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Impact of the 10-valent pneumococcal conjugate vaccine on hospital admissions in children under three years of age in Iceland

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ABSTRACT

Introduction: Pneumococcus is an important respiratory pathogen. The 10-valent pneumococcal vaccine (PHiD-CV) was introduced into the Icelandic vaccination programme in 2011. The aim was to estimate the impact of PHiD-CV on paediatric hospitalisations for respiratory tract infections and invasive disease.
Methods: The 2005–2015 birth-cohorts were followed until three years of age and hospitalisations were recorded for invasive pneumococcal disease (IPD), meningitis, sepsis, pneumonia and otitis media. Hospitalisations for upper- and lower respiratory tract infections (URTI, LRTI) were used as comparators. The 2005–2010 birth-cohorts were defined as vaccine non-eligible cohorts (VNEC) and 2011–2015 birth-cohorts as vaccine eligible cohorts (VEC). Incidence rates (IR) were estimated for diagnoses, birth-cohorts and age groups, and incidence rate ratios (IRR) between VNEC and VEC were calculated assuming Poisson variance. Cox regression was used to estimate the hazard ratio (HR) of hospitalisation between VNEC and VEC.
Results: 51,264 children were followed for 142,315 person-years, accumulating 1,703 hospitalisations for the respective study diagnoses. Hospitalisations for pneumonia decreased by 20% (HR 0.80, 95%CI:0.67–0.95) despite a 32% increase in admissions for LRTI (HR 1.32, 95%CI:1.14–1.53). Hospital admissions for culture-confirmed IPD decreased by 93% (HR 0.07, 95%CI:0.01–0.50) and no hospitalisations for IPD with vaccine-type pneumococci were observed in the VEC. Hospitalisations for meningitis and sepsis did not change. A decrease in hospital admissions for otitis media was observed, but did not coincide with PHiD-CV introduction.
Conclusion: Following the introduction of PHiD-CV in Iceland, hospitalisations for pneumonia and culture confirmed IPD decreased. Admissions for other LRTIs and URTIs increased during this period.

1. Introduction

Worldwide mortality in children under five years of age from acute lower respiratory tract infections (LRTI) is estimated to be 105 per 100,000 children. More than half of the LRTI deaths are estimated to be due to pneumonia caused by *Streptococcus pneumoniae* [1]. Mortality rates vary greatly between countries, ranging from 0.65 to 547 per 100,000 children in Finland and Somalia, respectively and have decreased by 37% globally since 2005 [1]. Hospitalisation rates also vary between countries. Immediately before a pneumococcal conjugate vaccine (PCV) was introduced into national immunization programmes, the rate of hospitalisations for pneumonia of children younger than two years of age was 293, 615 and up to 1274 per 100,000 children in Scotland [2], Sweden [3] and USA [4]. Pneumococci are the causative agent of 9–30% of community-acquired pneumonia in children, and this proportion is higher in severe pneumonia cases [5–9]. Pneumococci are also among the most common bacterial causes of meningitis and sepsis in unvaccinated children, associated with high morbidity and mortality [10]. Other clinical presentations of pneumococcal infections, such as otitis media (OM) are more common and less severe.

PCVs have been widely incorporated into national immunization programmes in recent years, and have successfully reduced

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invasive and non-invasive pneumococcal infections [2–4,11–17]. The 10-valent pneumococcal *Haemophilus influenzae* protein-D conjugated vaccine (PHiD-CV) was introduced into the Icelandic national immunisation programme in April 2011 for all children born in January 2011 and later, in a 2 + 1 schedule without a catch-up (at three, five and twelve months of age). Prior to the introduction of PHiD-CV, no systematic pneumococcal vaccination for children had been implemented. Vaccine uptake was excellent, with >97% of children receiving the two primary doses before their first birthday [18]. The aim of this study was to estimate the vaccine impact on admissions to the Children's Hospital in Iceland for culture-confirmed invasive pneumococcal disease (IPD), and all-cause meningitis, sepsis, pneumonia and OM.

2. Methods

2.1. Data sources

This study is a single-centre, individual-level, observational cohort study of paediatric hospital admissions due to IPD and diseases commonly caused by *S. pneumoniae*; all-cause OM, pneumonia, sepsis and meningitis. Hospitalisations for lower respiratory tract infections other than pneumonia (LRTI) and upper respiratory tract infections other than otitis media (URTI), as well as all-cause hospital admissions, were used as comparators. The Children's Hospital Iceland is the primary paediatric hospital for approximately 90% of the Icelandic population (www.statice.is) and serves as a secondary and tertiary paediatric hospital for the entire country.

