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REGULAR ARTICLE

Increase in tympanostomy tube placements despite pneumococcal vaccination, a population-based study

Elias Eythorsson[1], Samuel Sigurdsson[1], Helga Erlendsdóttir[1,2], Birgir Hrafnkelsson[3], Karl G. Kristinsson[1,2], Ásgeir Haraldsson (asgeir@lsh.is)[1,4]

1.Faculty of Medicine, University of Iceland, Reykjavik, Iceland
2.Department of Clinical Microbiology, Landspítali University Hospital, Reykjavik, Iceland
3.Department of Mathematics, University of Iceland, Reykjavik, Iceland
4.Children's Hospital Iceland, Landspítali University Hospital, Reykjavik, Iceland

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Correspondence
Ásgeir Haraldsson, Department of Paediatrics, University of Iceland, Children's Hospital Iceland, Landspítali–University Hospital, 101 Reykjavík, Iceland.
Tel: +354 5433050 |
Fax: +354 5521331 |
Email: asgeir@lsh.is

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ABSTRACT

Aim: The aim was to estimate the impact of the 10-valent pneumococcal vaccine (PHiD-CV) on tympanostomy tube placements (TTP) in children under five years of age in Iceland.

Methods: This population-based observational cohort study followed 11 consecutive birth-cohorts 2005–2015 from birth until their fifth birthday. Population registries were merged using national identification numbers. The risk of TTP was compared between birth-cohorts adjusted for the number of previous otitis media diagnoses and antimicrobial prescriptions. A Cox regression model was applied and the hazard ratio (HR) of TTP was estimated between each birth-cohort and the last vaccine non-eligible birth-cohort. The vaccine impact of PHiD-CV10 on TTP was estimated as 1-HR ×100%.

Results: In total, 51 247 children were followed for 210 724 person-years, of which 14 351 underwent 20 373 procedures. The estimated vaccine impact on TTP was −6% (95% CI −16% to 2.7%). Children in the vaccine-eligible cohorts had fewer previous otitis media diagnoses and had been prescribed fewer antimicrobials prior to the procedure than children in the vaccine non-eligible cohorts.

Conclusion: Despite high uptake of PHiD-CV10, tympanostomy procedures increased in Iceland during the study period. Vaccine-eligible children had milder disease prior to the procedure. The reason underlying these findings are speculative.

INTRODUCTION

Tympanostomy tube placements (TTP) are the most common paediatric surgical procedure in high-income countries (1,2). The most frequently cited indications for TTP are persistent serous otitis media and recurrent acute otitis media (3,4). Studies have consistently demonstrated the benefit of TTP in the treatment serous otitis media (3,4) while evidence for their use in the treatment of recurrent acute otitis media is inconsistent (3,5).

Prior to the general introduction of pneumococcal conjugate vaccines, the most common pathogens causing recurrent acute otitis media were *Haemophilus influenzae* and *Streptococcus pneumoniae* (6). Three randomized controlled trials of pneumococcal conjugate vaccines (PCV) evaluated the vaccine efficacy against TTP and revealed a trend towards fewer TTP in vaccinated children compared to unvaccinated, with vaccine efficacy estimates of 20.1% (95% CI 1.5% to 35.2%) (7), 6% (95% CI −14% to 23%) (8) and 13% (95% CI −2% to 26%) (9), respectively.

In 2011, the 10-valent pneumococcal *Haemophilus influenzae* Protein D conjugate vaccine (PHiD-CV, Synflorix®) was introduced into the paediatric vaccination programme in Iceland, with a two + one schedule given at

Abbreviations

ARD, Absolute risk difference; HR, Hazard ratio; IQR, Interquartile range; OM, Otitis media; PCV, Pneumococcal conjugate vaccine; PHiD-CV, The 10-valent pneumococcal *Haemophilus influenzae* Protein D conjugate vaccine; RR, Risk ratio; TTP, Tympanostomy tube placements; VEC, Vaccine-eligible cohort; VNEC, Vaccine non-eligible cohort.

