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Sex differences in invasive pneumococcal disease and the impact of pneumococcal conjugate vaccination in the Netherlands, 2004 to 2015

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Implementation of pneumococcal conjugate vaccines in the Netherlands (PCV7 in 2006 and PCV10 in 2011) for infants caused a shift in serotypes in invasive pneumococcal disease (IPD). We explored sex differences in serotype-specific IPD incidence before and after vaccine introduction. Incidences in the pre-PCV7 (June 2004–May 2006), post-PCV7 (June 2008–May 2011) and post-PCV10 period (June 2013–May 2015), stratified by age, were compared. Incidence was higher in men for all age groups (overall in men: 16.7, 15.5 and 14.4/100,000 and women: 15.4, 13.6 and 13.9/100,000 pre-PCV7, post-PCV7 and post-PCV10, respectively), except for 20–39 year-olds after PCV7 and 40–64 year-olds after PCV10 introduction. After PCV7 and PCV10 introduction, the overall IPD incidence decreased in men aged 20–39 years (from 5.3 pre-PCV7 to 4.7 and 2.6/100,000 post-PCV7 and post-PCV10, respectively), whereas it showed a temporary increase in women (from 3.9/100,000 pre-PCV7 to 5.0/100,000 post-PCV7 and back to 4.0/100,000 post-PCV10) due to replacement disease. PCV10 herd effects were observed throughout, but in women older than 40 years, a significant increase in non-PCV10 serotype offset a decrease in overall IPD incidence. Ongoing surveillance of IPD incidence by sex is important to evaluate the long-term effects of PCV implementation.

Introduction

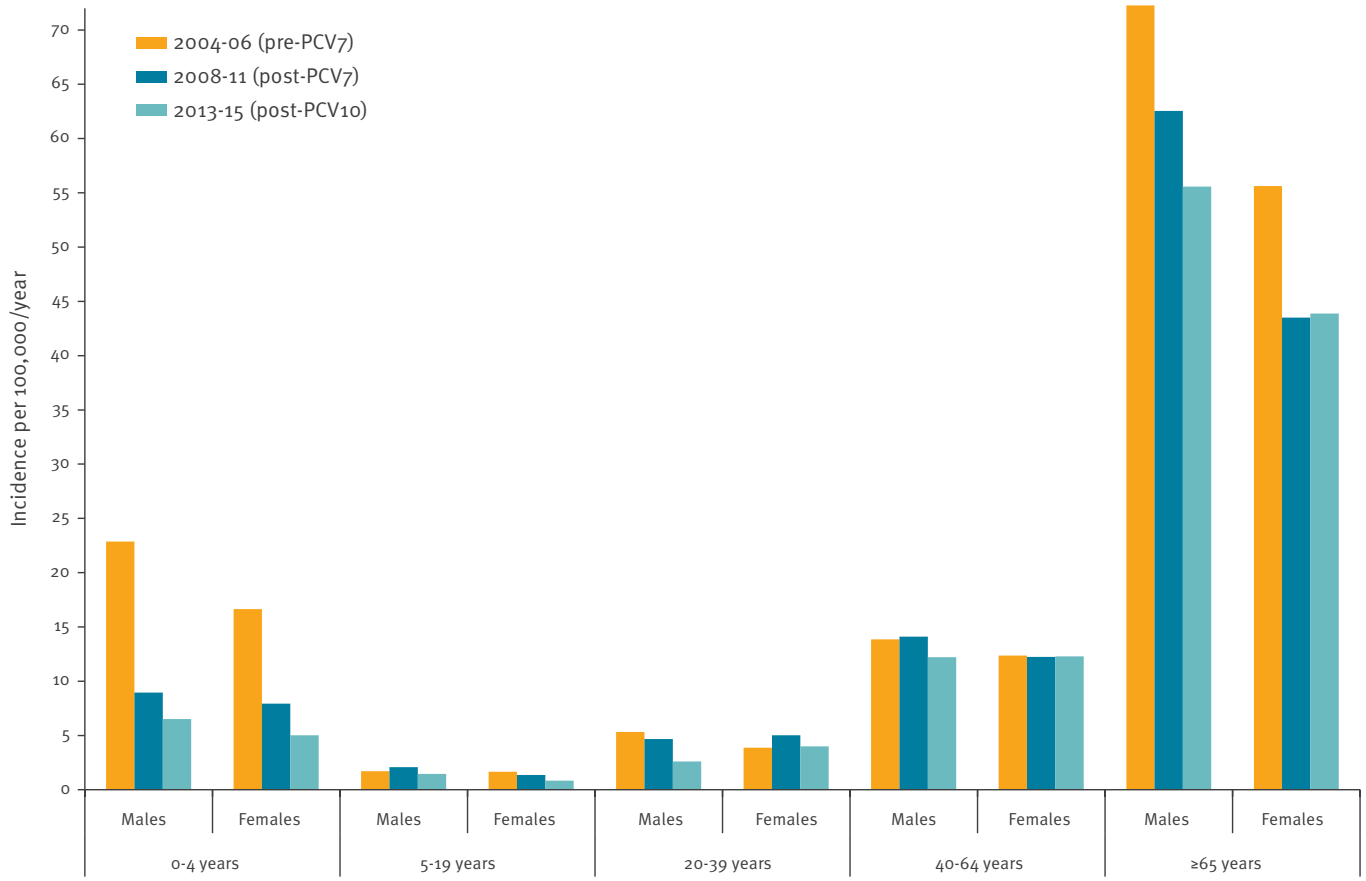
Sex differences play an important role in clinical disease susceptibility and outcome. In infectious diseases, the burden of bacterial, fungal, parasitic and viral disease is generally higher in men than in women [1-3]. However, with the exception of urinary tract infections, sex differences are often neglected in surveillance reports [4,5]. Also for *Streptococcus pneumoniae*, a frequent coloniser of the nasopharynx and cause of severe infections, the observed incidences of pneumococcal pneumonia and invasive pneumococcal disease (IPD) have been higher in men [6-8]. Young children have the highest pneumococcal carriage rates and are the key transmitters of *S. pneumoniae* in the population. However, no systematic age-specific differences in asymptomatic pneumococcal nasopharyngeal carriage rates have been observed between boys and girls [9-11]. Pneumococcal conjugate vaccination (PCV) has led to eradication of vaccine serotype carriage but immediate replacement by non-vaccine serotypes with a modest reduction in overall pneumococcal carriage in children [12,13].

In many countries, extensive IPD surveillance programmes were implemented before and after introduction of PCV in childhood immunisation programmes [14-17]. Although many surveillance reports described the impact of the first licensed 7-valent PCV (PCV7) on (serotype-specific) IPD incidences in different age groups [17], only limited data have been reported by sex [18-20]. In the Netherlands, PCV7 has been introduced for infants born after 1 April 2006 (in a 3+1 schedule) with a coverage of 94–95% since its introduction [21] and has led to a shift from vaccine to non-vaccine serotypes causing IPD ('replacement disease') in all age groups. In children eligible for vaccination, the decline in vaccine serotype IPD was strongest, but overall IPD incidence decreased due to herd protection in most age groups, in particular in persons 65 years and older [16,17].

Differences in the impact of pneumococcal conjugate vaccines between men and women do occur. Hak et al.

Figure 1

Age-specific incidence of invasive pneumococcal disease in men and women in the pre- and post-PCV periods, the Netherlands, 2004–15 (n = 4,303)



PCV: pneumococcal conjugate vaccine.

Study period: pre-PCV7 (June 2004–May 2006) post-PCV7 (June 2008–May 2011) and post-PCV10 (June 2013–May 2015).

reported an increase in the incidence of pneumococcal pneumonia in mothers of young infants after introduction of PCV7 in the United Kingdom (UK) [22]. In the Netherlands, a significant increase in IPD incidence was observed in middle-aged women 2–4 years after introduction of PCV7, mainly due to the emergence of serotype 1, which was not observed in men in the same age group [23]. Whether this was due to non-PCV7 serotype replacement or to a secular trend needs to be established because serotype 1 is a naturally fluctuating serotype [24]. In May 2011, the 10-valent pneumococcal conjugate vaccine (PCV10) including serotype 1 was introduced for Dutch infants.

The objective of this study was to explore differences in IPD incidence between men and women before and after PCV7 and PCV10 introduction by using national surveillance data up to May 2015.

