Impact of repeated influenza immunization on respiratory illness in children with pre-existing medical conditions

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Abstract

Purpose: Annual influenza immunization in medical risk groups is recommended in many countries. Recent evidence suggests that repeated inactivated influenza vaccine (IIV) immunization throughout childhood may impair long-term immunity against influenza. We assessed whether prior immunization altered the effect of IIV in children with pre-existing medical conditions on primary care diagnosed respiratory illness (RI) episodes during the influenza season.

Methods: Electronic records of IIV immunized children who met the criteria for annual IIV immunization according to Dutch guidelines were extracted from a primary care database over 2004-2015. For each year, we collected information on IIV immunization status, primary care attended RI episodes (including influenza-like illness, acute RI and asthma exacerbation) and potential confounders. Generalized estimating equations were used to model the association between prior IIV and occurrence of at least one RI episode during the influenza season with "current year immunized, but without IIV history" as reference group.

Results: 4,183 children (follow-up duration: 11,493 child-years) were IIV immunized at least once. Adjusted estimates showed lower odds for RI in current year immunized children with prior IIV compared to those without (OR: 0.61;95%CI:0.47-0.78 for "current year immunized and one IIV in previous two years"; OR:0.85;95%CI:0.68-1.07 for "current year immunized and ≥2 IIVs in previous three years, including prior year").

Conclusion: Repeated IIV immunization in children with pre-existing medical conditions has no negative impact on, and may even enhance, long-term protection against RI episodes diagnosed during the influenza season in primary care.

Keywords: Influenza, immunization, pre-existing medical condition, children, pediatrics, respiratory illness.

Abbreviations: ARTI: acute respiratory tract infection; ATC: anatomical therapeutic chemical; CI: confidence interval; GEE: generalized estimated equations; GP: general practitioner; ICPC: international classification for primary care; IIV: inactivated influenza vaccine; ILI: influenza like illness; JHN: Julius General Practitioner Network; OR: odds ratio; RI: respiratory illness; SCP: The Netherlands Institute for Social Research; SES: socio-economic status; URTI: upper respiratory tract infection; ZGA: The Healthcare Network Almere

Introduction

Influenza is a leading cause of respiratory illness (RI) and healthcare resource use worldwide.[1] Influenza infection and associated complications pose a particular threat to individuals with pre-existing medical conditions such as chronic respiratory or cardiovascular disease and diabetes mellitus.[2] In contrast with policies in some other countries like the US, where all children are recommended to receive annual influenza immunization, seasonal immunization with inactivated influenza vaccine (IIV) for individuals with pre-existing medical conditions aged six months and above is therefore recommended in many European countries, including the Netherlands.[3] However**,** concerns exist about possible attenuation of influenza immunity following repeated IIV immunization. This may be particularly relevant to children with pre-existing medical conditions as they tend to receive IIV repeatedly throughout childhood and possibly into adult life.

Possible immunological mechanisms for altering IIV effectiveness after repeated IIV immunization include interference with antibody and effector B-cell responses, depending on both the antigenic distance among vaccine strains and between the vaccine strains and circulating influenza strains [4, 5], and hampered development of cross-reactive virus-specific CD8+ T cells.[6] Children without any prior immunity from natural influenza could particularly be affected by the suppressed development of heterosubtypic immunity against antigenically distinct influenza strains.[7, 8]

Epidemiological studies have shown conflicting results as to whether these immunological mechanisms impact protection from annually repeated immunization against influenza and RI during the influenza season. Most studies included only a limited number of consecutive influenza seasons which may lead to biased results since IIV effectiveness can vary substantially from year-to-year.[9-15] Furthermore, previous studies focused either on healthy children or on adults.[11, 16-21] Data on the impact of repeated influenza immunization in children with pre-existing medical conditions are therefore lacking completely.

Using routine longitudinal primary care data over the years 2004-2015, we therefore assessed whether the impact of IIV on general practitioner (GP) diagnosed RI episodes during influenza season was altered in immunized children with pre-existing medical conditions with a history of IIV immunization. As confirmation of influenza infection is rarely obtained in primary care, we used a composite outcome of RI strongly associated with influenza.

