Effectiveness of live attenuated influenza vaccine in preventing amoxicillin prescribing in preschool children: a self-controlled case series study

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Short running title: Effectiveness of live attenuated influenza vaccine in preventing amoxicillin prescribing

Synopsis

Objectives: To determine the effectiveness of live attenuated influenza vaccine (LAIV) in reducing amoxicillin prescribing in preschool children in primary care.

Materials and methods: We used The Health Improvement Network (THIN), a large primary care database from the United Kingdom. We included children aged two to four years old at the start of either the 2013/14 or the 2014/15 winter season, with at least one amoxicillin prescription between September and May, irrespective of LAIV vaccination status. We used the self-controlled case series method to estimate influenza vaccine effectiveness (VE).

Results The total study sample included 33,137 children from 378 general practices during the two winter seasons. Of these children, 43.4% with at least one amoxicillin prescription had been vaccinated. The rate of amoxicillin prescribing was significantly reduced during periods of influenza vaccine immunity. The associated VE for amoxicillin prescribing was 12.8% (95% confidence interval (CI) 6.9%, 18.3%) in 2013/14 and 14.5% (9.6%, 19.2%) in 2014/15. Given a VE of 14.5%, we estimated that amoxicillin prescribing could have been reduced by 5.6% if LAIV uptake in two to four year old children increased to 50% in the 2014/15 winter season.

Discussion: Influenza vaccination of young children may contribute to a reduction in prescribing of amoxicillin, one of the most commonly prescribed antibiotics in primary care. Immunisation through the universal UK influenza vaccination programme should be encouraged in this age group. Further studies are required to confirm the size of the effect.

Introduction

Influenza causes a major burden on primary and secondary care services and families every winter in temperate countries.[1-3] Although influenza rarely results in secondary bacterial infection[4] it is linked with excess antibiotic prescribing in children.[5] The symptoms of influenza are diffuse[6] and may be difficult to distinguish from bacterial infections,[7] particularly in primary care where the majority of influenza cases present but diagnostic sampling is not widely available. Overuse of antibiotics is a major public health challenge due to increased antibiotic resistance.[8] It is therefore of interest to determine the role of influenza immunisation programmes in reducing antibiotic prescribing.[9]

Two clinical trials have examined the effect of influenza vaccination on antibiotic prescribing; one of live attenuated influenza vaccine (LAIV) in adults,[10] the other of inactivated influenza vaccine (IIV) in children aged six months to nine years.[11] The size of the effect in the paediatric trial was one less antibiotic prescription per child per season. Both these studies are now over 15 years old and antibiotic prescribing practices have changed over time.

A new policy of offering annual vaccination with intranasal LAIV to all children aged two to 16 years in the United Kingdom began in September 2013.[12] In 2015/16, between 34% and 57% (varying by UK country) of preschool children aged two to four years were vaccinated in primary care. [13,14]

Whether LAIV reduces antibiotic prescribing is of interest to clinicians, parents and policy makers evaluating the impact of the new influenza vaccination programme. There are no trials of the effect of LAIV on antibiotic prescribing in children, and further trials are unethical in the UK due to the recommendation to vaccinate all children. Observational studies comparing vaccinated and unvaccinated children lead to confounding by indication, since both influenza vaccination and complications are more common in children with chronic conditions.[14,15]

We evaluate the effectiveness of LAIV in reducing antibiotic prescribing in preschool children in primary care in the UK. We focus on prescribing of amoxicillin, indicated for two common complications of influenza: community acquired pneumonia and (in some children) acute otitis

media. We used a large primary care database and applied the self-controlled case series (SCCS) methodology[16,17] to minimise confounding by indication.

Methods

Ethics

All data in this study were anonymised. Data collection has been approved by the South East NHS Multicentre Research Ethics Committee. The analyses presented here were approved by the Scientific Review Committee of the data providers (QuintilesIMS), study reference number SRC 14–004.