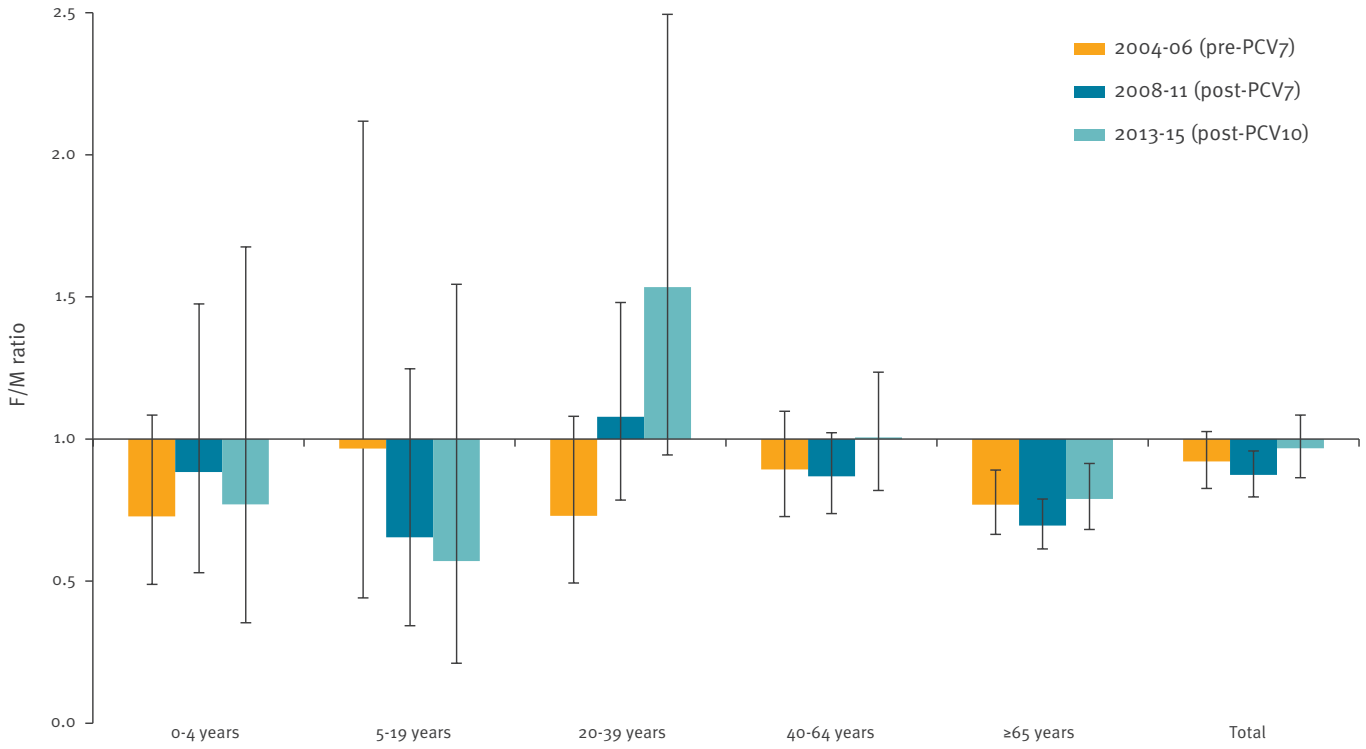
Methods

Study population and data collection

The Dutch pneumococcal surveillance is based on data from nine sentinel laboratories covering different regions of the Netherlands and ca 25% of the Dutch population (ca 4.2 million inhabitants, including 2.07 million men and 2.11 million women). The participant laboratories, selected for geographic location and reliability for submitting isolates, have not changed over time during the study period [14,16]. In addition, we have no indication that surveillance sensitivity has changed over the years. Pneumococcal isolates of all IPD patients, defined as patients with *S. pneumoniae* isolated from blood or cerebrospinal fluid (CSF), were submitted to the Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM) for serotyping by co-agglutination and capsular swelling (Quellung reaction) using specific antisera (Statens Serum Institute, Denmark). Pneumococcal serotypes and demographic data including age and sex were available for IPD cases from June 2004 up to May 2015.

Figure 2

Age-specific female/male incidence ratio of invasive pneumococcal disease in the pre- and post-PCV periods, the Netherlands, 2004–15 (n = 4,303)



F/M: female/male; PCV: pneumococcal conjugate vaccine.

Study period: pre-PCV7: June 2004–May 2006; post-PCV7: June 2008–May 2011; post-PCV10: June 2013–May 2015.

Black bars indicate 95% confidence intervals.

In addition, clinical information including clinical syndromes (categorised as (i) meningitis, (ii) invasive pneumonia (without meningitis), (iii) bacteraemia without focus and (iv) bacteraemia with other focus (without meningitis or invasive pneumonia)), clinical outcome (death in hospital and/or death within 30 days after first reported blood/CSF culture positive for *S. pneumoniae),* admission to an intensive care unit (ICU), and presence of underlying conditions (immunocompromising conditions and other comorbidities) were retrospectively extracted for IPD patients from June 2004 up to May 2012 from hospital medical records as described [15,16,25]. Clinical data from the post-PCV10 period (1 June 2013 to 31 May 2015) were not available.

Data analysis

We assessed sex-specific IPD incidences during a pre-PCV7 (1 June 2004 to 31 May 2006), post-PCV7 (1 June 2008 to 31 May 2011) and post-PCV10 period (1 June 2013 to 31 May 2015) and calculated the female/male (F/M) incidence ratio. The first two years after introduction of PCV7 and PCV10 (1 June 2006 to 31 May 2008 and 1 June 2011 to 31 May 2013) were regarded as transition period and not included.

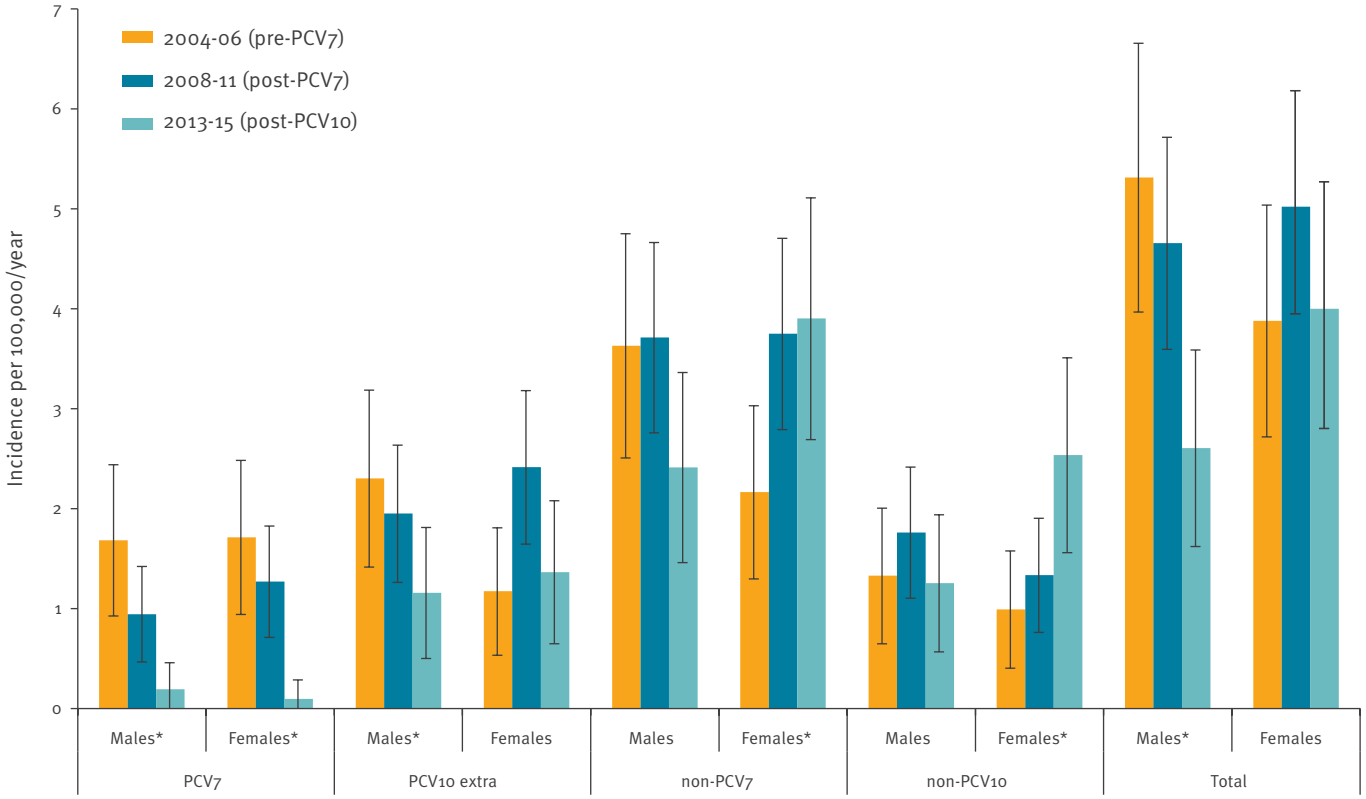
Changes in IPD incidences, comparing post-PCV7 to pre-PCV7 and post-PCV10 to post-PCV7 were assessed for men and women separately by calculating relative risks (RR). To investigate sex differences in direct and indirect effects (i.e. changes in IPD incidences) after PCV7 or PCV10 introduction, the interaction between sex and change in IPD incidence (RR post-PCV7 to pre-PCV7 or RR post-PCV10 to post-PCV7, respectively) was assessed by calculating the F/M risk ratio of RRs (dividing the RR in women by the RR in men).

Likewise, sex-specific differences in the proportion of clinical syndromes, in clinical outcome and in underlying conditions were assessed in the pre-PCV7 and post-PCV7 period (F/M ratio of proportions). Also changes in the proportion of clinical syndromes, in clinical outcome and in underlying conditions after PCV7 were assessed for men and women separately (RR post-PCV7 to pre-PCV7). The interaction between sex and change in proportions was assessed by calculating the F/M risk ratio of RRs. Cases without clinical data were excluded from these analyses.

