

Uptake and impact of vaccinating primary school-age children against influenza: experiences of a live attenuated influenza vaccine programme, England, 2015/16

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Citation style for this article:

Pebody Richard G, Sinnathamby Mary A, Warburton Fiona, Andrews Nick, Boddington Nicola L, Zhao Hongxin, Yonova Ivelina, Ellis Joanna, Tessier Elise, Donati Matthew, Elliot Alex J, Hughes Helen E, Pathirannehelage Sameera, Byford Rachel, Smith Gillian E, de Lusignan Simon, Zambon Maria. Uptake and impact of vaccinating primary school-age children against influenza: experiences of a live attenuated influenza vaccine programme, England, 2015/16. *Euro Surveill.* 2018;23(25):pii=1700496. <https://doi.org/10.2807/1560-7917.ES.2018.23.25.1700496>

Article submitted on 21 Jul 2017 / accepted on 21 Dec 2017 / published on 21 June 2018

The 2015/16 influenza season was the third season of the introduction of an intra-nasally administered live attenuated influenza vaccine (LAIV) for children in England. All children aged 2–6 years were offered LAIV, and in addition, a series of geographically discrete areas piloted vaccinating school-age children 7–11 years old. Influenza A(H1N1)pdm09 was the dominant circulating strain during 2015/16 followed by influenza B. We measured influenza vaccine uptake and the overall and indirect effect of vaccinating children of primary school-age, by comparing cumulative disease incidence in targeted and non-targeted age groups in vaccine pilot and non-pilot areas in England. Uptake of 57.9% (range: 43.6–72.0) was achieved in the five pilot areas for children aged 5–11 years. In pilot areas, cumulative emergency department respiratory attendances, influenza-confirmed hospitalisations and intensive care unit admissions were consistently lower, albeit mostly non-significantly, in targeted and non-targeted age groups compared with non-pilot areas. Effect sizes were less for adults and more severe endpoints. Vaccination of healthy primary school-age children with LAIV at moderately high levels continues to be associated with population-level reductions in influenza-related respiratory illness. Further work to evaluate the population-level impact of the programme is required.

Background

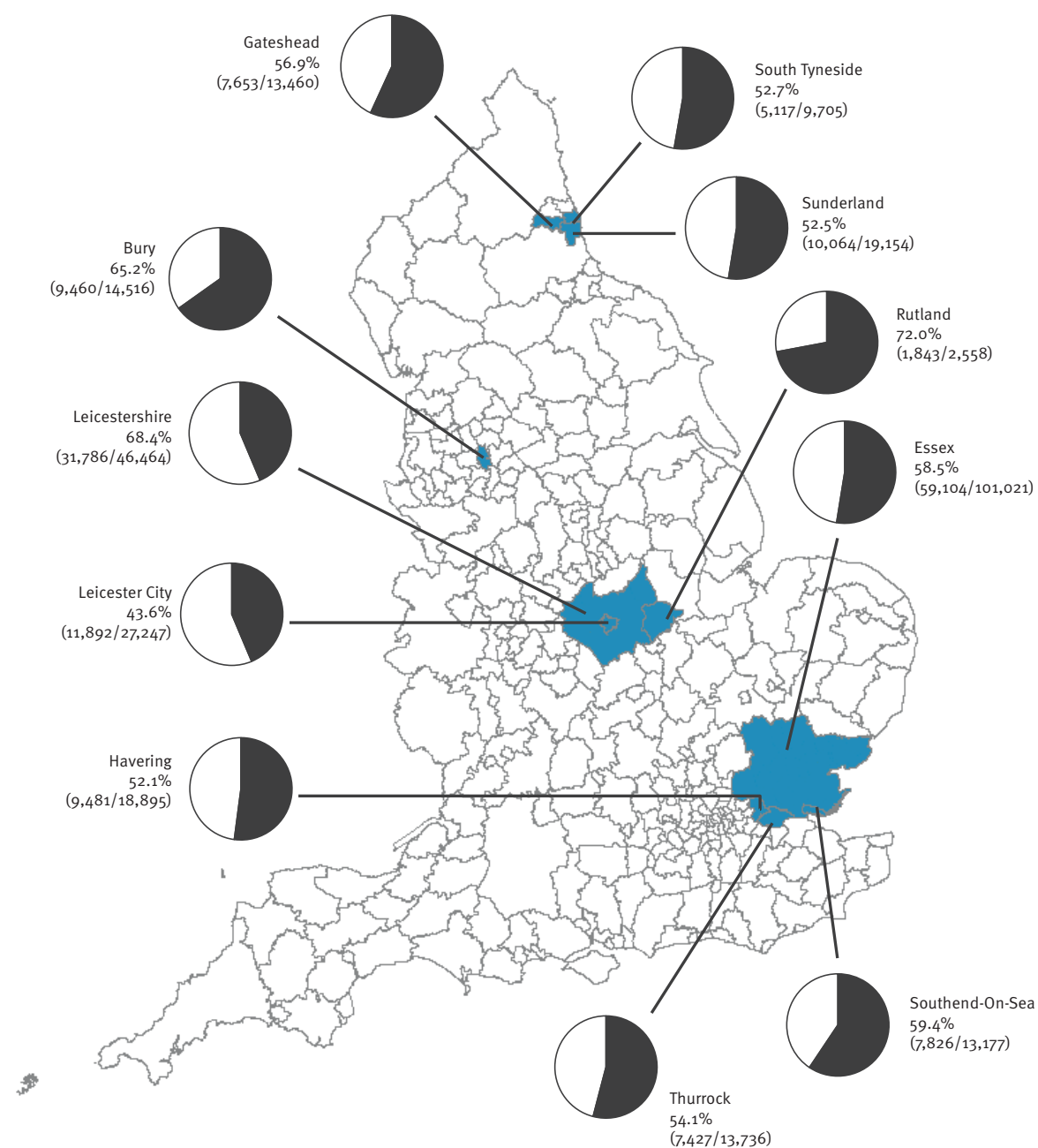
During the 2015/16 influenza season, England and the rest of the United Kingdom (UK) was in the third season of a new childhood influenza vaccination programme

targeting healthy children with a recently licensed intra-nasally administered live attenuated influenza vaccine (LAIV). The programme ultimately aims to offer annual influenza vaccination to all children 2–16 years of age to both directly protect them, and, by reducing their rate of infection, indirectly protect others in the community – particularly those who may be at higher risk of severe disease following influenza [1]. In this third season, the LAIV programme was extended from offering the vaccine to all healthy children 2–4 years of age to all children in school years 1 and 2, i.e. children 5 and 6 years of age across England. In addition, as in the 2 previous years, a series of five geographically discrete pilots were undertaken in England. In these pilots, the remaining healthy children of primary school age in school years 3 to 6 i.e. children aged 7–11 years, were also offered LAIV, with uptake exceeding 50% [2,3].

