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Newly introduced vaccines: effectiveness and determinants of acceptance

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2014

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gefenaite, G. (2014). *Newly introduced vaccines: effectiveness and determinants of acceptance*. s.n.

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Chapter 3. Pneumococcal vaccination campaign effectiveness

Did the Dutch pneumococcal vaccination campaign decrease the need of respiratory antibiotics in children?

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Submitted

Abstract

Background *Streptococcus pneumoniae* causes childhood respiratory mucosal infections that are frequently treated with antibiotics. In June 2006, an infant pneumococcal vaccination campaign (PVC) with a 7-valent vaccine was introduced in the Netherlands. In 2011, this vaccine was replaced with a 10-valent pneumococcal vaccine. To estimate the effectiveness of PVC we analysed the respiratory antibiotic use in the period of 2002-2012.

Methods This study was performed in 1-9 years old children included in the Dutch pharmacy-dispensing IADB.nl prescription database. Seasonal autoregressive integrated moving average models were applied to estimate the effectiveness of PVC (%) and its 95% confidence intervals (95%CI).

Results The models showed that introduction of the 7-valent PVC reduced antibiotic prescription proportions by 2.8% [95%CI 0.2-5.3] and 5.6% [95%CI 2.3-8.8] in 3 and 4 years old children. When the 10-valent PVC was added to the models, it reduced the proportion of antibiotic prescriptions only in 1 year old children by 24.5% [95%CI 6.0-39.3].

Conclusions There is a tendency towards a decrease in respiratory antibiotic prescription proportions after the introduction of 7-valent pneumococcal vaccination campaign. A 10-valent PVC demonstrated the reduction in antibiotic prescription proportions as well, but due to a relatively recent introduction the number of data points was limited and therefore the conclusions are preliminary.

Introduction

In 2001 in the Netherlands, 45% and 20% of all antibiotics in children were prescribed for respiratory tract and ear infections respectively, acute otitis media (AOM) being the leading cause [1]. One of the common pathogens responsible for these diseases, especially in young children, is *Streptococcus pneumoniae*. It has been found in 44% of children hospitalized with community-acquired lower respiratory tract infections [2]. Although it does not account for significant mortality in developed countries, it remains a public health concern due to its role in antibiotic use for respiratory mucosal infections [3].

In June 2006 a 7-valent pneumococcal vaccination campaign was introduced in the Netherlands as part of the National Dutch Immunisation Programme [4]. Although the prescription rates of oral antibiotics in children seemed to decrease after as compared to before vaccination introduction [5], no decline in ear-nose-throat problems has been observed [6]. The latter finding might be explained by the pneumococcal serotypes replacement: a decrease of vaccine-serotype invasive pneumococcal disease (IPD) was followed by an increase in IPD caused by non-vaccine serotypes [7][8]. There is no information, however, on changes in antibiotic prescriptions that are usually used for AOM and pneumonia in young children in the Netherlands after as compared to before the 7-valent pneumococcal vaccination campaign. Moreover, in 2011 the 7-valent pneumococcal vaccine was replaced by a 10-valent vaccine [9], whose effects have not yet been assessed in observational studies.

To reveal the patterns of respiratory antibiotic prescriptions in young children before and after the pneumococcal vaccination campaigns in the Netherlands we analysed the use of amoxicillin, azithromycin and cotrimoxazol from 2002 to 2012. Based on the Dutch general practitioner guidelines, these antibiotics are commonly prescribed from AOM and pneumonia in children up to nine years of age in general practice [10, 11]. We performed descriptive and time series analyses to assess whether the national pneumococcal vaccination campaign reduced the proportion of respiratory antibiotic prescriptions in children one to nine years of age.

Methods

The study population consisted of one to nine years old subjects from the IADB.nl database, which contains pharmacy-dispensing data from community pharmacies in the Netherlands. A more detailed description of this database is available elsewhere (<http://www.iadb.nl/> and [12]). The main outcome of the study was a proportion of monthly antibiotic prescriptions in a particular age group (a number of monthly prescriptions in the age group per month divided by a number of children in that age group in that month). The aggregated measure of antibiotic prescriptions per year (a number of monthly prescriptions in the age group per year divided by a number of children in that age group in that year) was calculated as well. The outcome measure was based on prescriptions for amoxicillin (ATC code J01CA04), azithromycin (J01FA10) and/or cotrimoxazol (ATC code J01EE01) as these are standardly prescribed antibiotics against AOM and pneumonia in children up to nine years of age in primary care [10, 11]. The name of the antibiotic dispensed, ATC (Anatomical Therapeutical Chemical) classification [13], date of prescription and birthdate of subjects were extracted from the IADB.nl database.