We further explored if there was a sex-specific preference in certain serotypes causing IPD, defined as an

Figure 3

Incidences of invasive pneumococcal disease per serotype group in 20–39 year-old men and women pre-PCV7, post-PCV7 and post-PCV10, the Netherlands, 2004–15 (n = 324)



IPD: invasive pneumococcal disease; PCV: pneumococcal conjugate vaccine.

Study period: pre-PCV7: June 2004–May 2006; post-PCV7: June 2008–May 2011; post-PCV10: June 2013–May 2015, Black bars indicate 95% confidence intervals.

* Indicates a significant difference (p value < 0.05) in IPD incidence comparing post-PCV10 to pre-PCV7.

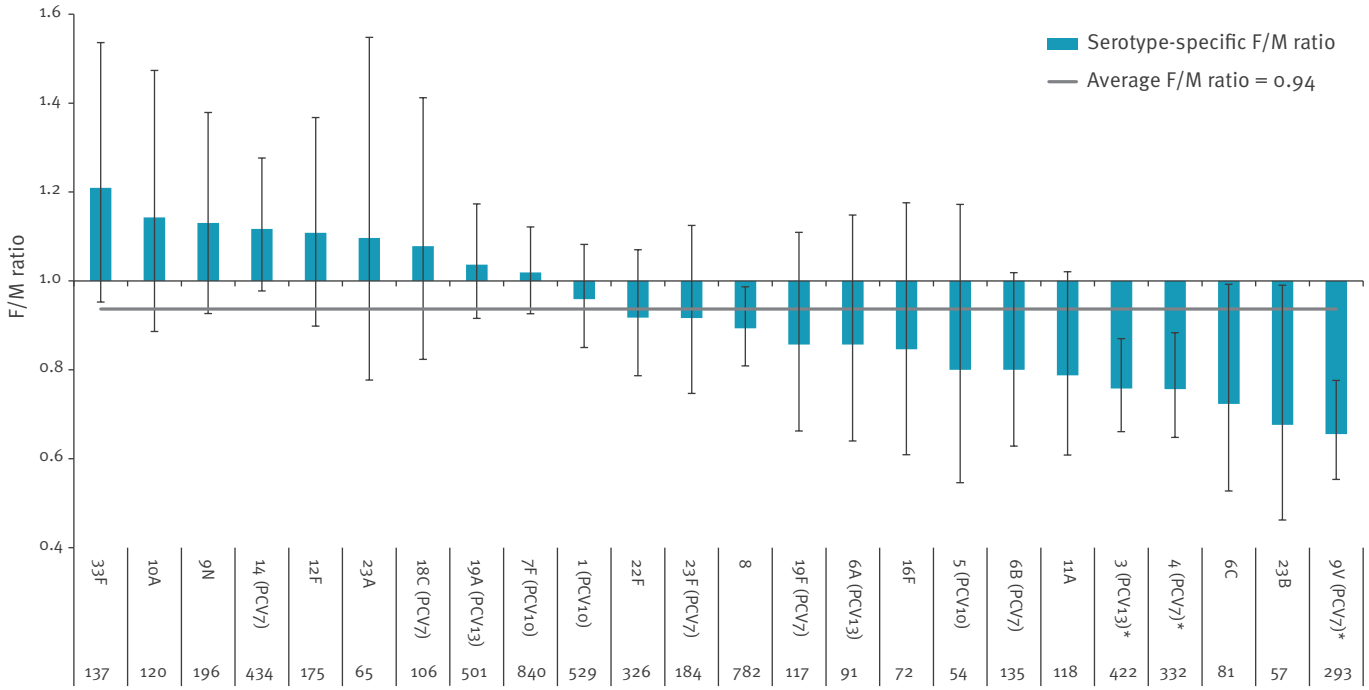
intrinsic and stable factor influencing the occurrence of a serotype that would potentially explain differences in overall IPD susceptibility between sexes. Potential sex-specific preferences in serotypes causing IPD were assessed by calculating the serotype-specific F/M ratio. We used all data from 2004 to 2015 (including the transition years) from patients aged 5 years and older (n = 6,628) to account for changes over time, without any exclusion. Younger children (n = 276) were not taken into account for this analysis because the numbers of IPD per serotype were too small to analyse them as a separate group. The serotype-specific F/M ratios were compared with the average F/M ratio (dividing the total number of cases in women by the total number of cases in men across all serotypes in patients aged 5 years and older) using Fisher's exact test (SPSS version 22). A p value of < 0.05 was considered statistically significant.

Analyses were stratified by age group (0–4, 5–19, 20–39, 40–64 and ≥ 65 years-old). Serotypes were divided in PCV7 serotypes (i.e. serotype 4, 6B, 9V, 14, 18C, 19F and 23F), additional PCV10 serotypes ('PCV10 extra': i.e. serotype 1, 5 and 7F) and non-PCV7 or non-PCV10 serotypes (all serotypes not included in PCV7 or PCV10, respectively). Also, as a sensitivity analysis, serotype 6A was included as a PCV7 serotype and results remained similar (data not shown).

Incidences were calculated as the number of cases per 100,000 persons per year. National incidences were calculated by dividing the population number for each year (StatLine Statistics, the Netherlands) by 4 reflecting the coverage of the sentinel surveillance laboratories (25% of the Dutch population). Differences in incidences and proportions were tested with chi-squared or Fisher's exact test, as appropriate, and for F/M incidence ratio, F/M ratio of proportions, serotype-specific F/M ratio, relative risks and F/M risk ratio of RRs, 95% confidence intervals (CI) were calculated using 2 × 2 tables (z-distribution) [26].

Figure 4

Serotype-specific female/male ratio for causing invasive pneumococcal disease in patients 5 years and older, the Netherlands, 2004–15 (n = 6,628)



F/M: female/male; IPD: invasive pneumococcal disease; PCV: pneumococcal vaccine.

All (additional) serotypes included in the 7, 10 and (not introduced) 13-valent PCV ('PCV13 extra': i.e. serotype 3, 6A and 19A) are shown. Of the non-vaccine serotypes, all serotypes with more than 50 cases during the entire study period are shown. The horizontal line represents the average F/M ratio across all serotypes (0.94). The numbers on the x axis represent the total number of isolates per serotype. Black bars indicate 95% confidence intervals.

* Indicates a significant difference (p value < 0.05) between the serotype-specific F/M ratio compared and the F/M ratio all other serotypes combined.

Results

Overall, 6,906 patients were affected by IPD in the period from 1 June 2004 to 31 May 2015; 3,592 males and 3,314 females, including 169 males and 107 females younger than 5 years. For the pre- and post-PCV periods (without the transition years included), overall 4,303 patients had IPD; 2,227 males and 2,076 females, including 106 males and 79 females younger than 5 years.

Incidence of invasive pneumococcal disease pre- and post-PCV7/10

Figure 1 shows the age and sex-specific IPD incidence in the pre-PCV7, post-PCV7 and post-PCV10 period. The IPD incidence in men was higher than in women for all age groups, except for the 20–39 year-olds in both post-PCV periods and the 40–64 year-olds in the post-PCV10 period. The largest difference in IPD incidence between men and women (in absolute numbers, Figure 1) was observed in those at highest risk, i.e. children younger than 5 years and persons 65 years and older, but the F/M ratio was only significant for those 65 years and older (Figure 2, F/M incidence ratio).

The Table presents IPD incidences (and absolute number of cases) for male and female IPD patients in the pre-PCV7, post-PCV7 and post-PCV10 periods and the change in IPD incidence for men and women separately (RR comparing post-PCV7 to pre-PCV7 and RR post-PCV10 to post-PCV7). In addition, we used the F/M risk ratio of RRs (post-PCV7 vs pre-PCV7 and post-PCV10 vs post-PCV10) to investigate sex differences in direct and indirect effects. Comparing post-PCV7 to pre-PCV7, there was a significant decrease in overall IPD incidence for children younger than 5 years and and people 65 years and older in both sexes (Table: in those younger than 5 years, the male RR was 0.39 (95% CI: 0.25–0.60) and the female RR was 0.48 (95% CI: 0.29–0.77), and in those 65 years and older, the male RR was 0.87 (95% CI: 0.76–0.99) and the female RR was 0.78 (95% CI: 0.68–0.90). The overall reduction (F/M risk ratio of RRs post-PCV7 vs pre-PCV7) in IPD was

Table A

IPD incidences for male and female invasive pneumococcal disease patients in the pre-PCV7, post-PCV7 and post-PCV10 period, the Netherlands, 2004–15 (n = 4,303)

