unvaccinated children were due to PCV13 serotypes, while most of the cases in vaccinated children (18 of 21) were caused by non-PCV13 serotypes.

The 34 cases and 272 matched controls presented similar sociodemographic characteristics and underlying medical conditions, with the exception of a higher proportion of males in cases (71% vs 51%, p = 0.037) (Table 4).

Cases and controls were similar in PCV vaccination history: 27 cases (79%) and 217 controls (80%) had received at least one dose of any PCV, and 24 cases (71%) and 198 controls (73%) had received PCV13. There were no children with a single dose given 0–14 days before the reference date. The adjusted direct effect of at least one dose of PCV13 (including schedules consisting of PCV13 and another PCV) in preventing IPD caused by PCV13 serotypes was 95% (OR: 0.05; 95% CI: 0.01–0.55; p = 0.014), and 93% (OR: 0.07; 95% CI: 0.01–0.70; p = 0.023) when restricting the analysis to IPD due to additional PCV13 serotypes. Conversely, cases due to non-PCV13 serotypes had a higher odds of PCV13 vaccination than controls, although with a wide CI including the null effect (OR: 6.75; 95% CI: 0.77–59.19; p = 0.085). As a result, we did not detect a significant direct effect of PCV13 in preventing all-serotype IPD (OR: 0.91; 95% CI: 0.33–2.49; p = 0.848). Similar findings were obtained for schedules of PCV13 only, when analysing the effect of at least three doses of PCV13, and when excluding children with any medical condition (Table 5).

Discussion

In a cohort of children younger than 5 years followed up during the 14 years in which PCV7 was introduced and its subsequent replacement by PCV13, we observed large reductions in the incidence of IPD, both in vaccinated children (total effect, 76%) and in those not vaccinated (indirect effect, 78%). The effect against PCV-serotype cases was earlier and more pronounced in vaccinated than in unvaccinated children, but these differences disappeared when we evaluated the effect against IPD due to all serotypes.

The replacement of PCV7 by PCV13 was followed by a reduction of 90% in the incidence of IPD due to PCV13 serotypes in children who had received PCV13.

PCV13 effectiveness (direct effect) was 95% against IPD due to PCV13 serotypes.

Other studies have also reported a high effectiveness of PCV13 against IPD due to vaccine serotypes: 86% in Quebec, Canada [8], and 75% in the UK [7], in the first 3 and 3.5 years after PCV13 introduction, respectively. In our case–control analysis, as in the study from Quebec, the effectiveness estimate for non-PCV13 serotypes was negative, although with a wide CI including the null effect.

In our cohort analysis, the incidence of IPD due to non-PCV13 serotypes among children who had received PCV13 increased compared with the incidence in unvaccinated children in the pre-PCV period. This finding suggests some vaccine-induced replacement, a phenomenon well-documented for PCV7 [3,24-27], which may be beginning to occur with PCV13 [12,19-21,28]. Nevertheless, the initial incidence of non-PCV13 serotype IPD was low, and its increase has been much smaller than the reduction in vaccine serotype incidence, resulting in a considerable net population benefit of vaccination. The replacement effect may be a potential source of bias to be corrected for in indirect cohort studies [6,7].

The two vaccine failures observed in children completely vaccinated with PCV13 were due to serotype 3, for which different studies suggest lower effectiveness [6,7,11,29].

To the best of our knowledge, ours is the first study to estimate the indirect effect of PCV13 against IPD in children younger than 5 years, and the results are consistent with those of other studies that have described reductions in IPD incidence in unvaccinated age groups after the change to PCV13 [10,11,17-19]. A study in Boston in the United States between July 2010 and June 2012 observed an indirect effect against nasopharyngeal colonisation in unimmunised children as vaccine uptake reached 75% [30], however, we observed an indirect effect against PCV7 serotypes starting in the period 2005–2007, when coverage reached only 48%. The strong indirect effect of PCV13, added to serotype

replacement in vaccinated children, leads to apparently paradoxical results, such as the low or absent direct effect of the vaccine against all-serotype IPD. In this situation the total effect is the measure that best reflects the benefit in the vaccinated population.