Methods

Study design and data collection

For this observational cohort study, we extracted data from two large electronic primary care databases; the Julius General Practitioner Network (JHN) and The Healthcare Network Almere (ZGA) databases. These contain anonymous routine healthcare data of all patients enlisted in the participating primary care practices in the Utrecht and Almere region, centrally located in the Netherlands. The patient populations are representative of the general Dutch population.[22, 23]

For Dutch residents, registration with a primary care practice is mandatory; GPs act as gatekeepers to specialized and hospital care, both during and outside office hours. Patient information in the databases includes diagnoses coded according to the International Classification for Primary Care (ICPC), drug prescriptions classified according to the Anatomical Therapeutic Chemical (ATC) Classification System and immunization codes.[24] GPs were trained to use this system and apply strict criteria for each ICPC code.

Study population

In the Netherlands, only children with pre-existing medical conditions are eligible for annual IIV immunization. Data for the years 2004-2015 of all children aged 6 months to 18 years eligible for annual

IIV immunization according to Dutch guidelines were extracted from the healthcare databases.[25, 26] Annual IIV immunization eligibility for this study was based upon pre-specified ICPC codes in the period between December 1st of the previous year and November 30th of the current year and pre-specified ATC codes in the period between July 1st and November 30th of the current year. This method was adopted from the national annual report on IIV coverage in the Dutch population.[25] The pre-existing medical conditions qualifying for IIV eligibility included respiratory (e.g. recurrent wheeze/asthma), pre-existing cardiovascular disease (e.g. congenital cardiovascular anomalies), diabetes mellitus, renal failure or immunocompromising conditions.[27]

All children receiving IIV at least once were included in the analysis. Each child was followed over time from the first IIV until either the i) year of last IIV immunization, ii) end of registration at the participating primary care practice or iii) or end of extraction date.

Definition of outcomes

As confirmation of influenza infection is rarely obtained in primary care, we used a composite outcome of RI strongly associated with influenza. The outcome was defined as occurrence of at least one GP-diagnosed RI episode during the influenza season (yes/no) and included the following conditions and ICPC codes: i) influenza-like illness (ILI); R80 (influenza), ii) acute respiratory infection (ARI); H71 (acute otitis media), R05 (cough), R78 (acute bronchitis/bronchiolitis), R81 (pneumonia), or iii) asthma exacerbation; R02 (dyspnea), R91 (chronic bronchitis), R96 (asthma). To exclude chronic RI not associated with an acute infection, ICPC codes R02, R05, R91 and R96 were only included if combined with a new prescription of inhaled or oral corticosteroids (ATC codes R03, H02AB) and/or oral antibiotics (ATC codes J01). To exclude ARI infections that are less specific for influenza, ICPC code R74 (URTI) was not included in the outcome. A new RI episode was documented after a consultation-free interval of at least 28 days. A medical prescription was considered related when dated seven days before until seven days after the RI episode.

Influenza seasons 2004-2015

Yearly influenza epidemic periods between 2004 and 2015 were defined as those weeks with at least 5% positive influenza isolates according to the sentinel surveillance of the National Institute for Public Health and the Environment (RIVM).[28] GPs participating in the sentinel surveillance randomly select patients presenting with ILI and/or ARI for collection of nasopharyngeal swabs. Samples are analyzed at the RIVM virological laboratory for respiratory pathogens.

