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Pneumococcal vaccination in older adults in the era of childhood vaccination: Public health insights from a Norwegian statistical prediction study

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ABSTRACT

Two different vaccines, a 23-valent polysaccharide vaccine (PPV23) and a 13-valent conjugate vaccine (PCV13), are available for prevention of invasive pneumococcal disease (IPD) in the population aged 65 years and older (65+). The IPD epidemiology in the 65+ is undergoing change due to indirect effects of childhood immunisation. Vaccine recommendations for the 65+ must take into account these trends in epidemiology. We therefore explored the preventive potential of vaccination strategies to prevent IPD in the 65+, including PPV23, PCV13 or PCV13 + PPV23 in 2014–2019. Quasi-Poisson regression models were fitted to 2004–2014 population-wide surveillance data and used to predict incidences for vaccine-type and non-vaccine type IPD. We determined the number of people needed to be vaccinated to prevent one case per season (NNV) for each strategy and estimated the public health impact on the IPD case counts from increasing the vaccine uptake to 28–45%. Our results indicate that PCV13-IPD will decrease by 71% from 58 (95% prediction interval 55–61) cases in 2014/15 to 17 (6–52) in 2018/19 and PPV23-IPD by 32% from 168 (162–175) to 115 (49–313) cases. The NNV will increase over time for all strategies because of a decreasing vaccine-type IPD incidence. In 2018/19, the PCV13-NNV will be 5.3 times higher than the PPV23-NNV. Increasing the vaccine uptake will lead to a larger public health impact for all scenarios. Combining PCV13 and PPV23 is most effective, but the additional effect of PCV13 will decrease and is only marginal in 2018/19. Our study demonstrates the importance of increasing PPV23 uptake and of developing vaccines that confer broader immunity.

1. Introduction

Streptococcus pneumoniae (pneumococci) are part of our normal nasopharyngeal flora, but can cause severe disease such as invasive pneumococcal disease (IPD; e.g. meningitis, febrile bacteraemia). Older adults aged 65 years and older (further called 65+) are among the most vulnerable population for IPD. In most Western societies, pneumococcal vaccination is therefore recommended for the 65+. In Norway, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been recommended to the 65+ since 1996, though uptake is estimated to be only about 15–30% (unpublished data NIPH). The effectiveness of PPV23 to prevent pneumococcal disease in older adults remains subject of controversy (Shapiro et al., 1991;Moberley et al., 2013;Huss et al., 2009;Jackson et al., 2003).

Recently, a 13-valent pneumococcal conjugate vaccine (PCV13) was licenced in the EU for use in all age groups (European Medicines Agency, 2013), and at present both PPV23 and PCV13 are available for prevention of IPD in the 65+. Twelve of the PCV13 serotypes are also included in PPV23. PCV13 likely provides better protection against pneumococcal disease due to different immunogenic properties (Bonten et al., 2014). PCV13 has been used in the Norwegian childhood immunisation programme since 2011. In order to make an informed choice between PPV23 and PCV13 for

Abbreviations: IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV13-7, six additional serotypes that are in PCV13 but not in PCV7; PPV2323, valent polysaccharide vaccine; PPV23-11, Twelve serotypes that are in PPV23 but not in PCV13; VE, vaccine effectiveness; NVT, Non-vaccine serotypes; NIPH, Norwegian Institute of Public Health; MSIS, Norwegian Surveillance System for Communicable Diseases; 95% PI, 95% Prediction intervals; NNV, Number needed to vaccinate; PHI_s, Public health impact per future season.

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the 65+ population, evaluation of the preventive potential of the vaccines is needed.

The potential of a vaccine to prevent disease depends on the incidence of disease caused by serotypes that are covered by the vaccine, the vaccine effectiveness (VE) and the vaccine uptake. Like in other settings where PCV has been implemented in childhood immunisation programmes (Lexau et al., 2005;Miller et al., 2011;Harboe et al., 2014), the epidemiology of IPD in Norway has substantially changed, both by direct protection of immunised children, and by indirect protection due to decreased transmission of vaccine serotype pneumococci to non-vaccinated age groups (Steens et al., 2013). Simultaneously, the incidence of IPD caused by non-vaccine serotypes (NVT) has slightly increased as a result of serotype replacement (Weinberger et al., 2011;Hicks et al., 2007;Miller et al., 2011;Steens et al., 2013). Further changes in the IPD epidemiology are expected for the near future, as it will take some years before the serotype distribution has stabilised after switching to PCV13 (Hanage et al., 2010). Such future changes in IPD epidemiology should be accounted for when designing vaccine recommendations.