The key evidence supporting the introduction of the UK childhood LAIV programme was mathematical transmission modelling that predicted and quantified the future impact, combined with an economic evaluation to determine the most cost-effective approach [4]. Since then, recently published evidence from the UK has shown that LAIV has been effective in children over these first three seasons [5]. Furthermore, the first 2 years of the LAIV programme provided encouraging evidence, albeit often not statistically significant, showing that vaccinating children of primary school age was associated with reductions in incidence for a range of influenza disease indicators in both targeted

FIGURE 1

Cumulative uptake of live attenuated influenza vaccine in primacy school-age children^a in pilot areas, England, week 40 2015–week 20 2016



^a Children 5 to 10 years of age, rising to 11 years of age.

The pilot areas are shown shaded on the map. The shaded area of each pie chart indicates the percentage of target children vaccinated.

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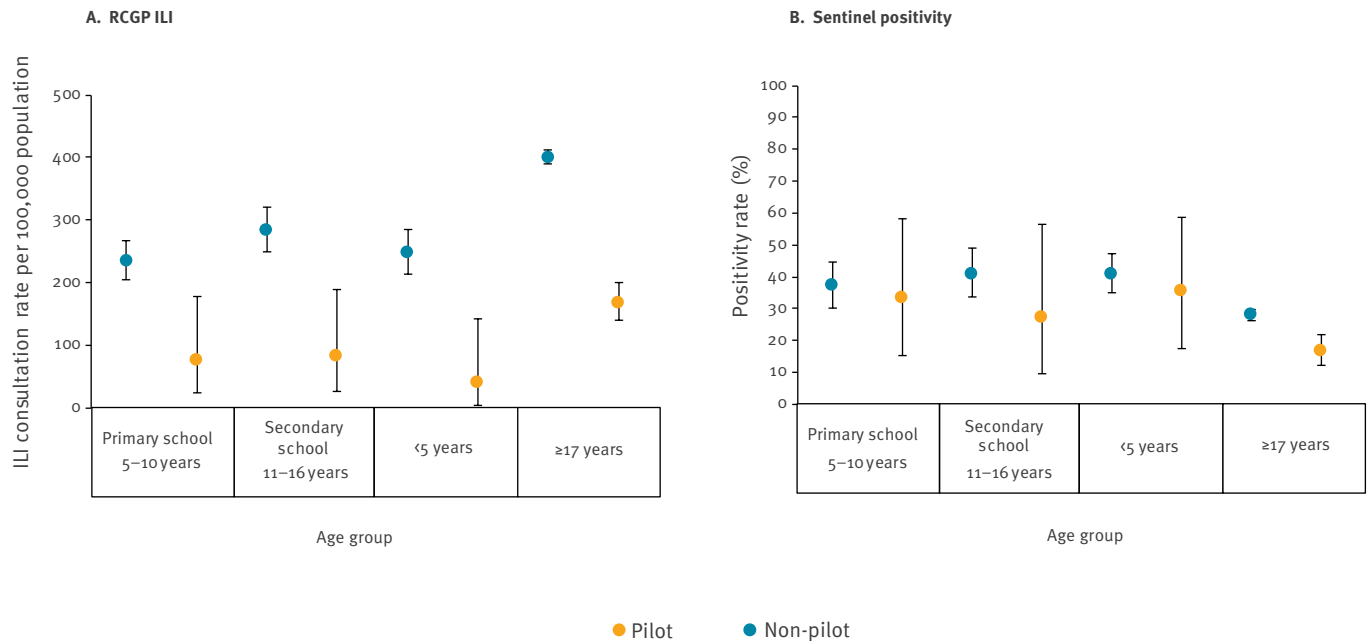
and non-targeted age groups when comparing pilot and non-pilot areas in England [6,7]. To date, only limited data has been published internationally of the observed impact of such programmes [8-10].

The 2015/16 influenza season in the UK started late, with peak activity in week 11/12, and was initially dominated by circulation of influenza A(H1N1)pdm09.

Disease impact was particularly seen in younger adults, resulting in large numbers of hospitalisations and intensive care unit (ICU) admissions in these age groups. However, neither level reached those observed in the last significant A(H1N1)pdm09 season of 2010/11. The latter part of this recent season saw influenza B circulation, particularly of the B/Victoria lineage [3]. End-of-season UK vaccine effectiveness (VE) analyses

FIGURE 2

Cumulative primary care ILI surveillance indicators in primary school pilot and non-pilot areas (A) consultation rate and (B) positivity rate^a from the RCGP ILI surveillance network with integrated microbiological surveillance, England, week 40 2015–week 20 2016



ILI: influenza-like illness; RCGP: Royal College of General Practitioners.

^a RCGP only for consultation rate; RCGP and Specialist Microbiology Network for positivity rate.

Black bars indicate 95% confidence intervals.

for the 2015/16 season reported that overall LAIV effectiveness in children 2 to 17 years of age in the UK was 57.6% (95% CI: 25.1–76.0) [5]. However, data emerging from the United States (US) found little evidence of the effectiveness of LAIV in protecting children during the 2015/16 season, resulting in the Advisory Committee on Immunization Practices temporarily suspending the recommendation to use LAIV in the US [11]. The reason for the discrepancy in VE between the US and UK remains under investigation: a description of the potential population impact of vaccinating children with LAIV for the 2015/16 season will help to guide the future paediatric vaccine strategy. The aim of this paper is to describe the uptake of influenza vaccine in children, to evaluate the indirect and total impact of vaccinating children of primary school age in England in the 2015/16 season against a range of influenza-related indicators, and to compare these indicators in the pre-and post-paediatric influenza vaccine era.

Methods

The majority of the England pilot areas that started vaccinating primary school-age children with LAIV in 2013/14 continued with the programme in 2015/16 [6,7]. All pilot areas delivered the programme through a school-based approach.