Definition of exposure and confounders

The exposure of interest was prior IIV immunization among those immunized. For each child contributing to the analysis, we determined the immunization status per year and the immunization history for that same year, defined as i) no prior IIV immunization in previous three years, ii) one IIV in previous two years, iii) at least two IIVs in previous three years, including prior year. Children eligible for immunization, but without receipt of IIV in the current year did not contribute to that year's analysis. Additional characteristics such as age, socio-economic status (SES), the total number of pre-existing medical conditions meeting eligibility criteria for IIV immunization per child, health-seeking behavior, and number of RI episodes outside the influenza season were considered as potential confounders. SES was derived from the postal code of each patient according to The Netherlands Institute for Social Research (SCP) containing information of income, percentage of people living in the area with low income, low education and unemployment.[29] SES levels were categorized according to postal code ranking in the Netherlands: high (top 20%), middle (20-80%) and low (lowest 20%). Health-seeking behavior was assessed by quantifying the number of primary care consultations for self-limiting diseases/complaints (ICPC codes). These included conditions such as exanthemaous diseases (chickenpox, exanthema subitum, hand foot mouth disease), acute gastrointestinal complaints (diarrhea, vomiting, abdominal pain) and focal symptoms (conjunctivitis, cold sore) To adjust for possible

confounding by indication, a co-variate representing the number of RI episodes in the months prior to the influenza season, between calendar weeks 20 to 36 (late spring and summer season), was added to the model.

Statistical analysis

For descriptive purposes, the incidence of RI episodes per 100 child-years was calculated by dividing the number of episodes by the total number of child-years per 5-year age categories. We used generalized estimating equations (GEE) with a binomial distribution and logit link function to assess the association between prior IIV immunization status and the presence of RI episodes during the influenza season with "current year vaccinated, but no prior IIV immunization" as the reference group. To test whether the effect of prior IIV immunization status on RI episodes was age-dependent, an interaction term for prior IIV immunization status with age was included in the fully adjusted GEE model. Effect modification was defined as p-value <0.10. The regression coefficients from the GEE model reflect odds ratios (OR). The fully adjusted model included age, SES, number of pre-existing medical conditions, health-seeking behavior and number of GP-diagnosed RI episodes outside the influenza season.

Results

Study population

Over the years 2004-2015, 225,045 children were registered in the JHN or ZGA databases and 12,916 children (5.7%) met the eligibility criteria for IIV immunization for at least one influenza season. Of these, 4,183 children (32% of 12,916) received IIV at least once during follow-up and were included in the analysis (total child-years of follow-up: 11,493). IIV immunization occurred in 10,017 follow-up years, whereas no IIV was administered in 1,476 child-years (Figure 1).

Baseline characteristics of the total study population and according to prior IIV immunization status are shown in Table 1. Immunized children with prior IIV immunization were older, had lower healthcare seeking and fewer RI episodes outside the influenza season than those without IIV history ($p<0.001$). The majority qualified for IIV due to pre-existing respiratory disease (78%) with asthma being the prime diagnosis. Overall, RI incidence rate was highest in the youngest age group and declined thereafter. The current year immunized group with prior IIV immunization had a lower RI incidence rate across all ages compared to those without IIV history.

Impact of repeated IIV immunization on respiratory illness episodes

Table 2 shows the association between prior IIV immunization and GP-diagnosed RI episodes during influenza seasons. Seasonal RI episodes occurred most frequently in IIV immunized children without history of IIV (7.0%). The adjusted model showed lower odds for having an RI episode during the influenza season in children with prior IIV immunization compared to those without prior IIV immunization (OR 0.61; 95%CI 0.47 to 0.78 for immunized in current year and one IIV in previous two years and OR 0.85, 95%CI 0.68 to 1.07 for immunized in current year and at least two IIVs in previous three years). The association between prior IIV immunization status and the occurrence of RI episodes during the influenza season was not age-dependent ($P_{interaction}$ =0.68).

Discussion

This study shows that protection against seasonal RI is not attenuated following repeated annual IIV immunization in children with pre-existing medical conditions. Interestingly, our findings suggest that repeated IIV immunization may even enhance protection.