Study design: The Self Controlled Case Series method

This method was originally developed to examine vaccine safety but has now been applied in a range of pharmacoepidemiological studies, including for evaluating the effect of influenza vaccination on asthma[18,19] and chronic obstructive pulmonary disease (COPD) exacerbations.[20] The method includes only individuals who have had the outcome of interest (cases), and compares the incidence rate within each case of the outcome of interest during a time-limited exposed period (eg. the period of vaccine protection) to rates during unexposed, or 'baseline' periods. Thus, the question is 'when' rather than 'who' experience the events. Since the analyses are conditional on each case, any characteristics such as gender or prevalence of chronic conditions which do not vary during the study period are inherently controlled for.[17] Any time-varying factors, like age or seasonal variation need to be adjusted for in the analyses.

Data source

We used The Health Improvement Network (THIN) primary care database for this study.[21] THIN contains anonymised longitudinal data on diagnoses, prescriptions, vaccinations and demographic information for around 6% of the UK population. THIN is approximately representative of the general UK population in terms of demographic characteristics, and primary care practices

92 contributing to THIN are representative of all UK general practices in terms of prescribing and
93 consultation rates.[22,23] Influenza vaccination uptake rates in THIN, including of LAIV, has been found
94 to be similar to uptake figures published by UK public health agencies.[24,25] Data are entered by the
95 general practitioner (GP, primary care clinician) during patient consultations. Prescriptions are
96 recorded in THIN using drug codes which map to the British National Formulary.[26]

97 *Study period and population*

98 We examined LAIV effectiveness during the first two winter seasons of the universal childhood
99 influenza vaccination programme: 2013/14 and 2014/15. Separate analyses were carried out for
100 each season since the influenza strains contained in the influenza vaccine were well matched to the
101 circulating strains in the 2013/14 season but less so in 2014/15.[12] Influenza A/H1N1 was the
102 dominant strain in 2013/14 and A/H3N2 in 2014/15. Children were eligible to be vaccinated from the
103 1st September each year. We defined each season from the first Monday in September until the 18th
104 May 2014 and 17th May 2015 (Sunday of week 20) respectively, when active surveillance for
105 respiratory infections by UK public health agencies end.[27]

106 Children were considered eligible for inclusion in one or both study cohorts if they were registered
107 with a THIN practice on the 1st September 2013 or 2014, met the age criteria for the target group to
108 receive LAIV in primary care in that respective season (children aged two to three years inclusive on
109 the 31st August 2013 for 2013/14 and children aged two to four years inclusive on the 31st August
110 2014 in 2014/15), and had at least one amoxicillin prescription during either of the two study
111 periods. That is, children were included in the analysis for 2013/14 if they had at least one
112 amoxicillin prescription in 2013/14; and in the analysis for 2014/15 if they had at least one
113 amoxicillin prescription in 2014/15.

114 Children were followed from the start to the end of the study period or until they deregistered from
115 the practice. Infections leading to a prescription of amoxicillin are likely to cluster within families. In
116 order to ensure independence of outcomes we randomly selected one child per family (identified via
117 the family number in THIN[24]) in the eligible age range for inclusion in the cohort.[24]

We included both vaccinated and unvaccinated cases. Since estimation of the relative risk of amoxicillin prescribing is within children only, unvaccinated children do not contribute to the estimation of the vaccine effect (only to estimation of the other time varying covariates in the model). The vaccinated periods are long in relation to the observation period (see below). It would be impossible to distinguish between seasonal variation and vaccine effects during periods when almost all cases have been vaccinated (as would happen during early spring). Therefore including unexposed (ie. unvaccinated) cases makes it possible to more accurately adjust for seasonal effects.[17]

Outcome

The outcome in this study was amoxicillin prescriptions. Amoxicillin is indicated for community acquired pneumonia and acute otitis media in children who are systemically unwell, at high risk of complications, or with persisting symptoms. Petersen et al[28] found that only 50-60% of antibiotic prescriptions had an associated indication recorded on the same day. Therefore we considered any prescription for amoxicillin irrespective of the indication. A child may receive more than one amoxicillin prescription each season. One of the assumptions of the SCCS method is that outcomes are independent, conditional on the time-varying covariates.[16,17] In order to meet this assumption we created prescribing episodes and assumed that all amoxicillin prescriptions in a 30-day period were associated with the same infection. Separate prescription episodes were assumed to be independent of each other. Only the first prescription in each 30 day period was included.