The aim of this work was to estimate the number of IPD cases caused by vaccine serotypes and NVT among the 65+ in the near future (2014–2019) using interrupted time series analyses based on population-wide surveillance data from 2004 through mid-2014. Furthermore, we aimed to determine the number of people needed to be vaccinated (NNV; Kelly et al., 2004) with PCV13 and/or PPV23 to prevent one IPD case per season and to calculate the potential public health impact on IPD of scenarios with different levels of vaccine uptake. Although the question of which vaccine to use in older adults has been addressed by others (Jiang et al., 2012; Smith et al., 2012; Vila-Corcoles and Ochoa-Gondar, 2013; Fedson and Guppy, 2013; Jiang et al., 2014), to our knowledge this study is the first to compare different vaccine strategies by predicting the public health impact based on data obtained in the PCV13 era.

2. Methods

2.1. Data sources

In Norway, notification of IPD is mandatory for microbiological laboratories and medical doctors and it is assumed to have a high and stable coverage. We used the serotype-specific notification data from the Norwegian Surveillance System for Communicable Diseases (MSIS; Norwegian Institute of Public Health, 2011) for IPD cases with a testing date between 1 January 2004 and 30 June 2014 and aged 65+. Data were extracted on 23 July 2014. All IPD cases, defined as a case in which *S. pneumoniae* was isolated from a normally sterile site, are notifiable to MSIS. Over 98% are isolated from blood and/or CSF and more than 90% of isolates are serotyped using the Quellung reaction with serotype-specific antisera (Vestrheim et al., 2010). According to the MSIS regulations, the NIPH does not require ethical approval for the use of notified data for this type of study.

Statistics Norway provided data on the number of Norwegian inhabitants per age group at the 1st of January of each corresponding year (Statistics Norway, 2014a), as well as predicted population sizes for the future (Statistics Norway, 2014b). We used the predicted population size at median growth and used linear interpolation to determine monthly population sizes as denominator. In 2014, Norway had 5.1 million inhabitants, of which 821,558 (16%) were 65+.

2.2. Interrupted time series analyses

We categorised our data by vaccine-type using the following designation: PCV13 serotypes, serotypes that are covered by PPV23 but not by PCV13 (PPV23–12), and NVT, defined as all serotypes not covered by PCV13 or PPV23; see Table 1.

Data were aggregated by months. Overall 7% (305/4365) of isolates missed serotype information; 58% of missings occurred in 2004/2005. Imputation of missing values was performed according to the distribution of known serotypes in the respective month, the preceding and the following month. The notified monthly IPD cases Y_t were regressed using a Poisson segmented time series analysis incorporating the changes in the Norwegian childhood immunisation programme, the population size and correcting for seasonality:

$$Y_t = \exp(\log(\mathrm{Pop}_t) + \beta_0 + \beta_1 \times \mathrm{month}_t + \beta_2 \times \mathrm{month}_t^{\mathrm{PCV7}} + \beta_3 \times \mathrm{month}_t^{\mathrm{PCV13}} + \beta_{\mathrm{seasonal}_k} + \varepsilon_t) \quad (1)$$

where month_t is the number of months from the start of the study period in January 2004, and $\mathrm{month}_t^{\mathrm{PCV7}}$ and $\mathrm{month}_t^{\mathrm{PCV13}}$ are the numbers of months after the introduction of PCV7 vaccination in July 2006 and the switch to PCV13 vaccination in April 2011, respectively; before the interventions these variables are set to zero. The term β_0 is the intercept coefficient, β_1 is the initial trend, β_2 is the change in trend post introduction of PCV7 vaccination, β_3 is the change in trend post introduction of PCV13 vaccination, $\beta_{\mathrm{seasonal}k}$ is the seasonality factor variable at month $k = 1, 2..12$, and ε_t is the error. To account for changes in the population size, the Norwegian population at month t (Pop_t) was used as an offset. To account for additional variation, we included a dispersion parameter, λ, resulting in a quasi-Poisson model.

The model Eq. (1) was fitted separately to PCV13 serotypes, PPV23–12 serotypes and NVT from 2004 through June 2014 (126 months; Fig. 1). Non-significant parameters ($p \geq 0.05$) were discarded from the final models; see Table 1. Data were analysed using GLM with the MASS package in the statistical software R version 3.1.0 (Swiss Federal Institute of Technology Zurich, 2014). The fitted models were used to predict IPD case counts for the period July 2014–June 2019 (60 months).

Seasons were defined to run from July to June the following year (e.g. July 2004–June 2005). Seasonal counts were calculated by summing the respective monthly counts. The PPV23 counts were calculated by adding the predicted values of the PCV13 and PPV23–12 models. Note that our PPV23 counts therefore include the counts for PCV13 serotype 6A, which is not included in PPV23. Due to low numbers, it was not possible to model this serotype separately and had limited effect on the final model. The frequency of serotype 6A decreased from an average of 24 cases per season in 2004–2009 to 11 in 2009/10 and further to two 6A cases in 2013/14.