Eleven consecutive Icelandic birth-cohorts 2005–2015 were followed from birth to three years of age, or until the end of the study period. Individual-level immigration and emigration data were collected from Statistics Iceland. Children born outside of Iceland and subsequently immigrated were excluded from the analysis. All hospital admissions to the Children's Hospital from 1 January 2005 to 31 December 2016 were included.

Data on admissions were collected from the hospital inpatient registry. Seven diagnostic groups were defined, of which six were based on International Classification of Diseases, 10th Revision (ICD-10) discharge diagnoses (Table 1). Only one diagnosis per hospital admission was used in the analysis. Diagnosis were sequentially searched in the following order: meningitis, sepsis, pneumonia, LRTI, AOM and finally URTI. An admission was considered to be due to IPD if the admitted child had culture- or PCR-confirmed *S. pneumoniae* sampled from blood, cerebrospinal or joint fluids and bones, regardless of ICD-10 discharge diagnosis. These microbiological data were extracted from laboratory information system of the Department of Clinical Microbiology at Landspitali University Hospital, the national reference laboratory for Iceland.

Using unique national identification numbers, culture data were linked to admissions data at individual-level. Data included date of birth, age, sex, the dates of admission and discharge, intensive care unit (ICU) stay and discharge diagnosis. All positive cultures linked to hospital admissions were included. Additionally, aggregate data on all admissions to the Children's Hospital Iceland, regardless of diagnosis were collected and compared to the study data.

Demographic information was collected from Statistics Iceland (www.statice.is).

3. Statistical methods

All Icelandic children born 2005–2015 were followed from birth until three years of age, death, emigration or the end of the study period. Based on the eligibility criteria of the PHiD-CV programme, birth-cohorts 2005–2010 were grouped as vaccine non-eligible cohorts (VNEC) and birth-cohorts 2011–2015 as vaccine eligible cohorts (VEC). When appropriate, the mean age at the time of admission and the median length of hospitalisations were calculated and diagnostic groups compared using Welch's two sample *t*-test and Wilcoxon rank sum test, respectively. The crude incidence rates (IR) of hospital admissions were calculated for each birth-cohort, diagnostic group and age group, and crude incidence rate ratios (IRR) were calculated between the VNEC and VEC assuming Poisson variance. A sub-analysis was performed within the pneumonia diagnostic group (ICD10: J10-J18), comparing each code between the VNEC and VEC. The proportion of admissions leading to an ICU stay was calculated by birth-cohort and diagnostic group.

The Kaplan-Meier product limit estimator was used to calculate the cumulative incidence of hospitalisations. This analysis included only the first hospitalisation for each child according to diagnostic group. For all other analyses, repeated hospitalisations were included, except if they occurred within 30 days of a previous hospitalisation for the same condition. Follow-up time was censored on both emigration and death. An unadjusted Cox regression was used to estimate the hazard ratio (HR) of hospitalisation between the VNEC and VEC for each diagnostic group. To evaluate whether the observed differences were likely to be due to direct effects of the PHiD-CV, the Cox regression was repeated by stratifying the data to two age-ranges; 0–90 days of age and 90 days and older.

The study was approved by The National Bioethics Committee (VSNb2013010015/03.07), The National Data Protection Authority (2013010100VEL/--) and medical director at the University Hospital.

4. Results

Information was available for 53,228 children. Of those, 1892 were excluded because they had immigrated to Iceland after birth.

Table 1
Definition and summary of the study's diagnostic groups. When applicable, the abbreviation used in the text is provided. Six of the seven diagnostic groups were defined based on the International Classification of Diseases, 10th Revision (ICD-10) codes associated with the hospitalisation. Invasive pneumococcal disease (IPD) was defined as any hospitalisation associated with positive pneumococcal culture from blood, cerebrospinal or joint fluid.