Influenza vaccination status

The exposure variable was receipt of LAIV. We used a code list developed for a previous study to identify children who have been vaccinated using LAIV and their date of vaccination each season.[24] Children with severe immunosuppression, asthma, or active wheezing are recommended to receive IIV rather than LAIV. Children receiving at least one dose of IIV was excluded from the analyses for a particular season. Children who are not in a clinical risk group (94.5% of preschool children [24]) are recommended to receive one dose of LAIV. We therefore did not have a sufficient number of cases

to examine the effectiveness of two versus one dose of LAIV. Children who had received two doses of vaccine were included in the study, but only the effect of one dose was assessed, that is, we did not further split the exposure period into subperiods following the first dose and the second dose.

LAIV vaccination status was treated as a time-varying covariate. The vaccination exposure periods are summarised in Figure S1. There is little evidence regarding how long influenza vaccine immunity lasts in children.[29-31] We assumed that vaccine-induced immunity lasts for six months in our baseline scenario, then varied assumptions about vaccine protection in sensitivity analyses.

Parents of children who required amoxicillin are likely to delay vaccination until symptoms have improved. In order for the SCCS model to be valid, the outcome of interest should not influence the exposure (LAIV receipt). Therefore, we included a `pre-vaccination' period in the analyses, lasting from the day of vaccination-14 to the day of vaccination-1. We assumed that vaccine induced immunity begins at 14 days after vaccination, in line with previous studies.[31-33] We therefore excluded a 14-day period after the date of vaccination. Excluding the immediate 14-day post-vaccination period also allowed us to take into account that amoxicillin prescription rates are likely to remain low immediately after vaccination, since children should be in good health at the time of vaccination.

Seasonality and influenza circulation periods

A number of different virus infections, including influenza, lead to amoxicillin prescribing in children during winter seasons. To allow for underlying seasonality of amoxicillin prescriptions (whatever the causative pathogen), we split the follow-up time into weeks of the winter season, and adjusted for week as a factor variable in the statistical models. By using this approach, we assumed that the underlying seasonality (i.e. timing) of respiratory virus circulation (including influenza) is the same among vaccinated and unvaccinated children. In terms of vaccine effects, the SCCS model tests whether the relative incidence is lower in vaccinated versus unvaccinated periods, adjusted for underlying seasonality of amoxicillin prescribing.

Since we hypothesised that LAIV would only be effective in preventing amoxicillin prescribing during periods when influenza virus was circulating in the community, we further split the follow-up time into influenza circulating and non-circulating periods and included this variable as a time varying covariate in the SCCS model. In the 2013/14 season, influenza circulated between end of December 2013 (week 52) and end of March (week 14) according to sentinel swabbing schemes run by Public Health England (PHE).[34] In 2014/15, influenza circulation was established by week beginning of December (week 49) and continued until beginning of April (week 15).[27]

Statistical analyses

Only children who had had at least one amoxicillin prescription were included in the analyses. We describe their characteristics in terms of age at cohort inception, sex, influenza vaccination status, and whether they were in a clinical risk group due to underlying chronic conditions, and therefore considered to be at increased risk of influenza-related complications, in each season. We used a code list used by PHE to measure vaccination uptake in primary care to define whether a child was in a clinical risk group.[35] A child was classified as being in a clinical risk group if they had any code recorded up to one year before the start of each winter season.

We plotted the proportion of cases who had been vaccinated and the number of prescriptions each week to assess the overlap in timing between exposure and outcome events. The SCCS models were fitted using a conditional Poisson regression model. Vaccine effectiveness (VE) was estimated as

$$VE = 1 - IRR$$

where the IRR is the relative rate ratio of amoxicillin prescribing in vaccinated periods, relative to unvaccinated periods, estimated by the fully adjusted SCCS model.