2.3. The prediction intervals

We determined the 95% prediction intervals (95% PI) by taking into account both the variation related to the uncertainty in the parameters (systematic part) and the uncertainty related to the future trend. First, we performed residual bootstrapping ($N = 1000$) and refitted the models to account for the systematic part of the variation. Then, for each of the 1000 samples, we introduced uncertainty in the predicted trend by adding a random component in terms of a random walk procedure (Pearson, 1905). In each time step (month), a random normally distributed number with mean zero and standard deviation 0.00137 was drawn and the cumulated values were exponentiated and added to the predicted values. This procedure was repeated 1000 times for each bootstrap sample and the 95% PI was obtained as the 2.5% and 97.5% values of the sorted counts in each season. The value of 0.00137 was chosen based on preliminary simulations and corresponded to a change of 5% in the trend of the PCV13 counts.

Table 1
Overview of the variables and their parameters of each vaccine-type specific quasi-Poisson regression model. If no parameter estimate is presented, the variable was discarded from the final model. The monthly denominator was included in all models as offset.

	PCV13		PPV23-12		NVT	
Included serotypes	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F		2, 8, 9N, 10A, 11A, 12F, 15B/C, 17F, 20, 22F, 33F		All serotypes not included in PCV13 or PPV23	
Variables	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value
Intercept β_0	−9.679	<2exp-16	−11.447	9.06exp-06	−12.153	<2exp-16
Time trend from January 2004 β_1			0.006	<2exp-16		
Change in time-trend from PCV7 introduction β_2	−0.015	<2exp-16			0.015	1.89exp-08
Change in time-trend from the switch to PCV13 β_3	−0.012	0.009	−0.011	0.011	−0.015	1.59exp-02
$\beta_{sesonalk}$ January	Reference		Reference		Reference	
February	−0.222	0.023	−0.229	0.092	−0.384	0.061
March	−0.071	0.445	−0.197	0.142	−0.019	0.917
April	−0.089	0.345	−0.165	0.213	−0.323	0.106
May	−0.174	0.072	−0.269	4.96exp-02	−0.093	0.618
June	−0.483	1.18exp-05	−0.561	2.37exp-04	−0.441	3.33exp-02
July	−0.814	4.87exp-10	−0.689	3.60exp-05	−0.710	2.94exp-03
August	−1.222	2.52exp-14	−0.978	0.000	−0.814	1.02exp-03
September	−0.260	0.011	−0.605	0.000	−0.408	0.055
October	−0.120	0.217	−0.479	0.002	−0.381	0.069
November	−0.099	0.309	−0.316	0.027	−0.436	0.041
December	0.119	0.196	0.115	0.360	0.106	0.560
Dispersion parameter λ	1.250		0.971		1.203	
Residual deviance (degrees of freedom)	141.25 (112)	0.032	117.32 (112)	0.347	138.67 (112)	0.044

2.4. Number needed to vaccinate

The NNV is analogous to the number needed to treat (Laupacis et al., 1988). In the present context, the NNV indicates the number of people aged 65+ who need to be vaccinated in a certain season to prevent one IPD case in that same season and age group. We determined the NNV for three vaccination strategies, PPV23-only, PCV13-only or use of PCV13 and PPV23 combined, using the method described by Kelly et al., 2004:

$$\mathrm{NNV} = 1/\mathrm{Inc}_{\mathrm{unvac}} \times \mathrm{VE} \quad (2)$$

where $\mathrm{Inc}_{\mathrm{unvac}}$ is the seasonal incidence in the unvaccinated population, which was calculated by dividing the predicted seasonal vaccine-type count, $\overline{\hat{Y}}_s$, by the size of the unvaccinated population; see Eq. (3). The size of the unvaccinated population was determined by correcting the predicted population size, Pop_s, for the assumed *immunised* population:

$$\mathrm{Inc}_{\mathrm{unvac}} = \overline{\hat{Y}}_s/(\mathrm{Pop}_s - (\mathrm{Pop}_s \times \mathrm{PPV23\ \ uptake} \times \mathrm{VE\ \ PPV23})) \quad (3)$$

The PPV23 uptake was assumed at 22% (median of the estimated vaccine uptake in Norway; unpublished data NIPH). We used VE 60% (range 40–70) for PPV23 (Table 2), and 75% (range 55–90) for PCV13 guided by results of the CAPiTA study (Bonten et al., 2014). In the combined scenario (PCV13 + PPV23), we used the VE of PCV13 for the PCV13 serotypes and the PPV23-VE for the PPV23–12 serotypes. We used the point estimates for VE to determine the most plausible NNV and the lower and upper bounds to determine its uncertainty. It is known that the VE is lower for some risk groups compared to the 65+ population without comorbidities (see for review Steens et al., 2014a). However, since this study focused on the general 65+ population this was not taken into account.