Age group	Pre-PCV7 (2004–06)		Post-PCV7 (2008–11)		Post-PCV10 (2013–15)		Men post-PCV7 vs pre-PCV7	Women post-PCV7 vs pre-PCV7	F/M risk ratio RRs post-PCV7 vs pre-PCV7	Men post-PCV10 vs post-PCV7	Women post-PCV10 vs post-PCV7	F/M risk ratio RRs post-PCV10-vs post-PCV7
	Male	Female	Male	Female	Male	Female						
	Incidence (n)	Incidence (n)	Incidence (n)	Incidence (n)	Incidence (n)	Incidence (n)	RR (95% CI)[a]	RR (95% CI)[b]	Risk ratio (95% CI)[c]	RR (95% CI)[d]	RR (95% CI)[e]	Risk ratio (95% CI)[f]
All ages	16.7 (674)	15.4 (634)	15.5 (953)	13.6 (850)	14.4 (599)	13.9 (591)	0.93 (0.84–1.03)	***0.88 (0.80–0.98)***	0.95 (0.82–1.09)	0.92 (0.83–1.02)	1.02 (0.92–1.14)	1.11 (0.96–1.28)
PCV7	8.0 (321)	6.9 (286)	3.2 (194)	2.9 (184)	0.8 (32)	0.6 (24)	*0.40 (0.33–0.47)*	***0.42 (0.35–0.51)***	1.06 (0.82–1.38)	***0.24 (0.17–0.35)***	***0.19 (0.13–0.29)***	0.79 (0.45–1.40)
PCV10 extra	3.3 (132)	2.7 (111)	3.6 (221)	3.7 (229)	2.5 (105)	2.4 (100)	1.10 (0.89–1.37)	***1.36 (1.08–1.70)***	1.23 (0.90–1.69)	***0.70 (0.55–0.88)***	***0.64 (0.51–0.81)***	0.92 (0.66–1.28)
non-PCV7	8.8 (353)	8.5 (348)	12.4 (759)	10.6 (666)	13.6 (567)	13.3 (567)	***1.41 (1.25–1.60)***	***1.26 (1.11–1.43)***	0.89 (0.74–1.07)	1.10 (0.99–1.23)	***1.25 (1.12–1.40)***	1.14 (0.98–1.33)
non-PCV10	5.5 (221)	5.8 (237)	8.8 (538)	7.0 (437)	11.1 (462)	11 (467)	***1.60 (1.37–1.87)***	***1.21 (1.04–1.42)***	***0.76 (0.61–0.95)***	***1.26 (1.12–1.43)***	***1.58 (1.38–1.79)***	***1.25 (1.04–1.49)***
<5 years	22.9 (59)	16.6 (41)	9.0 (32)	7.9 (27)	6.5 (15)	5.0 (11)	***0.39 (0.25–0.60)***	***0.48 (0.29–0.77)***	1.21 (0.63–2.32)	0.73 (0.39–1.34)	0.63 (0.31–1.28)	0.87 (0.34–2.21)
PCV7	14.7 (38)	12.2 (30)	0.6 (2)	0.6 (2)	0.4 (1)	0.0 (0)	***0.04 (0.01–0.16)***	***0.05 (0.01–0.20)***	1.27 (0.17–9.53)	0.78 (0.07–8.55)	NA	NA
PCV10 extra	3.5 (9)	1.2 (3)	2.5 (9)	2.6 (9)	0.9 (2)	0.5 (1)	0.72 (0.29–1.82)	2.17 (0.59–8.01)	3.00 (0.61–14.87)	0.34 (0.07–1.59)	0.17 (0.02–1.36)	0.50 (0.04–6.56)
non-PCV7	8.1 (21)	4.5 (11)	8.4 (30)	7.3 (25)	6.1 (14)	5.0 (11)	1.03 (0.59–1.80)	1.64 (0.81–3.34)	1.59 (0.65–3.92)	0.72 (0.38–1.36)	0.68 (0.34–1.39)	0.94 (0.36–2.45)
non-PCV10	4.6 (12)	3.2 (8)	5.9 (21)	4.7 (16)	5.2 (12)	4.6 (10)	1.26 (0.62–2.57)	1.45 (0.62–3.38)	1.14 (0.38–3.45)	0.89 (0.44–1.80)	0.97 (0.44–2.14)	1.10 (0.38–3.17)
5–19 years	1.7 (13)	1.7 (12)	2.1 (24)	1.4 (15)	1.5 (11)	0.8 (6)	1.22 (0.62–2.40)	0.83 (0.39–1.77)	0.68 (0.25–1.87)	0.70 (0.34–1.43)	0.61 (0.24–1.57)	0.87 (0.27–2.86)
PCV7	0.8 (6)	0.7 (5)	0.3 (4)	0.5 (5)	0.3 (2)	0.0 (0)	0.44 (0.12–1.56)	0.66 (0.19–2.28)	1.50 (0.26–8.81)	0.76 (0.14–4.16)	NA	NA
PCV10 extra	0.4 (3)	0.4 (3)	1.1 (13)	0.6 (7)	0.4 (3)	0.4 (3)	2.87 (0.82–10.06)	1.54 (0.40–5.97)	0.54 (0.09–3.41)	0.35 (0.1–1.24)	0.65 (0.17–2.53)	1.86 (0.29–11.76)
non-PCV7	0.9 (7)	1.0 (7)	1.7 (20)	0.9 (10)	1.2 (9)	0.8 (6)	1.89 (0.80–4.47)	0.94 (0.36–2.48)	0.50 (0.14–1.82)	0.69 (0.31–1.51)	0.92 (0.33–2.52)	1.33 (0.37–4.81)
non-PCV10	0.5 (4)	0.6 (4)	0.6 (7)	0.3 (3)	0.8 (6)	0.4 (3)	1.16 (0.34–3.96)	0.5 (0.11–2.22)	0.43 (0.06–2.97)	1.31 (0.44–3.89)	1.53 (0.31–7.56)	1.17 (0.17–8.09)

CI: confidence interval; F/M: female/male; PCV7: 7-valent pneumococcal conjugate vaccine; PCV10: 10-valent pneumococcal conjugate vaccine; RR: relative risk; PCV10 extra: serotypes 1, 5, 7F.

Difference in proportions were tested with chi-squared test, and RR and 95% CI were calculated. Incidences are shown as number of cases/100,000/year). Analyses were stratified by age group (<5, 5–19, 20–39, 40–64, ≥ 65 years). Numbers in italics indicates a significant difference.

Study period: pre-PCV7: June 2004–May 2006; post-PCV7: June 2008–May 2011; post-PCV10: June 2013–May 2015.

not significantly different between men and women of these age groups (Table).

Also in other age groups, there was no significant interaction between change in IPD incidence and sex comparing post-PCV7 to pre-PCV7. However, in the 20–39 year-olds, the F/M risk ratio of RRs for PCV10 serotype IPD was 2.43 (95% CI: 1.07–5.50), owing to a significant increase in PCV10 serotype IPD in women (RR = 2.06; 95% CI: 1.10–3.87) and a non-significant reduction in men (RR = 0.85; 95% CI: 0.50–1.43), which indicated a statistically significant difference in replacement disease by PCV10 serotypes (mainly 1 and 7F, data not shown). As a result, women showed a non-significant increase in IPD incidence comparing the pre-PCV7 to post-PCV7 (from 3.9/100,000 to 5.0/100,000) period, whereas the incidence decreased in men of the same age (from 5.3/100,000 to 4.7/100,000, Figure 3). In 40–64 year-olds of both sexes, IPD incidence remained stable after PCV7 introduction.

After PCV10 introduction, IPD caused by the additional PCV10 serotypes decreased in all age groups and in both sexes, suggesting PCV10 herd protection, although this was only significant for men aged 40–64 (RR = 0.67; 95% CI: 0.45–0.99) and women 65 years and older (RR = 0.60; 95% CI: 0.42–0.87, Table). In addition, PCV7 serotype IPD continued to decrease. These on-going effects of herd protection against PCV7 and recently introduced PCV10 resulted in a non-significant decline in overall IPD incidence for all except women aged 40 and older. In women 40 years and older, PCV7/10 herd protection was offset by a significant increase in non-PCV10 serotype IPD, which was not observed in men, a group where IPD incidence declined. As a result, IPD incidence in the 40–64 year-olds became similar in women and men (12.3/100,000 vs 12.2/100,000). However, we did not observe a significantly different change in overall IPD incidence between men and women in this age group (F/M risk ratio of RRs post-PCV10 vs post-PCV7, Table). Also in other age groups, there was no significant interaction between change in overall IPD incidence and sex comparing post-PCV10 to post-PCV7. After PCV10 introduction, non-PCV10 serotype IPD incidence in 20–39 year-old women increased (RR = 1.90; 95% CI: 1.07–3.38), whereas it decreased in men (RR = 0.71; 95% CI: 0.37–1.37, F/M risk ratio of RRs = 2.67; 95% CI: 1.11–6.39).

Clinical syndromes, outcomes and underlying conditions pre- and post-PCV7

Comparing post-PCV7 to pre-PCV7, no major differences were observed between sexes regarding shifts in the proportion of different clinical syndromes, outcomes and underlying conditions. However, some significant differences within the pre- and/or post-PCV7 periods, and small but significantly different shifts in proportions were observed between male and female IPD patients.

Clinical syndromes

In the pre-PCV7 period, the overall proportion (without stratification for age) of IPD patients with invasive pneumonia was significantly higher in male than female patients (76 vs 71%; F/M ratio of proportions: RR = 0.93; 95% CI: 0.87–0.98). After stratification for age, this remained significant for the 20–39 year-olds and those 65 years and older. In the post-PCV7 period (June 2008–May 2011), the distribution of clinical syndromes in all IPD patients was not significantly different between male and female patients. However, in male IPD patients aged 5–19 years, the proportion of pneumonia was significantly higher than in female patients (80 vs 40%: F/M ratio of proportions: RR = 0.50; 95% CI: 0.26–0.96), whereas for 20–39 year-old men, meningitis was significantly more common (20 vs 8%; F/M ratio of proportions: RR = 0.39; 95% CI: 0.16–0.96). The changes in distribution of clinical syndromes after PCV7 introduction (F/M risk ratio of RRs) were not significantly different between male and female patients except in 20–39 year-olds, in whom the increased proportion of pneumonia in female patients (from 68 to 77%) differed significantly from the decreased proportion (from 88 to 73%) in male patients (F/M risk ratio of RRs = 1.37; 95% CI: 1.01–1.86).