Diagnostic group	Abbreviation	Definition
Meningitis	–	ICD-10 discharge diagnosis of G00
Sepsis	–	ICD-10 discharge diagnosis of A41 or A42
Pneumonia	–	ICD-10 discharge diagnosis of J09-J18
Otitis Media and Complications	OM	ICD-10 discharge diagnosis of H65, H66, H70 or H72
Acute Upper Respiratory Tract Infections	URTI	ICD-10 discharge diagnosis of J00-J06
Acute Lower Respiratory Tract Infections	LRTI	ICD-10 discharge diagnosis of J20-J22
Invasive pneumococcal disease	IPD	Microbiologically confirmed pneumococcal infection from normally sterile site, regardless of ICD-10 diagnosis

A further 72 were excluded because of missing information on birth-date. The remaining 51,264 children were followed for a median of 1,096 days (range 6–1,096), resulting in 142,315 person-years of follow-up time. A total of 10,520 children had the follow-up time censored before their third birthday. Of those, 8,234 were censored at the end of the study period, 2,263 were censored due to emigration and 23 because of death. Birth-cohorts ranged from 4,026 to 5,130 children, and 51.3% were male.

A total of 1,414 children were hospitalised 1,703 times for diseases in the study's diagnostic groups. The total number of admissions, regardless of diagnosis, is shown in Table 2. Information on age, gender, number of admissions, rate and length of hospital and ICU admissions, stratified by study diagnosis and vaccine eligibility are shown in supplementary Table 1.

4.1. Admissions due to pneumonia and LRTI other than pneumonia

During the study period, 550 children were admitted 660 times with discharge diagnoses of pneumonia. Hospital admissions due to LRTI (other than pneumonia) were recorded 550 times for 508 children. The crude IR of admissions for pneumonia among children under three years of age was 4.94 and 4.18 per 1,000 person-years in the VNEC and VEC respectively. The corresponding crude IR of admissions for other LRTI was 2.94 and 5.23 in the VNEC and VEC respectively.

The crude IR for pneumonia admissions was highest in children 12–17 months of age, and significantly lower in the VEC compared to the VNEC (crude IRR: 0.52 (95%CI: 0.35–0.77, Fig. 1). The IR of admissions for LRTI was highest in children <6 months of age, and was significantly higher in the VEC compared to the VNEC (crude IRR 1.50, 95%CI 1.23–1.84, Fig. 1). The IR was not significantly different in other age groups for both diagnoses (Fig. 1).

A significant reduction in admissions, for the ICD-10 diagnosis pneumonia (organism unspecified, J18), was observed. The rates of admissions for other ICD-10 discharge diagnoses within the pneumonia diagnostic group did not differ significantly between the cohorts (Table 3).

For both pneumonia hospitalisations and other LRTI, a clear difference in the cumulative admission rates per 1,000 person-years was observed between VNEC and VEC (Fig. 2). The hazard ratio of pneumonia hospitalisation between the VEC and VNEC was 0.80 (95%CI:0.67–0.95). When stratified by age, the hazard ratio was 1.22 (95%CI 0.81–1.85) for children <90 days of age and 0.73 (95%CI 0.60–0.89) for children ≥90 days.

For LRTI hospitalisations the HR between VEC and VNEC was 1.32 (95%CI:1.14–1.53) (Fig. 3). The hazard ratio was larger for children <90 days of age, HR 1.54 (95%CI 1.23–1.94), and not significant for children ≥90, HR 1.18 (95%CI 0.97–1.44).

Supplementary Table 1 shows the proportion of children diagnosed with pneumonia at the Children's Hospital emergency room that were admitted to hospital, length of stay and proportion of admitted children transferred to ICU, stratified by birth-cohort.

4.2. Admissions due to OM and other URTI

For URTI and OM, 123 children and 256 children had 131 and 280 hospitalisations, respectively. The crude IR of admission for OM among children under three years of age was 2.32 and 1.45 per 1,000 person-years in the VNEC and VEC, respectively, and the crude IR for URTI admissions was 0.78 and 1.13 in the VNEC and VEC. The cumulative admission rate per 1,000 person-years for URTI and OM are shown in Fig. 2.

The hazard ratio of OM admission between the VEC and VNEC was 0.57 (95%CI:0.43–0.73). When stratified according to age groups, the hazard ratio was 0.72 (95%CI 0.33–1.57), and 0.55 (95%CI 0.42–0.72 for <90 days and ≥90 days, respectively. The hazard ratio for URTI hospitalisation was 1.56 (95%CI:1.11–2.19) (Fig. 3). Among children <90 days, and ≥90 days, the hazard ratios were 3.4 (95%CI 1.72–6.90) and 1.13 (95%CI 0.75–1.71), respectively.