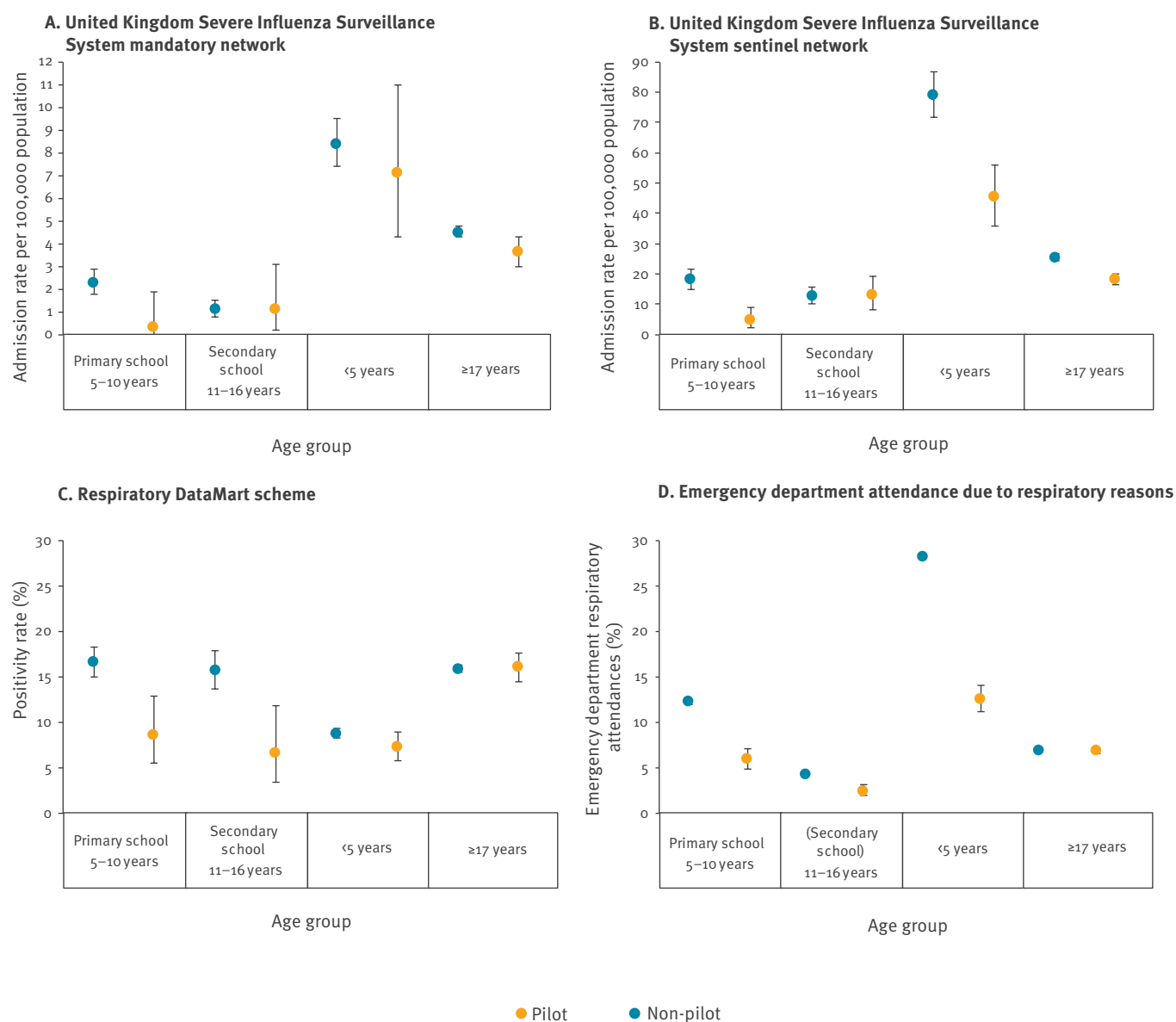
Measuring vaccine uptake

The target population for vaccination in pilot areas was defined as children of primary school age, i.e. children 5–10, but not 11 years or older (as defined by the child age on 1 September 2015) born between 1 September 2004 and 31 August 2010, resident in five areas in England: Greater Manchester (Bury); Leicestershire and Lincolnshire (Leicester City, Leicestershire, and Rutland); London (Havering); Essex (Essex, Southend-On-Sea, Thurrock); and Northumberland & Tyne and Wear (Gateshead, South Tyneside, Sunderland).

Commissioned data providers who were responsible for delivery of the childhood influenza programme in pilot areas collected and reported vaccination data to Public Health England (PHE) using ImmForm, a web-based reporting system [12]. Vaccine uptake was calculated from the number of children in the target population who received at least one dose of influenza vaccine in the period from 1 September 2015 until 31 January 2016. LAIV was offered to healthy children and at-risk children in whom vaccine was not contraindicated. For those at-risk children in whom LAIV was contraindicated, quadrivalent inactivated vaccine was offered instead.

FIGURE 3

Cumulative secondary care surveillance indicators in primary school pilot and non-pilot areas from four surveillance networks, England, week 40 2015–week 20 2016



Black bars indicate 95% confidence intervals.

Measuring school-age vaccine programme impact

The period of the impact study ran from week 40 2015 until week 20 2016, which is when influenza transmission ceased for the 2015/16 season [3].

The overall impact of the LAIV primary school-age programme for a range of virological and clinical endpoints in primary and secondary care as well as excess mortality was defined as Cumulative disease incidence in non-pilot areas – Cumulative disease incidence in primary school-age pilot areas.

As in previous studies, this was examined across four age groups to measure the impact of vaccination in targeted and non-targeted age groups. First, the impact

in children of primary school age, i.e. 5–10 years of age (targeted age group). Second, the indirect impact in children less than 5 years of age, individuals 11–16 years of age and individuals 17 years of age (non-targeted age-groups) [7].

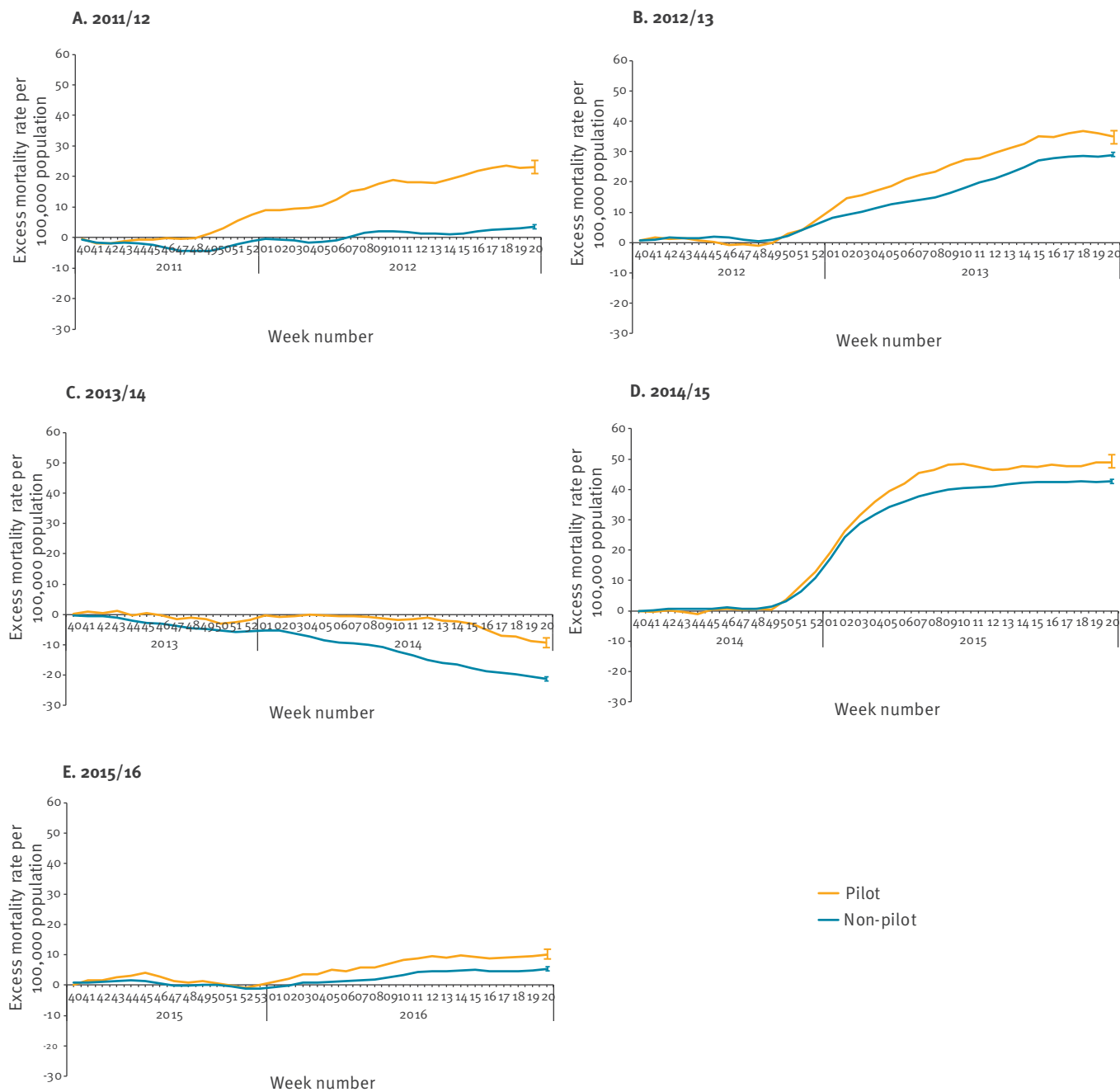
The cumulative, age-group-specific influenza indicators in pilot and non-pilot areas before vaccine programme introduction, i.e. 2011/12 and 2012/13, and after vaccine programme introduction, i.e. 2013/14, 2014/15 and 2015/16, in England were also compared.

