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# Inactivated influenza vaccine does not reduce all cause respiratory illness in children with pre-existing medical conditions

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ABSTRACT

*Background:* The effectiveness of inactivated influenza vaccine (IIV) immunization in preventing all cause respiratory illness (RI) in children with pre-existing medical conditions has not been fully established and varies from season to season. This study aims to quantify the overall impact of IIV immunization on primary care attended RI episodes in children with pre-existing medical conditions, using robust observational data spanning twelve influenza seasons.

*Methods:* Electronic records of IIV eligible children aged 6 months to 18 years were extracted from primary care databases over the years 2004–2015. IIV eligibility criteria according to Dutch guidelines included (chronic) respiratory and cardiovascular disease and diabetes mellitus. For each year, information on IIV immunization status, primary care attended RI episodes (including influenza, acute respiratory tract infections and asthma exacerbations) and potential confounders were collected. Generalized estimating equations were used to model the association between IIV status and occurrence of at least one RI episode during the influenza epidemic period with "current year immunized" as reference group. Robustness of findings were assessed by performing various sensitivity analyzes in which (i) seasons with a mismatch between the dominant circulating influenza virus and vaccine strain were excluded, (ii) influenza periods were further restricted to weeks with at least 30% influenza virus positive specimens in sentinel surveillance (instead of 5%), (iii) propensity scores were used to adjust for confounding.

*Results:* In total, 11,797 children (follow-up duration: 38,701 child-years) were eligible for IIV for $\geq$ one season with 29% immunized at least once. The adjusted odds for primary care attended RI episodes during the influenza epidemic period did not differ between current season immunized versus not immunized children (adjusted OR:1.01; 95%CI:0.90–1.13). The various sensitivity analysis showed comparable results.

*Conclusions:* IIV immunization in children with pre-existing medical conditions does not reduce all cause RI episodes encountered in primary care during the influenza season.



## 1. Introduction

Influenza is a major cause of respiratory illness (RI) and complications, in particular in individuals with pre-existing medical conditions such as (chronic) respiratory and cardiovascular disease and diabetes mellitus [1]. In contrast with policies in some other countries like the US, where all children are recommended to receive annual influenza immunization to control influenza disease burden, many countries, including the Netherlands, restrict annual immunization with the inactivated influenza vaccine (IIV) for individuals with pre-existing medical conditions aged six months and above [2]. However, this recommendation relies on a very thin evidence base [3].

Results of IIV field effectiveness in children are conflicting. Although IIV immunization reduces influenza incidence in case of adequate antigenic match between the vaccine and circulating influenza strains [4,5], estimated reductions in the overall incidence of all cause respiratory illness (RI) and its severity vary widely between studies and across seasons [3,5–8]. Yet, these measures of field effectiveness ultimately determine the impact and cost-effectiveness of IIV immunization policy.

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By using routine primary care data for twelve consecutive influenza seasons, we assessed the risk of primary care attended RI episodes among Dutch children aged 6 months to 18 years with pre-existing medical conditions who did and did not receive IIV immunization, while adjusting for important confounders.

## 2. Methods

### 2.1. Study design and definition of outcome, exposure and confounders

An extensive description of the methods has been described elsewhere [9].

In short, we collected observational data from two large electronic primary care databases over the years 2004–2015; the Julius General Practitioner Network (JGPN) and The Healthcare Network Almere (ZGA) database [10,11]. All children aged 6 months to 18 years eligible for annual IIV immunization according to Dutch guidelines were extracted from the primary care databases [12–14]. The pre-existing medical conditions qualifying for IIV eligibility included respiratory (e.g. recurrent wheeze/asthma) and (congenital) cardiovascular disease, diabetes mellitus, chronic kidney disease or immunocompromising conditions (e.g. primary immunodeficiency, auto-immune disease, HIV or use of immunosuppressive medication), according to primary care guidelines [15].

Annual IIV immunization eligibility was based on pre-specified assigned International Classification for Primary Care (ICPC) codes in the period between December 1st of the previous year and November 30th of the current year and pre-specified assigned Anatomical Therapeutic Chemical (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 among groups with pre-existing medical conditions in the Dutch population [13]. All children who met the criteria for IIV eligibility were included in the analysis. Person-time was included for each child from their first year of IIV indication until either the (i) year of their last IIV indication, (ii) end of registration at the participating primary care practice or (iii) end of extraction date. The study was deemed exempt from the Medical Research Involving Human subjects Act (WMO). We received a waiver of informed consent.