Key notes

- Tympanostomy tube placements are the most common paediatric surgical procedure and are commonly performed at private outpatient clinics.
- In this whole-population cohort study, the incidence of tympanostomy tube placements increased following the introduction of PHiD-CV10.
- Children in the vaccine-eligible cohorts had fewer documented physician visits for otitis media and had received fewer antimicrobial prescriptions prior to the tympanostomy procedure.

three, five and 12 months of age. All children born in 2011 and later were eligible. Vaccine uptake was immediately high with over 97% of each eligible birth-cohort receiving the primary vaccination by their first birthday (10). No systematic pneumococcal vaccination programme had previously been implemented.

The aim of this study is to estimate the vaccine impact of PHiD-CV against TTP in children under five years of age in Iceland and estimate the change in risk factors in children prior to undergoing the procedure.

METHODS

Data sources

This study was an individual level observational cohort study of all outpatient TTP in Iceland, from 1 January 2005 to 2031 December 2016. Consecutive birth-cohorts, 2005–2015 were included and followed from birth until 60 months of age or end of the study period.

Data were collected from three population-based registries and from Landspitali University Hospital's patient registry. The four registries were merged with Statistic Iceland's population registry, using unique national identification numbers. The population register contains demographic information, including gender, date of birth, immigration, emigration and death for every permanent resident of Iceland. Children who immigrated to Iceland after birth were excluded from the analysis. The observation time of children who emigrated was censored on the date of emigration. This allowed for accurate person-year at risk calculations.

Data on TTP were extracted from the Icelandic Health Insurance reimbursement database, using the reimbursement codes for TTP. The data included the calendar year and month of the procedure, the specific subtype of procedure and the surgeon's identification number. Additionally, information on all TTPs performed at Landspitali University Hospital was systematically extracted from the patient registry using procedural codes.

Data on primary care visits were obtained from the Primary Care Database of the Icelandic Directorate of Health, which covers all Primary Health Care Centres in Iceland. These data were only available until 31 December 2015. The Primary Care Database contains information on all primary care visits in Iceland. A visit was defined to be due to otitis media (OM) if an International Classification of Diseases, 10th Revision (ICD-10) diagnostic code for non-suppurative otitis media (H65), suppurative otitis media (H66), mastoiditis (H70) or perforation of tympanic membrane (H72) was recorded by the physician. Repeat visits within 30 days of the initial visit were assumed to be due to the same episode and were excluded from the analysis. Data on urgent care visits to the paediatric emergency department of the Children's Hospital Iceland during the same period were extracted from Landspitali University Hospital's patient registry using the same methodology.

Data on all filled prescriptions with the anatomical therapeutic chemical classification code J01 (antibacterials for systemic use) and subgroups were extracted from the National Drug Prescription Database of the Directorate of Health, which contains information on all outpatient drug prescriptions in the country.

Statistical methods

Statistical analysis was stratified by birth-cohorts and aggregate cohorts based on vaccine eligibility. Birth-cohorts 2005–2010 were classified as vaccine non-eligible cohorts (VNEC) and birth-cohorts 2011–2015 as vaccine-eligible cohorts (VEC). Statistical analysis was performed in R statistics version 3.3.3. using the survival package (11).

Crude incidence rates of TTP per 100 person-years were estimated for each birth-cohort by 6-month age groups, and crude incidence rate ratios between the VEC and VNEC were calculated assuming Poisson variance. The cumulative incidence of TTP procedures in each birth-cohort was assessed using the Kaplan–Meier estimator and confidence intervals calculated using the log delta method. The risk of TTP was compared between birth-cohorts with respect to two measures of risk; the number of previous diagnoses of otitis media and the number of previous antimicrobial prescriptions. In the subset of children who had undergone a TTP procedure and had full follow-up time (birth-cohorts 2011 and earlier), the distribution in the count of visits and prescriptions prior to the child's first TTP was compared between VNEC and VEC using an overall Chi-Squared Test of Independence. When assessing the previous visits, the observation age was four years of age due to restricted data. If a significant overall difference was detected, the risk ratio (RR) and absolute risk difference (ARD) within each level of the risk factor was estimated and tested using Chi-squared Tests of Independence. This was repeated for 36 month follow-up time.