The study period was from January 2002 to December 2012. It was chosen based on some preliminary analyses: we excluded the data prior to 2002 as we observed a rapid decrease in antibiotic use between 1995 and 2002, which was likely due to policies and interventions targeted at decreasing the antibiotic use, and it was not the aim to assess these interventions in our study.

The main study intervention was a 7-valent pneumococcal vaccination campaign that has been introduced in the Netherlands in June 2006 for all infants born after 1 April 2006. We also assessed the effects of a 10-valent pneumococcal vaccination campaign that targeted infants born after March 2011. The vaccinations were provided at two, three, four and eleven months of age with vaccination uptake rates of 94-95% (van Lier, 2012). We modelled the start of the main intervention as June 2007, as we anticipated all four doses of the vaccine, including the booster dose, to have been administered and had taken an effect by then. Because of few data points available in the dataset after the introduction of a 10-valent pneumococcal vaccination campaign, we assumed the

start of the 10-valent pneumococcal vaccination campaign as March 2012, and not May 2012, which might exclude the added effect of a booster dose. Children up to and six years old were assumed to have received only the 7-valent vaccine, children seven to nine years old were assumed to not have been vaccinated (potentially being indirectly protected by the vaccinated younger age groups), and children of 1 year of age were assumed to have received the 7-valent vaccine if born before June 2006, and the 10-valent vaccine if born after March 2011.

Statistical analysis

We first assessed the aggregated yearly respiratory antibiotic prescription proportions from 2002 to 2012 for each age group separately by plotting the data. We then assessed monthly antibiotic prescription proportions data by using multiplicative decomposition [14] that shows the observed trend of the outcome as well as seasonal and random patterns, and the trend after removing the seasonal and random components. To assess the effectiveness of the pneumococcal vaccination campaign we used seasonal autoregressive integrated moving average (SARIMA(p,d,q)(P,D,Q)_s) time series models [15] with intervention analysis [16], where p and P is the number of auto-regressive components, d and D stands for differencing applied in the series, q and Q indicates the number of moving average components, and s is equal to the number of units of seasonal period that are used in the model to remove additive seasonal effects. SARIMA allows us to estimate the effect of an intervention of interest by taking into account seasonal patterns. As pneumococcal illness tends to occur during the winter months, we assumed seasonal patterns occurring every twelve months, and therefore s was set to 12. We estimated the level (the abrupt change) in antibiotic prescription proportions and the change in trend (the slope) after as compared to before the introduction of the pneumococcal vaccination campaigns. The intervention variables were coded as 0 until June 2007 and March 2012, and 1 from June 2007 and March 2012 onwards for 7-valent and 10-valent pneumococcal vaccination campaigns respectively. To assess the change in trends after the interventions were introduced, slope change variables coded as 0 before the interventions, and 1 through 55 and 1 through 10 after the interventions, respectively for 7- and 10-valent vaccination campaigns were created [17][18]. The numbers 55 and 10 represent the number of months after each intervention.

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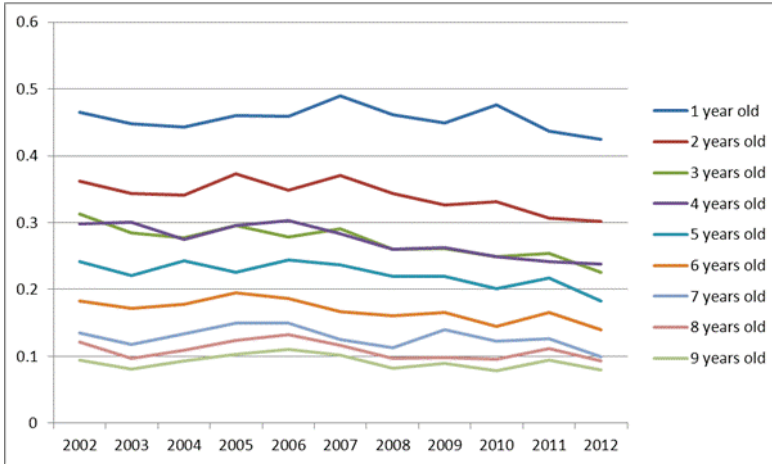
The best SARIMA models were identified based on the Akaike Information Criterion (AIC) before the 7-valent pneumococcal vaccination campaign took place for each age group separately [19]. They were then applied to estimate the 7-valent pneumococcal vaccination campaign effects throughout the post-intervention period. To assess the additional effect of the 10-valent pneumococcal vaccination campaign, the best model (the model with only 7-valent pneumococcal vaccination campaign versus the model with both interventions) were selected based on a likelihood ratio test. The coefficients and their standard errors were estimated by using maximum likelihood estimation. The percentage of change and its confidence intervals were calculated as $(\exp(\text{coefficient}) - 1) * 100\%$ and $(\exp(\text{coefficient} \pm 1.96 * \text{standard error}) - 1) * 100\%$. The adequacy of each model was verified by assessing the correlograms (there should be negligible residual autocorrelation) and the plots of the residuals (the residuals of the model should be randomly scattered). The analysis was performed with R 2.15.3 statistical software [20].