2.5. Public health impact of increased uptake of the different vaccines

We determined the public health impact per future season (PHI_s) by calculating the additional number of cases prevented by the three vaccination strategies, PPV23, PCV13 or PCV13 + PPV23, at different levels of vaccine uptake, which would not have been prevented if the current scenario with PPV23-only used by 22% of the 65+ would continue.

$$\mathrm{PHI}_s = (\mathrm{Scenario\ \ level\ \ uptake} - \mathrm{initial\ \ uptake}) \times \mathrm{VE} \times \overline{\hat{Y}}_s \quad (4)$$

The PHI_s for the combined scenario was determined by combining the PHI_s for PCV13 with the PHI_s for PPV23–12. The scenario levels for vaccine uptake were 28%, 36% or 45% in the 65+ population. These scenarios were partly based on the estimated influenza vaccine uptake in Norway in 2012/2013 (28% without underlying condition, 36% among the general 65+ population; personal communication KM Rydland, NIPH, 11 April 2014). Similar to the calculation of NNV, we used the point estimates of the predicted seasonal counts and VE to calculate the most plausible PHI_s, while the lower and upper bounds were used to quantify its uncertainty. We did not take into account waning immunity, but instead we used a constant value of VE for all five predicted seasons. The duration of protection of PPV23 is considered to be longer than 5 years (Andrews et al., 2012;Ochoa-Gondar et al., 2014), while currently no data is available for PCV13. We assumed that PCV13 vaccination would be initiated in the 65+ in 2014/15, and that the level of uptake of the vaccines would be reached within that season, with the exception for PCV13 because of the following: in Norway, PCV13 is recommended to be given at least 3 years after the last PPV23; PPV23 should be repeated every 10 years (Steens et al., 2014a). People who were vaccinated within the last three seasons

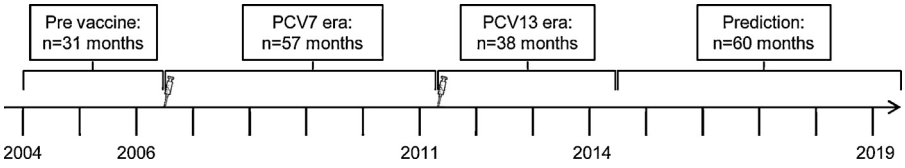

Fig. 1. Graphical representation of the period with observed and with predicted data. The syringes present the time that PCV7 was introduced (July 2006) and the switch to PCV13 (April 2011).

Table 2
Literature overview of estimates of the effectiveness of PPV23 to prevent vaccine-type IPD in the 65+. If different clinical pictures or age groups were used in the study, this is indicated in the table between brackets. Note that most of the empirical studies that are presented are also included in the meta-analyses..

Reference	Kind of study	Study period	VE (95%C.I.)
Butler et al., 1993	Indirect cohort analysis on surveillance data	1978–1992	70 (30–78) [immune-competent 65–74 years] 78 (54–89) [immune-competent ≥75 years]
Shapiro et al., 1991	Case-control study	1984–1990	80 (51–92)/71 (30–88) [65–74 years; <3 years/3–5 years after vaccination] 67 (20–87)/53 (−15 to 88) [75–84 years; <3/3–5 years] 46 (−31 to 78)/22 (−90–68) [≥85 years; <3/3–5 years]
Honkanen et al. 1999	Non-randomised trial	1993–1994	60 (−40 to 90)
Jackson et al., 2003	Retrospective cohort study	1998–2001	44 (7–67) [bacteraemia]
Andrews et al. 2004	Indirect cohort analysis on surveillance data	1997–1998, 2001–2002	79 (−14 to 96)
Dominguez et al. 2005	Case-control study with hospital controls	2001–2002	64 (31–82)
Mooney et al. 2008	Screening method on surveillance data	2003–2004	62 (45–73) [all-serotype IPD]
Vila-Corcoles et al. 2010	Case-control study	2002–2007	77 (40–92) [population 60+]
Andrews et al., 2012	Indirect cohort analysis on surveillance data	1998–2010	48 (32–60) [<2 years after vaccination] 24 (10–36) [overall]
Hutchison et al. 1999	Meta-analysis	1966–1996	83 (69–91)
Melegaro and Edmunds, 2004	Meta-analysis	1985–1999	65 (−49 to 92)
Puig-Barbera et al. 2002	Meta-analysis	1964–2000	32 (−18 to 61)
Moore et al. 2000	Meta-analysis	1966–2000	47 (−94 to 86) [bacteraemia]

were therefore not yet eligible to receive PCV13. The resulting levels of vaccine uptake that have been used in Eq. (4) are presented in Table 3.

Analyses were done in R (http://www.r-project.org/), Stata 13 and Excel 2010.

3. Results

3.1. Change in IPD trends following childhood vaccination

During the study period, 4365 IPD cases aged 65+ were notified in Norway, corresponding to 49% (4365/8847) of all notified IPD cases. The IPD case counts showed clear seasonality with high counts in the winter and significantly lower counts in the summer (Fig. 2; Table 1).

The average number of 65+ cases per season decreased from 498 (incidence 73/100,000) in 2004–2006 before the introduction of PCV7 to 400 (54/100,000) in 2010/11 before switching to PCV13. This dropped further to 274 (34/100,000) in 2013/14; see Table 4. The percentages of IPD cases caused by PCV13 and PPV23 serotypes decreased from 80% and 89% in 2004/05, respectively, to 26% and 64% in 2013/14.