Concerns about possible attenuation of influenza immunity following repeated IIV were first raised by Hoskins et al. in the late 70s.[9] They found a decreased protection against influenza in boys who had

been immunized annually compared with first-time immunized boys attending boarding school. Subsequent epidemiological studies, however, have been inconsistent.[9-20, 30] which could be due to methodological shortcomings (e.g. small sample sizes, short follow-up periods or insufficient data to adjust for confounding) or may mean that the hypothesis is incorrect. Recently, Ramsay and colleagues published a systematic review and meta-analysis including all epidemiological studies in this field. [31] They concluded that there is no overall evidence that prior season vaccination does negatively impact vaccine effectiveness. However, they emphasized the lack of studies including multiple seasons to evaluate repeated vaccination in more detail. Our study is the first that used a large and comprehensive longitudinal primary care dataset spanning eleven influenza seasons; it is powered to reliably detect differential effects of IIV history, rule out distortions by annual fluctuations in IIV effectiveness and adjust for a range of confounders.

Our study provides important evidence supporting that prior IIV immunization does not reduce, and in fact may even enhance vaccine effectiveness for seasonal RI by providing residual protection from earlier vaccinations.[15] Previous studies have primarily focused on laboratory confirmed influenza and we are the first to demonstrate this effect for seasonal RI. In addition, we found that the impact of repeated immunization was not modified by age. This is particularly reassuring in light of Bodewes et al's suggestion that annual influenza immunization in immunologically naive children may prevent the induction of heterosubtypic immunity, thereby enhancing susceptibility to genetically more distant strains.[6, 8] Our observations do not support this, although we note that we had no information on prior exposure to natural influenza among immunized children.

While laboratory confirmed influenza or markers of protective influenza immunity are considered the most specific endpoints to assess vaccine efficacy, the occurrence of RI during the annual influenza epidemic season, as studied here, is considered a reliable and comprehensive endpoint to assess IIV field effectiveness.[32] On average 25-30% of all GP-diagnosed RI episodes is attributed to influenza virus

infection during this period.[28] An advantage of studying these clinical, instead of microbiological or serological endpoints is that these are more relevant for daily practice. Our study was based on primary care attendance for RI, which reflects approximately 30-50% of respiratory symptom episodes occurring in the community.[33, 34] Although the effects of repeated IIV are likely similar for RI episodes that do or do not lead to GP consultation, our study was not designed to measure effects of repeated IIV stratified by disease severity. Future studies should therefore preferably also capture RI symptom episodes occurring in the community, as well as influenza and RI-associated hospitalizations.

Some methodological limitations deserve further attention. First, due to the observational design of this study, we cannot entirely rule out residual confounding by indication, meaning that the most severely affected children are more likely to receive repeated IIV and at highest risk for experiencing RI. This could have led to an underestimation of the protective effect of repeated IIV. By including RI episodes outside the influenza season as proxy for disease severity in our model, it is unlikely that this significantly influenced our findings. Second, misclassification of the cumulative number of influenza immunizations is possible, but likely to be low. Vaccinations are supplied almost exclusively by GPs, and adherence to coding vaccine administration is high because of the financial incentive. Third, misclassification of the outcome may be differential if GPs were less inclined to diagnose influenza among vaccinated children due to its perceived effectiveness. However, since we used a range of ICPC codes indicating RI of which only one was exclusively used for influenza infection (R80, representing 4.7% of RI episodes) we consider this unlikely. Finally, the dataset does not contain information on ethnicity. However, less than 13% of the population living in the Netherlands has a non-Western background.[35] Therefore, this study primarily looks at a white population in a high-income Northern European setting. This could have an effect on the generalizability of our results. However, we have no reason to assume that the impact of repeated IIV immunization differs by ethnic background or SES.

In summary, repeated IIV immunization has no negative impact on long-term vaccine effectiveness and may even enhance protection against RI among IIV immunized children with pre-existing medical conditions.

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Competing interests

No potential conflicts of interest to disclose.