This study has certain limitations. Although the study size was small, it was enough to sustain the statistically significant findings presented in the results but not for more disaggregated analysis. Some of the estimates' CIs were wide and should be interpreted with caution. In the comparisons between periods in the cohort study, we cannot rule out the possibility that some of the changes detected could have been due to temporal fluctuations in specific serotype incidence unrelated to vaccine use, giving an over- or underestimation of the indirect and total vaccine effects. However, the high effectiveness of PCV13 against vaccine serotypes was confirmed in the case–control study limited to the last period, in an analysis not affected by temporal fluctuations. The cohort analysis took into account age, sex, period and PCV status, but was not adjusted for other variables. Although some residual confounding could be possible, the results were consistent with those of the case–control analysis in which we did adjust for other variables. The fact that the same study has found a protective effect of PCVs for vaccine serotypes but not for non-vaccine serotypes also argues against important residual confounding. PCV7 was already available in the baseline period (2001–2004), with an average coverage of 11%; accordingly, some indirect effect cannot be ruled out. Nonetheless, the incidence of IPD in children younger than 5 years was still very high (75 per 100,000 PY), indicating little impact of vaccination. Few cases were not serotyped, and they were excluded from some analyses; however, sensitivity analyses were performed in the cohort study assigning these cases alternately to each serotype group (data not shown), and the main results were hardly affected. Only the indirect effect against PCV7 serotypes in the 2005–2007 period and the increased risk of non-PCV13 serotype IPD among vaccinated children in the 2011–2014 period lost statistical significance (p values 0.063 and 0.084, respectively).

This study also has a number of strengths. Population-based surveillance was active and consistent throughout the follow-up period. The case–control design achieved good comparability by individual matching, and was also adjusted for relevant covariables. The intermediate levels of vaccine coverage allowed a sufficient number of vaccinated and unvaccinated individuals to evaluate the direct and indirect effects.

In conclusion, PCV13 was highly effective in preventing vaccine-serotype IPD. With vaccine coverage around 76% in children, PCV benefits have been substantial and similar in vaccinated and unvaccinated children through strong total and indirect effects. Signs of possible serotype replacement in vaccinated children highlight the importance of ongoing surveillance and development of new pneumococcal vaccines. Joint assessment of vaccine effects at the individual and population level helps to better understand the complex dynamics of changes in the epidemiology of IPD that follow changes in the pneumococcal vaccination programme. The important vaccine benefit at the population level supports the recommendation for universal PCV vaccination in children.

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Acknowledgements

This work was partially supported by SpIDnet (Assessing the impact of vaccination with the conjugate vaccines on the epidemiology of invasive pneumococcal disease in Europe), a network funded by the European Centre for Disease Prevention and Control (ECDC/2012/038). We thank Dr Asunción Fenoll at the National Centre of Microbiology (Instituto de Salud Carlos III, Majadahonda, Spain) for serotyping of the pneumococcal isolates.

Conflict of interest

Enrique Bernaola has collaborated as a researcher in a clinical trial of PCV13 for Pfizer Inc. All other authors declare no competing interests.

Authors' contributions

MG, AB and JC designed the study. MG and JC performed the statistical analyses and drafted the manuscript. MH, FG and EB participated in the data review and manuscript revision. LT, AG and CE were responsible for the microbiological results and participated in the manuscript revision. Members of the Working Group for Surveillance of the Pneumococcal Invasive Disease in Navarra participated in the data collection and data review. All authors contributed to data interpretation, revised the article critically and approved the final version.

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Risk communication as a core public health competence in infectious disease management: Development of the ECDC training curriculum and programme

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Citation style for this article:
Dickmann P, Abraham T, Sarkar S, Wysocki P, Cecconi S, Apfel F, Nurm Ü. Risk communication as a core public health competence in infectious disease management: Development of the ECDC training curriculum and programme. Euro Surveill. 2016;21(14):pii=30188. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.14.30188

Article submitted on 10 June 2014 / accepted on 31 March 2015 / published on 07 April 2016