A Cox regression model was applied to the individual level data to accurately account for the influence of age and censored follow-up time. The hazard ratio (HR) of TTP was estimated between each of the study's birth-cohorts and the last VNEC (2010), which was used as a reference. The vaccine impact of PHiD-CV against TTP was then estimated as 1–(the hazard ratio between the last vaccine-eligible cohort and the reference cohort) $\times$ 100%. Additional Cox regression models that incorporated the number of previous otitis media visits and antimicrobial prescriptions as time-dependent covariates were fitted to further correct the vaccine impact estimate for confounding. The Cox regression model using the number of previous otitis media visits was censored at 31 December 2015 due to restricted data. Each Cox model was stratified by gender and accounted for the correlation between repeated observations of the same child with sandwich variance estimates.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). There was no patient or public involvement in this study.

RESULTS

Demographics

Information was available for 53 218 children born in 2005–2015. Of those, 1892 children immigrated to Iceland after birth and were therefore excluded from the analysis. A further 55 children were excluded due to lack of accurate information on their date of birth, and 24 children were excluded because their follow-up time was less than one month. The remaining 51 247 children were followed for a total of 210 724 person-years. A total of 14 351 children underwent 20 373 TTP procedures during the study period, 57% of whom were male. Study demographics are summarised in Table 1. The median age of the children at the time of their first TTP was 17 months (IQR 13-24). Of the children who underwent the procedure, 10 248 (71%) had only one TTP procedure, 2902 (20%) had two, and 1201 (8%) had three or more. Most of the procedures (98%) were performed in private outpatient clinics. The number of otolaryngologists performing outpatient TTP increased from 15 in 2005 to 2023 in 2016 with each surgeon performing a median of 123 (IQR 56.5-196) procedures per year (Table S1).

Crude incidence rates and cumulative incidence of TTP between VNEC and VEC

The overall crude incidence rate of TTP for children under five years of age was significantly higher in the VEC compared to the VNEC, 10.6 and 8.7 procedures per 100 person-years, respectively, (IRR 1.20, 95% CI 1.17 to 1.24). The crude incidence rate was highest among children 12–17 months of age, ranging from 19.2 to 28.5 procedures per 100 person-years. A significant increase in the crude incidence rate between VNEC and VEC was noted in children 12–17 and 18–23 months of age. No significant change in other age groups was observed (Fig. 1).

The cumulative incidence of each birth-cohort that underwent at least one TTP procedure by five years of age was highest in children born in 2010 and the lowest in children born in 2006, 32% and 29%, respectively (Table 2, Figure S1).

The mean (median) number of visits to a primary care physician or paediatric emergency department for otitis media prior to TTP was 2.05 (2) visits in the VNEC compared to 1.72 (1) visits in the VEC and the overall distribution was significantly different ($p < 0.001$). The proportion of children who had never visited a primary care physician or the paediatric emergency department for otitis media prior to the TTP procedure, increased from 21% of children in the VNEC to 29% of children in VEC (RR 1.40, 95% CI 1.28 to 1.54). Conversely, children in the VNEC who underwent TTP were significantly more likely to have visited a physician because of otitis media twice and three times prior to the procedure compared to children in the VEC (Table 3, Table S2).

The mean (median) number of previous prescriptions was lower for VEC than VNEC, 3.19 (4) and 3.62 (4), respectively, and the distribution between the groups was significantly different ($p < 0.001$). Children in the VEC were more likely to have never been prescribed antimicrobials, compared to VNEC, 5% vs 3% (RR 1.52, 95% CI 1.18 to 1.96).

Hazard ratio of TTP between VNEC and VEC

Model diagnostics of all Cox regression models did not reveal significant deviations from the model assumptions. Children who had visited a primary care physician for otitis media once had a HR of 3.12 (95% CI 2.93 to 3.32) for TTP compared to children who had never visited a physician. Children who had one previous antimicrobial prescription had a HR of 6.98 (95% CI 6.13 to 7.95) for TTP compared to those who had never received a prescription. The results of the three Cox models are illustrated in Figure 2. The hazard of TTP increased gradually from birth-cohort 2005 to 2015 irrespective of correction for previous otitis media visits or antimicrobial prescriptions. There was a slight pause in the rise in the hazard of TTP in the first vaccine-eligible cohorts in all Cox models. Using the pre-specified estimate, the estimated vaccine impact on TTP was −6% (95% CI −16% to 2.7%).