Contributors

Dr de Hoog developed the concept of the present study,conceptualized and designed the study, performed the statistical analyses, drafted the initial manuscript and revised the manuscript.
Dr Bruijning-Verhagen and Dr Venekamp developed the concept of the present study, conceptualized and designed the study, and reviewed and revised the manuscript for important intellectual content.
Prof Smit, Prof Schilder, Prof Sanders, and Prof Damoiseaux contributed to the analysis, interpreting the results and critically revised the manuscript for important intellectual content
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Table 1: Characteristics of the study population according immunization status

Study population	Total study population CY=11,493	Immunized in current year, but no prior IIV immunization CY=2,914	Immunized in current year, and one IIV in previous two years CY=2,450	Immunized in current year, and at least 2 IIVs in previous 3 years, including prior year CY=4,653
Sex (%)				
Boys	57.9	57.7	57.1	57.6
Girls	42.1	42.3	42.9	42.4
Socio-economic status score				
Low	16.4	17.0	16.1	14.6
Middle	50.7	48.5	50.2	54.3
High	32.7	34.5	33.5	31.0
Age groups (yr;%))				
0-5	8.4	20.9	8.8	1.2
6-10	15.6	20.2	19.0	10.5
11-15	45.3	37.5	44.7	48.3
>15	30.7	21.7	27.6	39.9

Health-seeking behavior; number of consultations (%)				
0	90.3	88.7	90.4	92.0
1	6.8	8.1	6.7	5.5
>1	2.9	3.2	2.8	2.6
Out-season RI in previous year (%)				
0	96.5	96.4	97.4	98.1
1	3.0	3.2	2.4	1.5
>1	0.5	0.3	0.2	0.3
Indicated diseases; % yes				
Pre-existing cardiovascular disease	10.7	10.5	10.0	10.2
Chronic lung disease	78.0	79.7	77.3	78.5
Diabetes	8.3	6.3	8.5	9.2
Chronic kidney disorder	0.1	0.1	0.1	0.1
Immunocompromising condition	3.9	3.7	4.6	3.3

Respiratory difficulties with neurological origin	1.7	1.3	1.8	1.8
Number of indications for IIV (%)				
1	97.4	98.3	97.7	96.8
>1	2.6	1.7	2.3	3.2
Incidence of RI during influenza season / 100 child-years (95% CI)				
All ages	18.4 (17.1-19.8)	27.8 (24.7-31.2)	13.1 (10.8-15.7)	13.4 (11.7-15.4)
0-5	56.4 (48.6-65.1)	66.2 (55.6-78.2)	37.9 (25.5-54.4)	49.4 (24.1-90.8)
6-10	30.3 (26.0-35.0)	30.0 (23.0-38.4)	22.8 (16.1-31.3)	26.9 (19.7-35.9)
11-15	13.2 (11.5-15.0)	14.8 (11.3-19.1)	9.4 (6.6-12.9)	12.4 (9.7-14.8)
>15	9.6 (7.9-11.6)	12.6 (8.5-18.1)	4.5 (2.3-8.0)	10.4 (8.1-13.2)
Boys	19.3 (17.6-21.3)	30.0 (25.7-34.7)	14.7 (11.5-18.5)	13.8 (11.5-16.5)
Girls	17.1 (15.1-19.2)	24.8 (20.4-29.9)	10.9 (7.7-14.9)	12.9 (10.3-15.9)

Number of consultations for RI during influenza season (%)				
0	95.2	93.0	96.5	96.3
1	3.0	3.9	2.3	2.5
>1	1.8	3.1	1.2	1.2