Data sources

A range of sentinel surveillance systems were used to measure the impact of vaccinating children of primary school age. Additional sentinel general practitioners

FIGURE 4

Cumulative weekly all-cause mortality in primary school pilot and non-pilot areas by influenza season, England, week 40 2011–20 2016

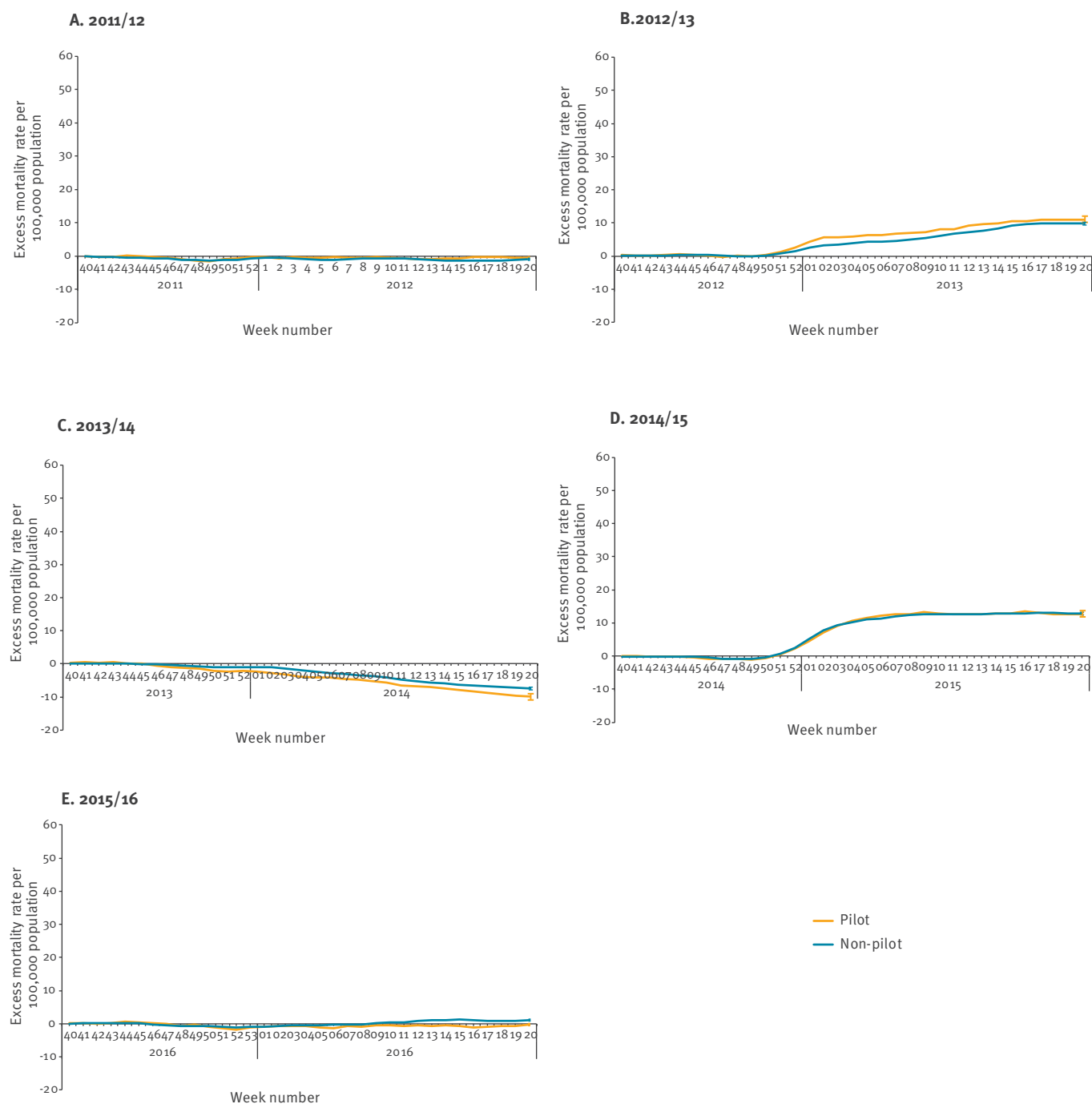


Panel A and B display pre-paediatric vaccination programme introduction seasons and C, D and E post-vaccination programme seasons.

Pre-paediatric vaccination programme introduction were influenza seasons 2011/12 and 2012/13, and post paediatric vaccine programme introduction were seasons 2013/14; 2014/15; 2015/16.

