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Short communication

Similar impact and replacement disease after pneumococcal conjugate vaccine introduction in hospitalised children with invasive pneumococcal disease in Europe and North America

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ABSTRACT

High incidence of childhood invasive pneumococcal disease (IPD) in the US declined steeply after 7-valent pneumococcal conjugate vaccine (PCV7) introduction, outweighing reductions observed elsewhere. We re-analysed aggregate published data and compared pre- and post-PCV IPD-incidence in different countries to explore PCV impact on hospitalised and outpatient IPD separately. The proportion of hospitalised IPD cases was consistently high (>80%) in England&Wales, Finland, the Netherlands, and Quebec/Canada, but only 32% in the US before PCV introduction, increasing to 69% during the PCV era. In the US, a higher reduction in outpatient IPD incidence (94% in 2015 versus 1998–99) was observed compared to hospitalised IPD (79%); a 51% reduction in the non-PCV13-type IPD incidence among outpatient cases was estimated compared to a >2-fold increase for hospitalised cases. After stratification by hospitalization status, PCV programmes resulted in similar impact and serotype replacement in hospitalised IPD in US when compared to other countries.

1. Background

The first pneumococcal conjugate vaccine against the seven most prevalent pneumococcal serotypes causing invasive disease in children (PCV7) was licensed in The United States in 2000 and in Europe in 2001. The US was the first to introduce PCV7 into the childhood vaccination programme in 2000, while other countries followed suit several years later. Higher-valent PCVs, PCV10 and PCV13, were licensed in 2009–2010, and PCV7 programs were subsequently replaced with one of these vaccines. In addition to the PCVs used, the infant vaccination schedules, number of doses, and use of catch-up programmes among older children as a part of the PCV introduction differed between the countries (Table 1) [1–5].

The steep reduction in overall invasive pneumococcal disease (IPD) following the PCV7 introduction in the US was remarkable [6], not only in the vaccinated target cohort of children but also in unvaccinated older children and adults because of the indirect (herd) effect through reduction in vaccine-type pneumococcal carriage in children and reduced onward transmission to others. The success of the US program encouraged other countries to introduce PCV in their infant vaccination programmes. Other countries, however, have reported less remarkable reductions in IPD incidence, mostly because of more rapid emergence of IPD due to non-PCV serotypes as a result of the replacement phenomenon [2–5,7]. The reasons for this differing epidemiology between the US and

Abbreviations: PCV, pneumococcal conjugate vaccine; IPD, invasive pneumococcal diseases.

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Table 1
PCV vaccination programmes and the incidence and PCV vaccination programme impact in the countries for children below 5 years of age.

Country/Provincewith references	PCV7 introduction year and infant vaccination schedule	PCV10/PCV13 introduction year and infant vaccination schedule	Estimated vaccination coverage	Pre-PCV* overall IPD incidence	Post-PCV overall IPD incidence**	Incidence Rate Ratio, overall IPD	Pre-PCV Non-vaccine*** type IPD incidence	Post-PCV non-vaccine type IPD incidence	Incidence Rate Ratio, Non-vaccine type IPD
United States [1,12]	2000; 3 + 1; catch-up for children < 5	PCV13 2010; 3 + 1; catch-up for children < 5	76% for at least three doses	94.5	9.0	0.10	6.5	7.0	1.08
USA, adjusted outpatients				64.5	2.8	0.04	4.4	2.2	0.49
USA, adjusted inpatients				30.0	6.2	0.21	2.1	4.8	2.34
Quebec, Canada [2,14]	2004; 2 + 1; catch-up for children < 5	PCV10 2009 and PCV13 2011; 2 + 1; no catch-up	97–98%, at least one dose	67.3	14.8	0.22	5.1	12.2	2.38
England & Wales [4]	2006; 2 + 1; catch-up for children < 2	PCV13 2010; 2 + 1; no catch-up	94%, two primary doses	31.6	9.2	0.29	3.1	8.0	2.60
The Netherlands [4,15]	2006; 3 + 1; no catch-up	PCV10 2011; 3 + 1; no catch-up, (2 + 1 from 2013 onwards)	93–95%	19.8	5.9	0.30	4.0	5.0	1.26
Finland [5]	Not introduced	PCV10 2010; 2 + 1; no catch-up	94–95%, at least one dose	32.2	9.5	0.30	6.3	8.5	1.35