Overall, the models fitted well the observed monthly IPD case counts (Fig. 2). The estimated number of IPD cases caused by PCV13 serotypes decreased significantly from the moment PCV7 was introduced, and the switch to PCV13 led to a further decline in cases (Fig. 2; Table 1). Both PPV23–12 and NVT IPD counts increased slightly in the period before the switch to PCV13. After switching to PCV13, the increase was halted for NVT-IPD, and the PPV23–12 IPD counts decreased slightly.

3.2. Trends for the near future

Our models predicted a continued decrease in PCV13-IPD counts in the near future, with an estimate of 17 (95% PI 6–52) cases in 2018/19, representing 8% of the total IPD case counts (Table 4). At that time, the PPV23–12 IPD count is predicted at 98 (95% PI 33–295) cases. Taken together, the results suggest a declining trend in PPV23-IPD counts to 52% of the total case counts in 2018/19; however, the prediction intervals are wide and inconclusive (Table 4). NVT-IPD counts may show a small increase to 104 cases (95%PI 35–313) in 2018/19, then accounting for 48% of the cases.

3.3. Number needed to be vaccinated to prevent one IPD case

Despite a higher VE for PCV13 than for PPV23, the NNV was larger for PCV13 because of its lower vaccine-type IPD incidence (Table 5). To prevent one IPD case in 2014/15, 16,524 persons (uncertainty 13,770–22,533) should be vaccinated with PCV13-only or 7149 (6128–10,724) with PPV23-only. This value will increase to 60,910 (50,759–83,060) and 11,508 (9864–17,262) in 2018/19, respectively; a 5.3 times difference between PCV13 and PPV23. The combination of PCV13 and PPV23 will have the lowest

Table 3
Example of the calculation of the level of vaccine uptake (=scenario – initial uptake) that was used to predict the public health impact of PPV23, PCV13 or PPV23 + PCV13. Here we only present the scenario level of 36%. Note that PCV13 is recommended to be given at least 3 years after the last PPV23; PPV23 should be repeated every 10 years (Steens et al., 2014a).

	PPV23	PCV13	PCV13 + PPV23
2014/15	14% PPV23 [a]	29.4% PCV13 [b]	29.4% PCV13 and 14% PPV23–12
2015/16	14% PPV23 [a]	31.6% PCV13 [b]	31.6% PCV13 and 14% PPV23–12
2016/17	14%PPV23 [a]	33.8% PCV13 [b]	33.8% PCV13 and 14% PPV23–12
2017/18	14% PPV23 [a]	36% PCV13	36% PCV13 and 14% PPV23–12
2018/19	14% PPV23 [a]	36% PCV13	36% PCV13 and 14% PPV23–12

[a] 14% = scenario level 36% – initial uptake of 22%.
[b] The PCV13 level = scenario level 36% – the population that is not yet eligible for PCV13 vaccination because of recent PPV23 vaccination. In the first season, 3/10 of the population that has initially been vaccinated (22%) is ineligible for vaccination, the second season 2/10 × 22% and the third season 1/10 × 22%.