Risk communication has been identified as a core competence for guiding public health responses to infectious disease threats. The International Health Regulations (2005) call for all countries to build capacity and a comprehensive understanding of health risks before a public health emergency to allow systematic and coherent communication, response and management. Research studies indicate that while outbreak and crisis communication concepts and tools have long been on the agenda of public health officials, there is still a need to clarify and integrate risk communication concepts into more standardised practices and improve risk communication and health, particularly among disadvantaged populations. To address these challenges, the European Centre for Disease Prevention and Control (ECDC) convened a group of risk communication experts to review and integrate existing approaches and emerging concepts in the development of a training curriculum. This curriculum articulates a new approach in risk communication moving beyond information conveyance to knowledge- and relationship-building. In a pilot training this approach was reflected both in the topics addressed and in the methods applied. This article introduces the new conceptual approach to risk communication capacity building that emerged from this process, presents the pilot training approach developed, and shares the results of the course evaluation.

Background

The International Health Regulations (IHR 2005) have been developed to help all countries better prepare and respond to public health emergencies of international concerns [1]. The importance of risk communication is recognised as one of the eight core capacities in the successful management of infectious diseases and other public health risks both in terms of gathering intelligence, and in enabling the functional flow of information, communication and coordination [2]. During a public health emergency time is short and important information, communication and coordination tasks such as identifying public communication focal points and stakeholders, developing and implementing reliable communication structures should be in place to allow systematic and coherent crisis communication and management [3].

Risk communication is understood in this context as serving a double role: risk communication should prepare for crisis management and it should build capacity for understanding and action competence as well as a comprehensive understanding of health risks among health officials and the general public. This capacity building is needed for peaks in demand and public health emergencies, as well as for managing continuous potential health threats, such as outbreaks of measles or the emergence of antimicrobial resistance.

Research studies indicate that while outbreak and crisis communication concepts and tools have long been on the agenda of public health officials, there is a need to better integrate conceptual approaches into sound practice in order to improve risk communication in health [4,5].

Currently, there is little consensus about the meaning, impact and methods of risk communication in infectious disease contexts. Risk communication as a technical term emerged during the early 1970s in the environmental health debates and has since then spread into different disciplines and discourses [6, 7]. The understanding of risk communication as '*information*

Table

Matrix of risk communication

Risk communication activities		Before Public health emergency Preparedness	During Public health emergency Response	After Public health emergency Legacy
Information	Gathering			
	Assessing			
	Sharing			
Communication	Communications (actions: flyer, website, etc.)		Crisis communications	
	Key messages / Content			
	Strategy / Methods			
Coordination	Local			
	Regional			
	National			
	International			

exchange about health risks caused by environment, industrial, or agricultural, processes, policies, or products among individuals, groups and institutions' [7] has become more prominent post 11 September 2001. The conceptual foundations of risk communication draw on complex social, cognitive and psychological research in a wide variety of areas including behavioural communications, environmental health, health promotion, governance and social marketing [7]. The public health practice of risk communication, however, has been slow to embrace such a broader perspective and mainly focussed on approaches to improve risk communication as the communication of risks from public health authorities to their public [8,9].

Efforts to broaden this approach face three substantial challenges:

It is not known how it is to be done. While there are a plethora of practical guidelines, best-practice examples and ad hoc advice (e.g. WHO outbreaks communications [10], United States Centers for Disease Control Crisis Emergency and Risk Communication [11]), this advice is mainly orientated towards communicating risks in outbreak and crisis situations [12]. While there is a multitude of conceptual approaches to risk perception and communication, e.g. Slovic [13,14], Fischhoff/ Morgan [15,16] and Kasperson [17], there is little integration of these approaches into risk communication in public health practice.

There is a lack of skilled individuals and formal training and practical experience is scarce as the approach has not entered into mainstream public health academia and learning [18].

Finally, there is a lack of supportive environments. Even though risk communication has been designated as a core IHR capacity, it has yet to be routinely implemented into public health organisation planning, its risk assessment, and management procedures [19].

Acknowledging these points, the European Centre for Disease Prevention and Control (ECDC) initiated the development of a training curriculum and programme to address the need for both conceptual and practical capacity building in risk communication as an integral component of disease prevention and control. Practitioners and researchers on the forefront of risk communication practise were invited to develop a new conceptual approach to capacity building and develop a teaching curriculum. The initial focus of the training was on vaccine preventable diseases, in particular enhancing measles vaccination uptake, and was first tested with ECDC and European Commission experts in January 2013.

