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Impact of 7-valent versus 10-valent pneumococcal conjugate vaccines on primary care consultations across various age groups in the Netherlands, 5 years after the switch: A time-series analysis

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ABSTRACT

Background: In 2011, 10-valent pneumococcal conjugate vaccine (PCV10) replaced PCV7 in The Netherlands. We aimed to assess the impact of this switch on non-invasive pneumococcal disease in primary care across various age-groups, including pneumonia-bronchitis, otitis media (OM) and sinusitis with and without considering pre-PCV10 secular trends.

Methods: Electronic records of 397,441 individuals included in a regional primary care database from July 2006 to June 2016 were extracted (2,408,762 person-years). We fitted interrupted time-series on annual incidence rates (IR) of primary care diagnosed pneumonia-bronchitis, OM and sinusitis episodes per age-group. We performed these two types of analyses, comparing; 1) the post-PCV10 observed versus expected trend if PCV10 had not been implemented and pre-PCV10 secular trends had continued 2), the pre- versus post-PCV10 observed, model fitted trend. The latter assumes no secular trend. Incidence rate ratios (IRR) were calculated using both methods.

Results: We found significant reductions following PCV10 introduction with both analysis methods for pneumonia-bronchitis in the pediatric and adult age-groups, for sinusitis in the age-group 20–50 years and for OM, the effect across various age-groups are uncertain given contradictory results. For other outcomes and age-groups, the effect estimates were not consistent across the two-method used and heavily depended on the strength of the underlying trend. No consistent effects were observed in the elderly population, considering the two methods used.

Conclusion: Our study supports some direct and indirect-effect of PCV10 introduction on non-IPD, mainly on pneumonia-bronchitis, but estimates heavily depend on the method of analysis used. Estimates from the two different approaches may differ substantially if underlying trends are strong.

1. Introduction

Streptococcus pneumoniae (pneumococcus) is an important cause of both bacterial respiratory tract infections (RTI) and invasive disease worldwide, that affects predominantly young children and the elderly population. There are over 90 distinct pneumococcal serotypes that frequently colonize the nasopharynx asymptomatically, mostly in young children. Nasopharyngeal colonization serves as an important reservoir of transmission to other individuals. Infection occurs when pneumococci spread beyond the nasopharynx to the lower respiratory tract (bronchitis-pneumonia), middle ear (otitis media) and sinuses (sinusitis). In addition, pneumococci can also cause invasive disease, including septicaemia and meningitis [1–4]. Prior to the widespread implementation of conjugate vaccines for infants, pneumococcal disease accounted for approximately 826,000 deaths in children aged 0–5 years globally in the year 2000 [5]. In Europe, before pneumococcal conjugate vaccine (PCV) introduction, pneumococcal infection was estimated to be responsible for about 28–37% of childhood pneumonia cases [6,7] and 25–70% pneumonia cases in adults [8–10], 30% of otitis media (OM) cases and 13–27% of cases of acute sinusitis[11–13].

Given the notable health impact of pneumococcal disease, pneumococcal vaccine programs have been implemented in many countries. In the Netherlands, seven valent pneumococcal conjugate vaccine (PCV7) was introduced in June 2006 as a 3 + 1 infant schedule with doses at 2,3,4 months of age, and a booster at 11 months for children born after 1st April 2006. PCV7 covers the pneumococcal

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serotypes 4, 6B, 9 V,14,18C,19F and 23F [14,15]. Because of broader coverage and the serotype replacement, such as serotypes 1, 5, and 7F observed in invasive pneumococcal disease (IPD) following introduction of PCV7, it was decided to replace PCV7 in the infant immunisation programme by ten valent pneumococcal conjugate vaccines (PCV10) in March 2011. PCV10 covers additional serotypes 1, 5 and 7F. Two years later, in November 2013, the doses were reduced from 3 + 1 to 2 + 1 schedule at 2, 4 and booster at 11 months of age because studies showed that a 2 + 1 infant schedule was non-inferior to a 3 + 1 schedule [16]. The coverage of infant PCV vaccination has been consistently high since its introduction, varying between 94.4% in 2011 and 92.8% in 2018 [14].

The implementation of PCV7 in the Netherlands decreased vaccine-serotype IPD incidence in vaccinated children [17,18]. Further reductions in IPD cases were observed after PCV10 introduction in children, while in non-vaccinated older children and adults, IPD cases also reduced through herd protection[18,19], but the decrease was less strong due to an increase in IPD incidence due to pneumococcal serotypes 1, 5, and 7F not covered by PCV7 and later PCV10 [18,20].

While several studies have evaluated the impact of PCVs on IPD incidence, the impact of PCV on non-invasive pneumococcal diseases (non-IPD) is far less studied. This is because the impact of PCVs on non-IPD can be difficult to assess, as diagnostic confirmation of pneumococcal infection is difficult to obtain and most times not performed. Alternative proxies for non-IPD are therefore often used such as all-cause OM or pneumonia incidence. Studies in Europe and USA have demonstrated reductions in all-cause OM and pneumonia in children younger than 2 years following PCV7 introduction [21–27]. For older children and adults, impact of PCV7 on non-IPD is less convincing. A reduction in OM incidence in older children (>2 years) was observed shortly after PCV7 introduction for infants, suggesting herd-effects. Observed effects of PCV7 introduction on pneumonia are inconsistent. Some studies did see a decline in children and adults [25,27,28]. While others did not [22,25]. To what extent in The Netherlands has a switch to PCV10 generated additional non-IPD reductions through direct and indirect effects has been little studied thus far [23,28]. Reported effects include a further decline in all causes OM and pneumonia outpatient visit and hospitalization in children [21,29,38,30–37] and adults[21,37] in Europe, America and South Pacific. There is also limited information on the effectiveness of PCV7 and PCV10 on the incidence of sinusitis [30,39]. Most, but not all studies used time series analysis with adjustment for secular trends to evaluate the difference in incidence between PCV7 vs PCV10 period. There is however no consensus in the literature whether this adjustment generates more valid estimates of effect, compared to models that assume trends may be temporary and fluctuate over time and should therefore not be accounted for.

In the Netherlands, studies describing the impact of PCVs across various age-groups have focused on IPD or on pneumonia hospitalizations [18–20,23]. To the best of our knowledge, its population impact on diseases associated with non-IPD in primary care settings has not been assessed. This study aims to assess the impact of switch from PCV7 to PCV10 on the incidence of primary care attended lower respiratory tract infections (pneumonia-bronchitis), OM and sinusitis across various age-groups. For this purpose, we evaluated the occurrence of these conditions in a large cohort of primary care patients between 2006 and 2015. We use two different time series methods to estimate the impact, one with, and one without adjustment for secular trends.