FIGURE 5

Cumulative weekly respiratory excess mortality in primary school pilot and non-pilot areas by influenza season, England, week 40 2011–week 20 2016

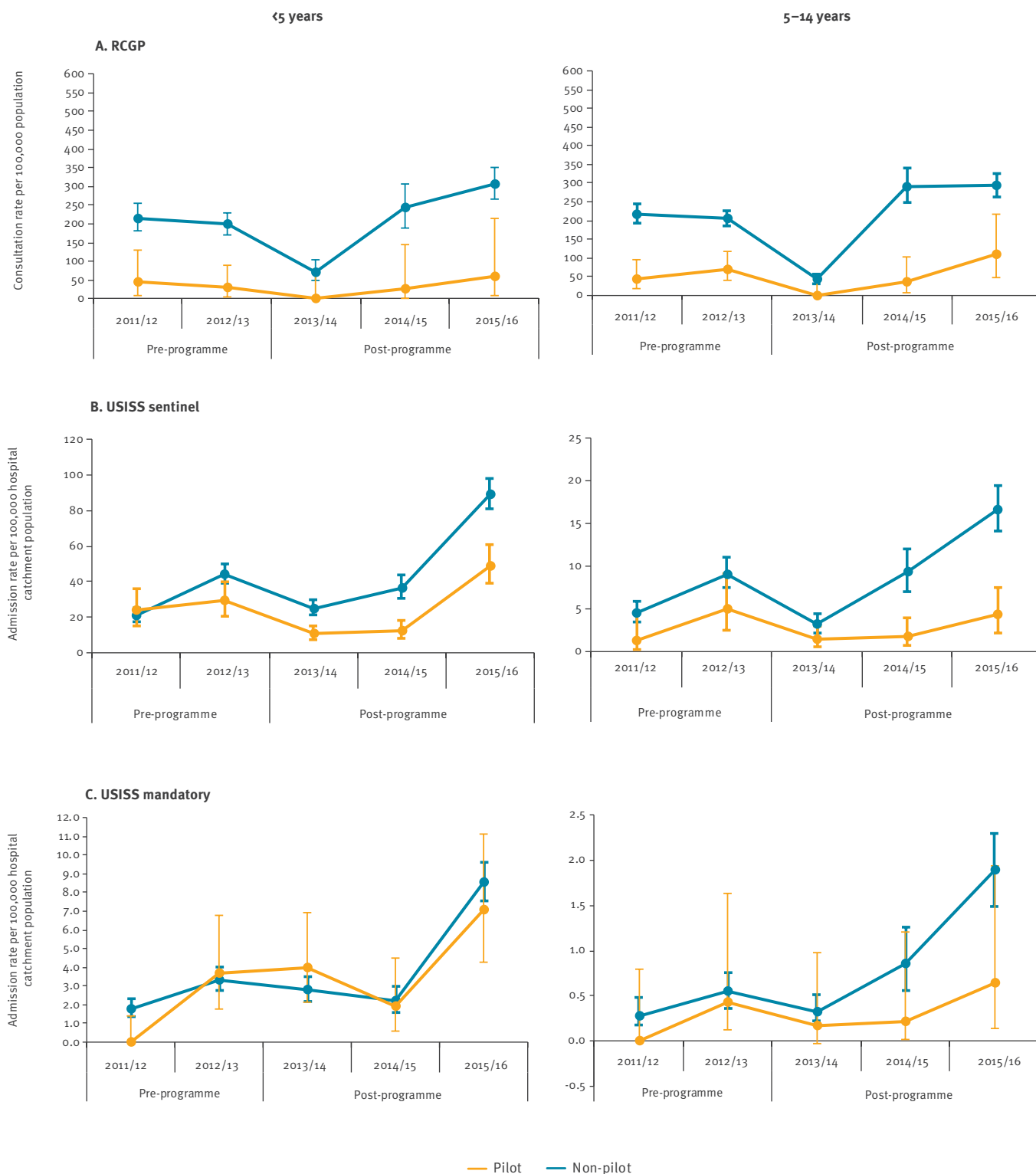


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FIGURE 6

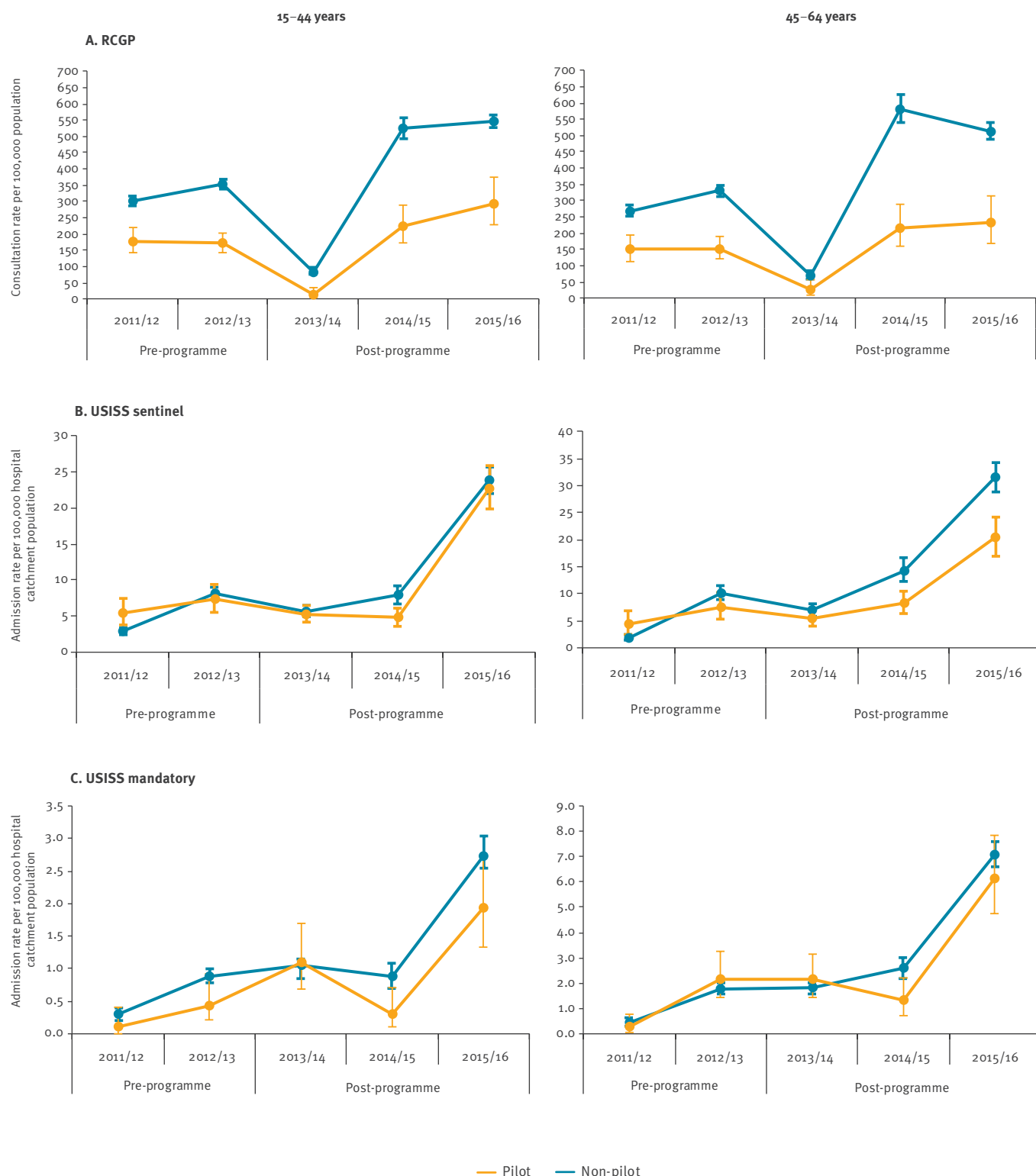
Cumulative, age-specific influenza indicators in pilot and non-pilot areas, by notification systems, England, week 40 2011–week 20 2016^a



ILI: influenza-like illness; RCGP: Royal College of General Practitioners; USISS: United Kingdom Severe Influenza Surveillance System.