Statistically significant VE in preventing amoxicillin prescriptions was defined as a Wald test *p*-value<0.05. Separate models were fitted for each of the two seasons. We adjusted for single years of age (2, 3, 4 and 5 years) as a categorical variable, active influenza circulation and week number as time varying covariates.

We conducted sensitivity analyses to determine the impact of changing assumptions about the effect of age and the duration of vaccination protection on VE estimates:

1) restricting analyses to period of active influenza circulation only (scenario 1).

2) increasing the number of age groups to six month age groups rather than single years of age (scenario 2)

3) assuming vaccine protection lasts for nine months (scenario 3). This means that vaccine protection extends beyond the end of the study period in this scenario.

4) splitting the six month vaccinated period into two subperiods from 14 days to less than three months and three months to less than six months after vaccination (scenario 4)

Absolute risk differences cannot be obtained using SCCS. We conducted a simple calculation (not allowing for herd immunity) to examine the impact of increasing LAIV uptake in two to four year old children in England beyond current levels, given our estimated VE. First, we obtained the current number of amoxicillin prescriptions in England by estimating the amoxicillin prescribing rate in two to four year old children in English THIN practices between September 2014 and April 2015, and applying these rates to mid-year population estimates from the Office for National Statistics.[36] Second, by assuming a constant ratio between VE and uptake, with VE set at the estimated value for the 2014/15 season, we calculated the expected number of amoxicillin prescriptions (*Prescriptions*$_{exp}$) for a given scenario of vaccination uptake (*VU*$_S$) as:

$$Prescriptions_{exp} = \frac{Prescriptions_{Obs}}{1 - VE}\left(1 - \frac{VU_S VE}{VU_{Obs}}\right)$$

Where *Prescriptions*$_{Obs}$ is the observed number of prescriptions in 2014/15, *VU*$_{Obs}$ is observed vaccination uptake in England in the 2014/15 season (37.6%[37]), and *VE* is the vaccine effectiveness estimated from our study for 2014/15 (see Text S1).

We used Stata 13[38] for data management and model fitting and R 3.3.1 for graphical output.

Results

We identified 90,788 children aged 2 to 3 years in 2013 and 142,273 children aged two to four years in 2014 (Figure 1). There were 33,137 children from 378 general practices who had at least one amoxicillin prescription during either of the two seasons. Of these children, 14,368 (43.4%) had received at least one dose of LAIV in either of the two seasons. Overall, 5,071 children (15.3%) contributed person time to both study periods. The characteristics of the children in each cohort are shown in Table 1. The vast majority of children in either cohort had only one prescription episode each season.

Half of the vaccines had been administered by the beginning of November in both seasons (Figure 2). Amoxicillin prescriptions displayed several peaks, one in the beginning of December, followed by two more peaks in mid-February and mid-March. The amoxicillin prescribing rate was lower in the 14 days before and the 14 days after vaccination among the vaccinated cases in both seasons (Figure S2).

Influenza vaccination was associated with a significant decrease in amoxicillin prescriptions in both winter seasons. LAIV VE in preventing amoxicillin prescriptions was 12.8% in 2013/14 and 14.5% in 2014/15 (Table 2). Overlapping 95% confidence intervals from the two seasons suggest a similar effect size. Including the indicator of influenza circulation had negligible effect on influenza VE estimates in either season.

Subdividing the age groups had negligible effect, whereas restricting the study period to weeks with active influenza circulation led to a reduction in the number of cases included in the model and greater variability in the VE estimates. When vaccine protection was assumed to be nine instead of six months, VE estimates increased in both seasons. When we split the vaccinated period into two sub-periods, VE point estimates were similar across the two shorter periods. The CIs for the VE estimates from all sensitivity analyses overlapped with those for the baseline scenario for both seasons.