The outcome was defined as the presence of any general practitioner (GP)-diagnosed RI episode which occurred during an influenza epidemic period. This included the following conditions and ICPC codes: (i) influenza; R80 (influenza), (ii) respiratory complications that are often accompanied by influenza; R78 (acute bronchitis/bronchiolitis), R05 (cough) in combination with a prescription of oral antibiotics (ATC codes J01), R81 (pneumonia) and H71 (acute otitis media), or (iii) asthma exacerbation; R91 (chronic bronchitis), R96 (asthma), R02 (dyspnea), R05 (cough). The ICPC codes of (i) and (ii) have shown good correlation with the case-definitions of influenza like illness (ILI) and ARI used in the European Influenza Surveillance Network [16]. The recommendation to immunize children with asthma against influenza is based on the rationale that IIV may prevent influenza induced asthma exacerbations and lower respiratory tract infections [17]. In order to capture vaccination effects on asthma exacerbations that occur during the influenza season we have included (combination of) ICPC codes that may indicate such exacerbations. These include: R91 (chronic bronchitis), asthma exacerbation (R96), dyspnea (R02), or cough (R05) when accompanied by a new prescription of inhaled corticosteroids (ATC codes R03), oral corticosteroids (ATC codes H02AB) and/or oral antibiotics (ATC codes J01) suggesting the episode was acute. To exclude ARTI infections that are less specific for influenza [18], ICPC code R74 (URTI/common cold) was not included in the outcome. A new RI episode was documented after a disease-free interval of at least 28 days. A medical prescription was considered related when dated seven days before until seven days after the consultation for RI episode.

Yearly influenza epidemic periods from 2004 through 2016 were defined as those weeks with the longest consecutive period of at least 5% influenza virus positive specimens from patients with influenza-like illness (ILI) using data from the national virological sentinel surveillance of ILI by the National Institute for Public Health and the Environment (RIVM) and Nivel Netherlands institute for health services research [19,20].

The exposure of interest was IIV immunization status (ICPC code R44 or ATC code J07BB02 divided in current year vs no current year IIV immunization). In the Netherlands influenza vaccination is available free of charge for target groups. The general practitioner receives a reimbursement for the costs incurred and work carried. To claim the reimbursement, the doctor must register in the electronic patient file which patient has received the vaccination. According to the Dutch guideline, for children younger than nine years of age, who have not been fully vaccinated at least once in the past two seasons, the vaccination is repeated after four weeks in order to achieve sufficient antibody formation [15]. Additional characteristics such as age, socio-economic status (SES), the total number of pre-existing medical conditions per child, health-seeking behavior, and number of RI episodes prior to the influenza epidemic period were considered as potential confounders. Health-seeking behavior was assessed by quantifying the number of primary care encounters for self-limiting diseases/complaints (ICPC codes) which usually run a favorable natural disease course. 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, herpes simplex labialis).

### 2.2. Statistical analysis

For descriptive purposes, the incidence of primary care attended RI episodes during the influenza epidemic period 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 IIV immunization status and the presence of all cause RI episodes during the influenza epidemic period with "no current year immunization" as the reference group. To test whether the effect of 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. Age (in categories 0–5, 6–10, 11–15 and > 15 year) was considered as an effect modifier when the p-value for interaction was < 0.10. The regression coefficients from the GEE model reflect odds ratios (OR). The fully adjusted model included SES, age, number of pre-existing medical conditions, presence or absence of pre-existing respiratory disease, diabetes or immunocompromising conditions, health-seeking behavior and number of primary care attended all cause RI episodes outside the influenza season as potential confounders. In secondary analyses, we restricted (i) the outcome to seasonal influenza (ICPC code R80) and (ii) the study population to those with asthma which is the largest subgroup of children qualifying for influenza immunization.