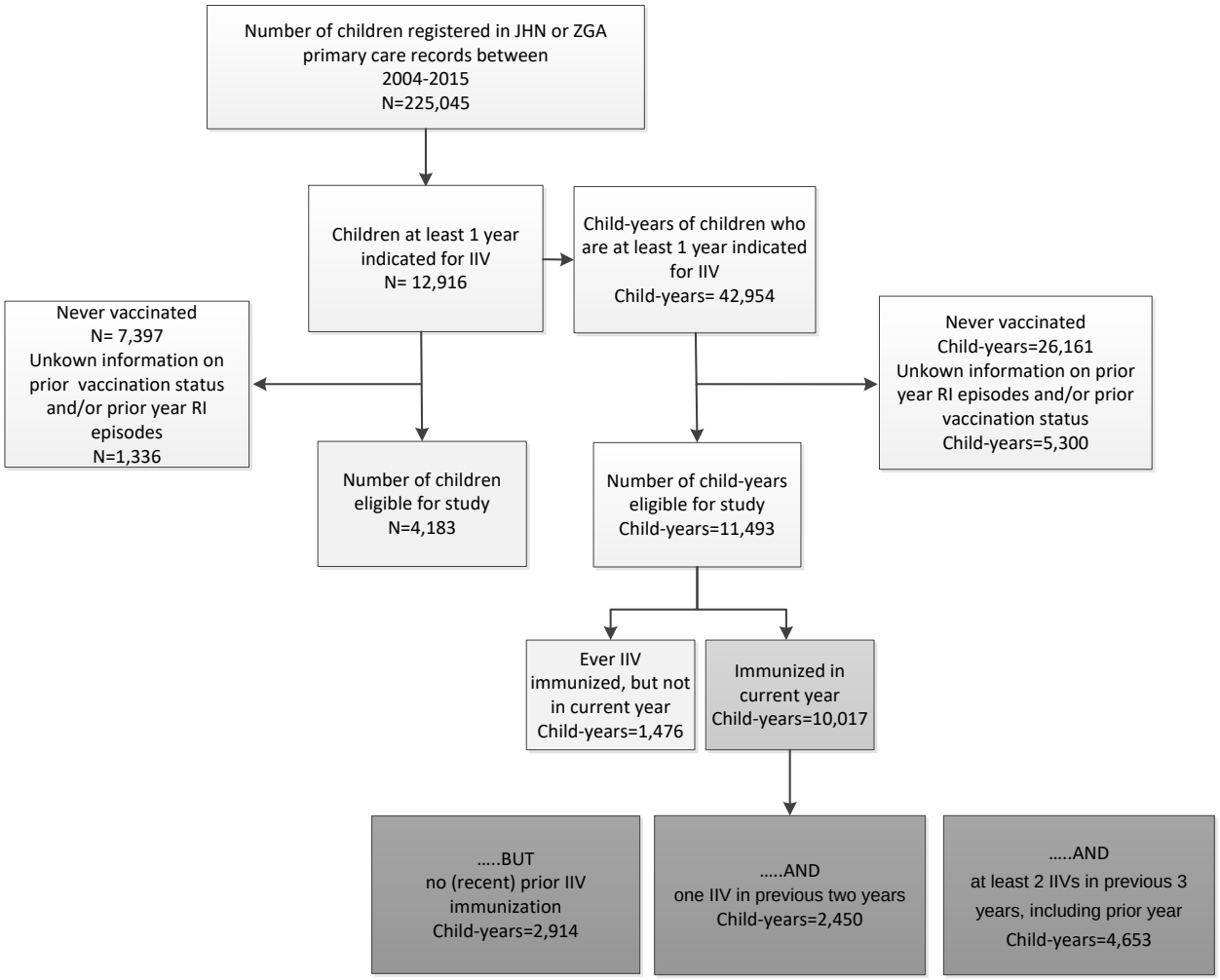
Abbreviations: CY: Child-years, RI: respiratory infections, CI: confidence interval

Table 2: Association between immunization history and occurrence of at least one RI episode during influenza season

	% RI episodes	Crude OR (95% CI)	Adjusted OR (95% CI)
Immunized in current year, but no (recent) prior IIV immunization	7.0	ref	ref
Immunized in current year, and one IIV in previous two years	3.5	0.48 (0.37-0.61)	0.61 (0.47-0.78)
Immunized in current year, and at least 2 IIVs in previous 3 years, including prior year	3.7	0.50 (0.41-0.62)	0.85 (0.68-1.07)

*Adjusted for socio-economic status (SES), age, number of indication categories for IIV, health-seeking behavior, and number of out-season summer GP-diagnosed RI episodes.

Figure 1: Flowchart of the study population



Note: The results of the 1,476 child-years of follow-up of children eligible for IIV immunization, but without receipt of IIV in the current year are not reported in the results.