We estimate that 626,932 amoxicillin prescriptions were issued to two to four year old children in England between September 2014 and April 2015. Assuming a VE of 14.5%, only 591,868 amoxicillin prescriptions would have been prescribed in this season had vaccine uptake been 50% in two to four year olds (Figure S3) rather than the observed uptake of 37.6%. This amounts to a decrease of 35,064 prescriptions or 5.6%.

Discussion

We found a 12.8% to 14.5% reduced rate of amoxicillin prescribing during periods of LAIV-induced immunity in preschool children. The effectiveness of LAIV in preventing amoxicillin prescribing episodes was robust to assumptions about the duration of LAIV protection and age effects.

The study included over 30,000 children during the first two seasons of the universal paediatric influenza vaccination programme in the UK. Only a small proportion of amoxicillin prescriptions are likely to be prescribed due to influenza complications, and hence any effect of influenza vaccination is likely to be small. Therefore, a large study is required to detect a vaccination effect. The large number of cases also allowed us to finely adjust for the seasonal pattern of amoxicillin prescribing using week of the winter season.

We used the SCCS method to estimate relative amoxicillin prescribing rates during vaccinated and unvaccinated periods within each child. This is the first time SCCS is used to estimate influenza VE in children. Use of the SCCS method means any confounding by indication, which often arises in cohort studies of influenza VE,[39] is implicitly controlled for.

We could not examine the effect on prescriptions due to particular symptoms. However, we were still able to detect a significantly reduced risk of amoxicillin prescribing during periods of LAIV-induced immunity. Since such a small proportion of children received two doses of LAIV, we examined effectiveness after only one dose. However, these results are relevant to the vast majority of children in the UK who are only recommended to receive one LAIV dose.

One alternative explanation for our result is that GPs are less likely to prescribe antibiotics to children who have been vaccinated, if they consider these children to be at lower risk of influenza complications. However, GPs are advised to decide on antibiotic prescribing based only on the severity and longevity of symptoms and the presence of chronic conditions, not on whether the infection is caused by a particular pathogen.[40] We therefore consider it unlikely that decisions regarding antibiotic prescriptions are based on a child's vaccination status.

Three aspects of our study results were unexpected. First, the effect sizes were similar in the two seasons under study, despite varying degrees of vaccine strain. We note that significant VE in preventing laboratory confirmed influenza was still reported by PHE in 2014/15.[12] Rather than simply reducing the incidence of influenza-related complications leading GPs to prescribe amoxicillin, LAIV may lead to non-specific protection against respiratory infections. Large, randomised clinical trials of LAIV in young children with antibiotic prescribing as an outcome are required to address this question.

Second, when we increased the assumed period of LAIV-induced immunity to nine months, the point estimate of LAIV VE increased. If protection persists beyond six months, inclusion of the 6-9 month period in the reference category of the base scenario will have caused the effect to be underestimated. When the assumed period of LAIV immunity is nine months, the immunity period extends to the end of observation and the analysis relies heavily on non-vaccinated cases to estimate the weekly seasonal effects. However, there is no reason why seasonal effects should differ between vaccinated and unvaccinated cases.

Third, we hypothesised that VE estimate would be highest during the months immediately following vaccination. Amoxicillin prescribing is a non-influenza specific outcome. The seasonal pattern of overall amoxicillin prescribing is not in alignment with that of influenza, whereas the seasonal pattern of prescribing attributable to influenza should be (with some lag). The burden due to influenza cannot be deciphered from the data and no method can disentangle the effect of waning vaccine immunity from the effect of other circulating viruses leading to amoxicillin prescriptions. Overall, our sensitivity analyses are useful in showing that effects beyond six months are protective, indicating that LAIV effectiveness is often long lasting throughout the season.