Table 1 Demographic information about the study birth-cohorts

Birth-cohort	Number of children	Person-years	Number of procedures (number of children)	Median age in months (IQR)
2005	4541	21 409	1946 (1280)	17 (12-25)
2006	4665	21 988	1931 (1303)	18 (13-27)
2007	4770	22 500	1974 (1335)	18 (13-27)
2008	4949	23 313	2140 (1428)	18 (13-26)
2009	5128	24 141	2145 (1514)	18 (13-25)
2010	4984	23 580	2203 (1547)	18 (13-26)
2011	4641	22 052	1997 (1382)	18 (13-24)
2012	4667	20 191*	2057 (1419)*	16 (12-23)*
2013	4438	14 951*	1642 (1200)*	16 (13-23)*
2014	4438	10 731*	1582 (1251)*	16 (13-23)*
2015	4026	5866*	756 (692)*	13 (11-15)*
Total	51 247	210 723	20 373 (14 351)	17 (13-24)

The number of tympanostomy tube procedures is shown along with the total number of children who underwent at least one procedure. The median age at the time of the child's first procedure is provided. Birth-cohorts 2012–2015 did not reach full five-year follow-up time due to censoring. Values which are not directly comparable to previous birth-cohorts due to censoring are marked with an asterix (*).

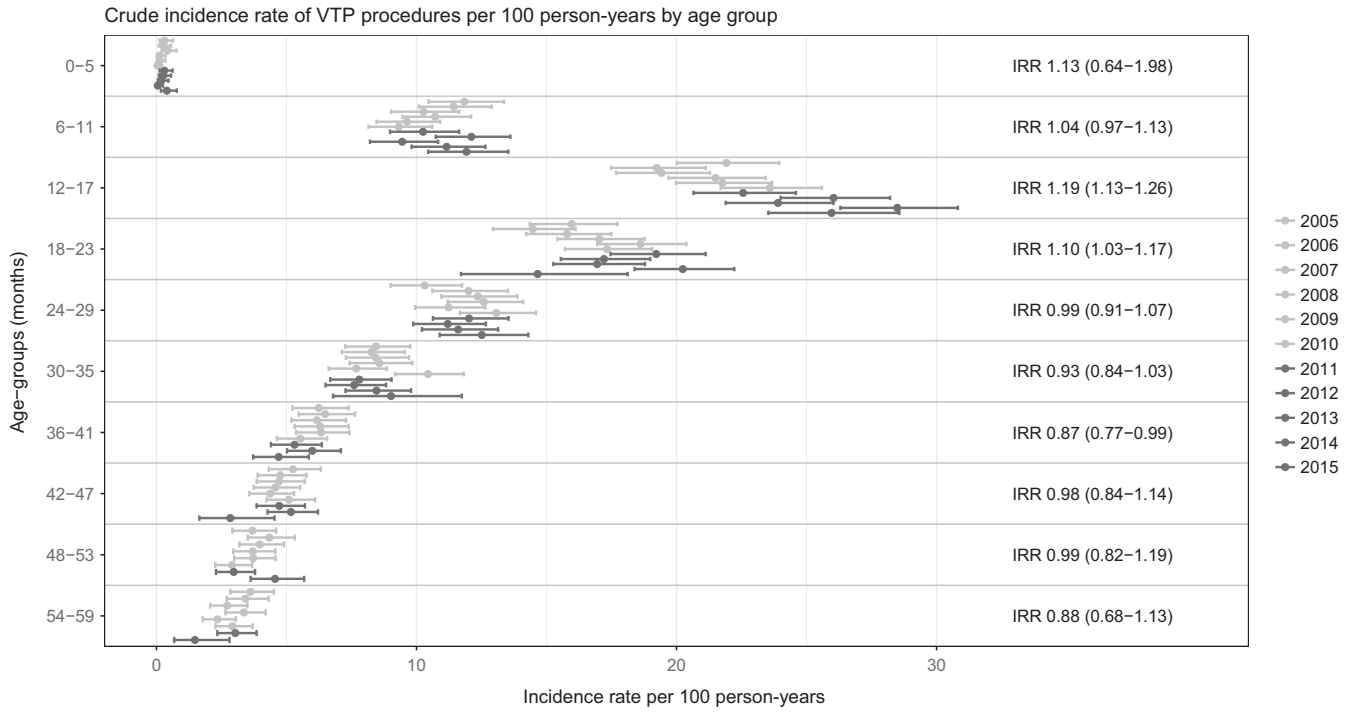

Figure 1 The incidence rate of tympanostomy tube procedures per 100 person-years for each birth-cohort is depicted, stratified by six-month age groups. Estimates are illustrated as points with error-bars indicating 95% confidence intervals. Vaccine non-eligible cohorts (VNEC) are illustrated in light grey and vaccine-eligible cohorts (VEC) in dark grey. The incidence rate ratios between VEC and VNEC are written in along with 95% confidence intervals.