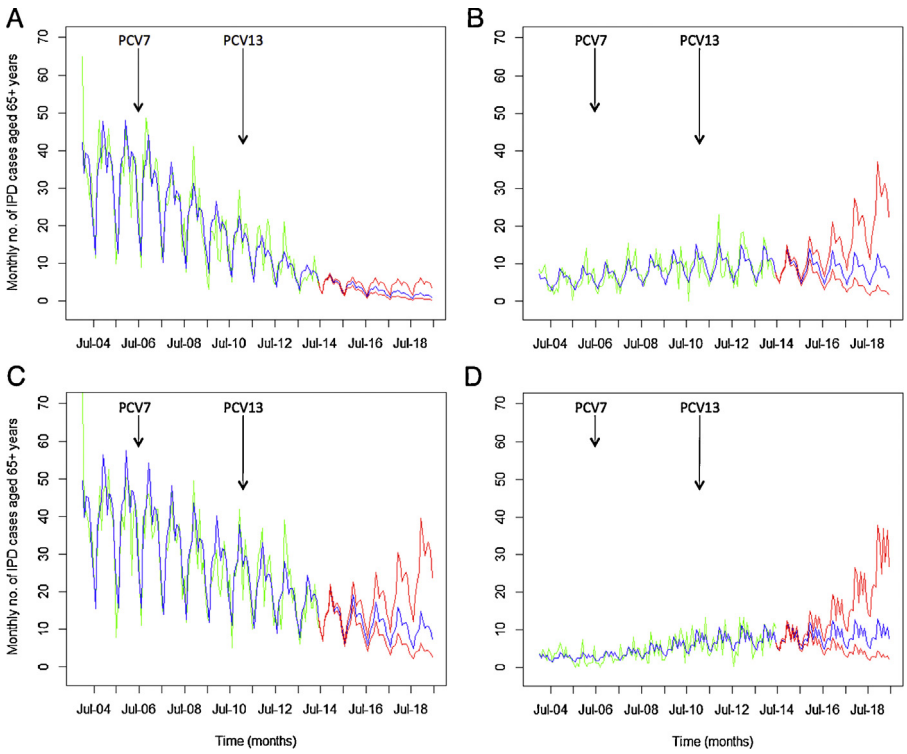

Fig. 2. The observed data (in green) and predicted monthly number of IPD cases (in blue) with 95% prediction intervals (in red). A: PCV13, B: PPV23–12, C: PPV23 (including serotype 6A), D: NVT. The arrows indicate the timing of vaccine introduction.

NNV, indicating the largest preventive effect. Because of the further decrease in vaccine-type IPD incidence, the NNV will increase over time for all scenarios.

3.4. Public health impact of increased uptake of the different vaccines

The combination of PCV13 and PPV23 is found to prevent most cases during all predicted seasons and at all investigated levels of vaccine uptake (Fig. 3), although the difference compared to PPV23-only is predicted to be only three cases in 2018/19. Increasing the vaccine uptake will lead to a larger public health impact; an increase in PPV23 uptake affects the public health impact more substantially than an increase in PCV13 uptake, mainly as a results of the steeper decrease in PCV13-IPD incidence compared to PPV23–12 IPD incidence. The impact of all scenarios will decrease over time as a result of the decrease in vaccine-type IPD counts.

The public health impact of a scenario where vaccination with PCV13 is added to the 22% of 65+ that are currently vaccinated with PPV23 is estimated to prevent additionally 7 (5–8) cases in 2014/15, which is similar to the expected impact from increasing the PPV23-only uptake to 28%, which may prevent further 6 (4–7) cases. These numbers will have decreased to 3 (2–3) and 4 cases (3–5) in 2018/19, respectively. At a higher level of vaccine

Table 4
Observed and predicted number of IPD cases aged ≥65 year per season (July–June), by vaccine-type. Behind the observed number of IPD cases in the surveillance data, the percentage of all IPD cases in its season caused by serotypes covered by the respective vaccines is presented in brackets. For the predicted results, the 95% prediction interval (95%PI) is presented in brackets.

Surveillance data		PCV13 (%)	PPV23–12 (%)	PPV23 (%)	NVT (%)
Pre-vaccination	2004/05	416 (80)	61 (12)	461 (89)	43 (8)
	2005/06	377 (79)	74 (16)	431 (91)	25 (5)
PCV7 period	2006/07	395 (82)	65 (13)	423 (88)	23 (5)
	2007/08	292 (66)	101 (23)	370 (84)	49 (11)
	2008/09	271 (64)	106 (25)	347 (81)	49 (12)
	2009/10	179 (50)	109 (30)	277 (77)	69 (19)
	2010/11	205 (51)	108 (27)	303 (76)	88 (22)
PCV13 period	2011/12	162 (45)	117 (32)	274 (76)	83 (23)
	2012/13	118 (36)	133 (40)	247 (74)	82 (25)
	2013/14	71 (26)	106 (39)	175 (64)	97 (35)
Predicted results		**PCV13 (95%PI)**	**PPV23–12 (95%PI)**	**PPV23[a] (95%PI)**	**NVT (95%PI)**
PCV13 period	2014/15	58 (55–61)	110 (105–116)	168 (162–175)	95 (90–101)
	2015/16	43 (35–54)	107 (86–133)	150 (127–178)	98 (78–122)
	2016/17	32 (20–50)	104 (66–164)	135 (96–199)	100 (63–159)
	2017/18	23 (11–50)	100 (48–214)	124 (70–241)	102 (48–218)
	2018/19	17 (6–52)	98 (33–292)	115 (49–313)	104 (35–313)

[a] Note that for the predicted results, PPV23 includes serotype 6a, as this estimate was determined based on the sum of the prediction by models PCV13 and PPV23–12.

Table 5
Number needed to vaccinate to prevent one IPD case per season (July–June), presented by vaccine-type. As VE we used for PPV23: 60% (range 40–70), and for PCV13: 75% (range 55–90).The uncertainty, presented between brackets, is determined by the uncertainty in VE.

Season	PPV23[a]	PCV13	PCV13 + PPV23
2014/15	7149 (6128–10,724)	16,524 (13,770–22,533)	6580 (5577–9492)
2015/16	8223 (7048–12,334)	22,896 (19,080–31,222)	7672 (6514–11,135)
2016/17	9315 (7,985–13,973)	31,725 (26,438–43,261)	8799 (7482–12,842)
2017/18	10,413 (8926–15,620)	43,959 (36,632–59,944)	9942 (8467–14,583)
2018/19	11,508 (9864–17,262)	60,910 (50,759–83,060)	11,089 (9456–16,336)

[a] Including serotype 6A.