Results

The aggregated yearly estimates revealed that very young children, in particular one and two years old, had the most prescriptions of respiratory antibiotics that decreased with older age (Figure 1). We observed a slight decrease in respiratory antibiotic prescriptions after 2006 and 2011 pneumococcal vaccination campaigns (Figure 1). We observed similar patterns when we inspected decomposed monthly trends of antibiotic prescriptions.

To reveal the effects of the pneumococcal vaccination campaign on the antibiotic prescriptions we performed time series analysis from 2002 to 2012. The best time series SARIMA models were identified based on AIC before the 7-valent pneumococcal vaccination campaign (see Table 1 for the best models for every age group) and the likelihood ratio test when the additional effect of a 10-valent pneumococcal vaccination campaign was assessed. The final models did not show evidence of autocorrelation and we could not detect clear patterns in the residual autocorrelation for most of the age groups. Only the model for the 4 years old children showed significant autocorrelation at lag 12 indicating a remaining seasonal effect. However, it is unlikely that this will have had a strong effect on the overall result.

Figure 1. The proportion of yearly antibiotic prescriptions by different age



y-axis: year; x-axis: proportion of antibiotic use (number of users per year/number of children in a particular age group in that year). Different colours indicate different age groups (different age at which the antibiotic was prescribed).

The level of respiratory antibiotic prescriptions decreased after the introduction of the 7-valent pneumococcal vaccination introduction in most of the age groups (Table 1). The statistically significant reduction, however, was only present in 3 and 4 years old children, 2.8% [95%CI 0.2-5.3] and 5.6% [95%CI 2.3-8.8] respectively. The month-to-month trends of antibiotic prescription proportions were similar before and after the 7-valent pneumococcal vaccination campaign in five to nine years old children, but they showed a decreasing pattern (by 0.2-0.3%) in one to four years old children.

One year old children showed a significant increase in the level of the antibiotic prescription proportions after the introduction of the 7-valent pneumococcal vaccination campaign (Table 1). Similar, but not significant increase was found in the two years old children as well.

After adding the 10-valent pneumococcal vaccine into the model, the level of antibiotic prescription proportions in one year old children increased for the 7-valent pneumococcal vaccine by 6.2% [95% CI 4.0 to 8.5%]; after the 10-valent vaccine introduction it decreased by 24.5% [95% CI 6.0 to 39.3%]. The month-to-month trends in

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antibiotic prescriptions were similar after as compared to before the introduction of the 7-valent (-0.02% [95% CI -0.04 to 0.08]) and 10-valent pneumococcal vaccination campaigns (2.9% [95% CI -1.54 to 7.63]). The 10-valent vaccination campaign did not have significant effects in other age groups.

Table 1. The results of the best fitting SARIMA models for different age groups: change in level and trend of antibiotic prescription proportions.

Age group	Change in level % 95% CI	Change in trend % 95% CI	Best SARIMA (p,d,q)(P,D,Q) ₁₂ model
1 year old	8.58 4.50 to 12.28	-0.23 -0.31 to -0.15	SARIMA (8,0,9)(6,1,6) ₁₂
2 years old	3.69 -0.71 to 8.28	-0.36 -0.46 to -0.26	SARIMA (8,0,7)(9,0,4) ₁₂
3 year old	-2.77 -5.31 to -0.16	-0.29 -0.39 to -0.19	SARIMA (7,0,7)(8,0,4) ₁₂
4 year old	-5.63 -8.84 to -2.29	-0.26 -0.36 to -0.16	SARIMA (6,0,4)(5,1,5) ₁₂
5 years old	-1.04 -5.37 to 3.5	-0.31 -0.43 to -0.19	SARIMA (5,0,0)(9,0,9) ₁₂
6 years old	-6.49 -16.18 to 4.32	-0.22 -0.48 to 0.02	SARIMA (5,0,2)(0,1,4) ₁₂
7 years old	-5.95 -21.37 to 12.51	-0.27 -0.68 to 0.14	SARIMA (2,0,2)(6,0,4) ₁₂
8 years old	-18.08 -33.65 to 1.16	0.18 -0.56 to 0.93	SARIMA (3,0,8)(6,1,3) ₁₂
9 years old	-5.19 -21.81 to 14.95	-0.18 -0.63 to 0.27	SARIMA (0,0,0)(7,1,7) ₁₂