Three sensitivity analyzes were performed to assess the robustness of the findings, First, seasons with a mismatch between the dominant circulating influenza virus and the vaccine strain were excluded. Classification of match/mismatch was based on data from the sentinel national influenza surveillance in primary care [21] as described elsewhere [22]. Data on influenza match/mismatch for seasons 2004–2014 have been published previously

[22] and additional data for seasons 2015 and 2016 were added for this study. An overview of circulating strains per season and the degree of mismatch can be found in the appendix (appendix Table 1). Mismatched seasons included 2004/2005, 2009/2010, 2011/2012, 2014/2015 and were excluded from the analysis [22]. Second, only periods with 30% influenza virus positive specimens in sentinel surveillance (instead of the 5% applied in primary analysis) were studied. As a result the mean duration of the annual influenza epidemic periods decreases from 17.08 weeks in the primary analysis (5% positive specimens) to 10.09 weeks (30% positive specimens) in the sensitivity analysis. Finally, propensity scores were used to adjust for confounding. Scores were calculated for the set of confounders with propensity score regression analysis and included as a single, continuous covariate in the GEE model estimating the association between IIV immunization status and RI episodes. All statistical analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, ILL, USA) and OpenEpi: Open Source Epidemiologic Statistics for Public Health (version 3.01, updated April 2013).

## 3. Results

### 3.1. Study population

Over the years 2004–2015, 225,045 children were registered in the JGPN or ZGA databases and 11,947 children (5.3%) with a total follow-up of 38,701 child-years met the eligibility criteria for IIV immunization for at least one influenza season (Fig. 1).

Baseline characteristics of the total study population and according to IIV immunization status are listed in Table 1. In general, immunized children were older and had fewer RI episodes during the influenza season than the non-immunized children. Diabetes and pre-existing respiratory disease were more prevalent in immunized children and immunosuppressive conditions in non-immunized children. The majority qualified for IIV due to pre-existing respiratory disease (73%) with asthma (R96) being the prime diagnosis (>90%).Overall, the RI incidence rate was highest in the youngest age group and declined thereafter; whereas the vaccine coverage was highest in the oldest age group (Appendix Fig. 1). Acute otitis media (ICPC code H71) was the most common diagnostic code (37.6%). Influenza (R80) represents 6.1% of all RI episodes (data not shown).

### 3.2. Impact of IIV immunization on respiratory illness episodes

Table 2 shows the association between IIV immunization status and primary care attended all cause RI episodes during the influenza season. Seasonal RI episodes occurred most frequently in children without current year IIV (5.4%). However, the adjusted odds for primary care attended RI episodes during the influenza season did not significantly differ between children receiving IIV in current year and those who did not receive IIV (adjusted OR (aOR): 1.01; 95% CI 0.90 to 1.13). The association between IIV immunization status and the occurrence of RI episodes during influenza seasons was not age-dependent ($P_{interaction} = 0.14$). This means that the association is comparable for each age group. The secondary analysis, where only children with asthma were included, showed similar results (OR 1.00; 95% CI: 0.87 to 1.16; Table 3). The association between IIV immunization status and seasonal influenza showed 30% lower odds for developing influenza when immunized with IIV (aOR: 0.70; 95% CI: 0.46 to 1.07). Sensitivity analyzes results are summarized in Table 4. The effect estimates derived from these analyzes were comparable with the estimate from the main analysis.

## 4. Discussion

This large observational study including twelve consecutive influenza seasons found no impact of IIV in preventing primary care attended all cause RI in children with pre-existing medical conditions, while applying rigorous control for confounding. Our findings were robust in subgroup and several sensitivity analysis.

Other studies also found no, or only a very limited, impact of annual IIV on seasonal RI occurrence in (medical risk) children [6,23,24], but results are conflicting [25]. While seasonal influenza vaccination may reduce the actual RI episodes caused by influenza