2. Methods

We conducted a retrospective observational study using electronic medical records from a large cohort of primary care patients covering the period between 2006 and 2016. The Julius General Practitioner Network (JGPN) contains healthcare data from patients registered at one of the participating primary care practices located in the central region of the Netherlands. Variables in the database were patient age, sex, date of registration/discharge at the primary care practice, medical diagnosis coded based on International Classification of Primary Care (ICPC) codes, antibiotics prescriptions registered according to the Anatomical Therapeutic Chemical (ATC) classification. All participating GPs are trained according this system and using strict criteria for ICPC codes. For example, ICPC code H71 is based on the Dutch general practitioner AOM guidelines [40]. The study population comprises of all patients that were registered for at least one month in the JGPN database between 2006 and 2016. Patients were stratified into 9 age-groups: 0–5, 5–10, 10–20, 20–40, 40–50, 50–60, 60–70, 70–80 and > 80 years. We stratified by different age groups because direct and indirect effects of infant vaccination may vary with age, both in magnitude and in timing. Stratification by age is mostly per 10-year period, except for the youngest age group: 0–5 and 5–10 years in which much evolution can occur. We also merged age group 20–30 and 30–40 together because we do not expect substantial differences between the two age groups with low incidence overall, thereby increasing statistical power. As we followed patients longitudinally, they could move from one age-category to the next during the follow-up time.

2.1. Outcome

The outcome of interest was defined as a primary care consultation for any of the diseases associated with non-invasive pneumococcal infection. Occurrence of a disease episodes was identified through assigned ICPC codes, as registered in the JHN database. Codes included were: pneumonia/bronchitis (R81/R78), OM (H71) and sinusitis (R75). Multiple GP-visits of the same patient and for the same indication within a period of 28 days were considered as a single episode of disease.

2.2. Exposure

The exposure of interest was the use of 7-Valent versus 10-Valent pneumococcal vaccine in the infant immunization programme. Individual immunization status was not available in the dataset. Instead, we defined the exposure by epidemiological year. An epidemiological calendar year was defined to run from 1 July to 30 June of the next year because the outcomes of interest occur more during the winter periods. The transition period is the year when PCV10 was implemented (2011). This epidemiological year was excluded from the analysis. Thus, the following periods were defined: between July 2006 to June 2011: PCV7 period; July 2011 to June 2012: transition period; and July 2012 to June 2016: PCV10 period. For the older age-groups, it is known that indirect effects of infant pneumococcal vaccination become manifest only after some lag-time [18,23]. Therefore, for age-groups above 20 years, we adapted the PCV periods as follows: PCV7 period July 2006 to June 2012, transition period July 2012 to June 2013, PCV10 period July 2013 to June 2016. This lag of 2 years in herd effects corresponds to findings by Knol et al [18,23].

3. Statistical analysis

Incidence rates for primary care attended pneumonia/bronchitis, OM and sinusitis were calculated per year and per age-group as the number of episodes divided by the person-time of observation. For each age-group, we assessed the impact of the switch from PCV7 to PCV10 on the rate of diseases associated with

pneumococcal infections using segmented regression analysis. Individual level patient data were fitted using Generalized Estimating Equations (GEE) with a negative binomial distribution and log of the person-time as offset variable. Models were fitted to the following outcomes: pneumonia-bronchitis, OM and sinusitis. The intervention (PCV7 vs PCV10), along with two variables for baseline time trend and time after intervention were added to the model. Each model thus had 4 explanatory variables: time, intervention (PCV7/PCV10), time after intervention and age. These variables estimate the baseline trend during the PCV7 period, the change in level immediately following PC10 introduction, the change in trend in the PCV10 versus PCV7 periods and the effect of age of the individual, respectively.

Next, we performed two types of analysis in order to determine vaccine impact. In time series analysis, it may be important to consider any underlying time trends, which affects the observed incidence of an outcome over time. We choose to perform two types of analyses; one that assumes continuation of any time trends already present in the PCV7 period, and one that assumes no trends, apart from those related to the intervention, based on the rational that 1) it is unclear if those underlying trends would have continued without PCV10 vaccination, 2) we are unsure which analysis will represent the true effect of vaccine impact and 3) authors of previous research in this topic usually picked either one of the two approaches and we hypothesize that the two approaches might lead to different results and conclusions in settings where the underlying time-trend is strong. In the first analysis, we compared the post-PCV10 incidence rate to the expected incidence rates if PCV10 had not been implemented (the counterfactual state), based on secular trends during the PCV7 period, that were extrapolated to the PCV10 period. We expressed vaccination impact as the absolute difference between the incidence rate with intervention and the expected incidence for the counterfactual state (i.e., if PCV10 introduction had not occurred). Similarly, we calculated the incidence rate ratio (IRR) as the ratio of mean incidence rates/1000 person years with intervention and expected without intervention for each age group. In the second analysis, we compared observed, model fitted, pre- and post-PCV10 trends. The impact was determined based on the IRRs and their 95% confidence intervals (CI) taking the model-based mean of the IRs in pre- and post-periods. We considered PCV10 effects that were consistently present in both analyses as a significant result. PCV 10 effects were considered negative when both analysis yield non-significant effects/no effect and inconclusive when only one analyses yields significant effect, but the other does not; or the direction of effect differs between the two analyses.

We conducted all analysis using SPSS version 25 and p-values of < 0.05 were considered statistically significant.

4. Results

The study population obtained from the Julius Primary Care Network Database included 397,441 individuals contributing in total 2,408,762 person-years (PY) of observation between July 2006 and June 2016. In total, we recorded 65,400 primary care diagnosed episodes of pneumonia-bronchitis, 50,662 OM episodes and 45,644 episodes of sinusitis throughout the study period (Fig. 1).