4.3. Admissions due to all-cause meningitis and sepsis, and IPD

For meningitis and sepsis, 15 and 61 children had 19 and 63 hospitalisations, respectively. The crude IR for meningitis hospitalisation was 16.5 and 8.7 per 100,000 person-years in the VNEC and VEC respectively, and the crude IR for sepsis hospitalisations was 38.8 and 52.3. Twenty three hospitalised children had culture-confirmed IPD. The crude IR for IPD was 24.7 per 100,000 person-years in the VNEC compared to 1.74 per 100,000 person-years in the VEC. The proportion of IPD caused by vaccine-type pneumococci was 77% in the VNEC and 0% in the VEC.

The cumulative admission rates per 1000 person-years for sepsis and IPD are shown in Fig. 2. For meningitis, the hazard ratio of hospitalisation between the VEC and VNEC was 0.45 (95%CI 0.15–1.41). The hazard ratio of hospital admission for IPD between VEC and VNEC was 0.07 (95%CI:0.01–0.50). The hazard ratio of sepsis hospitalisation between the VEC and VNEC was 1.26 (95% CI:0.75–2.13) (Fig. 3). Survival analyses stratified according to age for these three diagnostic groups did not alter results (data not shown).

Table 2
Overview of admissions in the study birth-cohorts. Asterisk (*) signifies incomplete follow-up due to censoring at the end of the study period before all children in the birth-cohort had reached 3 years of age.

Birth-cohort	Children followed, *n*	Follow-up time, person-years	All cause admissions, *n*	Rate of admissions per 1000 person-years	Study admissions, *n* (children, *n*)	Rate of study admissions per 1000 person-years	Proportion due to study diagnosis, %	ICU admissions, *n* (children, *n*)
2005	4,541	13,278	446	33.59	219 (160)	16.49	49.1	7 (7)
2006	4,668	13,658	415	30.39	176 (140)	12.89	42.4	10 (8)
2007	4,770	13,985	423	30.25	186 (160)	13.30	43.9	6 (5)
2008	4,953	14,472	442	30.54	117 (101)	8.08	26.5	5 (4)
2009	5,130	14,965	484	32.34	124 (109)	8.29	25.6	7 (6)
2010	4,988	14,593	384	26.31	158 (138)	10.83	41.1	7 (7)
2011	4,643	13,638	392	28.74	129 (112)	9.46	32.9	4 (4)
2012	4,667	13,750	576	41.89	196 (155)	14.25	34	0 (0)
2013	4,438	13,033	472	36.22	149 (119)	11.43	31.6	9 (8)
2014*	4,440	10,916*	431*	39.48	144 (122)*	13.19	33.4	6 (5)*
2015*	4,026	6,027*	377*	62.55	105 (98)*	17.42	27.9	3 (3)*
Total	51,264	142,315	4,842	34.02	1,703 (1,414)	11.97		64 (57)