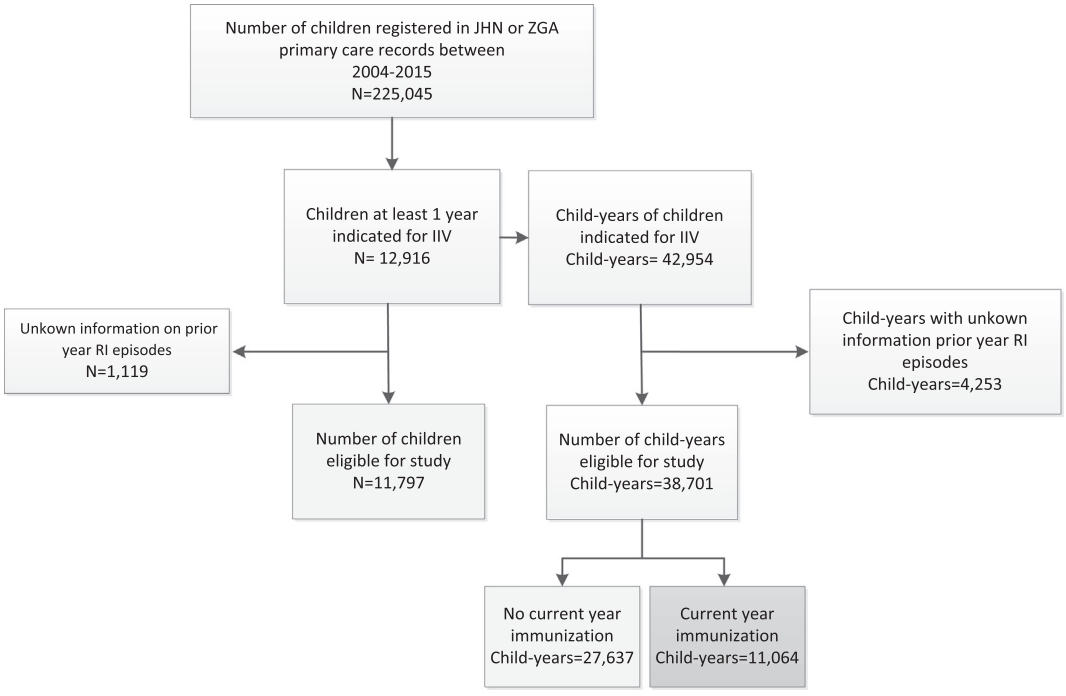


**Fig. 1.** Flowchart of the study population.

**Table 1**
Characteristics of the study population according to immunization status.

| Study population | Total population CY = 38,701 | No current year immunization CY = 27,637 | Current year immunization CY = 11,064 |
|---|---|---|---|
| Sex (% boys) | 58.6 | 58.9 | 57.9 |
| *Socio-economic status score* | | | |
| Low | 15.4 | 15.7 | 14.8 |
| Middle | 50.1 | 49.0 | 53.0 |
| High | 34.4 | 35.3 | 32.1 |
| *Age groups (yr %)* | | | |
| 0–5 | 16.8 | 20.0 | 8.4 |
| 6–10 | 18.6 | 19.9 | 15.4 |
| 11–15 | 39.3 | 37.4 | 44.4 |
| >15 | 25.3 | 22.7 | 31.9 |
| *Healthcare seeking (number of consultations; %)* | | | |
| 0 | 91.0 | 91.1 | 91.1 |
| 1 | 6.4 | 6.4 | 6.3 |
| >1 | 2.6 | 2.5 | 2.6 |
| *Out-season RI episodes in previous year (week 20–36)* | | | |
| 0 | 97.7 | 97.7 | 97.6 |
| 1 | 2.1 | 2.0 | 2.1 |
| >1 | 0.2 | 0.3 | 0.4 |
| *Indicated diseases (% yes)* | | | |
| Pre-existing cardiovascular disease | 12.4 | 13.3 | 10.0 |
| Chronic lung disease | 73.2 | 70.8 | 79.2 |
| Diabetes | 6.2 | 5.4 | 8.1 |
| Chronic kidney disorder | 0.2 | 0.3 | 0.1 |
| Immunocompromising condition | 7.0 | 8.4 | 3.7 |
| Respiratory difficulties with neurological origin | 2.9 | 3.4 | 1.6 |
| *Number of indications for IIV* | | | |
| 1 | 98.1 | 98.4 | 97.4 |
| >1 | 1.9 | 1.6 | 2.6 |
| *Incidence of RI during influenza season/100 CY (95% CI)* | | | |
| All ages | 19.4 (18.6–20.2) | 20.6 (19.7–21.6) | 16.4 (15.2–17.8) |
| 0–5 | 49.7 (46.8–52.8) | 48.7 (45.5–52.0) | 55.8 (47.9–64.8) |
| 6–10 | 26.8 (24.8–29.8) | 27.3 (25.0–29.8) | 25.2 (21.3–29.7) |
| 11–15 | 10.7 (9.8–11.7) | 10.5 (9.4–11.6) | 11.3 (9.7–13.0) |
| >15 | 7.2 (6.3–8.2) | 6.3 (5.3–7.5) | 8.8 (7.2–10.6) |
| *Number of consultations for RI during influenza season (%)* | | | |
| 0 | 94.9 | 94.6 | 95.7 |
| 1 | 3.4 | 3.8 | 2.7 |
| >1 | 1.6 | 1.6 | 1.6 |

Abbreviations: CY: Child-years, RI: respiratory infections, CI: confidence interval, IIV: inactivated influenza vaccine.