FIGURE 7

Cumulative, age-specific influenza indicators in pilot and non-pilot areas, by notification system, England, week 40 2011–week 20 2016^a

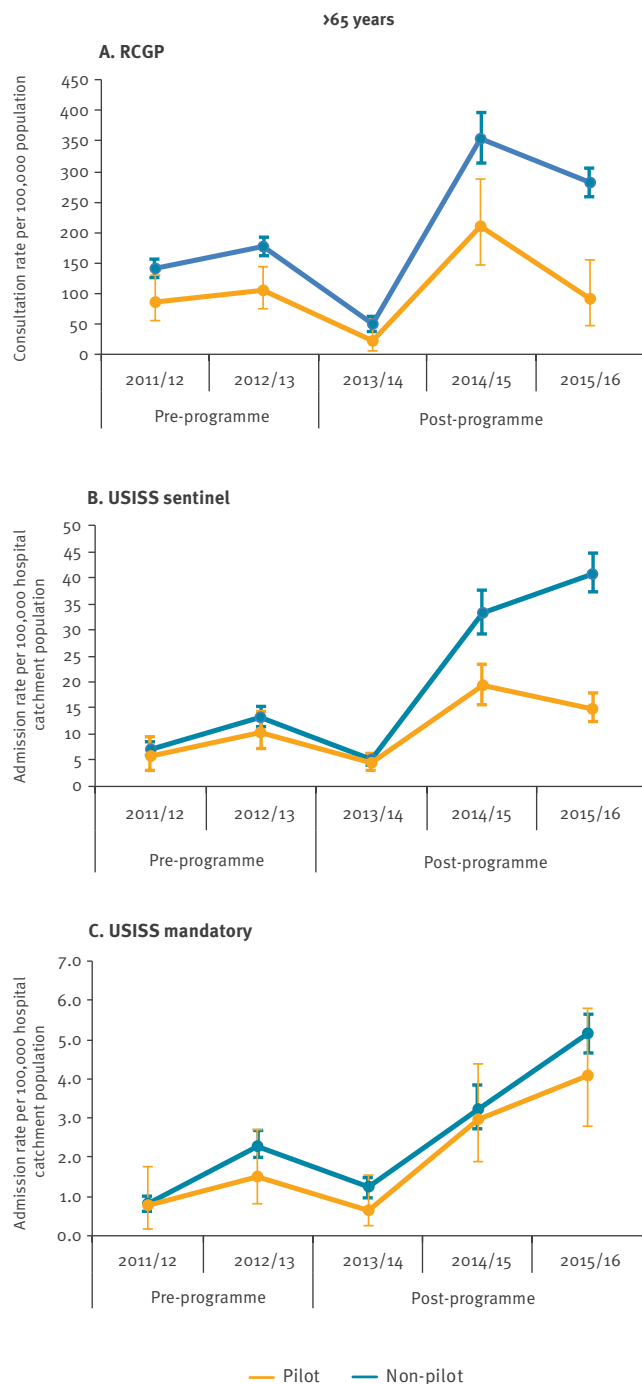


ILI: influenza-like illness; RCGP: Royal College of General Practitioners; USISS: United Kingdom Severe Influenza Surveillance System.

^a For the 2013/14 season, the data are based on week 40 2013 to week 15 2014, as per previously published work [6]. The primary pilot areas in the 2013/14 season were applied to calculate rates at each reporting level. Similarly, for the 2014/15 season, the data are based on week 40 2014 to week 14 2015 as per previously published work [7]. The primary pilot areas in the 2014/15 season were applied to calculate rates at each reporting level, excluded secondary pilots areas.

FIGURE 8

Cumulative, age-specific influenza indicators in pilot and non-pilot areas, England, week 40 2011–week 20 2016^a



ILI: influenza-like illness; RCGP: Royal College of General Practitioners; USISS: United Kingdom Severe Influenza Surveillance System.

^a For the 2013/14 season, the data are based on week 40 2013 to week 15 2014 as per previously published work [6]. The primary pilot areas in the 2013/14 season were applied to calculate rates at each reporting level. Similarly, for the 2014/15 season, the data are based on week 40 2014 to week 14 2015 as per previously published work [7]. The primary pilot areas in the 2014/15 season were applied to calculate rates at each reporting level, excluded secondary pilot areas.

(GPs), emergency departments (ED) and hospitals were recruited in the pilot areas since the first season of the introduction of the LAIV programme in 2013/14.

Primary care

Primary care surveillance was undertaken through the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) Weekly Returns Service sentinel GP network. This system reported weekly influenza-like illness (ILI) consultations in primary care. One hundred-forty-six RCGP practices participated in non-pilot areas and 10 practices in pilot areas. Seventy of these RCGP practices together with 22 practices from a further sentinel network, the Specialist Microbiology Network (SMN), collected respiratory swabs from a sample of patients consulting with ILI, regardless of vaccination status.

Secondary care

The UK Severe Influenza Surveillance System (USISS) includes two schemes. First, USISS sentinel, a voluntary network of 27 National Health Service (NHS) hospital trusts across England (22 in non-pilot areas and five in pilot areas in 2015/16), reported the weekly number of laboratory-confirmed influenza hospital admissions [13]. Estimated hospital catchment populations were used to calculate weekly laboratory confirmed hospitalisation rates per 100,000 population [14] as previously documented by pilot area and age group. Second, USISS mandatory, which involves all ICU and high dependency units (HDU) in England (136 units in non-pilot areas and 11 in pilot areas in 2015/16), reported the number of laboratory-confirmed influenza admissions each week. Admission rates by age group and pilot area were calculated as for the USISS sentinel scheme [13].

The Emergency Department Syndromic Surveillance System (EDSSS), is a sentinel network of emergency departments (ED) that monitors weekly ED attendances [15] and the proportion of all weekly attendances coded as respiratory in pilot (one ED) and non-pilot areas (24 EDs) by age group.

The Respiratory DataMart scheme (RDMS), collates and reports all influenza reverse-transcription-PCR (RT-PCR) respiratory swab results in a network of PHE and NHS laboratories in England; the majority of samples (>90%) came from secondary care [16] and were used to compare the influenza cumulative positivity over the study period. Postcode of residence was used to classify whether a sample was taken from a patient residing in a pilot or non-pilot area. Swab positivity was compared by age group and pilot area.