4.1. Pneumonia/Bronchitis

The mean pneumonia-bronchitis incidence rate in the PCV7 period varied between 9.99 (95 %CI: 8.98–11.10)/1000 person-years (PY) for the age-group 10–20 years and 82.43 (95 %CI: 75.77–89.72)/1000 PY for adults > 80 years. During the PCV10 period, incidence rates varied between 8.45 (95 %CI:

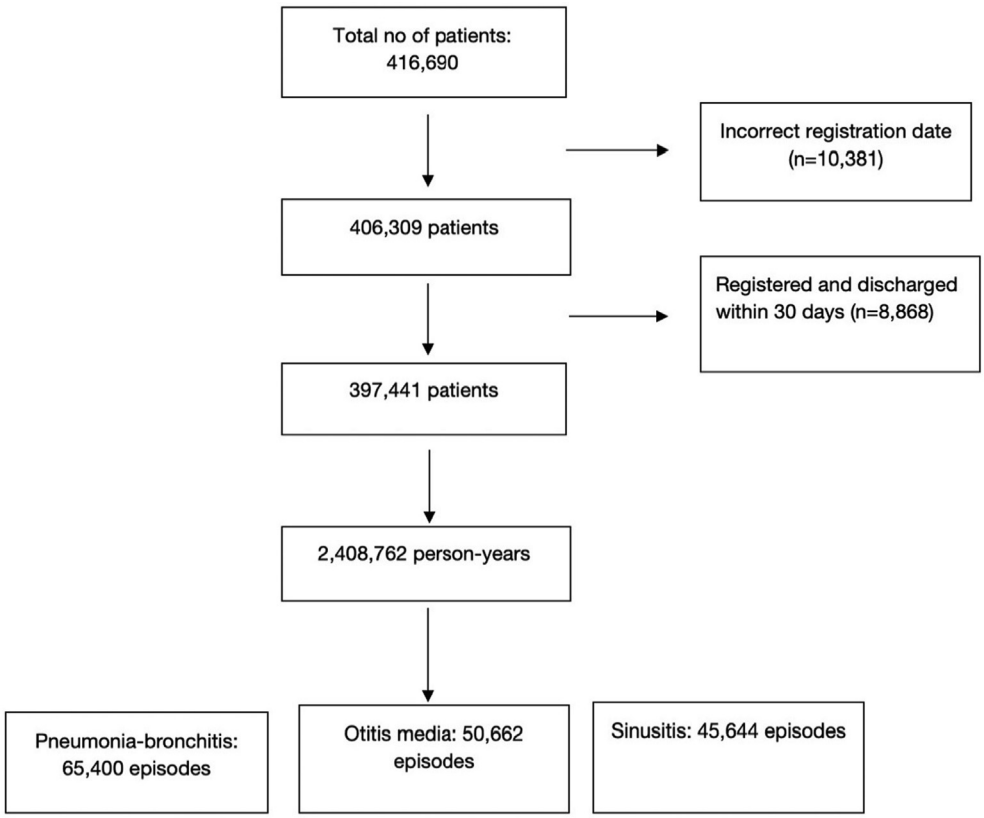

Fig. 1. Flowchart of the study population.

7.54–9.47)/1000 PY and 96.00 (95 %CI: 88.31–104.41)/1000 PY, respectively (Table 1 and Fig. 2a).

Comparing the expected incidence rates based on PCV7 secular trends, the model estimated significant reductions in the post-PCV10 period for all age-groups with mean IRRs varying between 0.58 (95 %CI: 0.51–0.64) to 0.80 (95 %CI: 0.74–0.86), and mean absolute reductions varying from 6.24 (95 %CI: 5.25–7.13) to 24.79 (95 %CI: 22.17–27.24) /1000 PY. (Table 2).

Based on the observed, model fitted, pre- and post-PCV10 incidence rate, reductions in post-PCV10 were less pronounced but still significant for the age-group 0–5 years (IRR: 0.85; 95% CI 0.78–0.92), 5–10 years (IRR: 0.83; 95% CI 0.70–0.98), 20–40 years (IRR: 0.79; 95% CI 0.72–0.86), 40–50 year (IRR: 0.88; 95% CI 0.80–0.97), 50–60 year (IRR: 0.90; 95% CI 0.82–0.99). A significant increase was seen for 80 years and above (IRR: 1.16; 95% CI 1,03–1,31). In the other age-group, mean IRRs did not reach statistical significance (Table 1).

4.2. Otitis media

The mean OM incidence rate in the PCV7 period varied between 160.51(95 %CI: 155.53–165.66) /1000 PY for the age group 0–5 years and 1.08 (95 %CI: 0.60–2.00)/1000 PY for adults > 80 years. In the PCV10 period, incidence rates varied between 173.26 (95 %CI: 167.97–178.72) and 1.61 (95 %CI: 0.94–2.81) /1000 PY for age group 0–5 years and > 80 years respectively (Table.1 and Fig. 2b).

Comparing the expected incidence rates based on PCV7 secular trends, the model estimated significant reductions in the post-PCV10 period for age-groups below 20 years and age groups between 50 and 70 years with mean IRRs varying between 0.66 (95 %CI: 0.64–0.68) and 0.81 (95 %CI: 0.73–0.86), corresponding to mean absolute reductions of 88.73 (95 %CI: 84.55–92.76) – 2.84 (95 %CI: 2.06–4.21)/1000 PY. By contrast, a significant increase in post-PCV10 was observed for the age-gro up > 80 year (IRR: 1.93 (95 %CI: 1.14–3.35)). (Table 2).

Based on the observed, model fitted, pre- and post-PCV10 incidence rate, significant increases in post-PCV10 were observed for age-groups 0–5 year (IRR: 1.08; 95% CI 1.03–1.13), 5–10 years (IRR: 1.22; 95% CI 1.09–1.36), 10–20 years IRR: 1.33; 95% CI 1.12–1.59). In the other age-groups, mean IRRs did not reach statistical significance (Table.1).

4.3. Sinusitis

The mean sinusitis incidence rate in the PCV7 period varied between 1.42 (95 %CI: 1.02–1.99)/1000 PY for age-group children < 5 years and 27.37 (95 %CI: 25.89–28.93)/1000 PY for 40–50 years. In the PCV10 period, incidence rates varied between 0.73 (95 %CI: 0.45–1.19)/1000 PY and 24.81 (95 %CI: 23.30–26.42)/1000 PY for age-group < 5 and 40–50 years, respectively (Table.1 and Fig. 2c).

Comparing the expected incidence rates based on PCV7 secular trends, the model estimated significant reductions in the post-PCV10 period for all age-groups above 10 years with mean IRRs varying between 0.61(95 %CI: 0.56–0.67) to 0.82 (95 %CI: 0.75–0.90), and mean absolute reductions varying from 2.22 (95 %CI: 1.20–3.14) to 14.11 (95 %CI: 12.03–16.00)/1000 PY. By contrast, in children aged 0–5 years the expected time trend suggested a further decline was limited by PCV10 introduction (IRR: 4.09 (95 %CI: 2.54–6.62)). (Table 2).