Further, we found that restricting the observation period to weeks of active influenza circulation led to highly variable estimates of the VE estimates. Restricting the study period leads to a reduction in statistical power through three mechanisms. First, it reduces the number of cases included in the model, as highlighted in the footnote to Table 2. Second, restricting the study period will in this case

mean that the ratio of exposed versus unexposed time is even larger, leading to a loss of efficiency. Third, restricting the study period will mean some vaccinated cases do not contribute any unexposed time to the model, meaning that the vaccine effects are estimated based on an even smaller number of children. Hence, restricting the study period led to much more variable estimates of VE and larger CIs, particularly for the 2013/14 season when the period of influenza circulation was shorter than in 2014/15. We note that the CIs for Scenario 1 and the baseline scenario overlap in both seasons. In the absence of reliable data on the duration of LAIV-induced immunity among children, the size of the effect of LAIV on amoxicillin prescribing should therefore not be overestimated. Ongoing monitoring of the effect of LAIV on amoxicillin prescribing in preschool children is required.

Several other viruses, and in particular respiratory syncytial virus (RSV), is known to cause substantial morbidity in young children[41] and may lead to amoxicillin prescribing. RSV circulation in the UK peaks in early December. Since we adjust for week of the winter season, this should not bias our results, as long as the incidence of RSV-related prescribing is the same in vaccinated and unvaccinated children. One small study has shown an increase in the risk of non-influenza respiratory viruses following IIV receipt,[42] but these results have not been replicated for LAIV. The risk of bias caused by differential timing of RSV circulation in relation to influenza vaccination is therefore likely to be minimal.

Our results add to a growing body of evidence showing a reduction in antibiotic prescribing associated with influenza vaccination.[43] Universal influenza vaccination of children could contribute to the effort to decrease antibiotic prescribing in primary care, where three quarters of antibiotics are prescribed in the UK.[44] Based on a simple calculation, we estimated that up to 5.6% of amoxicillin prescriptions could be prevented if LAIV uptake in two to four year old children in England had been 50% rather than the observed 37.6%. More detailed studies are required to model the potential impact of increases in influenza vaccination uptake on antibiotic prescribing.

We found a significantly reduced risk of amoxicillin prescribing during periods of influenza vaccine immunity in preschool children vaccinated with LAIV. Influenza vaccination of children may lead to

328 reductions in amoxicillin prescribing, but the effect may be small. Further efforts should be made to
329 increase uptake of LAIV in preschool children under the universal influenza vaccination programme.
330

Declarations

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Transparency declarations

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449 **Table 1. Characteristics of the children who had received amoxicillin prescriptions according to**

450 **winter season**

	Winter season	
	2013/14	**2014/15**
Variable	***n* (%)**	***n* (%)**
Age at start of season (years)		
2	8254 (53.1)	8475 (37.4)
3	7289 (46.9)	7842 (34.6)
4		6348 (28)
Sex		
Male	8088 (52.0)	11613 (51.2)
Female	7455 (48.0)	11052 (48.8)
Vaccinated during the season		
No	9226 (59.4)	13272 (58.6)
Yes – one dose	6162 (39.6)	9281 (41)
Yes – two doses	155 (1.0)	112 (0.5)
Clinical risk group		
No	14480 (93.2)	20801 (91.8)
Yes	1063 (6.8)	1864 (8.2)
Number of outcome episodes during season		
1	11648 (74.9)	17473 (77.1)
2	2977 (19.2)	4088 (18)
3 or more	918 (5.9)	1104 (4.9)
Total *N*	**15543**	**22665**

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Table 2 Main model results and sensitivity analyses for influenza vaccine effectiveness (VE) in preventing amoxicillin prescriptions, according to season, with 95% confidence intervals (CI)

	Winter season	
Analysis scenario	**2013/14**	**2014/15**
Main analysis (baseline scenario)	12.6% (6.7%, 18.2%)	14.5% (9.6%, 19.2%)
Sensitivity analyses		
Scenario 1: restricting to periods of active influenza circulation*	4.2% (-47.4%, 37.7%)	29.5% (13.9%, 42.3%)
Scenario 2: Six month age groups	12.5% (6.6%, 18.1%)	14.4% (9.5%, 19.1%)
Scenario 3: vaccine protection lasts for 9 months	21.2% (14.9%, 27.1%)	19.0% (13.7%, 24.0%)
Scenario 4: two vaccination sub periods:		
14 days - <3 months	13.3% (6.8%, 19.2%)	13.9% (8.6%, 18.8%)
3 - <6 months	11.9% (51%, 18.2%)	15.6% (10.0%, 20.9%)