**Table 2**
Association between immunization status and occurrence of at least one RI episode during influenza season.

| Immunization status | % RI episodes | Crude Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI)* |
|---|---|---|---|
| Not immunized in current year | 5.4 | ref | ref |
| Immunized in current year | 4.3 | 0.76 (0.68–0.84) | 1.01 (0.90–1.13) |

Abbreviations: RI: respiratory infections.
* Adjusted for socio-economic status, age, number of indication categories for IIV, having a chronic lung disease, diabetes or immunocompromising condition, health-seeking behavior, and number of out-season primary care attended RI episodes.

**Table 3**
Association between immunization status and occurrence of at least one RI episode during influenza season in children with asthma.

| Immunization | % RI episodes | Crude Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI)* |
|---|---|---|---|
| Not immunized in current year | 5.6 | ref | ref |
| Immunized in current year | 4.2 | 0.72 (0.63–0.83) | 1.00 (0.87–1.16) |

Abbreviations: RI: respiratory infections.
* Adjusted for socio-economic status, age, number of indication categories for IIV, having diabetes or a immunocompromising condition, health-seeking behavior, and number of out-season primary care attended RI episodes.

virus [4,5], it may not prevent other viral episodes and primary care consultations. In all, the lack of convincing evidence that IIV immunization reduces overall RI incidence in children with pre-existing medical conditions raises concerns as to whether the current policy actually generates the intended health benefits and qualifies as an efficient allocation of healthcare budgets.

Scientifically, the lack of impact of IIV immunization in preventing seasonal all cause RI episodes is incompletely understood. High-quality evidence shows that IIV efficacy and effectiveness against laboratory-confirmed influenza infection in children varies between 42% and 83% [17,26]. In this study, we found 30% lower odds for seasonal influenza when IIV immunized. With the estimated contribution of influenza to ILI (defined as symptoms of fever, cough, and respiratory-tract illness) during the annual influenza season varying between 10% and 50% [27], a net reduction between 5% and 41% in seasonal RI episodes would be expected.

Evidence is accumulating on the existence of viral interference where infection by one virus may alter susceptibility to another

**Table 4**
Association between immunization status and occurrence of at least one RI episode during influenza season in the sensitivity analysis.

| Sensitivity analysis | Immunization status | % RI episodes | Crude Odds Ratio (95% CI) | Adjusted Odds Ratio (95% CI)* |
|---|---|---|---|---|
| Propensity score regression | Not immunized in current year | – | – | ref |
| | Immunized in current year | – | – | 0.96 (0.86–1.08) |
| Excluding seasons with virus mismatch | Not immunized in current year | 5.3 | ref | ref |
| | Immunized in current year | 4.0 | 0.72 (0.63–0.82) | 1.00 (0.87–1.15) |
| 30% influenza positive samples | Not immunized in current year | 3.3 | ref | ref |
| | Immunized in current year | 2.7 | 0.80 (0.70–0.92) | 1.08 (0.94–1.24) |

Abbreviations: RI: respiratory infections.
* Adjusted for socio-economic status, age, number of indication categories for IIV, having a chronic lung disease, diabetes or immunocompromising condition, health-seeking behavior, and number of out-season primary care attended RI episodes.

virus infection due to temporary non-specific immunity following the initial infection [28–31]. This phenomenon could in theory increase susceptibility to other viruses following vaccine-induced prevention of influenza infection, and could explain the lack of impact of IIV on all-cause RI episodes. This hypothesis is supported by ecological studies [29,31], a pediatric IIV trial [30], and a respiratory syncytial virus (RSV) prophylaxis trial in preterm infants [28]. Furthermore, a recent Dutch study among older adults showed an increased incidence of non-influenza infections in vaccinated versus unvaccinated persons [32]. If non-influenza infections increase in IIV immunized individuals, the health benefits from influenza immunization only arise when the non-influenza infections that 'fill in the gap" are less severe and result in fewer complications. This is plausible, as influenza virus in particular is associated with secondary bacterial infections and more severe clinical disease. Yet, is should be noted that in our population, the most common indication (>70%) for immunization was prevention of asthma exacerbations. Previous studies have shown that rhinovirus (RV) and not influenza virus is the predominant pathogen associated with acute asthma exacerbations [33–36]. It is therefore uncertain if reductions in asthma exacerbations from influenza immunization can be expected. Whether viral interference can explain the lack of IIV impact on RI episodes in our study is unknown and requires further investigation.