Outcomes

In the pre- and post-PCV7 period, the overall case fatality and the proportion of ICU admissions (without stratification for age) were not significantly different between male and female IPD patients. The decline in case fatality after PCV7 introduction did not differ significantly between male (from 15 to 12%) and female patients (from 18 to 11%; F/M risk ratio of RRs = 0.79; 95% CI: 0.54–1.13). Nor were changes in case fatality and proportion of ICU admissions significantly different between male and female patients after stratification for age.

Underlying conditions

In the pre- and post-PCV7 period, the overall proportion (without stratification for age) of male IPD patients with an immunocompromising condition was significantly higher compared with that of female patients, with 21 vs 16% pre-PCV7 (F/M ratio of proportions = 0.78; 95% CI: 0.61–0.99) and 21 vs 13% post-PCV7 (F/M ratio of proportions = 0.64; 95% CI: 0.51–0.79), respectively. After stratification for age, this remained significant for patients 65 years and older. Also the change in the overall proportion of patients with an immunocompromising condition after PCV7 introduction was significantly different between male and female patients (F/M risk ratio of RRs = 0.82; 95% CI: 0.67–0.99), indicating a significantly higher decrease in women compared with the stable proportion in men. However, after stratification for age, there were no significant differences in changes in immunocompromising conditions between male and female patients following PCV7 introduction. The overall proportion of patients with any comorbidity was higher in male IPD patients than in female patients, with 76 vs 74% pre-PCV7 (F/M ratio of

Table B

IPD incidences for male and female invasive pneumococcal disease patients in the pre-PCV7, post-PCV7 and post-PCV10 period, the Netherlands, 2004–15 (n = 4,303)

Age group	Pre-PCV7 (2004–06)		Post-PCV7 (2008–11)		Post-PCV10 (2013–15)		Men post-PCV7 vs pre-PCV7	Women post-PCV7 vs pre-PCV7	F/M risk ratio RRs post-PCV7 vs pre-PCV7	Men post-PCV10 vs post-PCV7	Women post-PCV10 vs post-PCV7	F/M risk ratio RRs post-PCV10-vs post-PCV7
	Male	Female	Male	Female	Male	Female						
	Incidence (n)	Incidence (n)	Incidence (n)	Incidence (n)	Incidence (n)	Incidence (n)	RR (95% CI)[a]	RR (95% CI)[b]	Risk ratio (95% CI)[c]	RR (95% CI)[d]	RR (95% CI)[e]	Risk ratio (95% CI)[f]
20–39 years	5.3 (60)	3.9 (43)	4.7 (74)	5.0 (79)	2.6 (27)	4.0 (41)	0.88 (0.62–1.23)	1.29 (0.89–1.88)	1.48 (0.89–2.44)	***0.56 (0.36–0.87)***	0.80 (0.55–1.16)	1.42 (0.80–2.54)
PCV7	1.7 (19)	1.7 (19)	0.9 (15)	1.3 (20)	0.2 (2)	0.1 (1)	0.56 (0.29–1.10)	0.74 (0.40–1.39)	1.32 (0.53–3.33)	***0.20 (0.05–0.89)***	***0.08 (0.01–0.57)***	0.38 (0.03–4.54)
PCV10 extra	2.3 (26)	1.2 (13)	2.0 (31)	2.4 (38)	1.2 (12)	1.4 (14)	0.85 (0.50–1.43)	**2.06 (1.10–3.87)**	***2.43 (1.07–5.50)***	0.59 (0.3–1.16)	0.57 (0.31–1.04)	0.95 (0.39–2.35)
non-PCV7	3.6 (41)	2.2 (24)	3.7 (59)	3.7 (59)	2.4 (25)	3.9 (40)	1.02 (0.69–1.52)	**1.73 (1.08–2.78)**	1.69 (0.91–3.15)	0.65 (0.41–1.04)	1.04 (0.70–1.55)	1.60 (0.86–2.97)
non-PCV10	1.3 (15)	1.0 (11)	1.8 (28)	1.3 (21)	1.3 (13)	2.5 (26)	1.33 (0.71–2.48)	1.34 (0.65–2.79)	1.01 (0.39–2.65)	0.71 (0.37–1.37)	***1.90 (1.07–3.38)***	***2.67 (1.11–6.39)***
40–64 years	13.8 (194)	12.4 (170)	14.1 (313)	12.2 (268)	12.2 (182)	12.3 (182)	1.02 (0.85–1.22)	0.99 (0.82–1.20)	0.97 (0.75–1.26)	0.87 (0.72–1.04)	1.00 (0.83–1.21)	1.16 (0.89–1.51)
PCV7	5.9 (82)	4.6 (63)	2.9 (64)	2.4 (52)	0.5 (7)	0.3 (5)	***0.49 (0.36–0.68)***	***0.52 (0.36–0.75)***	1.05 (0.64–1.72)	***0.16 (0.07–0.36)***	***0.14 (0.06–0.36)***	0.87 (0.26–2.91)
PCV10 extra	2.6 (37)	2.5 (35)	3.6 (80)	3.8 (83)	2.4 (36)	2.7 (40)	1.37 (0.92–2.02)	***1.49 (1.00–2.21)***	1.09 (0.63–1.90)	***0.67 (0.45–0.99)***	0.71 (0.49–1.04)	1.06 (0.62–1.83)
non-PCV7	8.0 (112)	7.8 (107)	11.2 (249)	9.9 (216)	11.7 (175)	11.9 (177)	***1.40 (1.12–1.75)***	***1.27 (1.01–1.60)***	0.90 (0.65–1.25)	1.05 (0.86–1.27)	1.21 (0.99–1.48)	1.16 (0.88–1.53)
non-PCV10	5.4 (75)	5.2 (72)	7.6 (169)	6.1 (133)	9.3 (139)	9.2 (137)	***1.42 (1.08–1.87)***	1.16 (0.87–1.55)	0.82 (0.55–1.21)	1.22 (0.98–1.53)	**1.52 (1.20–1.93)**	1.24 (0.90–1.72)
≥65 years	72.3 (348)	55.6 (368)	62.5 (510)	43.5 (461)	55.6 (364)	43.9 (351)	***0.87 (0.76–0.99)***	***0.78 (0.68–0.90)***	0.90 (0.75–1.10)	0.89 (0.78–1.02)	1.01 (0.88–1.16)	1.13 (0.94–1.38)
PCV7	36.3 (175)	25.5 (169)	13.4 (109)	9.8 (104)	3.1 (20)	2.3 (18)	***0.37 (0.29–0.47)***	***0.38 (0.30–0.49)***	1.04 (0.74–1.47)	***0.23 (0.14–0.37)***	***0.23 (0.14–0.38)***	1.00 (0.50–2.00)
PCV10 extra	11.8 (57)	8.6 (57)	10.8 (88)	8.7 (92)	7.9 (52)	5.3 (42)	0.91 (0.65–1.27)	1.01 (0.72–1.40)	1.11 (0.69–1.77)	0.74 (0.52–1.04)	***0.60 (0.42–0.87)***	0.82 (0.50–1.36)
non-PCV7	35.9 (173)	30.1 (199)	49.2 (401)	33.7 (357)	52.5 (344)	41.6 (333)	***1.37 (1.15–1.64)***	1.12 (0.94–1.33)	0.82 (0.64–1.05)	1.07 (0.92–1.23)	***1.24 (1.06–1.43)***	1.16 (0.94–1.42)
non-PCV10	24.1 (116)	21.5 (142)	38.4 (313)	25.0 (265)	44.6 (292)	36.4 (291)	***1.59 (1.29–1.97)***	1.17 (0.95–1.43)	***0.73 (0.54–0.98)***	1.16 (0.99–1.36)	***1.45 (1.23–1.72)***	1.25 (0.99–1.58)

CI: confidence interval; F/M: female/male; PCV7: 7-valent pneumococcal conjugate vaccine; PCV10: 10-valent pneumococcal conjugate vaccine; RR: relative risk; PCV10 extra: serotypes 1, 5, 7F.

Difference in proportions were tested with chi-squared test, and RR and 95% CI were calculated. Incidences are shown as number of cases/100,000/year). Analyses were stratified by age group (<5, 5–19, 20–39, 40–64, ≥65 years). Numbers in italics indicates a significant difference.

Study period: pre-PCV7: June 2004–May 2006; post-PCV7: June 2008–May 2011; post-PCV10: June 2013–May 2015.

proportions = 0.98; 95% CI: 0.92–1.05) and 77 vs 72% post-PCV7 (F/M ratio of proportions = 0.94; 95% CI: 0.89–0.99). After stratification for age, this was significant for patients 65 years and older pre-PCV7 and for 40–64 year-old patients post-PCV7. The overall change in the proportion of patients with any comorbidity following PCV7 introduction was not significantly different between male and female patients (F/M risk ratio of RRs = 0.96; 95% CI: 0.88–1.04) with or without stratification for age.