Table 2 The cumulative incidence of each birth-cohort that has undergone at least one tympanostomy tube placement (TTP) by six-month age intervals

Birth-cohort	6 m (%)	12 m (%)	18 m (%)	24 m (%)	30 m (%)	36 m (%)	42 m (%)	48 m (%)	54 m (%)	60 m (%)
2005	0.4	7.2	16.4	21.1	23.7	25.8	26.9	27.8	28.4	28.8
2006	0.3	7.1	14.8	19.5	22.9	24.8	26.5	27.4	28.3	28.6
2007	0.4	6.6	14.9	19.7	23.4	25.3	26.7	27.8	28.4	28.6
2008	0.2	7.2	15.9	21.0	24.5	26.5	27.7	28.5	29.1	29.5
2009	0.3	6.5	15.7	22.0	25.1	27.2	28.5	29.1	29.9	30.2
2010	0.1	6.6	16.5	22.4	26.3	28.8	30.1	31.0	31.4	31.7
2011	0.4	6.6	16.3	23.3	26.3	27.9	28.7	29.4	30.1	30.5
2012	0.2	7.8	18.3	23.9	26.7	28.3	29.5	30.4	30.9	–
2013	0.3	6.5	16.3	21.7	25.0	26.9	27.5	–	–	–
2014	0.2	6.9	19.1	26.1	29.1	–	–	–	–	–
2015	0.5	7.8	18.6	–	–	–	–	–	–	–

Birth-cohorts 2005-2010 are vaccine non-eligible cohorts (VNEC), and birth-cohorts 2011–2015 are vaccine-eligible cohorts (VEC). Birth-cohorts 2012–2015 did not complete the full five-year follow-up time. In those cases were no child in the birth-cohort reached the beginning of the six-month age interval during the study period, the unknown proportion is represented with a hyphen (–).

DISCUSSION

This observational cohort study of 11 consecutive birth-cohorts from 2005 to 2015 demonstrated an unusually high incidence rate of TTP among young Icelandic children. Both the incidence and cumulative incidence of TTP increased over the study period despite the introduction of PHiD-CV. Children in the vaccine-eligible cohorts who underwent the procedure had visited a physician less often for the treatment of otitis media and had filled antimicrobial prescriptions than children in the VNEC, before undergoing the procedure. The largest increase in the incidence of TTP was observed in children 12–17 and 18–23 months of age, despite a considerable reduction in the incidence of acute otitis media in those age groups (10).

These results are unexpected. Our research group has previously published studies on the impact of the PHiD-CV vaccination programme in Iceland showing a 24% decrease in paediatric emergency department visits for otitis media (12), a 22% decrease in all-cause acute otitis media in primary care (10), a 6% decrease in all-cause outpatient antimicrobial prescriptions (13) and a 55% reduction in otitis media with treatment failure, as measured by the

Table 3 The cumulative number of previous otitis media visits and antimicrobial prescriptions are shown for those children in the vaccine non-eligible cohorts (VNEC) and the vaccine-eligible cohorts (VEC) who underwent at least one tympanostomy tube placement

	Previous visits for otitis media			Previous antimicrobial prescriptions		
Cum No.	VNEC % (n)	VEC % (n)	RR (95% CI)	VNEC % (n)	VEC % (n)	RR (95% CI)
Zero	20.6 (1716)	28.9 (398)	1.40 (1.28 to 1.54)	3.4 (286)	5.2 (72)	1.52 (1.18 to 1.96)
One	24.9 (2076)	24.4 (337)	0.98 (0.89 to 1.09)	11.6 (966)	12.8 (177)	1.11 (0.95 to 1.29)
Two	20.4 (1705)	19.6 (270)	0.96 (0.85 to 1.07)	19.3 (1608)	22.6 (311)	1.27 (1.05 to 1.30)
Three to four	24.9 (2075)	20.2 (279)	0.81 (0.73 to 0.91)	37.8 (3154)	37.4 (516)	0.99 (0.92 to 1.07)
Five to seven	8.0 (666)	6.4 (89)	0.81 (0.65 to 1.00)	22.3 (1860)	19.3 (266)	0.87 (0.77 to 0.97)
Eight or more	1.2 (104)	0.4 (6)	0.35 (0.15 to 0.79)	5.6 (468)	2.7 (37)	0.48 (0.34 to 0.67)