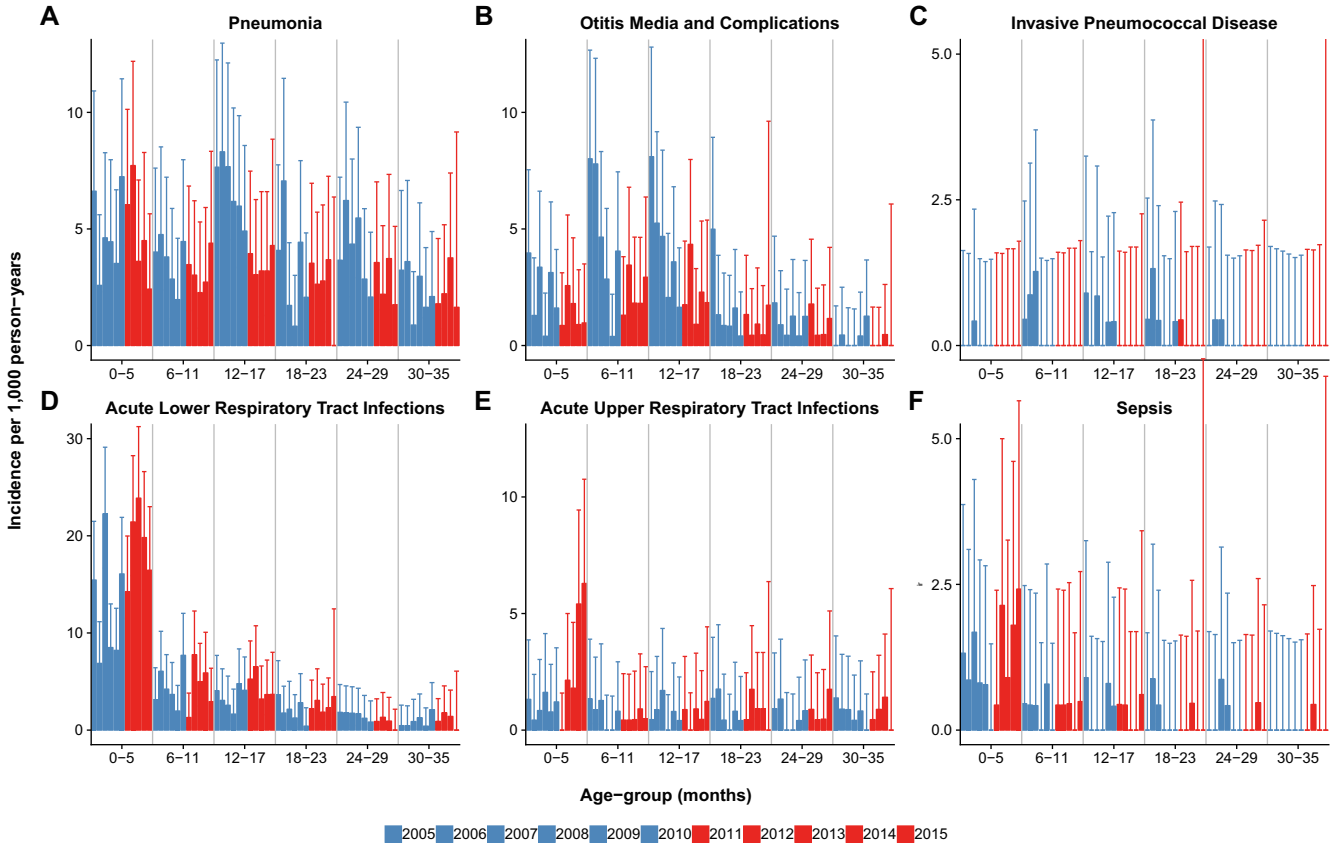

Fig. 1. Crude incidence rates (IR) of the six diagnostic groups (A-F) per 1,000 person-years for each of the birth-cohorts. Fig. 1 A–D and F depict the incidence rate of admissions due to corresponding diagnosis, while Fig. 1E depicts the incidence rate of admissions with culture confirmed IPD, regardless of diagnosis. The comparison is split into 6-month age-brackets which are illustrated in the Y-axis. The vaccine non-eligible cohorts (VNEC) are illustrated in light-gray and the vaccine eligible cohorts in dark-gray.

Table 3
Comparison of the number of hospitalisations and the incidence rates of hospitalisations for individual ICD-10 diagnoses of the pneumonia diagnostic group. Incidence rate ratios between the Vaccine eligible and Vaccine non-eligible cohorts are shown.

Sub-group diagnosis	Vaccine non-eligible cohorts		Vaccine eligible cohorts		Comparison between VEC and VNEC
	n	IR (95%CI)	n	IR (95%CI)	IRR (95%CI)
J10: Influenza with pneumonia, virus identified	5	0.06 (0.02–0.14)	1	0.02 (0.00–0.10)	0.30 (0.01–2.65)
J11: Influenza with pneumonia, virus not identified	1	0.01 (0.00–0.07)	0	0.00 (0.00–0.06)	0.00 (0.00–57.76)
J12: Viral pneumonia	68	0.80 (0.62–1.01)	48	0.84 (0.62–1.11)	1.05 (0.71–1.53)
J13: Pneumonia due to *S. pneumoniae*	3	0.04 (0.01–0.10)	3	0.05 (0.01–0.15)	1.48 (0.20–11.06)
J15: Bacterial pneumonia, not elsewhere classified	90	1.06 (0.85–1.30)	55	0.96 (0.72–1.25)	0.91 (0.64–1.28)
J16: Pneumonia due to other infectious organisms	3	0.04 (0.01–0.10)	2	0.03 (0.00–0.13)	0.99 (0.08–8.62)
J17: Pneumonia in diseases classified elsewhere	1	0.01 (0.00–0.07)	1	0.02 (0.00–0.10)	1.48 (0.02–116.25)
J18: Pneumonia, organism unspecified	234	2.75 (2.41–3.13)	111	1.94 (1.59–2.33)	0.70 (0.56–0.88)

5. Discussion

This population-based study of eleven consecutive birth-cohorts demonstrated a 20% reduction in pneumonia hospitalisations among children younger than three years of age, following the introduction of PHiD-CV into the national immunisation program. Hospitalisations due to culture-confirmed IPD decreased by 93% and there were no hospital admissions due to vaccine-type IPD among the vaccine eligible cohorts.