Based on the observed, model fitted, pre- and post-PCV10 incidence rate, significant reductions in post-PCV10 were observed for age-groups 0–5 (IRR: 0.52; 95 %CI 0.27–0.97), 20–40 (IRR: 0.80; 95% CI 0.75–0.86) and 40–50 years (IRR: 0.91; 95 %CI 0.83–0.99).

Table 1
Observed, model fitted pre- and post-PCV10 age-group specific mean incidence/1000PY, IRR and absolute difference.

Age-group in years	Mean incidence/1000PY (95 %CI)PCV7 Period	PCV10 Period	IRR (95 %CL)	Absolute difference/1000PY
Pneumonia-Bronchitis				
0–5	62.74 (59.61–66.05)	53.09 (50.24–56.11)	0.85 (0.78–0.92)	−9.65 (-9.94, −9.37)
5–10	18.30 (16.54–20.27)	15.17 (13.64–16.89)	0.83 (0.70–0.98)	−3.13 (-3.38, −2.90)
10–20	9.99 (8.98–11.10)	8.45 (7.54–9.47)	0.85 (0.71–1.01)	−1.53 (-1.63, −1.44)
20–40	13.70 (13.00–14.43)	10.77 (10.09–11.50)	0.79 (0.72–0.86)	−2.92 (-2.93, −2.91)
40–50	22.76 (21.46–24.14)	20.03 (18.70–21.45)	0.88 (0.80–0.97)	−2.74 (-2.76, −2.69)
50–60	31.70 (29.87–33.64)	28.55 (26.64–30.60)	0.90 (0.82–0.99)	−3.15 (-3.23, −3.04)
60–70	44.09 (41.51–46.84)	45.20 (42.39–48.20)	1.03 (0.94–1.12)	1.10 (0.88, 1.36)
70–80	58.84 (54.85–63.13)	64.25 (59.79–69.04)	1.09 (0.99–1.21)	5.40 (4.94, 5.91)
> 80	82.43 (75.77–89.72)	96.00 (88.31–104.41)	1.16 (1.03–1.31)	13.57 (12.54, 14.69)
Otitis-media				
0–5	160.51 (155.53–165.66)	173.26 (167.97–178.72)	1.08 (1.03–1.13)	12.74 (12.44, 13.06)
5–10	36.56 (34.13–39.16)	44.67 (41.88–47.66)	1.22 (1.09–1.36)	8.12 (7.75, 8.50)
10–20	8.88 (7.96–9.91)	11.85 (10.77–13.04)	1.33 (1.12–1.59)	2.97 (2.81, 3.13)
20–40	5.38 (5.00–5.78)	6.06 (5.57–6.59)	1.13 (0.99–1.28)	0.68 (0.57, 0.81)
40–50	3.99 (3.47–4.58)	4.58 (3.98–5.28)	1.15 (0.92–1.43)	0.60 (0.51, 0.70)
50–60	3.61 (3.07–4.24)	3.87 (3.24–4.63)	1.07 (0.82–1.41)	0.27 (0.17, 0.39)
60–70	3.61 (2.99–4.36)	3.79 (3.07–4.70)	1.05 (0.77–1.44)	0.18 (0.08, 0.34)
70–80	2.39 (1.76–3.25)	2.25 (1.61–3.16)	0.94 (0.56–1.59)	−0.14 (-0.09, −0.15)
> 80	1.08 (0.60–2.00)	1.61 (0.94–2.81)	1.49 (0.55–4.02)	0.53 (0.34, 0.81)
Sinusitis				
0–5	1.42 (1.02–1.99)	0.73 (0.45–1.19)	0.52 (0.27–0.97)	−0.69 (-0.8, −0.57)
5–10	3.14 (2.49–3.96)	2.63 (2.06–3.36)	0.84 (0.56–1.26)	−0.51 (-0.6, −0.43)
10–20	10.99 (9.96–12.13)	10.36 (9.39–11.44)	0.94 (0.80–1.11)	−0.63 (-0.69, −0.57)
20–40	25.41 (24.46–26.40)	20.45 (19.52–21.42)	0.80 (0.75–0.86)	−4.96 (-4.98, −4.94)
40–50	27.37 (25.89–28.93)	24.81 (23.30–26.42)	0.91 (0.83–0.99)	−2.56 (-2.59, −2.51)
50–60	25.01 (23.40–26.72)	24.66 (22.89–26.56)	0.99 (0.89–1.10)	−0.35 (-0.51, −0.16)
60–70	21.61 (19.80–23.58)	21.97 (20.01–24.12)	1.02 (0.89–1.16)	0.36 (0.21, 0.54)
70–80	15.09 (13.28–17.15)	15.38 (13.36–17.71)	1.02 (0.83–1.25)	0.30 (0.08, 0.56)
> 80	8.17 (6.48–10.35)	8.33 (6.43–10.81)	1.02 (0.69–1.50)	0.15 (-0.05, 0.46)

PY: Person-years.
IRR: Incidence rate ratio.
- Reductions in the post-PCV10 period when comparing pre- and post-PCV10 age-group specific mean incidence rates.