Concept review, integration and development

Working definitions

Risk and crisis communication differ in many aspects and there is terminological and epistemological ambiguity in international fora and discussions regarding definitions and approaches [20]. As a working definition we used *time*, *method* and *content* to distinguish between risk communication and crisis communication. Risk communication starts before crisis and continues throughout and after a crisis, is less directive compared with crisis communication, and has more time to explain even difficult and contradicting scientific positions. It also has the time and opportunity to offer diverse approaches to bridge the gap between the scientific assessment of health risks and public perceptions of health risks. The main activity areas of risk communication are information gathering, sharing

and assessing, communication strategy, key messages and communications and coordination on different geographical and organisations levels (Table 1). Crisis communication is the communication during an outbreak when people need to know exactly what to do if they are affected and how to protect themselves and others. Effective communications is vital to prevent surges of low risk patients blocking medical infrastructures and to prevent the further transmission of the disease by enabling people to adopt e.g. the right behaviours. During an outbreak, time is short and crisis communication therefore needs to be concise and often unidirectional. Table 1 displays the main activity areas of risk communication and can be used to structure the strategic thinking around risk communication needs and gaps. It also helps clarify the distinction between working definitions of risk communication and crisis communications.

Conceptual approach communication models

Risk communication goes beyond communications of risks. It entails building public health capacity to enable, encourage and empower different publics to understand and act on health risks [21,22] Yet, public health officials often see their tasks as predominantly providing information. They tend to rely mainly on an early information technology paradigm that assumes a rather static and unilateral sender who conveys messages to addressable recipients [23]. The reality of communication and information has been transformed. The public is no longer seen as a passive entity to be given recommendations and guidelines to follow by institutions which are to be trusted. The sender-message-recipient communication model does not cater for understanding how humans process information, communicate and make behavioural decisions. The popularity and increasingly important intelligence gathering and information dissemination functions of interactive social media (e.g. Facebook, Twitter, LinkedIn, etc.) is a strong indicator of the growing influence of decentralised and user-generated connectivity and is rapidly changing communication marketplaces [24].

A new approach for risk communication in public health

The proposed risk communication concept for public health builds on theories and models from a variety of disciplines and applies a reflective approach. It calls for strategic shifts in thinking and approach to risk communication namely:

1. *From telling to listening*: Risk communication is viewed as a complex process. It is as concerned with listening and understanding as it is with providing information and advice. Having listened and understood peoples' different perceptions and behaviours allows for quicker and more effective communication when time is short. Much can be learned in this area from behavioural communications models; which, for example, emphasise listening and gathering insights about what really motivates and moves the people to whom you are trying to communicate [25].

2. *From information transfer to relationship building:* Risk communication is not seen as exclusively based on information transmission, but as a strategic activity concerned with relationship building between authorities and the public over time [26]. Engaging affected populations early in development, planning, ongoing monitoring and evaluation enhances peoples' sense of empowerment and ownership. Much can be learned in this area from social marketing approaches; which, for example, emphasise the importance of 'exchange theory'- to understand the benefits and rewards for a given behaviour [27,28].

3. *From 'command and control' to creating supportive environments:* Risk communication is not just about directive action, but is concerned with creating supportive environments where people can make their own informed decisions. Much can be learned in this area from health promotion approaches; which, for example emphasises the importance of 'environmental' factors on behaviour and the need 'to make the healthy choice the easy choice.' [29]

4. *From siloed to coordinated approaches*: Multiple actors and sectors are inevitably involved with all risk communication related issues. Risk communication is concerned with integration and partnership. Much can be learned in this area from new governance approaches which, for example, emphasise 'whole-of-government' and 'whole-of-society' approaches [30,31].

Conceptual approach to training curriculum: methods and contents

This conceptual re-framing was reflected both in the topics addressed and in the methods applied.

The new risk communication training views risk and crisis communication as related but distinct realities. Although risk communication is seen as the foundation on which successful crisis communication can refer and rely on, risk communication is seen as having a different broader social format, rationale and rules. Risk communication has more to do with knowledge- and relationship building than simple information conveyance.