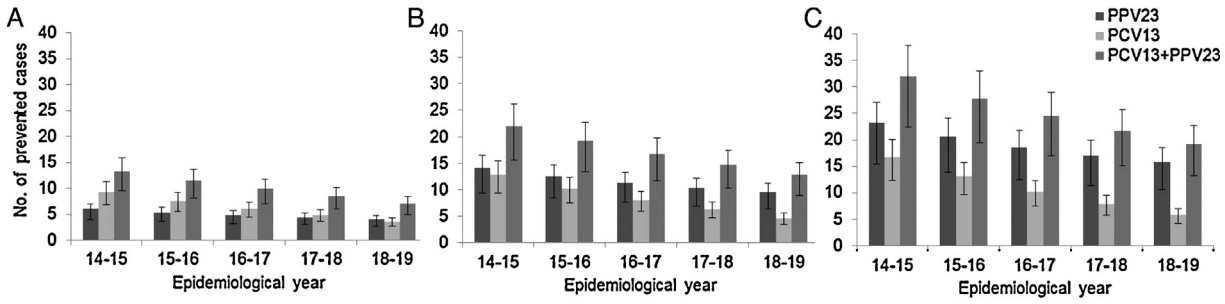

Fig. 3. The public health impact: the predicted number of IPD cases prevented by PPV23 (dark grey), PCV13 (light grey) and a combination of PCV13 and PPV23 (grey) in comparison to the current scenario (PPV23-only at 22% uptake). A: 28% vaccine uptake, B: 36% uptake, C: 45% uptake. The error bars indicate the uncertainty in the public health impact based on the uncertainty in VE.

uptake, an increase in PPV23-only uptake will have a larger effect than adding PCV13, and PPV23 will account for a larger proportion of the impact of the combined regimen (Fig. 3).

4. Discussion

We have shown that the implementation of PCV in the childhood immunisation programme has substantially decreased the PCV13-IPD incidence among the 65+ as a result of indirect protection. The number of IPD cases will likely continue to decrease further, with limited or no increase in NVT-IPD. The NNV for PCV13 will consequently increase considerably. The potential for PCV13 to prevent IPD in the 65+ in Norway will therefore be limited. In the longer run, increasing PPV23 uptake will have a higher public health impact than adding PCV13 to PPV23 with unchanged levels of vaccine uptake. An increased vaccine uptake with PCV13 and PPV23 combined will prevent most cases, although the additional effect of PCV13 will decrease and is only marginal in 2018/19.

This study focused on IPD, while the highest burden of pneumococcal infections is on lower respiratory tract infections/non-invasive pneumonia. Can we extrapolate the results from this study to non-invasive pneumonia? Although PPV23 is thought to be effective in preventing IPD in older individuals, particularly in healthy individuals under 75 years (Moberley et al., 2013;Andrews et al., 2012), its protection against non-invasive pneumonia is debated (Moberley et al., 2013; Melegaro and Edmunds, 2004; Jackson et al., 2003; Ochoa-Gondar et al., 2014). PCV13 can prevent about half of the PCV13-pneumonia cases aged 65+ (Bonten et al., 2014). So, there might be a potential for PCV13 in pneumonia prevention. There is no information available about the incidence of PCV13-pneumonia in Norway. Results of a large trial among 65+ in the Netherlands estimated that about 14% of all community acquired pneumonia cases were caused by PCV13 serotypes (Bonten et al., 2014). Note that in the Netherlands, the 10-valent PCV instead of PCV13 is used in children. PCV13-serotypes have been shown to be less often the cause of non-invasive compared to invasive pneumococcal pneumonia (Benfield et al., 2013). Together with the further decrease in PCV13-IPD incidence, this suggests also a limited role for PCV13 in pneumonia prevention in Norway. Still, more research is needed on the incidence of PCV13-pneumonia to estimate its real preventive potential in the 65+.

We used a simple statistical prediction model fitted on notification data. We explored several ways of implementing the changes in the childhood immunisation programme in the model, including constant intervention effects and a gradual build-up of the intervention effect. As the more complex models did not significantly improve the model fit, we decided on using a simple approach as a time trend starting at the moment of intervention. We modelled the vaccine-type serotypes in groups instead of individual serotypes as this has been shown to provide the best estimates for changes in IPD incidence (Weinberger et al., 2013). The advantage of our approach is that we did not need to make assumptions on the size of the indirect effect and serotype replacement, as these were intrinsic to the data. Still, the predictions are based on extrapolation of current trends. To prevent too strict conclusions for the future, we added stochasticity to our prediction intervals through a random walk process. Data on pneumococcal carriage in children, the main transmitters of pneumococci, indicate that the substantial indirect protection of PCV13 is indeed likely to continue in the future (Lee et al., 2014; Gounder et al., 2014; van Hoek et al., 2014; Ricketson et al., 2014; Steens et al., 2014b). It is unlikely that use of PCV13 among the 65+ will induce indirect protection because of the low carriage rates among older age groups (<5%; Flamaing et al., 2010). The very limited or absence of serotype replacement as predicted by our models is less certain, as reflected in the wide 95%PIs. Several studies indicate that serotype replacement may be occurring after switching to PCV13, though to a lesser degree than that observed after PCV7 introduction (Moore et al., 2014;Steens et al., 2013;Kaplan et al., 2013). As it was shown after PCV7 implementation that serotype replacement was complete only after a few years (Hanage et al., 2010), serotype replacement might still occur. If serotype replacement will still occur, depending on the replacing serotypes, PPV23 may have larger public health impact than predicted by this study.