* Average for 2 pre-PCV years in each country, per 100 000 person-years.
** Average for years 5 and 6 for post higher-valency PCVs, per 100 000 person-years.
*** Non-PCV13 for the US, Quebec and England & Wales; non-PCV10 for The Netherlands and Finland.

the other countries have remained largely unknown, yet several hypotheses have been proposed: differences in pre-vaccination serotype distribution, environmental and sociologic factors influencing transmission and replacement, antimicrobial use influencing the emergence of antibiotic-resistant clones, and variation in diagnostic and hospitalisation practices [8].

One major difference in the pre-PCV era was the higher IPD incidence in the US compared to many other countries and inclusion of a high proportion of outpatient cases without hospitalisation in the Active Bacterial Core (ABC) IPD surveillance [6,9]. The high proportion of non-hospitalised IPD cases diminished with time since PCV7 introduction, with most reported cases in recent years being hospitalised [6,10–11]. To date, a formal analysis comparing PCV impact on hospitalised and outpatient IPD cases in different settings has been missing.

Therefore, we reanalysed the published data in children to explore impact of PCV7 and higher-valent PCVs in the US on hospitalised and outpatient IPD incidence separately, and compared those to results from countries with well-established surveillance systems including England & Wales, Finland, The Netherlands and Quebec (Canada).

2. Methods

We performed a descriptive analysis for the surveillance data published previously or specifically extracted the data for the present analysis. Details of the PCV vaccination programmes in different countries are presented in Table 1 [1–5].

US CDC researchers were invited as co-authors, but they declined and thus we had no access to the ABC surveillance individual data. Therefore, the US incidence rates were extracted from the public website for 1998–2015 [12].

The IPD surveillance is nationwide in England and Wales, Quebec (for children) and Finland. Sentinel surveillance is used in the Netherlands (9 sites, approximately 25% of the Netherlands population) and in the US ABC surveillance (currently 10 sites, approximately 10% of the US population).

We extracted the proportions of hospitalised and outpatient IPD cases in children less than 5 years of age from the national dataset for Quebec and Finland. Hospitalisation was defined as an inpatient admission into a hospital ward. Data for the US [1,6,10–11] were extracted from the published literature as reported (no definitions given). In England and Wales and The Netherlands, blood cultures, especially in children, are nearly always only performed in the hospital setting [4,9,13].

We divided the IPD incidence into hospitalised and outpatient categories for the US-ABC data. We assumed similar vaccine/non-vaccine serotype distributions in hospitalised and outpatient categories in the absence of detailed published data for the post-PCV13 era, and therefore, used adjusted incidence rates for hospitalised and outpatient non-PCV serotypes, based on the overall distribution of annual hospitalised and outpatient categories. Analysis of data reported from US ABC surveillance [10], however, allowed comparison of the serotype distribution between PCV7 and non-PCV7 serotypes in the pre- and post-PCV7 era. This showed similar proportions of IPD cases due to non-PCV7 serotypes in hospitalised and non-hospitalised cases (19% and 16%, respectively) in the pre-PCV7 baseline period (1998–1999) and in the post-PCV7 period from 2006 to 2007 (98% and 99%, respectively). As the proportions of hospitalised IPD cases in the other countries except the US were stable without any trends, we report for those overall IPD only.

Using a before-after design, we compared the average incidence during the two years prior to first PCV introduction up until years 5 and 6 (average of either calendar years or epidemiological years as available for each surveillance region) after the extended-valency

PCV (either PCV10 or PCV13) and calculated the incidence rate ratios (IRR) by dividing the post-PCV incidence rate by the pre-PCV incidence rate.