Excess mortality

Routine death registration data from the Office for National Statistics was used to calculate excess mortality each week using the European Monitoring of Excess Mortality for Public Health Action (EuroMOMO) standard algorithm [17]. The observed number of

TABLE 1

 Adjusted impact of vaccinating primary school-age children on selected primary care influenza surveillance indicators, England, influenza season, 2015/16^a

Age group		Measure	RCGP ILI consultation rate (per 100,000 population)		Sentinel influenza swab positivity (%)	
			Non-pilot area	Pilot area ^b	Non-pilot area	Pilot area ^b
Primary school	5–10 years	Rate	234.7	75.8	37.3	33.3
		(n/N)	(225/95,857)	(5/6,593)	(63/169)	(5/15)
		Risk difference	Ref	-158.9	Ref	-4.0
		OR (95% CI)		0.31 (0.08 to 1.15)		0.96 (0.23 to 4.03)
		p value		0.080		0.961
Secondary school	11–16 years	Rate	283.0	81.1	40.9	27.3
		(n/N)	(249/87,979)	(5/6,164)	(63/154)	(3/11)
		Risk difference	Ref	-201.9	Ref	-13.6
		OR (95% CI)		0.28 (0.08 to 0.91)		0.54 (0.14 to 2.12)
		p value		0.034		0.379
Other age groups	<5 years	Rate	248	39.5	41.1	35.3
		(n/N)	(197/79,449)	(2/5,057)	(99/241)	(6/17)
		Risk difference	Ref	-208.5	Ref	-5.8
		OR (95% CI)		0.14 (0.02 to 1.18)		0.97 (0.16 to 5.71)
		p value		0.071		0.971
	≥17 years	Rate	400.3	167.5	28.1	16.5
		(n/N)	(4,529/1,131,418)	(122/72,842)	(648/2,308)	(39/237)
		Risk difference	Ref	-232.8	Ref	-11.6
		OR (95% CI)		0.37 (0.16 to 0.90)		0.52 (0.32 to 0.84)
p value		0.029		0.008		

CI: confidence interval; ILI: influenza-like illness; OR: odds ratio; RCGP: Royal College of General Practitioners.

^a Week 40 2015 to week 20 2016.

^b Includes primary school pilot areas.

p values < 0.05 are in bold.

weekly death occurrences, corrected for reporting delay, was compared with the expected number of deaths, based upon historical patterns, to determine if there was statistically significant excess mortality. Excess mortality was estimated in both non-pilot and pilot areas based upon place of usual residence. The algorithm was applied to both all-cause mortality and death registrations where respiratory, ICD-10 'J' code, was the primary cause of death [18].

Statistical methods

Cumulative disease incidence rates per 100,000 population were calculated for the RCGP, USISS sentinel and USISS mandatory schemes, by summing the number of weekly disease episodes (from week 40 2015 to week 20 2016) over the average weekly population at risk based on the GP registered or hospital catchment population respectively. Calculations were undertaken overall and by age group for both pilot and non-pilot areas. Exact Poisson confidence intervals (CI) were calculated.

Cumulative influenza swab positivity for the GP swabbing (from RCGP and SMN) and RDMS were calculated

by summing the number of positive samples over the total number of samples tested in the study period. Cumulative proportion of ED attendances coded as respiratory were calculated by summing the total number of respiratory coded ED attendances over the total number of ED attendances with a diagnosis during the study period. Calculations were undertaken overall and by age group and pilot area. Exact CIs were calculated. To measure the impact of primary school vaccination, the non-pilot areas were set as reference and odds ratios (ORs) and 95% CIs were calculated by age group and surveillance system. To adjust for clustering at the reporting unit level, e.g. by GP, hospital, laboratory, data were converted to binomial individual level across schemes and random effects logistic regression was undertaken.

Cumulative excess mortality rates by pilot and non-pilot area were calculated by summing the difference between observed and expected weekly deaths over the study period, and using the resident population in pilot and non-pilot areas.

TABLE 2

Adjusted impact of vaccinating primary and/or secondary school-age children on selected secondary care influenza surveillance indicators, England, influenza season, 2015/16^a

Age group	Measure		Influenza-confirmed ICU admission rate, USISS mandatory (per 100,000 population)		Influenza-confirmed hospitalisation rate, USISS sentinel (per 100,000 population)		Proportion influenza positive, Datamart (%)		Emergency Department respiratory attendance proportion (%)	
	Non-pilot area	Pilot area	Non-pilot area	Pilot area	Non-pilot area	Pilot area	Non-pilot area	Pilot area	Non-pilot area	Pilot area
Primary school	Rate	2.3	0.3	18.3	4.8	16.6	8.5	12.3	5.9	
	(n/N)	(78/3,341,020)	(1/291,687)	(120/657,495)	(9/487,220)	(317/1,911)	(19/224)	(8,944/72,980)	(106/1,800)	
	Risk difference	Ref	-2.0	Ref	-13.4	Ref	-8.1	Ref	-6.4	
	OR (95% CI)	Ref	0.24 (0.01 to 3.83)	Ref	0.15 (0.02 to 1.00)	Ref	0.66 (0.35 to 1.22)	Ref	0.64 (0.16 to 2.56)	
Secondary school	p value	1.1	0.312	12.6	0.050	15.7	0.184	4.2	0.528	
	Rate	1.1	1.0	12.6	12.8	15.7	6.5	4.2	2.4	
	(n/N)	(36/3,244,504)	(3/281,903)	(77/609,913)	(23/179,278)	(177/1,130)	(9/139)	(3,470/74,888)	(58/2,407)	
	Risk difference	Ref	-0.1	Ref	0.2	Ref	-9.2	Ref	-1.8	
Other age groups	OR (95% CI)	Ref	0.95 (0.08 to 10.66)	Ref	0.90 (0.39 to 2.06)	Ref	0.41 (0.19 to 0.90)	Ref	0.77 (0.22 to 2.67)	
	p value	8.4	0.966	78.9	0.801	8.7	0.026	28.2	0.680	
	Rate	8.4	7.1	78.9	45.1	8.7	7.2	28.2	12.5	
	(n/N)	(253/2,999,969)	(19/269,118)	(453/573,865)	(81/179,577)	(863/9,932)	(78/1,087)	(38,785/137,383)	(267/2,129)	
<5 years	Risk difference	Ref	-1.3	Ref	-33.8	Ref	-1.5	Ref	-15.7	
	OR (95% CI)	Ref	0.56 (0.04 to 7.45)	Ref	0.76 (0.18 to 3.22)	Ref	1.22 (0.86 to 1.72)	Ref	0.48 (0.12 to 1.88)	
	p value	4.5	0.662	25.5	0.709	15.8	0.265	6.9	0.295	
	Rate	4.5	3.6	25.5	18.2	15.8	16.0	6.9	6.8	
≥17 years	(n/N)	(1,700/37,376,608)	(125/3,432,083)	(1,671/6,548,444)	(390/2,139,664)	(4,509/28,557)	(350/2,190)	(67,563/977,078)	(2,371/34,874)	
	Risk difference	Ref	-0.9	Ref	-7.3	Ref	0.2	Ref	-0.1	
	OR (95% CI)	Ref	0.98 (0.58 to 1.66)	Ref	0.66 (0.20 to 2.22)	Ref	0.87 (0.75 to 1.01)	Ref	1.20 (0.36 to 4.07)	
	p value	Ref	0.948	Ref	0.505	Ref	0.061	Ref	0.761	

ICU: intensive care unit; OR: odds ratio; RCGP: Royal College of General Practitioners; USISS: United Kingdom Severe Influenza Surveillance System.

p values < 0.05 are in bold.