The training adopted a deconstructive approach and facilitated a look at the discourses that shape people's decisions and behaviour.

The training aimed to help participants to understand the concepts that underlie risk communication advice before they are able to really implement 'good advice' on risk communication strategies into their own realities. The new risk communication adopts a reflective approach. Rather than emphasising detailed guidance that lists the steps to go from A to B, the training aimed

to provide participants with a map, the skill and literacy to read the map and the ability to design their own risk communication strategies that work in their realities. Finally, an interactive, critical and reflective process in groups is emphasised. Rather than listening to lectures, a hands-on approach was used that engaged with participants and facilitated active learning, understanding and networking.

Objectives, organisational and methodological approach

The pilot training addressed public health and communication experts working at ECDC and the Commission of the European Union. The overall objective was to develop the competencies of public health programme managers and practitioners to analyse, understand and apply risk communication concepts, principles and approaches to the prevention and control of communicable disease threats on regional, national and/or local levels.

Each day of the two-day course was organised into reflection and action sessions. The days started with reflection sessions introducing terms, definitions, approaches, and gave time to discuss these. The afternoons were dedicated to actions: exploring ways to put concepts into practice, testing ideas, working on scenarios related to both on-going and crisis challenges, discussing and getting feedback from others within small working groups and in the plenum.

In order to maximise the utility of the discussions and ensure 'real-life' learning, each participant was asked to complete a pre-course assignment that included the development of a case study based on their own contextually specific experience. These case studies informed group work and plenum discussions.

The training was evaluated with a pre- and post-course questionnaire as well as day assessments at the end of first and the second day.

Pre-course assessment

Seven of 14 respondents considered themselves as having good knowledge of risk communication theories and 7 of 15 respondents had 'significant' or better experience in applying risk communication. The reason to participate in the training was mainly to receive a more formal training in risk communication as this was considered important for their field of work.

Expectations were practical and conceptual: participants wished for a structured approach, practical examples and tools; they also hoped for a better understanding of the different concepts and approaches.

Asked for a working understanding of risk communication, participants saw communication and risk communication as instruments to ensure trust and transparency; they stressed the importance of risk communication in the prevention of infectious diseases and as foundation for crisis communication. The nature of risk communication was seen in the communication of risks and to provide information adapted to various people; risk communication in this meaning was seen as ability to respond to public information needs. Ultimately risk communication should empower people as better-informed people are more likely to modify their behaviour.

Post-course assessment

After the course, 14 of 15 respondents reported that their expectations had been fully met and 14 of 16 stated that their understanding of concepts and approaches had increased considerably.

Participants, who said earlier that they had good knowledge and understanding of risk communication, expressed the need for a paradigmatic change in the understanding and institutional practice of risk communication and felt better prepared to advocate for this change. The majority felt that the training was very useful and they provided constructive feedback to individual sections in the day assessments. Overall, they appreciated that the training was based on a reflective and reframing approach rather than on providing tips, checklists and concrete guidance.

Conclusion

The training pilot was successful in conceptualising, articulating and introducing a new approach towards training the trainers in risk communication in public health. Further systematic analysis and evaluations of risk communication approaches and trainings are necessary to develop the capacity on the ground that is needed for the prevention of and response to public health incidents and emergencies. Future training in national and local settings will improve the curriculum and practice of risk communication and provide insights into the situation and landscape of risk communication on the ground and enhance our understanding of the practice of risk communication.

The ECDC as developer and advocate of this training and approach is in a unique position to be an efficient broker of knowledge and experience between the many centres of expertise around and beyond Europe and those in the EU countries responsible for risk communication policy and practice in public health.

Acknowledgements

The training was founded by Specific contract N. Twelve - ECDC3442 Implementing Framework Contract N: ECDC/09/030 between World Health Communication Associates (WHCA) and ECDC.

Authors' contributions

All authors have been involved in concept development and training design. PD wrote the draft and did the evaluation; all authors have commented on the draft and approve the final version.

Conflicts of Interest

The authors declare that they do not have a conflict of interest.

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