Another possible explanation for the lack of IIV impact in our study is that immunization predominantly protects against severe influenza disease and associated complications [37–40]. If so, immunization would reduce influenza severity instead of incidence. Results from a RCT in children indeed indicate that vaccine efficacy is highest for severe (laboratory confirmed) influenza disease [41]. Other studies showed protective effects against influenza-associated mortality and hospitalizations in children [38–40,42]. Our research studied primary care attendance for RI and was not designed to capture this. Whether IIV immunization in children with pre-existing medical conditions is associated with reductions in hospital admissions and mortality from respiratory illness during influenza seasons is therefore unknown. Future research should ideally measure vaccine impact across the full spectrum of RI disease severity including hospital admission, and mortality, and also consider health economics and vaccine adverse events data to fully balance the benefits and harms of IIV immunization in this population.

Some methodological limitations deserve further attention. First, we cannot entirely rule out residual confounding by indication, meaning that the most severely affected children (i.e. those at highest risk for experiencing RI) are more likely to receive IIV. This could have led to an underestimation of the protective effect of IIV. However, by including RI episodes outside the influenza season as a proxy for disease severity in our model and adjustment for age, number and type of pre-existing medical conditions, as well as health seeking behavior, it is unlikely that this has significantly influenced our findings. Second, the impact of IIV immunization in young children under the age of nine years could be underestimated since we cannot rule out the possibility that these children are insufficiently vaccinated (received one instead of two doses of IIV). Unfortunately we do not have reliable information whether the child received a double dose of IIV when indicated. Overall, 29% of eligible children received IIV immunization in our study which closely resembles the IIV coverage estimates based on nationwide surveillance data [43]. Third, if the magnitude of the effect of IIV on RI is very small, our study may have been underpowered to detect this effect. We performed however two sensitivity analyses to assess if an effect was detectable when more stringent definitions of influenza epidemic periods were applied or when selecting only influenza seasons with adequate IIV effectiveness. The results of these analyses confirmed those of the primary analysis with no effect detectable. Furthermore, misclassification of the outcome may be differential if GPs were less inclined to diagnose RI among vaccinated children due to its perceived effectiveness against influenza disease. However, since we used a range of ICPC codes of which only one was exclusive to influenza infection (R80, representing 6.1% of RI episodes) we consider this unlikely. In addition, this would not explain the higher incidence of RI in the immunized group. The observed 30% lower odds for developing influenza (ICPC R80) when IIV immunized should be interpreted with caution. First, whilst microbiological testing is rarely performed in children with ILI in Dutch primary care, the number of influenza codes was relatively low - and with 6.1% of all RI episodes lower than anticipated based on previous estimations [27] - leaving our study underpowered to draw any definite conclusions. Second, we cannot rule out misclassification since it is unknown whether the participating GPs exclusively used the influenza code (R80) for laboratory-confirmed cases.

In conclusion, we found that IIV immunization in children with pre-existing medical conditions does not reduce all cause RI episodes encountered in primary care during influenza epidemic periods.

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## Author contributions

MdH performed the analyses and wrote the manuscript, RV helped designing the study and assisted in the analyses, helped interpret the results and revised the manuscript, AM and ES helped

interpret the results and revised the manuscript, PBV supervised the project and revised the manuscript.

## CRediT authorship contribution statement

**MdH**: Performed the formal analyses and wrote the original draft of the manuscript. **RV**: Helped conceptualizing the study and assisted in the analyses, helped interpret the results and reviewed and edited the manuscript. **AM** and **ES**: Helped interpret the results and reviewed and edited the manuscript. **PBV**: Supervised the project and reviewed and edited the manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Role of the funding source

The funder of this research, The Netherlands Organization for Health Research and Development, had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.11.086.

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