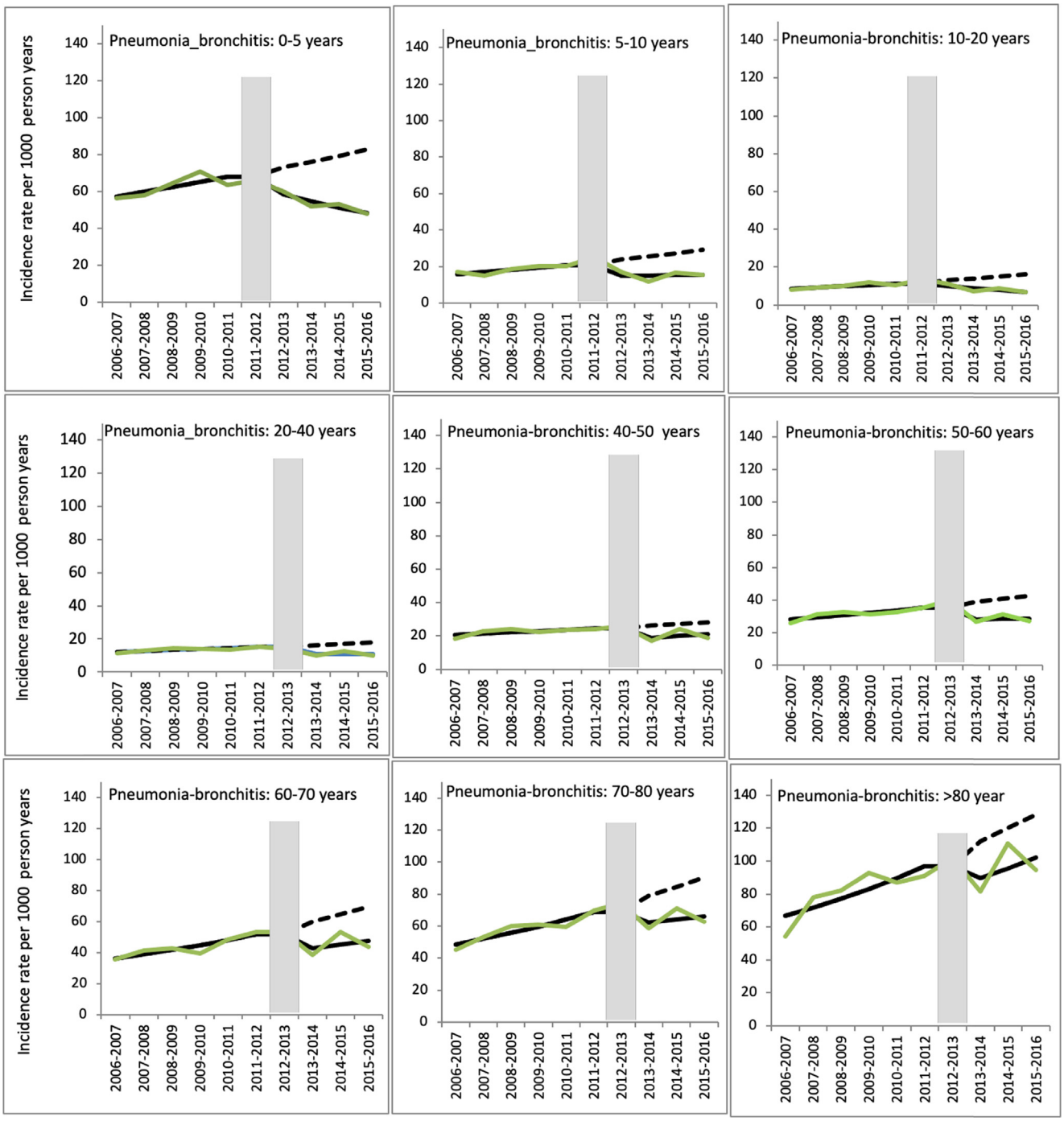

Fig. 2a. Age-specific trends in incidence rate for pneumonia-bronchitis between 2006 and 2007 and 2015–2016 covering the PCV7 and PCV10 periods. Incidence rates are presented per 1000 person years. The green line represents the observed incidence rate over time. The black line represents the model fitted incidence including the model coefficient for intervention (i.e. switch from PCV7 to PCV10). The interrupted black line represents the predicted incidence rate without intervention (i.e. if the switch from PCV 7 & to PCV 10 had not occurred), based on the secular time trend in the PCV7 period. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In the other age groups, mean IRRs did not reach statistical significance (Table.1).

5. Discussion

While the impact of higher valent PCVs on IPD and pneumonia hospitalizations has been described in several studies, the impact on pneumococcal associated infections in primary care settings has been much less studied. In this study, we applied two different time-series methods to estimate the impact of switch from PCV7 to PCV10 on the incidence of primary care attended lower respiratory tract infections (pneumonia-bronchitis), OM and sinusitis across various age-groups in The Netherlands. In both types of analyses, we found a consistent decrease in incidence of pneumonia-bronchitis following PCV10 introduction in age-groups 0–5, 5–10 and 20 to 60 years, with IRR varying between 0.58 (95 %CI: 0.52–0.64) in ages 5–10 years to 0.80 (95 %CI: 0.74–0.86) for age-grou p > 80 years in the first-analysis (which compared post PCV10 inci-

Table 2
Observed versus expected age-group specific mean IR/1000PY for PCV10 period based on pre-PCV10 secular time trends.