The NNV and public health impact are dependent on the assumption on the initial level of vaccine uptake. The vaccine recommendations for risk-groups changed in May 2013, such that patients with certain comorbidities are recommended to use PCV13 in addition to PPV23, but for the general 65+ population,

PPV23 is still the only recommended vaccine (Steens et al., 2014a). Although the exact vaccine uptake among the 65+ is unknown, data on the number of vaccines sold for common risk-groups (including the 65+) indicate that PPV23 uptake has not changed substantially (unpublished data NIPH). If we have underestimated the current vaccine uptake for PPV23, the estimated NNV would be higher for PPV23 but lower for both, the PCV13-only scenario and the scenario with combined use of PCV13 and PPV23. Furthermore, the public health impact of PPV23-only and the combined scenario would be lower, while the impact of PCV13 would basically be unchanged. Note that all public health impact scenarios are presented in comparison to the baseline scenario where PPV23 was used at a level of 22%. Unfortunately we were not able to compare the public health impact of the different vaccination scenarios to a scenario in the absence of any pneumococcal vaccination, as we estimated the future incidence by fitting notification data from a period where PPV23 had been recommended for the 65+. The public health impact of a PCV13-only strategy would be slightly larger in a scenario where PPV23 vaccination were to cease. However, as the duration of protection from PPV23 among those already vaccinated is assumed to last longer than the number of years we predicted for in this study, the underestimation from using a PPV23 baseline is likely limited.

Several countries have likewise investigated the best approach to prevent IPD in older adults. Population-based Markov modelling studies from Germany and UK concluded that vaccination with PPV23 remains the optimal vaccination strategy from public health and budget perspectives (Jiang et al., 2012;Jiang et al., 2014). A Markov state-transition model used on US data predicted that PCV13 will have more impact than PPV23, but only in case of moderate indirect protection by childhood immunisation (Smith et al., 2012). A static cohort model on US data showed that a combined strategy would prevent most cases (Chen et al., 2014). A study using a more similar approach to ours (Poisson model; Link-Gelles et al., 2013) concluded on a stable rate of PCV13-IPD, suggesting that PCV13 might have a stable preventive potential in the 65+ up to 2020. None of these models implemented surveillance data of the PCV13 era, and all were sensitive to the size of the indirect effect of childhood immunisation. As we used surveillance data up to three years after the switch to PCV13, we could implement the real size of the indirect effect up to mid-2014, and showed that the substantial indirect protection likely decreases the public health impact of PCV13 in Norway.

Pneumococci can be an important cause of super-infections during influenza infections (O'Brien et al., 2000;Kuster et al., 2011;Fleming-Dutra et al., 2013;Talbot et al., 2005). We therefore evaluated the effect of influenza illness (including the pandemic season) on our estimates by adding the incidence of influence-like illness (ILI) determined by the ILI sentinel surveillance (Hauge et al., 2009) to the models, but this did not significantly improve the models if we already corrected for seasonality. Still, influenza vaccination has been shown to play a role in the prevention of IPD (Christenson et al., 2004;Gilchrist et al., 2012), and in an optimal strategy for IPD prevention, pneumococcal vaccination is combined with influenza vaccination. Increasing the uptake of both vaccines is needed. Healthcare providers should be involved in encouraging uptake of vaccination (Schneeberg et al., 2014).

5. Conclusions

Although our results should be interpreted with caution due to their predictive nature, this study suggests that in Norway vaccine-type IPD in the 65+ will continue to decrease. Further reductions in IPD in the era of childhood vaccination can be achieved by increasing the PPV23 uptake. Still, as the NNV was lowest for the combination of PCV13 and PPV23, the use of PCV13 and PPV23 combined should be considered for the most fragile population, including the 65+ with comorbidities, as is currently recommended in Norway. As the preventive potential of the currently available pneumococcal vaccines is predicted to decrease, vaccines conferring broader protection should be developed.

Conflict of Interest

None declared

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Author contributions

AS, DFV and BFdB contributed to the conception of the study and the study design, BFdB wrote the initial R-syntax, AS and BFdB performed the final data analysis, AS, DFV and BFdB interpreted the results, AS drafted the manuscript, and BFdB and DFV critically revised the manuscript. All authors have seen and approved the final manuscript.

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