3. Results

Before PCV introduction, only 32% of IPD cases in children below 5 years were hospitalised in the US but this proportion increased to 69% after PCV introduction by 2012. In contrast, 67 to 99% of childhood IPD cases were hospitalised in the other countries and this proportion remained relatively constant over the surveillance period (Fig. 1, Supplement Figure 1).

IPD incidence prior to PCV introduction and up until 5 to 6 years after introduction of higher-valent PCVs (PCV10/PCV13), with their respective IRRs are shown in Table 1. While the decreases in overall IPD were similar for other countries, the results for the US differed. When the US results were stratified by hospitalisation status, the results for hospitalised IPD cases were consistent with the results of the other countries (Table 1, Fig. 2).

The US ABC results diverged especially for replacement disease due to non-PCV serotypes, with a greater than 2-fold increase in the adjusted incidence of hospitalised cases of IPD due to non-PCV13 serotypes compared to 51% reduction in outpatient IPD cases due to non-PCV13 serotypes (Table 1, Fig. 2). The incidence and trends in replacement disease due to non-PCV13 serotypes that was observed among hospitalised IPD cases in US children was similar to that observed for the other countries (Fig. 2).

4. Discussion

Our analysis shows that the impact of PCVs on overall IPD incidence in hospitalised children younger than 5 years was similar in the US ABC surveillance compared to the other countries in North America and Europe. Strikingly, in the US the relative changes for non-PCV IPD representing replacement disease diverged between hospitalised and outpatient cases. This differential impact would be consistent with a reduction in routine blood cultures taken from young children in the emergency departments and outpatient clinics during the post-PCV era; this change in diagnostic practice has been suggested in many published reports since PCV introduction in the US [16–18], yet has not been formally reported in any impact evaluation.

Another possible reason for the differential reduction in hospitalised and outpatient IPD cases within the US ABC surveillance could be due to differences in serotype distribution between these two patient groups, i.e. if IPD cases among outpatients were more commonly caused by vaccine serotypes. However, this does not seem be the case as, in children younger than 5 years of age, 84% of outpatient IPD cases in the pre-vaccine era were due to PCV7 types, compared to 81% of the hospitalised IPD cases in the US (Ref. 10, Table 3) [10].

The 3-fold higher incidence of IPD prior to PCV introduction in the US compared to most other countries is likely due to differences in detection and diagnosis of IPD, especially taking blood cultures from febrile children in outpatient settings. Outside the US, the blood cultures are mostly taken in inpatient settings. In the present study, most laboratory-confirmed IPD cases were hospitalised; 97–98% in the Netherlands [12], 86–95% in Finland, 67–91% in Quebec (Supplement Figure) and almost all cases in England and Wales. Obtaining blood cultures in the outpatient setting would increase the number of laboratory-confirmed IPD cases (i.e. true positives), which would not be included in routine IPD surveillance in the other countries. Finnish vaccine probe studies have shown that in addition to laboratory-confirmed IPD, PCV can prevent a considerably higher disease burden of clinically suspected IPD cases in which blood cultures remained negative [19–20]. Thus, the true incidence of IPD is higher than estimated trough most laboratory-based surveillance systems. The estimation of the relative impact of any vaccination programme is not biased by low sensitivity of case detection (e.g. by exclusion of cases presenting or being treated outside the hospital setting) as long as the situation remains stable. However, any changes in case ascertainment during the vaccine evaluation period (e.g. reduced blood culturing in the outpatient setting) can cause a differential bias and distort the evaluation.

Ecological before/after studies are particularly vulnerable to different sources of bias. Regarding the evaluation of PCV impact, differences in the IPD reduction after PCV introduction and the degree of replacement disease may be due to different serotype distributions during the pre-vaccination era including the contribution of vaccine-preventable serotypes to overall IPD, contemporaneous implementation of other interventions such as influenza vaccination, changes in hospitalisation practices and/or outpatient management, changes in severity of clinical disease leading to differential presentation to primary care or the hospital, or changes