*Models include 7523 children in 2013/14 and 14616 children in 2014/15

457 **Figures**

458 **Figure 1: Flowchart of the final selection of cases included in the SCCS analysis**

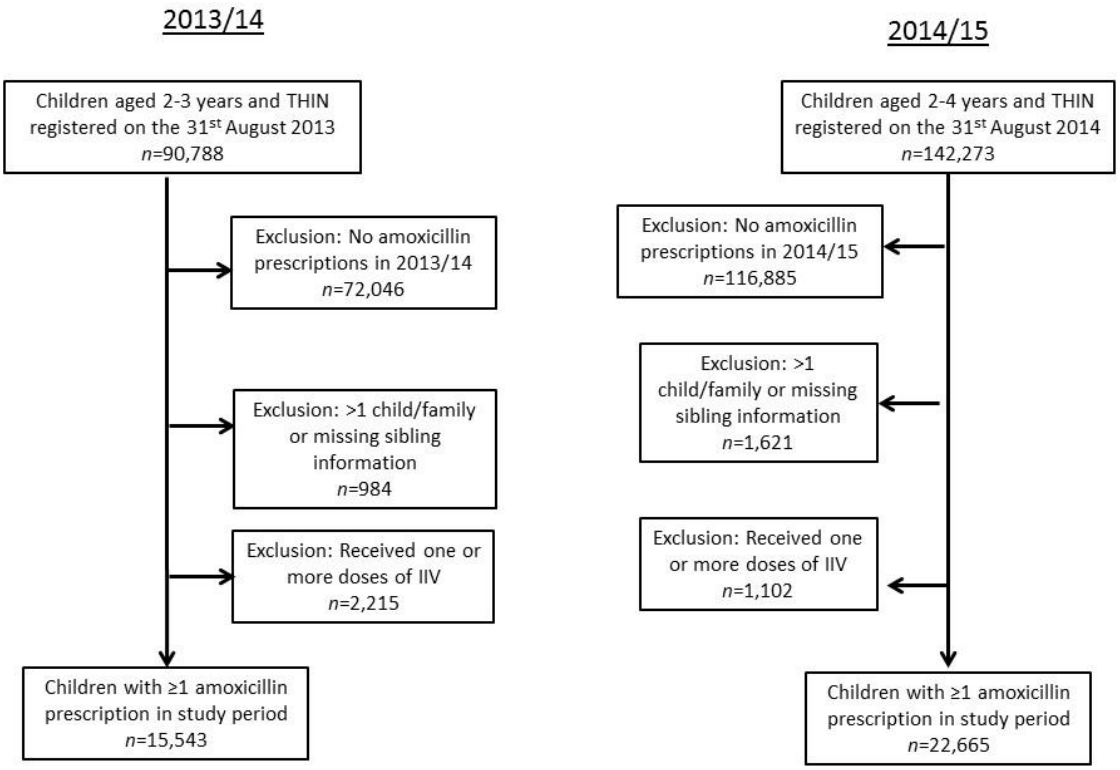

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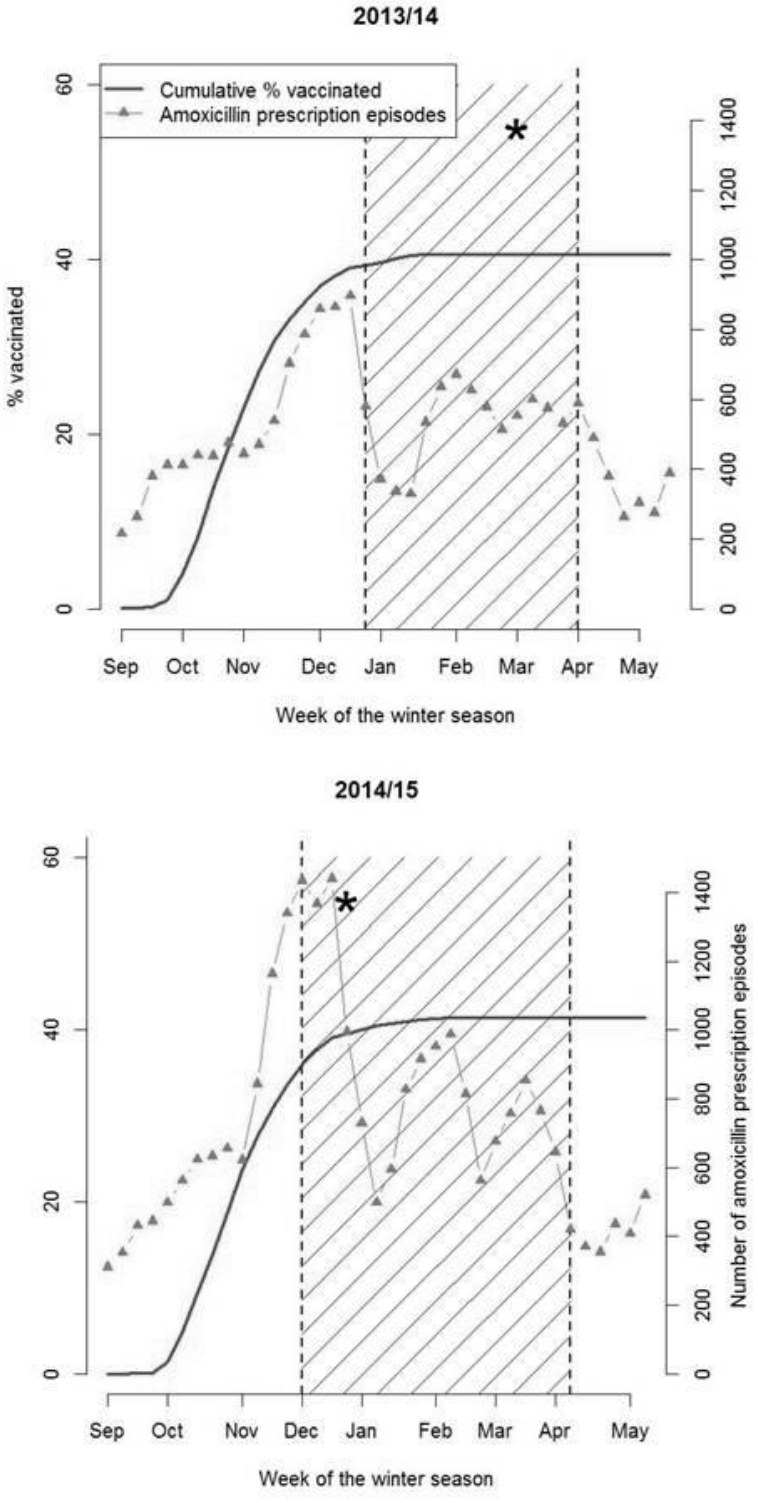
Figure 2. Cumulative proportion of cases in each cohort vaccinated and the number of amoxicillin prescriptions, by week of the study period†



†The shaded area shows period of active influenza circulation, and *indicates peak week of influenza circulation according to Public Health England sentinel swabbing schemes.[27,34]

Supplementary file information

- Supplementary Text S1: Deriving a formula for number of amoxicillin prescriptions given different vaccination uptake scenarios

- Supplementary Figure S1. Influenza vaccine periods in the SCCS analyses for vaccinated and unvaccinated children

- Supplementary Figure S2. Number of days between vaccination and amoxicillin prescription episodes among vaccinated amoxicillin prescription cases (numbers above the plot indicate the number of events per day in the specified time period)*

*Note that x-axes for the two seasons are not the same

- Supplementary Figure S3. Expected number of amoxicillin prescriptions in two to four year old children between September 2014 and April 2015 under varying scenarios of LAIV uptake.