Serotype-specific female/male ratio for invasive pneumococcal disease

Figure 4 shows the serotype-specific F/M ratio. Overall, 6,628 patients aged 5 years and older (3,422 males, 3,206 females) were affected by IPD in the period from 1 June 2004 to 31 May 2015. The average F/M ratio across all serotypes was 0.94. Only serotypes 3, 4 and 9V were significantly associated with male sex (F/M ratio = 0.76; p = 0.026, F/M ratio = 0.76; p = 0.047 and F/M ratio = 0.66; p = 0.002, respectively).

Discussion

Our findings confirm the importance of sex as an epidemiological factor in IPD. We observed structurally higher IPD incidences in men in all age groups, with the exception of 20–39 year-olds after implementation of PCV7 and of 40–64 year-olds after implementation of PCV10. These observations illustrate a sex-specific differential impact of post-PCV dynamics.

The structural excess in IPD incidence in boys younger than 5 years has been attributed to anatomical or early hormonal differences predisposing to differences in immunity [27-29]. Likewise, the higher susceptibility for IPD in elderly men could be explained by sex-based inactivation of the X chromosome, resulting in differences in immunity [1,4,5]. Also a higher prevalence of underlying conditions in the male population such as chronic cardiovascular and renal disease, malignancies [30] or tobacco use is likely to play a role [31]. This is reflected in a significantly higher proportion of immunocompromising conditions in male IPD patients pre- and post-PCV7. We only found a serotype-specific preference to affect men and women differently in three of 24 serotypes; therefore an individual serotype-specific (or serotype-related) factor for explaining the difference in IPD susceptibility is unlikely.

In 20–39 year-olds, IPD incidence in women increased post-PCV7 and became higher than in men, in whom IPD incidence had decreased. This reflected a significant increase in IPD caused by the additional PCV10 serotypes (mainly serotypes 1 and 7F). Likewise, previous analysis of Dutch surveillance data 2–4 years after PCV7 introduction showed an increase in IPD incidence in women (20–44 years-old) caused by an increase in serotype 1 [23]. After PCV7 was replaced by PCV10, covering serotypes 1 and 7F, herd effects may have reduced the elevated burden of IPD in 20–39 year-old women. Indeed, herd protection of PCV10 was established, and overall IPD incidence as well as IPD caused by PCV10 serotypes decreased in both sexes. However, a significant increase in non-PCV10 type IPD was, again, exclusively observed in women and IPD incidence remained higher in women than in men post-PCV10. The increase in non-PCV10 type IPD (attributable to several serotypes) suggests a vaccine induced effect rather than natural fluctuation of a single serotype.

Also, in a recent study from the United States, IPD incidence was generally higher in male people, but after PCV13 introduction, IPD incidence among 18–39 year-old black women became slightly higher than in men [20]. Socially defined roles may explain this phenomenon. Women of childbearing age could be at increased risk for replacement disease because of close contact with PCV7/10-vaccinated children as was hypothesised in other studies [22,23]. In Scotland before PCV7 introduction, a higher IPD incidence was observed in 35–49 year-old women based on data from 1992 to 2007 [32]. Increased carriage of non-vaccine pneumococcal serotypes in parents of vaccinated children compared with parents of unvaccinated children has been well established [12,33]. Although these studies did not analyse men and women separately, the importance of sex is further supported by a study on pertussis, which showed a higher transmission rate between infants and mothers compared with fathers [34].

In other non-vaccinated age groups, PCV10 herd effects became apparent as well, but again with a sex-specific differential impact. In men 40 years and older, IPD incidence declined further during the post-PCV10 period, whereas herd effects in women of the same age groups were offset by a significant increase in IPD caused by non-PCV10 serotypes. This could suggest that for women 40 years and older, after an initial overall reduction in IPD due to PCV7 herd effects, a new plateau phase in IPD incidence has been reached using current vaccination strategies.

After introduction of PCV7, shifts in circulating serotypes were associated with significant changes in clinical outcome, such as a lower overall case fatality [25]. Our findings confirm that this is the case for both sexes at the time point 5 years after PCV7 introduction. Pre- and post-PCV7, the case fatality and ICU admission rates between male and female patients were not significantly different.

A limitation of our study is that it was an ecological study, so one should be cautious about interpreting findings as causally related to introduction of vaccination. In addition, not accounting for multiple testing in statistical analysis and some results being borderline significant, our results should be regarded as explorative analysis and need to be interpreted with caution. Furthermore, we had no information whether or not IPD patients were parents and/or had close contact with children and therefore could not further assess the proposed mechanism which could have resulted in

the observed differences in 20–39 year-old patients. Nevertheless, our study provides important insights into structural sex differences in IPD incidence and different indirect effects after PCV7/10 introduction. This finding indicates that an intervention in a complex ecosystem can result in (temporary) changes in IPD dynamics but needs to be confirmed by others.

Conclusion

This study confirms the importance of sex in IPD incidence. We have shown that shifts in serotypes can cause increased IPD incidence rates. Although IPD surveillance studies have been performed in many countries, data on sex differences are scarce. We invite other investigators to stratify their pre- and post-pneumococcal vaccination IPD data by sex. Continued surveillance of IPD incidence and outcome by sex is important to evaluate the direct and indirect long-term effects of pneumococcal conjugate vaccination in the population.

Conflict of interest

Gertjan Wagenvoort received a lecturing fee from Pfizer.

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Authors' contributions

Data administration, data analysis, interpretation of data, drafting of the manuscript: Gertjan Wagenvoort and Mirjam Knol. Interpretation of data, drafting of the manuscript: Elisabeth Sanders, Hester E. de Melker, Bart Vlaminckx. Drafting manuscript, interpretation of data and serotyping: Arie van der Ende.

References

1. Fish EN. The X-files in immunity: sex-based differences predispose immune responses.Nat Rev Immunol. 2008;8(9):737-44. DOI: 10.1038/nri2394 PMID: 18728636
2. Roberts CW, Walker W, Alexander J. Sex-associated hormones and immunity to protozoan parasites.Clin Microbiol Rev. 2001;14(3):476-88. DOI: 10.1128/CMR.14.3.476-488.2001 PMID: 11432809
3. Kadioglu A, Cuppone AM, Trappetti C, List T, Spreafico A, Pozzi G, et al. Sex-based differences in susceptibility to respiratory and systemic pneumococcal disease in mice. J Infect Dis. 2011;204(12):1971-9. DOI: 10.1093/infdis/jir657 PMID: 22021621
4. van Lunzen J, Altfeld M. Sex differences in infectious diseases-common but neglected.J Infect Dis. 2014;209(Suppl 3):S79-80. DOI: 10.1093/infdis/jiu159 PMID: 24966193
5. Falagas ME, Mourtzoukou EG, Vardakas KZ. Sex differences in the incidence and severity of respiratory tract infections.Respir Med. 2007;101(9):1845-63. DOI: 10.1016/j.rmed.2007.04.011 PMID: 17544265
6. Gutiérrez F, Masiá M, Mirete C, Soldán B, Rodríguez JC, Padilla S, et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. J Infect. 2006;53(3):166-74. DOI: 10.1016/j.jinf.2005.11.006 PMID: 16375972
7. Jensen-Fangel S, Mohey R, Johnsen SP, Andersen PL, Sørensen HT, Ostergaard L. Gender differences in hospitalization rates for respiratory tract infections in Danish youth.Scand J Infect Dis. 2004;36(1):31-6. DOI: 10.1080/00365540310017618 PMID: 15000556
8. Millett ER, Quint JK, Smeeth L, Daniel RM, Thomas SL. Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study.PLoS One. 2013;8(9):e75131. DOI: 10.1371/journal.pone.0075131 PMID: 24040394
9. Usuf E, Bottomley C, Adegbola RA, Hall A. Pneumococcal carriage in sub-Saharan Africa--a systematic review.PLoS One. 2014;9(1):e85001. DOI: 10.1371/journal.pone.0085001 PMID: 24465464
10. Watson K, Carville K, Bowman J, Jacoby P, Riley TV, Leach AJ, et al. Upper respiratory tract bacterial carriage in Aboriginal and non-Aboriginal children in a semi-arid area of Western Australia. Pediatr Infect Dis J. 2006;25(9):782-90. DOI: 10.1097/01.inf.0000232705.49634.68 PMID: 16940834
11. Syrjänen RK, Kilpi TM, Kaijalainen TH, Herva EE, Takala AK. Nasopharyngeal carriage of Streptococcus pneumoniae in Finnish children younger than 2 years old.J Infect Dis. 2001;184(4):451-9. DOI: 10.1086/322048 PMID: 11471103
12. van Gils EJ, Veenhoven RH, Hak E, Rodenburg GD, Bogaert D, Ijzerman EP, et al. Effect of reduced-dose schedules with 7-valent pneumococcal conjugate vaccine on nasopharyngeal pneumococcal carriage in children: a randomized controlled trial. JAMA. 2009;302(2):159-67. DOI: 10.1001/jama.2009.975 PMID: 19584345
13. Spijkerman J, van Gils EJ, Veenhoven RH, Hak E, Yzerman EP, van der Ende A, et al. Carriage of Streptococcus pneumoniae 3 years after start of vaccination program, the Netherlands. Emerg Infect Dis. 2011;17(4):584-91. DOI: 10.3201/eid1704.101115 PMID: 21470445
14. Jansen AG, Rodenburg GD, van der Ende A, van Alphen L, Veenhoven RH, Spanjaard L, et al. Invasive pneumococcal disease among adults: associations among serotypes, disease characteristics, and outcome. Clin Infect Dis. 2009;49(2):e23-9. DOI: 10.1086/600045 PMID: 19522653
15. Rodenburg GD, de Greeff SC, Jansen AG, de Melker HE, Schouls LM, Hak E, et al. Effects of pneumococcal conjugate vaccine 2 years after its introduction, the Netherlands. Emerg Infect Dis. 2010;16(5):816-23. DOI: 10.3201/eid1605.091223 PMID: 20409372
16. van Deursen AM, van Mens SP, Sanders EA, Vlaminckx BJ, de Melker HE, Schouls LM, et al. Invasive pneumococcal disease and 7-valent pneumococcal conjugate vaccine, the Netherlands. Emerg Infect Dis. 2012;18(11):1729-37. DOI: 10.3201/eid1811.120329 PMID: 23092683
17. Myint TT, Madhava H, Balmer P, Christopoulou D, Attal S, Menegas D, et al. The impact of 7-valent pneumococcal conjugate vaccine on invasive pneumococcal disease: a literature review. Adv Ther. 2013;30(2):127-51. DOI: 10.1007/s12325-013-0007-6 PMID: 23397399
18. Ladhani SN, Slack MP, Andrews NJ, Waight PA, Borrow R, Miller E. Invasive pneumococcal disease after routine pneumococcal conjugate vaccination in children, England and Wales.Emerg Infect Dis. 2013;19(1):61-8. DOI: 10.3201/eid1901.120741 PMID: 23259937
19. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CGUS. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination.N Engl J Med. 2013;369(2):155-63. DOI: 10.1056/NEJMoa1209165 PMID: 23841730
20. de St Maurice A, Schaffner W, Griffin MR, Halasa N, Grijalva CG. Persistent Sex Disparities in Invasive Pneumococcal Diseases in the Conjugate Vaccine Era.J Infect Dis. 2016;214(5):792-7. DOI: 10.1093/infdis/jiw222 PMID: 27247342
21. van Lier EA, Oomen PJ, Mulder M, Conyn-van Spaendonck MAE, Drijfhout IH, de Hoogh PAAM, de Melker HE. Vaccinatiegraad Rijksvaccinatieprogramma Nederland Verslagjaar 2013. [Immunisation coverage national immunisation programme in the Netherlands: year of report 2013]. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu. 2013. RIVM Rapport 150202001. Dutch. Available from: http://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2013/juni/Immunisation_coverage_National_Immunisation_Programme_in_the_Netherlands_Year_of_report_2013
22. Hak E, Shea KM, Jick SS. Association of infant pneumococcal vaccination with pneumococcal pneumonia among mothers: a nested case-control study using the GPRD.Vaccine. 2013;31(12):1590-6. DOI: 10.1016/j.vaccine.2013.01.018 PMID: 23357195
23. Van Mens SP, Van Deursen AM, Meijvis SC, Vlaminckx BJ, Sanders EA, De Melker HE, et al. Increased incidence of serotype-1 invasive pneumococcal disease in young female adults in The Netherlands. Epidemiol Infect. 2014;142(9):1996-9. DOI: 10.1017/S0950268813002860 PMID: 24229845