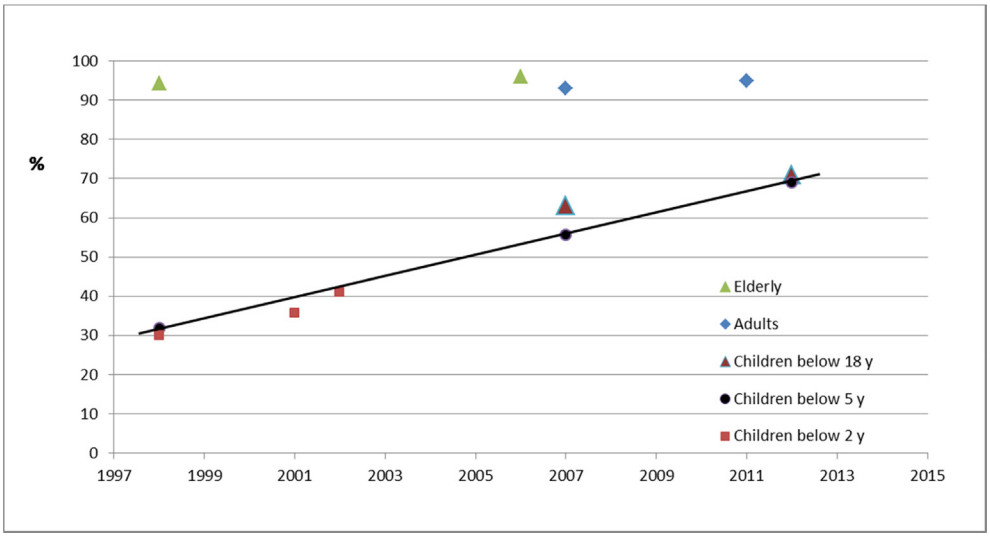

Fig. 1. Proportion of hospitalised cases out of all reported IPD cases in the US ABC surveillance by calendar year in children and adults based on published reports [6,10–11].