95% CI: 95% confidence intervals; SARIMA(p,d,q)(P,D,Q)_s: Seasonal Autoregressive Integrated Moving Average model with intervention analysis, where p and P is the number of auto-regressive components, d and D stands for differencing applied in the series, q and Q indicates the number of moving average components, and s is equal to the number of units of seasonal period that are used in the model.

Discussion

This study is the first to assess the effects of the 7- and 10-valent national pneumococcal vaccination campaigns together on the standard antibiotic prescriptions for mucosal infections, such as AOM and pneumonia in children. We showed that there was a slight decrease in the level of antibiotic prescription proportions after the introduction of the 7-valent pneumococcal vaccination campaign in three and four years old children (2.8% and 5.6% respectively), but not in one, two and five to nine years old children. When we assessed the effect of a 10-valent vaccination campaign, we observed a 24% decrease in the level of antibiotic prescription proportions in 1 year old children, while there was no

effect in other age groups. Although we did not have specific information about the causes of antibiotic prescriptions, these drugs are specifically recommended to treat AOM and pneumonia in young children in the Netherlands [10, 11] and *S.pneumoniae* is one of the leading causes of mucosal infections [3]. Therefore our results are likely to indicate the effect of the pneumococcal vaccination campaigns on health problems caused by *S.pneumoniae*.

We found that in very young children the antibiotic prescription proportions increased after the introduction of the 7-valent pneumococcal vaccination campaign. In older children the point estimates showed a decrease, but it was only significant in three and four year old children. The not significant effects of the vaccination campaign could be due to relatively low overall use of antibiotics in the Netherlands and therefore it is difficult to obtain statistically significant estimates. Moreover, it has been documented that after the introduction of the 7-valent pneumococcal vaccination campaign in the Netherlands, IPD rates caused by non-vaccine serotypes increased [7][8]. This could be an explanation for the increase in antibiotic prescription proportions in very young children as well as the not significant differences in older children. However, in our study we were not able to explore the effect of serotype replacement since serotype specific clinical outcome data was not part of the dataset.

We found a 24% decrease in one year old children after the introduction of a 10-valent pneumococcal vaccination campaign. This could be explained both, by the observed increase of antibiotic prescription proportions after the 7-valent pneumococcal vaccination campaign, and by a better effectiveness of the 10-valent pneumococcal vaccine against the circulating serotypes. This should further be explored when the data on more data points and for more age groups becomes available.

Because pneumococcal vaccination campaign was targeting well defined population groups at the national level at well-known time points and vaccination uptake rates were high (94-95%) [4][9], we were able to study the effects of the interventions on the population rather than individual level. This is advantageous as large databases that do not include individual vaccination information can still be used to assess the impact of population-based interventions. By using SARIMA time series models we were able to

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estimate direct (among one to six years old children) and indirect (among seven to nine years old children) effect of pneumococcal vaccination campaigns. We were able to take seasonal effects into account as well as model both, 7-valent and 10-valent pneumococcal vaccination campaigns.

In conclusion, our study provides some evidence that the 7-valent pneumococcal vaccination campaign was effective in reducing antibiotic prescriptions, especially in 3-4 years old children. The 10-valent pneumococcal vaccination campaign demonstrated a reduction in antibiotic prescriptions in one-year-old children, but not in older children. Due to a relatively recent introduction of a 10-valent pneumococcal vaccination campaign the number of data points was limited and therefore the conclusions are preliminary. Future studies should focus on revealing the effects of the 7-valent and (the added effects of) the 10-valent pneumococcal vaccination campaigns.

Author's contributions

Designed the study: GG. Prepared and analysed data: GG, MJB, JB. Interpreted the results: GG, MJB. Wrote the first draft: GG. Revised the article: GG, MJB, JB, EH. All authors read and approved the final manuscript.

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