Age-group in years	Mean incidence/1000PY Observed PCV10 (95 %CI)	Mean incidence/1000PYExpected PCV10 (95 %CI)	IRR (95 %CI)	Absolute difference (95 %CI) / 1000PY
Pneumonia-Bronchitis				
0–5	53.09 (50.24–56.11)	77.88 (77.48–78.28)	0.68 (0.65–0.71)	−24.79 (-27.24, −22.17)
5–10	15.17 (13.64–16.89)	26.30 (26.19–26.42)	0.58 (0.52–0.64)	−11.13 (-12.55, −9.52)
10–20	8.45 (7.54–9.47)	14.69 (14.67–14.72)	0.58 (0.51–0.64)	−6.24 (-7.13, −5.25)
20–40	10.77 (10.09–11.50)	17.06 (17.01–17.11)	0.63 (0.59–0.67)	−6.29 (-6.92, −5.61)
40–50	20.03 (18.70–21.45)	27.43 (27.40–27.47)	0.73 (0.68–0.78)	−7.40 (-8.70, −6.02)
50–60	28.55 (26.64–30.60)	40.89 (40.80–40.97)	0.70 (0.65–0.75)	−12.34 (-14.16, −10.37)
60–70	45.20 (42.39–48.20)	64.66 (64.54–64.79)	0.70 (0.66–0.74)	−19.46 (-22.15, −16.59)
70–80	64.25 (59.79–69.04)	84.60 (84.39–84.81)	0.76 (0.71–0.81)	−20.35 (-24.60, −15.77)
> 80	96.00 (88.31–104.41)	120.15 (119.51–120.79)	0.80 (0.74–0.86)	−24.15 (-31.20, −16.38,)
Otitis- media				
0–5	173.26 (167.97–178.72)	261.99 (260.73–263.27)	0.66 (0.64–0.68)	−88.73 (-92.76, −84.55)
5–10	44.67 (41.88–47.66)	65.81 (65.35–66.25)	0.68 (0.64–0.72)	−21.14 (-23.47, −18.58)
10–20	11.85 (10.77–13.04)	14.69 (14.98–15.10)	0.81 (0.73–0.86)	−2.84 (-4.21, −2.06)
20–40	6.06 (5.57–6.59)	6.47 (6.46–6.48)	0.94 (0.86–1.02)	−0.41 (-0.89, 0.11)
40–50	4.58 (3.98–5.28)	5.25 (5.24–5.25)	0.87 (0.76–1.01)	−0.66 (-1.26, 0.03)
50–60	3.87 (3.24–4.63)	5.34 (5.33–5.34)	0.73 (0.61–0.87)	−1.46 (-2.09, −0.71)
60–70	3.79 (3.07–4.70)	5.28 (5.27–5.30)	0.72 (0.58–0.89)	−1.49 (-2.21, −0.60)
70–80	2.25 (1.61–3.16)	3.06 (3.05–3.07)	0.74 (0.53–1.03)	−0.81 (-1.44, 0.09)
> 80	1.61 (0.94–2.81)	0.83 (0.82–0.84)	1.93 (1.14–3.35)	0.78 (0.11, 1.97)
Sinusitis				
0–5	0.73 (0.45–1.19)	0.178 (0.177–0.179)	4.09 (2.54–6.62)	0.55 (0.27–1.01)
5–10	2.63 (2.06–3.36)	3.08 (3.07–3.09)	0.85 (0.67–1.09)	−0.45(-1.00, 0.27)
10–20	10.36 (9.39–11.44)	12.58 (12.52–12.64)	0.82 (0.75–0.90)	−2.22 (-3.14, −1.20)
20–40	20.45 (19.52–21.42)	30.28 (30.21–30.35)	0.68 (0.65–0.71)	−9.83 (-10.70, −8.93)
40–50	24.81(23.30–26.42)	36.64 (36.59–36.70)	0.68 (0.64–0.72)	−11.84 (-13.29, −10.28)
50–60	24.66 (22.89–26.56)	38.64(38.58–38.65)	0.64 (0.59–0.69)	−13.98 (-15.69, −12.09)
60–70	21.97 (20.01–24.12)	36.08 (36.01–36.15)	0.61 (0.56–0.67)	−14.11 (-16.00, −12.03)
70–80	15.38 (13.36–17.71)	21.99 (21.94–22.05)	0.70 (0.61–0.80)	−6.61 (-8.58, −4.33)
>80	8.33 (6.43–10.81)	13.30 (13.16–13.45)	0.63 (0.49–0.80)	−4.97 (-6.73, −2.64)

PY = Person-years
IRR: Incidence rate ratio
- Reductions in the post-PCV10 period when comparing the observed versus expected incidence rates based on PCV7 secular trends

dence rate to the expected incidence rates based on PCV7 secular trends) and between 0.79 (95 %CI: 0.86–0.72) for age-group 20–40 years to 0.90 (95 %CI: 0.82–0.99) for age-group 50–60 years in the second-analysis (which compared observed, model fitted, pre- and post-PCV10 incidence rates). Results for OM were inconsistent; a significant decline for age-groups < 20 years and age group 50–70 years were estimated based on first-analysis, while the second-analysis estimated a significant increase for age-groups up to 20 years. For sinusitis, significant reductions with both analyses were only observed in age-group 40–50 years (IRR: 0.68 (95 %CI: 0.64–0.72) and 0.91(95 %CI: 0.83–0.99) in first- and second-analysis, respectively), but a trend towards a decline was also observed for age-groups 20–40 years (IRR varying between 0.68 (95 %CI: 0.65–0.71) and 0.80 (95 %CI: 0.75–0.86) in the first and second analysis respectively).

We used two different methods of time series analysis; one that accounts for underlying secular trends and assumed continuation of such trends, and one that does not assume this.

Using both methods in parallel increased the robustness of our findings on PCV10 effects, as we only considered effects significant if both analyses yielded significant results in the same direction. For some outcomes and age-groups, there were considerable differences between the estimates from either analysis. These raised a lot of uncertainty, as it is impossible to know which of these estimates best represents the true effect. It is important to realize that any approach used in estimating vaccine impact will have a huge impact on the result. Authors of previous research in this topic picked either one of the two approaches [23,33,35]. We are actually showing that results of one approach can lead to a different results and conclusions than the other approach. The difference in estimated effect is particularly pronounced, if the underlying trend in pre-period is strong. In the context of uncertainty about the stability of underlying time trends, we recommend that both methods should be explored before definite conclusions are drawn. In the absence of an increasing or decreasing time trends, both methods yield comparable results and there is no clear advantage of one over the other.

5.1. Pneumonia

Our findings that PCV10 contributed to a decline in pneumonia-bronchitis incidence in children in primary care are in line with studies that looked at effects of PCV10 introduction on pneumonia hospitalizations. Reported reductions in all-cause pneumonia hospitalizations based on before-after comparative studies vary between 15% and 38% in children < 5 years, and between 16.8% and 27.1% for children between ages 5 years and 17 years. For adults, the effect of PCV10 versus PCV7 on all-cause pneumonia hospitalizations is generally less pronounced i.e. from 11.1% to 17.1% [23,30,33,36,37,41]. We observed no reductions in primary care consultations of pneumonia-bronchitis in the elderly, which is consistent with findings that serotype replacement is much more pronounced in the elderly population [19], limiting the impact of infant pneumococcal immunization. An interrupted time series study reported PCVs impact on pneumonia specifically in an outpatient setting, but this study, conducted in Peru, included only children<1 year of age. An overall reduction of 18.7% in outpatient visits for pneumonia was estimated after PCV7 and PCV10 period