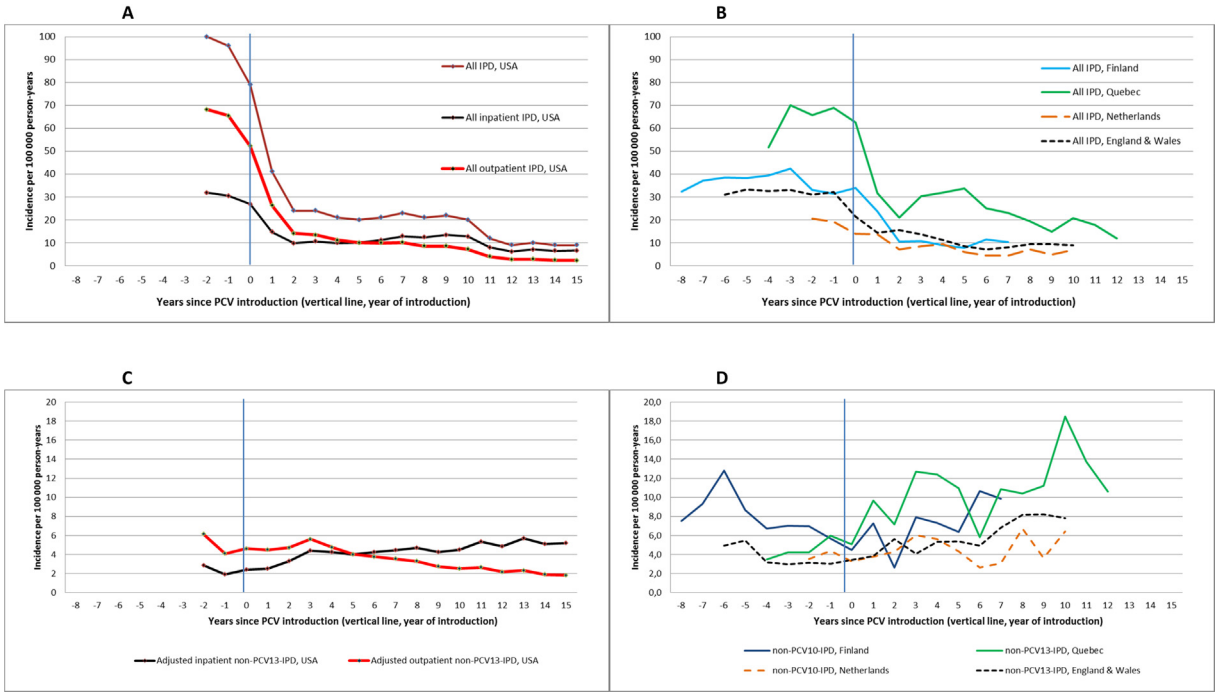

Fig. 2. Incidence of all IPD in children below 5 years of age in US (panel A) and in Quebec, Canada and European countries (panel B) before and after infant PCV introduction*, panels C and D for non-PCV serotypes.

in the management of cases with underlying comorbidities and other risk factors. Evaluation of vaccine impact is also complicated by changes in transmission dynamics over time and secular or geographic trends within pneumococcal serotypes or clonal lineages that may be unrelated (e.g. changes in serotype 1 IPD prior to PCV13 introduction) [8] or related (e.g. selection pressure) to the immunisation programme. These can be partially controlled by using trend analyses, external controls, or a combination of these.

A limitation of this analysis includes the lack of data for IPD cases in the ABC surveillance stratified by inpatient/outpatient status and serotype grouping. We therefore assumed similar proportions of vaccine serotypes causing IPD in the outpatient and inpatient cases in the US. One US study, which did report IPD cases by serotype grouping and inpatient/outpatients status for the pre and post-PCV7 era, showed a significant increase in IPD due to non-PCV7 serotypes for hospitalised cases from 6.1 to 12.3 per 100 000 person-years but a non-significant decrease in outpatient NVT IPD cases (from 10.7 to 9.7) by 2006–2007 [10]. Our results are in line with these, taking into account that we reported changes over a longer time-period when further reductions in the proportion of outpatient IPD cases were reported in the ABC surveillance. The sole aim of the current analysis was to compare the US-ABC hospitalised IPD cases to overall IPD for the other countries, where most IPD cases are routinely hospitalised; therefore, differences in the vaccination programmes, schedules, vaccines uptake or other surveillance factors between the different countries were not considered in detail. For example, increase in non-PCV-types (replacement disease) seemed lower in the PCV10 countries Netherlands and Finland (Table 1), probably due to the cross-protection against 19A and 6A, here included as non-PCV10 types.

The US-ABC surveillance has also reported a divergent indirect impact of the childhood PCV programme on older adults aged 65 years or more. While disease replacement with non-PCV serotypes increased 2–4-fold in other countries, the increase reported by US-ABC has been minimal [1,8]. The reason for this discrepancy is not the same as in the children, since nearly all IPD cases among older adults were routinely hospitalised prior to vaccine introduction (Fig. 1). However, this difference could be explained by changes in blood culture or hospital admission practices within the ABC surveillance. The published data [10] suggest changes mainly in the clinical syndrome of bacteraemia without a focus; among 65+ year-olds, non-PCV type invasive pneumonia incidence increased significantly (from 18.5 to 26.6/100 000) as did pneumococcal meningitis (from 1.1 to 1.4/100 000) while bacteraemia without focus decreased slightly (from 6.5 to 5.9) [10].

In conclusion, we suggest that the reduction in outpatient blood culture practice after the PCV introduction in US has contributed to the discordant results observed in the US ABC surveillance data compared to other high-income countries for IPD in children. Therefore, for scientific reports and for cross-country comparison purposes, the analysis of IPD surveillance data should be stratified by hospitalisation status.

Authors contributions

AAP conceived and proposed the study idea and drafted the first analyses with PDW, EAMS, and EM. PDW, MT, SNL, GD, MJK, EAMS, and EM provided the surveillance data, and contributed to the interpretation of the data. AAP drafted the manuscript. All authors had access to the data, reviewed the manuscript, and commented on and approved the final version.

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Declaration of Competing Interest

AAP and MT report grants from GlaxoSmithKline, Pfizer, and Sanofi to the Finnish Institute for Health and Welfare for research

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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.2021.01.070.

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