The 20% impact of the PHiD-CV for all-cause pneumonia hospitalisations is in line with previous studies, which have demonstrated a 7.4–30% reduction for clinically diagnosed pneumonia [2,12,19,20].

As in any vaccine ecological study, careful consideration must be paid to the possibility of unmeasured confounders. By including all children in Iceland for eleven consecutive birth-cohorts, sampling bias could be excluded. This means that differences in the distribution of risk factors among children in the VNEC compared

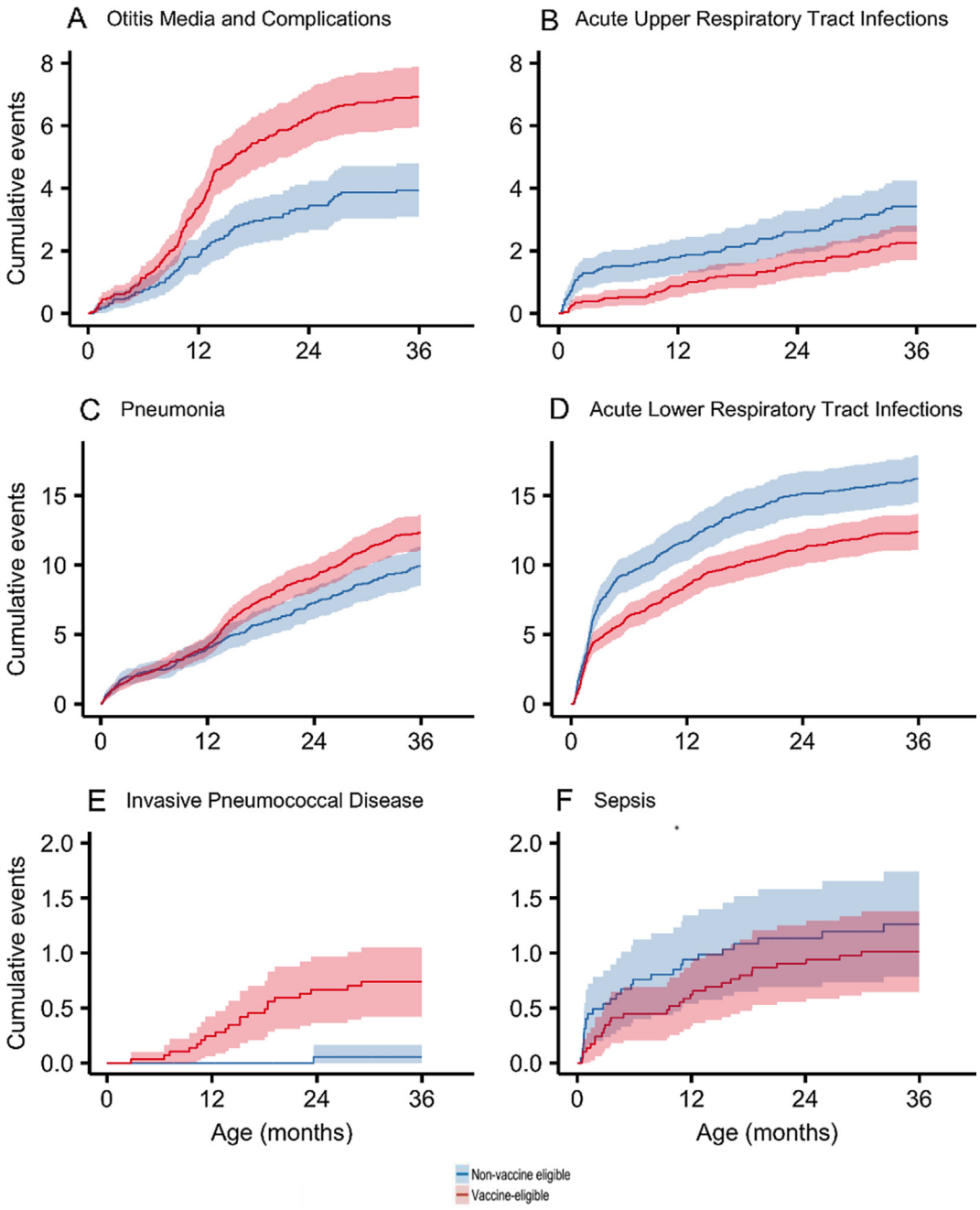

Fig. 2. Kaplan-Meier cumulative event curves per 1,000 person-year for each of the diagnostic groups (A-F). The vaccine non-eligible cohorts (VNEC) are illustrated in blue and the vaccine eligible cohorts (VEC) are illustrated in red. Censored observations are depicted with a cross and the 95% confidence intervals (CI) are represented by a shaded area. The Y-axis is scaled independently for each pair of diagnostic groups (A-B, C-D and E-F). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to VEC could only be due to systematic changes in the whole population. We are unaware of any systematic changes that could have reduced the incidence of paediatric pneumonia requiring hospitalisation, except the introduction of PHiD-CV. Temporal changes in referral habits of pneumonia cases could possibly explain the observed association, if physicians who previously tended to admit low-risk paediatric pneumonia, later tended to treat them as outpatients. If this was true, hospitalisations for other related diseases would be expected to decrease concurrently, due to comparative cultural change. The proportion of pneumonia hospitalisations admitted to the ICU and the hospital length of stay would be expected to increase, as the proportion of serious pneumonia cases would be higher. None of these predictions were observed (Table 2, Supplementary Table 1). In addition, we have demonstrated that visits to the emergency department for pneumonia decreased after the vaccination [16]. A possible confounder is a shift in coding practices. In a recent Swedish study, comparing the use of ICD-10 discharge coding before and