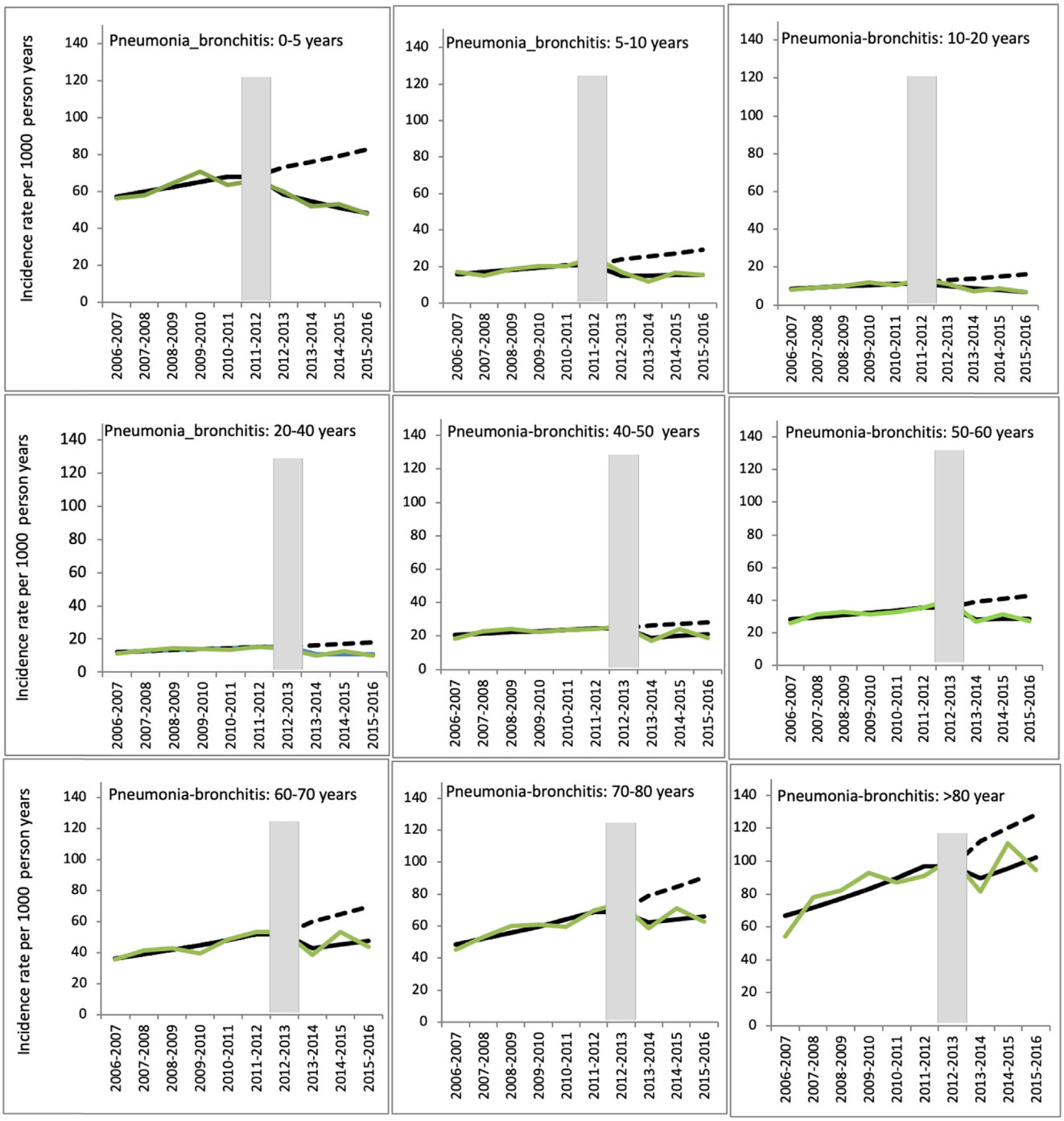

Fig. 2b. Age-specific trends in incidence rate for otitis media between 2006 and 2007 and 2015–2016 covering the PCV7 and PCV10 periods. Incidence rates are presented per 1000 person years. The green line represents the observed incidence rate over time. The black line represents the model fitted incidence including the model coefficient for intervention (i.e. switch from PCV7 to PCV10). The interrupted black line represents the predicted incidence rate without intervention (i.e. if the switch from PCV 7 & to PCV 10 had not occurred), based on the secular time trend in the PCV7 period.

compared to pre-vaccine period [35]. The analysis was not corrected for secular trends. While using interrupted time series to compare observed versus estimated number of pnumonia cases if vaccine had not been implemented, based on pre PCV10 period, that were extrapolated to the PCV10 period, Reyburn et al. reported a 26% reduction in all causes pneumonia hospital admissions in children aged 24–59 months, 5 years after PCV10 introduction.

5.2. Otitis media

Our findings in the first-analysis which showed that PCV10 contributed to a decline in OM incidence in children < 20 years in primary care are in line with studies that looked at effects of PCV10 introduction on OM outpatient visit. Reported reductions in OM outpatient visit in those studies vary between 6.6% and 50.7% in children < 5 years, and 20.0% for children between ages 5 and 9 years [21,29,31,35]. By contrast, we observed no reductions in