24. Harboe ZB, Benfield TL, Valentiner-Branth P, Hjuler T, Lambertsen L, Kaltoft M, et al. Temporal trends in invasive pneumococcal disease and pneumococcal serotypes over 7 decades. Clin Infect Dis. 2010;50(3):329-37. DOI: 10.1086/649872 PMID: 20047478
25. Wagenvoort GH, Sanders EA, Vlaminckx BJ, Elberse KE, de Melker HE, van der Ende A, et al. Invasive pneumococcal disease: Clinical outcomes and patient characteristics 2-6 years after introduction of 7-valent pneumococcal conjugate vaccine compared to the pre-vaccine period, the Netherlands. Vaccine. 2016;34(8):1077-85. DOI: 10.1016/j.vaccine.2015.12.066 PMID: 26778420
26. Rothman K, Greenland S. Chapter 15: Introduction to stratified analysis. In: Rothman K, Greenland S, editors. Modern epidemiology. 3rd ed. Philadelphia: Wolters Kluwer; 2008. p. 258-282.
27. Muenchhoff M, Goulder PJ. Sex differences in pediatric infectious diseases.J Infect Dis. 2014;209(Suppl 3):S120-6. DOI: 10.1093/infdis/jiu232 PMID: 24966192
28. Liptzin DR, Landau LI, Taussig LM. Sex and the lung: Observations, hypotheses, and future directions.Pediatr Pulmonol. 2015;50(12):1159-69. DOI: 10.1002/ppul.23178 PMID: 25906765
29. Voysey M, Barker CI, Snape MD, Kelly DF, Trück J, Pollard AJ. Sex-dependent immune responses to infant vaccination: an individual participant data meta-analysis of antibody and memory B cells.Vaccine. 2016;34(14):1657-64. DOI: 10.1016/j.vaccine.2016.02.036 PMID: 26920472
30. Jungers P, Chauveau P, Descamps-Latscha B, Labrunie M, Giraud E, Man NK, et al. Age and gender-related incidence of chronic renal failure in a French urban area: a prospective epidemiologic study. Nephrol Dial Transplant. 1996;11(8):1542-6. DOI: 10.1093/oxfordjournals.ndt.a027610 PMID: 8856208
31. Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, et al. Cigarette smoking and invasive pneumococcal disease. N Engl J Med. 2000;342(10):681-9. DOI: 10.1056/NEJM200003093421002 PMID: 10706897
32. Inverarity D, Lamb K, Diggle M, Robertson C, Greenhalgh D, Mitchell TJ, et al. Death or survival from invasive pneumococcal disease in Scotland: associations with serogroups and multilocus sequence types. J Med Microbiol. 2011;60(Pt 6):793-802. DOI: 10.1099/jmm.0.028803-0 PMID: 21393453
33. Flasche S, Van Hoek AJ, Sheasby E, Waight P, Andrews N, Sheppard C, et al. Effect of pneumococcal conjugate vaccination on serotype-specific carriage and invasive disease in England: a cross-sectional study. PLoS Med. 2011;8(4):e1001017. DOI: 10.1371/journal.pmed.1001017 PMID: 21483718
34. de Greeff SC, de Melker HE, Westerhof A, Schellekens JF, Mooi FR, van Boven M. Estimation of household transmission rates of pertussis and the effect of cocooning vaccination strategies on infant pertussis.Epidemiology. 2012;23(6):852-60. DOI: 10.1097/EDE.0b013e31826c2b9e PMID: 23018969

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Letter to the editor: Just a coincidence? Two severe human cases due to swine influenza (SIV) A(H1N1)v in Europe, October 2016

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To the editor: We read with concern the reports of two human cases infected with swine influenza virus (SIV) that both occurred in October 2016 in Europe [1,2]. One case was a school-aged child in the Netherlands with history of eczema, while the other was a middle-aged man in Italy with obesity as underlying condition. The similarities of these cases were striking: both developed severe respiratory symptoms with a rapid progression, finally requiring admission to intensive care and use of extracorporeal membrane oxygenation (ECMO). Antiviral treatment was initiated in both cases more than three days after onset of symptoms, and only after the symptoms worsened, invasive mechanical ventilation and ECMO support were initiated. Both cases recovered and were discharged from hospital.

Eurasian avian-like SIV A(H1N1)v were identified in both patients. In Europe, these viruses circulate widely in the pig population [3]. The viruses isolated from the patients differed genetically from each other. Both cases had presumably visited pig farms before onset of symptoms, suggesting direct contact or indirect exposure to infected pigs, e.g. through contaminated surfaces or via aerosol. In both cases, an initial positive influenza A detection with subsequent inconclusive typing results was followed by whole genome sequencing, which identified the swine virus origin. The same virus was also detected in the pigs at the visited farm in the Netherlands.

These two cases are the first severe human cases of SIV A(H1N1)v reported to the European Centre for Disease Prevention and Control (ECDC) or the World Health Organization Regional Office for Europe (WHO/Europe) since the 2009 influenza A(H1N1) pandemic, apart from a few sporadic detections in mild or asymptomatic persons during research projects [4]. The detection of these cases may have benefited from the availability of whole genome sequencing for specimens with inconclusive results or nontypeable influenza. That reports of human cases in Europe are rare is in contrast to the more frequent sporadic reports of human cases caused by SIV A(H1N1)v, A(H1N2)v or A(H3N2)v in the United States (US) and highlights the continuous possibility of spill-over of influenza viruses from swine to humans [5]. This is probably a result of the fact that more individuals in the US are exposed to infected animals because of the popularity of regular local and state fairs and agricultural exhibitions with ca 150 million visitors each year where swine are openly accessible for the visitors [6]. Because there is no continuous surveillance of influenza viruses in pigs in Europe, data mainly derive from research projects that may only provide a fragment of the overall picture. Especially little is known about the impact of trade-related network and transport structures between pig producers that may contribute to a rapid spread of new influenza viruses across Europe [3].