The proportion of each cohort who had the corresponding number of prior visits or prescriptions is shown with the absolute number of children within parentheses. The relative risk (RR) of having each number of previous visits or prescriptions between the VEC and VNEC is shown with 95% confidence intervals.

incidence of ceftriaxone use for otitis media (14). Taken together, these results strongly indicate a reduction in the burden of disease associated with otitis media following PHiD-CV introduction. This however is not reflected in a decrease in TTP, as demonstrated by the current study.

Three randomized controlled trials have evaluated the effect of PCV on rates of TTP. In the Northern California Kaiser Permenente trial, 37 868 children were randomized in a double-blinded study to receive either PCV7 or meningococcus type C vaccine. A 20.1% (95% CI 1.5% to 35.2%) reduction in TTP was noted in the PCV7 cohort compared to the control (7). A similar trial conducted in Finland randomized 1662 children to receive either PCV7 or Hepatitis B vaccine and followed them with repeat examinations up to 24 months of age. A non-significant odds ratio 0.94 (95% CI 0.77 to 1.14) for TTP in the PCV7 was demonstrated (8). Finally, in Finland in 2014, a cluster randomized trial in which over 47 000 children were randomized to either PHiD-CV or Hepatitis B vaccine, found a non-significant decrease of 13% (95% CI −2% to 26%) (9). Observational studies have generally shown a decrease in TTP following vaccination. TTP was shown to have decreased by 16% (95% CI 11% to 21%) and 23% (95% CI 10% to 35%) in Tennessee and New York, respectively, following PCV7 introduction (15). Similarly, there was a 23%, 16% and 6% reduction in rates of TTP in children under one, one and two years of age in Australia following PCV7 introduction (16). However, not all countries have seen decreases following PCV introduction. Denmark implemented PCV7 in a two + one schedule into their paediatric vaccine scheme in October 2007. They have noted increasing TTP rates since 1998, and this upward trend remained unchanged following vaccine introduction (17).

Our study confirms the previously reported high incidence rate and prevalence of TTP in Iceland, compared to other countries. The prevalence of children one to six years of age who underwent one or more TTP in Iceland was 29% in 1998 (18) and 34% in 2003 (19). Our data show that 31% of children in the latest birth-cohort with full five years of follow-up had undergone TTP. This is higher than; Australia (6% of five-year-old children) (20); Canada (7% of three-year-olds) (21); Denmark (29% of five-years-olds) (22); Norway (9% of four-year-olds) (23); Sweden (1% of ten-year-olds) (24) and USA (7% of three-year-olds) (25).

These numbers are concerning. It is difficult to explain the reasons for a continued increase in the number of TTP performed in a country that already has one of the highest incidence of these procedures in the world (18,19). The burden of otitis media is dwindling, while the proportion of children undergoing the procedure is rising. The children in the VEC had fewer diagnoses of otitis media and were prescribed fewer doses of antimicrobials than children in the VNEC prior to the procedure, and thus seem to have less severe disease. All antimicrobial prescriptions regardless of provider or indication were included. However, patient data on visits to otolaryngologists and paediatricians in independent practice were unavailable due to coding differences and may be considered a confounder.

Data from Statistics Iceland's website show that visits to private practicing specialists have increased in Iceland, including visits to paediatricians and otolaryngologists. It is possible that a portion of non-emergent cases has moved from primary care to specialist care. Nevertheless, after-hours and urgent visits to private paediatricians were unchanged during the study period (personal correspondence with head of largest private paediatrician clinic), which suggests that paediatricians do not see acutely ill children with otitis media more often than previously. No urgent or after-hour clinic is operated by otolaryngologists.