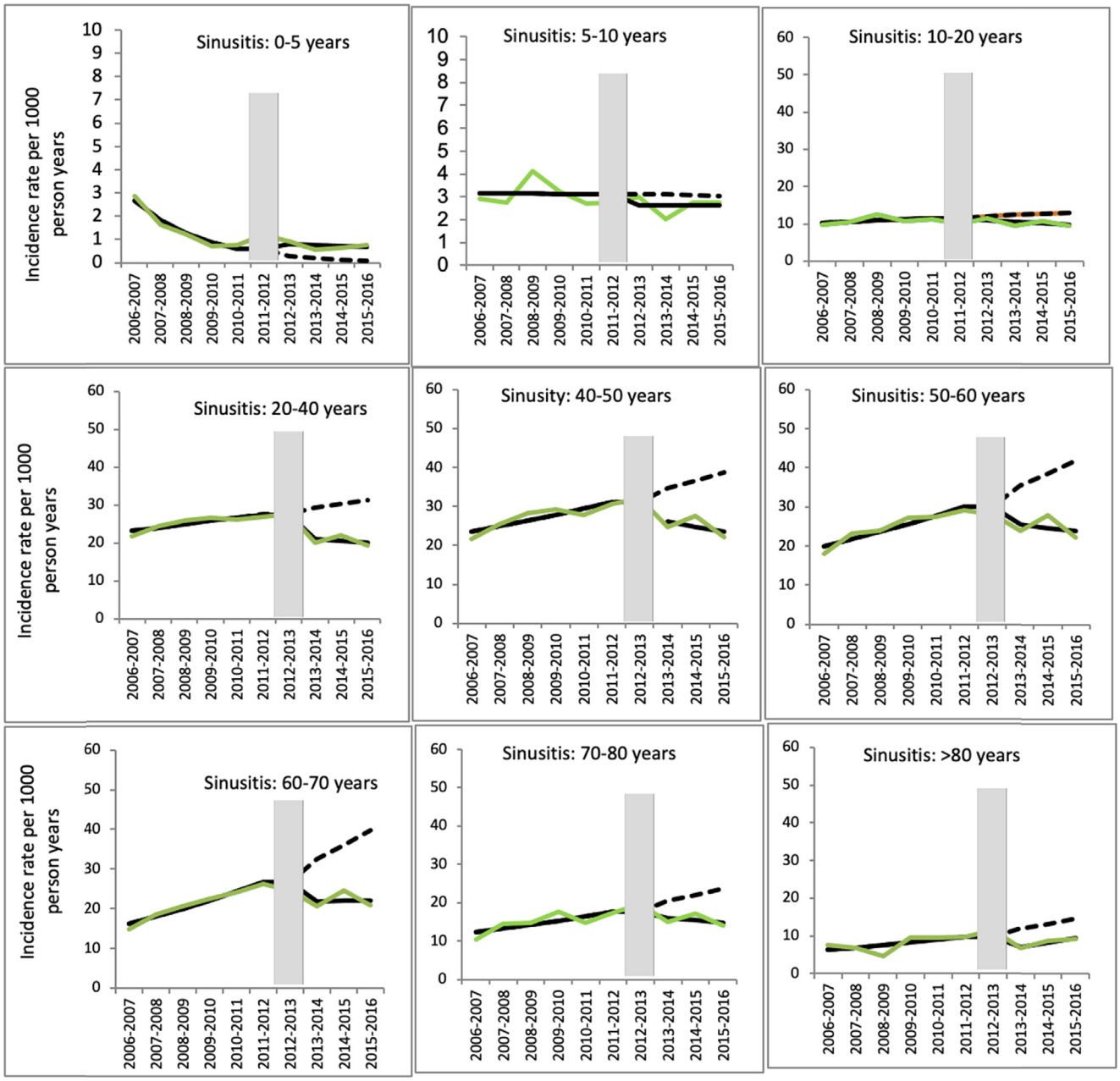

Fig. 2c. Age-specific trends in incidence rate for sinusitis between 2006 and 2007 and 2015–2016 covering the PCV7 and PCV10 periods. Incidence rates are presented per 1000 person years. The green line represents the observed incidence rate over time. The black line represents the model fitted incidence including the model coefficient for intervention (i.e. switch from PCV7 to PCV10). The interrupted black line represents the predicted incidence rate without intervention (i.e. if the switch from PCV 7 & to PCV 10 had not occurred), based on the secular time trend in the PCV7 period.

OM incidence in the second-analysis. Our findings in the second-analysis suggested an increase after PCV10 introduction in age-group 0–20 years. Given the inconsistency in results, we remain uncertain about the true impact of PCV10 on OM.

5.3. Sinusitis

The impact of higher valent PCVs on the incidence of sinusitis has been very little studied. Only one study conducted in the US reported PCV13 impact on chronic sinusitis inpatients aged < 18 years. All patients had a positive sinus culture for streptococcus pneumonia. PCV13 reduced chronic sinusitis cases by 31% compared to PCV7 [39]. Our findings suggest a reduction in adult sinusitis may be an additional benefit of infant PCV10 immunization. Reductions were significant in age-groups with the highest incidence of sinusitis. Interestingly, no substantial changes were observed in sinusitis incidence in pediatric and adolescent age-groups. In children < 5 years of age, the first-analysis even suggested an increase after PCV10 introduction. Sinusitis in young children is however difficult to diagnose and extremely uncommon as most sinuses have not yet fully developed. Any impact of PCV immunization in this age-group would be very small.

6. Strengths and limitations

It is important to highlight some of the limitations of our study. Firstly, our study is an ecological study and might be subject to

ecological fallacy, i.e., faulty conclusion that arise when inference on individuals is based on the group they belong.

The study relied on the routine healthcare data, provided in the JGPN database that does not contain information on for example, chest × ray orders and tube placement. Thus, we could not increase the specificity of our study outcomes. This issue is acknowledged by the field. For example, Lau et al [21] mentioned that a general limitation in UK primary care database is that microbiology cultures are rarely taken from patients presenting to primary care with otitis media and Grijalva et al [22] noted in their limitation section that they relied on diagnosis made by physicians, since radiological information supporting pneumonia diagnosis was limited in primary care. However, despite these limitations, ICPC codes are considered a valuable proxy for non-invasive pneumococcal infections and have been frequently used to conduct impact studies like ours [42–45]. Since patient information was derived from a primary care database, misclassification of ICPC codes cannot be ruled out. We consider it however unlikely that the switch from PCV7 to PCV10 would affect coding practices. Our first analysis approach adjusted for any secular time trends in coding practices. In our analyses we did not adjust for changes in the influenza immunization policy or coverage. In the Netherlands, annual influenza immunization in recommended for medical risk groups and for elderly. In 2008, the eligible age for influenza immunization in elderly was changed from 65 to 60 years [46]. In addition, the influenza immunization coverage in elderly has been gradually decreasing from 72% in 2006 to 50% in 2017. As influenza infection is associated with secondary pneumococcal disease these changes may have some effect on pneumonia-bronchitis incidence measured in primary care, but those effects are considered to be small and would be captured in the first-analysis [47]. The strength of this study is the size of the primary care cohort studied, the number of years included in the analyses used to evaluate PCV10 effects on non-invasive disease in a community with high vaccine coverage and the robust methodology with dual approach.

6.1. Conclusion

Five years after PCV10 replaced PCV7 in the Netherlands, PCV10 has contributed to a reduction in pneumonia-bronchitis incidence in primary care in children and adults and a reduction in sinusitis incidence in some adult age-groups, while no clear effect was seen on OM incidence. Our study therefore supports evidence of direct and indirect effect of PCV10 on non-invasive pneumococcal disease. Our study shows that it is important to consider the approach used to estimate vaccine impact because it can have a large impact on the result. Estimate from the two different approaches can only be comparable, if there is less underlying trend.

7. Contributors

PCJIBV, MLAdH and OAA designed the study, PCJIBV led the project and MLAdH advised the team throughout the planning and execution of the project. OAA managed the data and performed statistical analysis. PCJIBV MLAdH and OAA interpreted the results. OAA wrote the draft of the paper while PCJIBV and MLAdH revised the paper to provide more clear information and quality standard.

CRediT authorship contribution statement

Ogechukwu Asogwa: Conceptualization, Data curation, Formal analysis, Methodology, Software, Visualization, Writing – original draft. **Marieke de Hoog:** Conceptualization, Formal analysis, Methodology, Writing/review & editing; Project administration. **Patricia Bruijning-Verhagen:** Conceptualization, Methodology, Formal analysis, Supervision, Visualization Writing/review & editing

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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