after introduction of PCV-7, a shift from J12.1 (respiratory syncytial virus (RSV) pneumonia) to J21.0 (RSV bronchiolitis) was observed. A 52% reduction in bacterial pneumonia (J13-J18) in children <2 years of age was also observed, suggesting that a part of that reduction might be a diagnostic shift due to an increase in virology testing [21]. In our study, no change was observed for viral pneumonia J12, while a 32% increase was

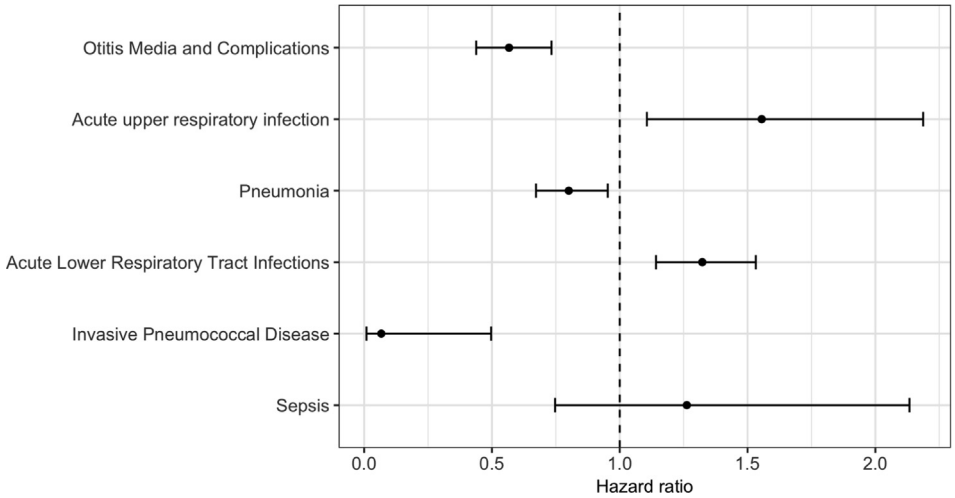

Fig. 3. Hazard ratio between the vaccine eligible cohorts (VEC) and the vaccine non-eligible cohorts (VNEC) for each of the diagnostic groups. The point estimate is illustrated as a point and the 95 percent confidence intervals (CI) are depicted with error-bars. The vertical dotted line represents the equivalency border of a hazard ratio of 1.

found in non-pneumonia LRTI (J20-J22). While differentiating between clinical pneumonia and other LRTI in young children can be challenging, we argue that the observed decrease in pneumonia is not the result of a drift in diagnostic coding practices, for the following reasons. Firstly, only children admitted to the paediatric ward were included, representing a subgroup with more severe illnesses, that probably had greater number of diagnostic tests done to confirm the diagnosis. This should reduce the risk of misdiagnosis. Secondly, the increase in admissions due to LRTI was only observed in children younger than six months of age, while the decrease in pneumonia admissions was only noted in children between 12 and 18 months of age. Similarly, when the result of the survival analysis was stratified to children younger than 90 days and older than 90 days the increase in non-pneumonia LRTIs was attenuated in the <90 days old group, with no significant change found in children >90 days of age. The same trend could also be noted in the analysis for non otitis media URTI. The opposite however was observed for the analysis on pneumonia admissions, with no significant change noted in children <90 days and an attenuated difference in children >90 days of age. This suggests that the changes were independent, and not due to a shift in diagnostic coding.