Health care in Iceland is a single-payer system with the government guaranteeing equal access for all permanent residents through a single national health insurance scheme. Healthcare providers are either salaried governmental employees or independent practitioners who work within a framework agreement with Icelandic Health Insurance, and are reimbursed on a per case basis, according to pre-determined negotiations. There are no set regulations regarding the indication for, or the number of TTPs which may be performed annually at clinics in Iceland, and patients did not require a referral to make an appointment during the study period. The number of operating otolaryngologists increased during the study period. The out-of-pocket fee for TTP is low, a nominal outlay in a high-income country. Furthermore, data from Statistics Iceland's website show that the employment for

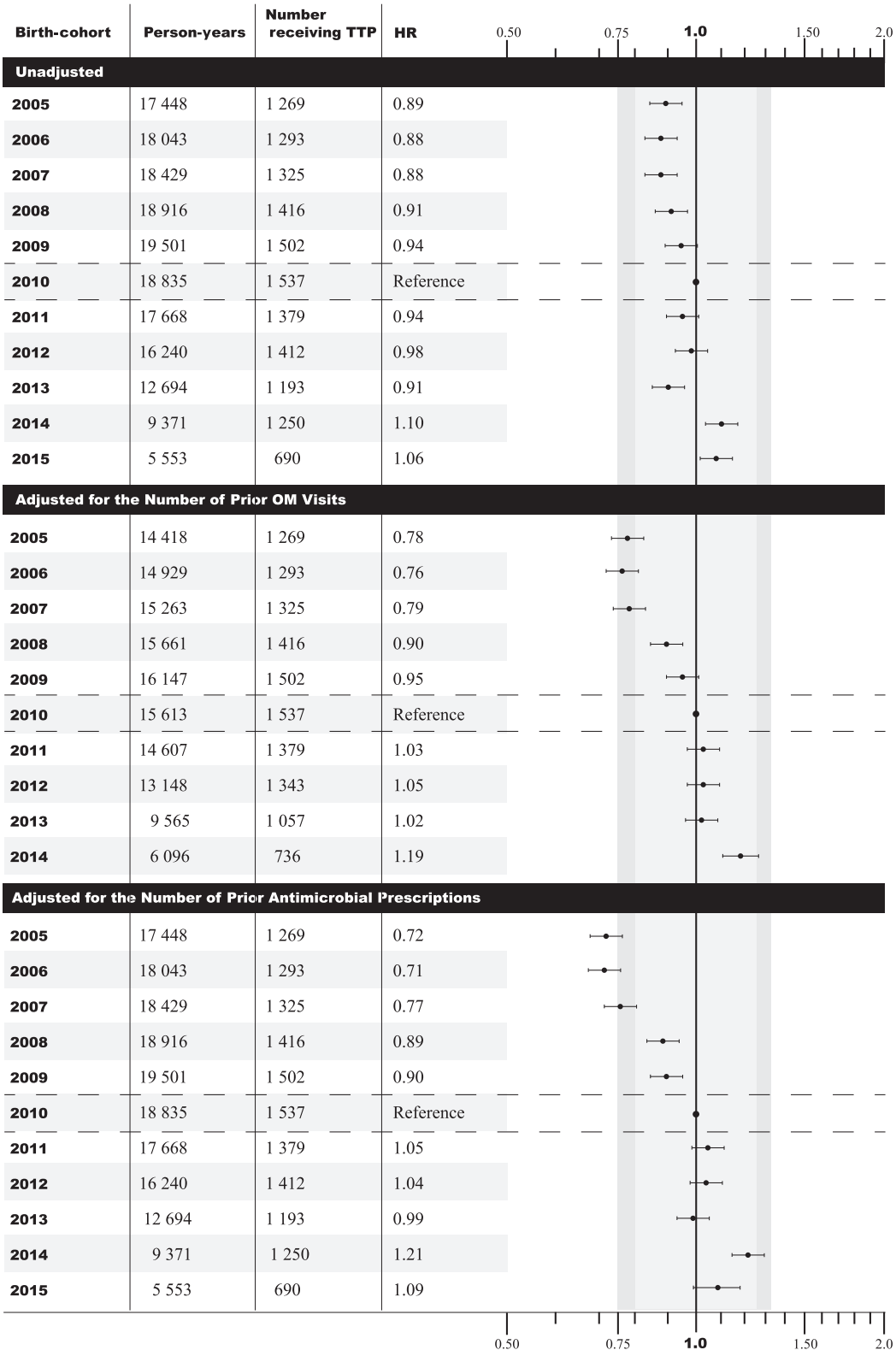

Figure 2 The hazard ratio (HR) of tympanostomy tube placement between each birth-cohort and the last vaccine non-eligible birth-cohort are depicted, as estimated by three Cox regression models. At the top, unadjusted HR estimates are illustrated. HR estimates adjusted for the number of prior otitis media visits compromises the middle and prior antimicrobial prescriptions are illustrated at the bottom.