The 2009 pandemic was the latest of several pandemics caused by a swine-origin influenza virus [7]. The two recent human cases of swine influenza should serve as a reminder that zoonotic transmission events from pigs to humans, causing severe illnesses, can happen in Europe as well. They should also raise awareness of the need for cautious SIV case management, particularly during the seasonal influenza epidemic, in order to avoid re-assortment events between swine and human viruses and to detect any human-to-human transmission as early as possible.

People who develop influenza-like symptoms after exposure to pigs should be promptly assessed for influenza infection. Specimens should be characterised virologically and isolates should be shared with the WHO Collaborating Centres. Early treatment with neuraminidase inhibitors should be considered and patients isolated to reduce risk of further transmission, in line with relevant national recommendations. Follow-up of other exposed individuals and contacts of

the index cases should be considered to identify further cases and to detect any human-to-human transmission of the virus. A rapid sharing of such information nationally as well as internationally through the European Union's Early Warning and Response System (EWRS), the International Health Regulations [7] or directly contacting the respective authorities is a prerequisite for early identification of new emerging pandemic threats and initiation of containment and prevention measures.

Conflict of interest

None declared.

References

1. Rovida F, Piralla A, Marzani FC, Moreno A, Campanini G, Mojoli F, et al. Swine influenza A (H1N1) virus (SIV) infection requiring extracorporeal life support in an immunocompetent adult patient with indirect exposure to pigs, Italy, October 2016. Euro Surveill. 2017;22(5):30456. DOI: 10.2807/1560-7917.ES.2017.22.5.30456 PMID: 28183395
2. Fraaij PL, Wildschut ED, Houmes RJ, Swaan CM, Hoebe CJ, de Jonge HC, et al. Severe acute respiratory infection caused by swine influenza virus in a child necessitating extracorporeal membrane oxygenation (ECMO), the Netherlands, October 2016. Euro Surveill. 2016;21(48):30416. DOI: 10.2807/1560-7917.ES.2016.21.48.30416 PMID: 27934581
3. Watson SJ, Langat P, Reid SM, Lam TT, Cotten M, Kelly M, et al. Molecular Epidemiology and Evolution of Influenza Viruses Circulating within European Swine between 2009 and 2013. J Virol. 2015;89(19):9920-31. DOI: 10.1128/JVI.00840-15 PMID: 26202246
4. European Centre for Disease Prevention and Control (ECDC). Annual epidemiological report. zoonotic influenza. Reporting on 2014 data retrieved from TESSy. Stockholm: ECDC. [Accessed: 15 Feb 2017]. Available from: http://ecdc.europa.eu/en/healthtopics/avian_influenza/Pages/Annual-Epidemiological-Report.aspx
5. Centers for Disease Control and Prevention (CDC). 4 variant virus infections linked to pig exposures. Atlanta: CDC. [Accessed: 15 Feb 2017]. Available from: https://www.cdc.gov/flu/news/variant-virus-pig-exposure.htm
6. National Assembly of State Animal Health Officials (NASAHO) and National Association of State Public Health Veterinarians (NASPHV). Measures to minimize influenza transmission at swine exhibitions, 2013. Arlington: NASAHO; 2013 [22/02/2017]. Available from: http://www.nj.gov/agriculture/divisions/ah/pdf/swineexhibitions.pdf
7. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009;360(25):2605-15. DOI: 10.1056/NEJMoa0903810 PMID: 19423869
8. World Health Organization (WHO). International health regulations (2005) - Third edition. Geneva: WHO; 2016. Available from: http://www.who.int/ihr/publications/9789241580496/en/

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Authors' reply: Two severe human cases due to swine influenza A (H1N1)v in October 2016 in Europe were chronologic coincident yet distinct events

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To the editor: Indeed, the similarities between the cases reported by Fraaij et al. from the Netherlands [1] and our group in Italy [2] are somewhat striking. Both cases occurred in October 2016, both cases presented with severe respiratory syndrome and in both cases, a swine influenza virus (SIV) strain circulating in a nearby pig farm was detected in the patient. In the paper by Fraaij et al., the patient had visited a pig farm, but not had direct contact with pigs [1]. In our paper, the patient stated that he had no contact with infected pigs, but his brother worked on a pig farm. Although the data presented in our paper strictly adhere with official reports [2], we also agree that unreported visits to a pig farm or direct contact with infected pigs through contaminated surfaces or via aerosol are possibilities that cannot be excluded. However, a major difference between the Dutch and Italian case were the SIV strains recovered from the patients, indicating the occurrence of chronologically coincidental yet distinct events.

We share all the concerns raised by the Authors of the Letter to the editor [3]. In particular: (i) attention to severe zoonotic influenza A infections in humans should be as high in Europe as in any other region of the world. (ii) Both reported cases occurred earlier than the influenza season in humans and this event may have had an impact on established surveillance procedures and reporting which are activated at the beginning of the season. (iii) Virus whole genome sequencing should be the gold standard for specimens with inconclusive results or nontypeable influenza strains (indeed, this approach was followed by both the Dutch and Italian groups). (iv) We strongly recommend the inclusion of pan-influenza A molecular assays in the work-up of all patients with severe respiratory syndromes, irrespective of seasonality. (v) We fully support the need for unrestricted sharing of biological materials as well as epidemiological, clinical and sequence data.

In addition, we support the suggestion for follow-up investigations in patients with a documented SIV infection, a task that might not be easy to achieve. As far as our recent experience is concerned, at a follow-up telephone visit on 7 February 2017 [2]. As confirmed by his brother, the former patient was well, but not available for further questions.

Finally, we would like to emphasise that swine influenza monitoring programmes at the Istituto Zooprofilattico Sperimentale della Lombardia e dell'Emilia Romagna (IZSLER) have been in place since the late 1990s, especially in northern Italy where more than 75% of the Italian swine industry is located. These programmes (further improved since 2009) are mainly based on genome detection, virus isolation and sequencing of all respiratory forms and revealing continuous circulation of H1N1, H3N2 and H1N2 SIVs as well as the isolation of influenza A(H1N1)pdm09 viruses in pigs.

Moreover, surveillance of SIV circulating in European pigs is carried out in many countries, mainly in western

Europe, involving the networks *European Surveillance Network for Influenza in Pigs* (ESNIP 1, 2 and 3) which are aimed at expanding our knowledge on European SIV epidemiology [4]. However, judging by the small number of available SIV sequences, SIV surveillance appears to be less rigorous and systematic in other parts of Europe.

Conflict of interest

None declared.

References

1. Fraaij PL, Wildschut ED, Houmes RJ, Swaan CM, Hoebe CJ, de Jonge HC, et al. Severe acute respiratory infection caused by swine influenza virus in a child necessitating extracorporeal membrane oxygenation (ECMO), the Netherlands, October 2016. Euro Surveill. 2016;21(48):30416. DOI: 10.2807/1560-7917.ES.2016.21.48.30416 PMID: 27934581
2. Rovida F, Piralla A, Marzani FC, Moreno A, Campanini G, Mojoli F, et al. Swine influenza A (H1N1) virus (SIV) infection requiring extracorporeal life support in an immunocompetent adult patient with indirect exposure to pigs, Italy, October 2016. Euro Surveill. 2017;22(5):30456. DOI: 10.2807/1560-7917.ES.2017.22.5.30456 PMID: 28183395
3. Adlhoch C, Penttinen P. Letter to the editor: Just a coincidence? Two severe human cases due to swine influenza (SIV) A(H1N1)v in Europe, October 2016. Euro Surveill. 2017;22(10):pii=30478.
4. Simon G, Larsen LE, Dürrwald R, Foni E, Harder T, Van Reeth K, et al. European Surveillance Network for Influenza in Pigs: Surveillance programs, diagnostic tools and swine influenza virus subtypes identified in 14 European countries from 2010 to 2013. PLoS One. 2014;9(12):e115815. http://dx.doi.org/DOI: 10.1371/journal.pone.0115815 , 2014.

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WHO recommendations on the composition of the 2017/18 influenza virus vaccines in the northern hemisphere

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On 2 March 2017, the World Health Organization (WHO) published recommendations on the composition of the trivalent and quadrivalent vaccines for the 2017/18 northern hemisphere influenza season [1]. WHO recommends that trivalent vaccines for use in the 2017/18 northern hemisphere influenza season contain the following:

- an A/Michigan/45/2015 (H1N1)pdm09-like virus;
- an A/Hong Kong/4801/2014 (H3N2)-like virus; and
- a B/Brisbane/60/2008-like virus.

For the quadrivalent vaccines containing two influenza B viruses, WHO recommends that they contain the above three viruses and a B/Phuket/3073/2013-like virus.

As in previous years, national or regional authorities approve the composition and formulation of vaccines used in each country. National public health authorities are responsible for making recommendations regarding the use of the vaccine.

WHO organises consultations with an advisory group of experts twice every year to analyse influenza virus surveillance data generated by the WHO Global Influenza Surveillance and Response System (GISRS), and issues recommendations on the composition of the influenza vaccines for the following influenza season.

References

1. World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2017-2018 northern hemisphere influenza season. Geneva: WHO; Mar 2017. Available from: http://www.who.int/influenza/vaccines/virus/recommendations/201703_recommendation.pdf?ua=1

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