An increase in positive RSV and human metapneumovirus tests was noted in Iceland [22] and other countries [23–26] in the post-vaccination era. An increase in viral respiratory infections, such as those caused by RSV, influenza and human metapneumovirus generally result in an increase in pneumococcal acquisition [27,28]. This may lead to subsequent bacterial diseases, including OM, pneumonia and IPD [28–31].

There was a slight decrease in the incidence rate of pneumonia hospitalisations in vaccine non-eligible birth-cohorts 2009 and 2010 aged 12–17 months (Fig. 1). This could be due to a combination of two factors, i.e. herd effect on the 2010 birth-cohort and selective vaccination of high-risk children, which was implemented in the years prior to vaccine introduction. This is supported by our data, which show that 6% and 22% of children in the 2009 and 2010 birth-cohorts received the primary PCV doses before their second birthday [18].

The 93% reduction observed in admissions due to IPD reported in this study was greater than the 55–83% reduction in IPD reported in other studies [12,32–37]. The decrease in IPD was evident right from the beginning of the study period, before the vaccination program was introduced (Fig. 1). As it is a rare infection occurring in a small population, year to year variations in IPD cases can be considerable. Similar variations have been previously reported on the incidence of meningitis in Iceland from 1975 to 2014 [38]. Some of the observed decrease could also be explained by vaccination of at-risk children, as has been previously discussed.

The present study was not able to detect an impact on all-cause meningitis and sepsis hospitalisations. This may be because of a too small sample size to detect a change on diagnoses which are less specific to pneumococcal disease than IPD and pneumonia.

A large reduction was found in admissions due to OM in the VEC compared to VNEC. This appears to be due to a higher incidence of OM hospitalisations among the first three vaccine non-eligible birth-cohorts compared to all other study birth-cohorts, rather than a decrease due to the introduction of the vaccine.

Three observational studies from the USA, Sweden and Italy have demonstrated a decrease in OM hospitalisations following the introduction of a PCV [14,15,39]. In an USA and a Swedish studies, the admission rates prior to the introduction of the PCV-7 vaccine was compared to rates following the introduction of PCV10/PCV13 showing 66% and 42% reduction in hospital admission, respectively [14,15]. In an Italian study a 36.4% reduction in OM hospitalisation was noted in birth-cohorts eligible for the vaccination following PCV-7 introduction, compared to prior birth-cohorts [39]. None of the above studies considered the impact of decreasing trends in OM hospitalisations prior to the introduction of PCV or the possibility of unmeasured confounding. In our study, the importance of carefully interpreting the results with regard to temporal trends and possible confounders was demonstrated to have significant impact on the results. A recent Israeli study did not find a decrease in hospital admissions due to OM [40].

Clinical practices in treating OM can vary greatly between countries and often depend on factors such as the feasibility of strict follow-up. In Iceland, outpatient treatment of OM is favoured over admissions whenever possible, with reassessment often scheduled. While further studies are required to determine the full extent of the impact of PCVs on OM admissions, the effect on OM in outpatient care has been well established, including in Iceland [11,17,41,42].

When comparing only children too young to have receive the first primary does of the vaccine, no herd effect was noted for any of the study diagnoses. However, the number of admissions in that age group was low.

6. Conclusion

There was a significant impact of PHiD-CV on the rate of hospital admissions due to pneumonia and IPD among Icelandic children younger than three years of age, adding to the growing literature on the impact of PHiD-CV on pneumococcal diseases.

Ethics approval

The study was approved by The National Bioethics Committee (VSNb2013010015/03.07), the National Data Protection Authority (2013010100VEL/--) and the Directorate of Health, Iceland (1301266/5.6.1/gkg).

Consent for publication

Not applicable.

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Authorś contributions

Authors Sigurdsson and Eythorsson contributed equally to this manuscript.

ÁH, KGK and HE had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: SS, ESE, HE, ÁH, KGK

Acquisition, analysis, or interpretation of data: SS, ESE

Drafting of the manuscript: SS, ESE

Critical revision of the manuscript for important intellectual content: SS, ESE, HE, BH, KGK, ÁH

Statistical analysis: ESE, BH

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Obtained funding: HE, KGK, ÁH

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.01.094.

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