both genders has increased in recent years, and is among the highest in Europe (26). This may account for increased parental pressures for early intervention to avoid work absence. Antimicrobial usage, which like other paediatric interventions, may often be driven by parental pressure (27,28), is also comparably high in Iceland, but has decreased following the introduction of PHiD-CV (13).

There were two main limitations to our study. First, as discussed above, we were unable to include visits to specialists in this study. Second, as with any vaccine ecology study we cannot exclude the possibility of unmeasured confounding. Because the data are extracted from a reimbursement database, we do not have information concerning the indications for TTP. We therefore cannot exclude the possibility that, during the study period, there has been a shift towards indications that are not associated with the number of previous otitis media diagnoses in primary care or antimicrobial usage. However, we are unaware of any evidence supporting this hypothesis. Even if it were the case, there is evidence to suggest that PCV decreases both recurrent acute otitis media and serous otitis media (8,29). This study group has previously shown that recurrent acute otitis media has decreased in Iceland following the introduction of PHiD-CV10 (10). There is an increasing trend in the incidence of TTP in the vaccine non-eligible cohorts among children 12–17 and 18–23 months of age, as seen in Figure 1. However, interpreting changes in specific age groups within cohorts must be done with caution. Whether or not a child has a procedure at a young age modifies his or her risk of having a procedure later, and therefore a survival analysis approach was age is taken into account is more appropriate. The hazard of TTP is also shown to increase in the VNEC in Fig. 2. Visually, the increasing trend then seems to plateau in vaccine-eligible cohorts. It is possible that the incidence and cumulative incidence of TTP would have increased more sharply, had PHiD-CV10 not been introduced. The current study's design is however unable to provide evidence for or against this hypothesis.

The study has several strengths. The study population is well defined, including every child in the age group in the entire country. Individual level data on all TTP reimbursements spanning the six years before and after the vaccine introduction were extracted from databases of the Icelandic Health Insurance, which is the only Health Insurance provider in the country. This fact enables the accurate analysis of prevalence rate, incidence rates, incidence proportions and survival rate of TTP. In addition, it makes possible an accurate depiction of the burdens of the disease in children prior to receiving tubes, and of the indications for the procedures and the risk factors involved.

CONCLUSION

The incidence, cumulative incidence and hazard of TTP increased significantly during the study period, which spans a six-year period before and after the introduction of the PHiD-CV into the Icelandic paediatric vaccination programme. There was some evidence of increasing trend prior to vaccine introduction, which did not appear to have an impact on the incidence of TTP procedures. The reason for this is unclear and is neither in concordance with other studies evaluating PCV impact on TTP, nor does it reflect previous studies on the impact of PHiD-CV in Iceland. Our results suggest that children with softer indications or milder disease are receiving TTP. Further research is warranted. The data underlying the current study can be used to evaluate the impact of TTP on the risk of future otitis media and antimicrobial prescriptions compared to match children. The results could then be used to inform the development of national guidelines regarding the indication for tympanostomy tube placements.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose relevant to this article other than above.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Figure S1 The cumulative incidence of tympanostomy tube placements from birth to 60 months of age is shown for children in the vaccine non-eligible cohorts (illustrated in light grey) and the vaccine-eligible cohorts (illustrated in dark grey).

Table S1 A summary of the study data by calendar year. The number of tympanostomy tube placements (TTP) performed on Icelandic children younger than five years of age is shown with the number of children undergoing at least one procedure presented within parentheses.

Table S2 The absolute risk difference (ARD) in the number of previous otitis media visits and antimicrobial prescriptions between the vaccine non-eligible cohorts (VNEC) and the vaccine eligible cohorts (VEC).

Table S3 The risk ratio (RR) and the absolute risk difference (ARD) in the number of previous otitis media visits and antimicrobial prescriptions between the vaccine non-eligible cohorts (VNEC) and the vaccine eligible cohorts (VEC).