^a Week 40 2015 to week 20 2016.

Comparison for the post-introduction (2013/14, 2014/15, 2015/16) and pre-introduction periods (2011/12, 2012/13) was undertaken for the cumulative, age-specific influenza incidence in pilot and non-pilot areas. The pre-vaccination pilot areas were the same as those defined for the 2015/16 season.

Laboratory methods

Influenza laboratory confirmation of samples from primary and secondary care was undertaken on respiratory samples using comparable real-time PCR methods able to detect circulating influenza A and influenza B viruses [19,20]. Samples from the RCGP sentinel GP scheme were sent to the PHE Reference Virus Unit in Colindale; samples from the SMN sentinel GP scheme and secondary care were sent to one of the network of specialist PHE microbiology laboratories (SMN scheme) or NHS laboratories elsewhere in England (secondary care).

Results

Vaccine uptake

The total target population for the primary school pilots was estimated to be 279,933 primary school-age children.

An estimated 162,013 primary school-age children in pilot areas received at least one dose of influenza vaccine resulting in an overall uptake of 57.9%. This ranged from 43.6% to 72.0% at the pilot-site level (Figure 1). Uptake by school year group ranged from 62.6% in year 1 (children 5 to 6 years of age), 60.1% in year 2 (children 6 to 7 years of age), 57.2% in year 3 (children 7 to 8 years of age), 56.2% in year 4 (children 8 to 9 years of age), 56.0% in year 5 (children 9 to 10 years of age), to 54.7% in year 6 (children 10 to 11 years of age).

Influenza vaccine uptake achieved in children 2–4 years of age in primary school pilot areas was 34.0% in 584 GP practices compared with 34.4% in 7,029 GP practices in non-pilot areas elsewhere in England. For children in school years 1 and 2, i.e. children 5 and 6 years of age, uptake was 61.4% (58,920/96,036) in pilot areas compared with 53% (658,008/1,240,567) in non-pilot areas elsewhere in England.

School age vaccine programme impact

Patterns of activity

The cumulative ILI consultation rate and sentinel GP swab positivity in primary care, ED respiratory attendances, RDMS influenza positivity and ICU/HDU rates in secondary care from week 40 2015 to week 20 2016 were consistently lower in primary school-age pilot areas compared with non-pilot areas in both the targeted and non-targeted age groups (Figures 2 and 3). These differences were less marked for the sentinel GP swab positivity, RDMS indicators and laboratory-confirmed ICU admissions particularly in the older,

non-targeted age group of individuals 17 years of age and over.

All-cause and respiratory excess mortality

All-cause excess mortality was significantly higher in pilot areas during both the pre-vaccine (2011/12 and 2012/13) and post-vaccine period (2013/14, 2014/15 and 2015/16) (Figure 4). For all-age respiratory deaths, there was no significant difference between pilot and non-pilot areas during the pre-vaccine period (2011/12 and 2012/13). However, in the post-vaccine period, cumulative excess respiratory deaths were significantly lower in both 2013/14 and 2015/16 seasons (Figure 5).

Pre-vaccination information for indicators with available data

Data were available for RCGP ILI and influenza confirmed hospitalisations and ICU admissions. During the two seasons before the start of the childhood vaccination programmes, the cumulative ICU/HDU admission and hospitalisation rates for influenza were similar between the targeted and non-targeted age groups in pilot areas compared to those in non-pilot areas. In comparison, GP ILI consultation rates were consistently lower during the two seasons prior to the programme introduction in the pilot areas compared with non-pilot areas. For all indicators, there was a divergence between pilot and non-pilot areas in both targeted and non-targeted age groups with the introduction of the childhood influenza vaccine programme in 2013/14 with a relative reduction for indicators in pilot areas compared to non-pilot areas (Figure 6, 7, 8).

Adjusted impact for primary and secondary care surveillance indicators

Vaccinating primary school age children resulted in significant reductions in cumulative incidence/laboratory-confirmed positivity in primary care indicators for ILI and swab positivity in adults when comparing pilot with non-pilot areas and adjusting for clustering (Table 1). There were also non-significant reductions for ILI GP consultations and swab positivity in both children of primary school age and those less than 5 years of age (Table 1)

For the secondary care indicators, i.e. for influenza-confirmed hospitalisations and ICU admissions, ED attendances and DataMart positivity, reductions were seen in all instances in the targeted age group when comparing pilot to non-pilot areas, though this was only statistically significant for laboratory-confirmed hospitalisations (Table 2). The size of these reductions was less and non-significant when examining children less than 5 years of age and those of secondary school age. There was little evidence of any reduction for these indicators when comparing pilot and non-pilot areas among adults (Table 2).

Discussion

This study assesses the uptake of LAIV and evaluates the impact of the recently implemented LAIV programme for children in England that was targeted at primary school-age children in discrete geographical pilot areas during the 2015/16 influenza season. We found similar levels of uptake during this season, when compared with the first two seasons and that vaccinating children of primary school age was associated with reductions in incidence for a range of surveillance indicators in England. This effect was most evident in areas where all children of primary school age had been targeted, with the impact most noticeable in targeted age groups. The size of the effect was less for more severe endpoints such as excess respiratory mortality, and for non-targeted age groups e.g. adults and secondary school-age children.

The 2015/16 influenza season was characterised by significant numbers of hospitalisations and ICU admissions and some fatalities among younger adults, an observation consistent with the circulation of influenza A(H1N1)pdm09 virus [3]. We observed decreases in influenza in primary school-age children (and indirectly in children under the age of 5 years, where the burden of influenza is recognised to be highest) together with smaller indirect reductions in secondary school-age children and adults in primary school age pilot areas. These indirect reductions seen for primary care consultations, laboratory-confirmed hospitalisations, ICU/HDU admissions and ED attendances, however, were not statistically significant. As seen in the first two seasons of the programme, the effect sizes generally became smaller as the endpoints were more severe [6,7], which is consistent with publications from elsewhere [8-10]; in particular, a study by King et al., who reported significant reductions in medically attended acute respiratory illnesses (MAARI) emergency department visits in children and young adults, but less so for hospitalisations (particularly in the elderly) associated with increases in LAIV uptake in primary school-age children [10].

We report good uptake levels in primary school-age children in pilot areas. A study by Calder et al. found that school-based influenza vaccine programmes achieved better equity by ethnicity and deprivation, though primary care delivery can also achieve important increases in uptake [21]. This reinforces this approach as a model of delivery for vaccinating children of school age.

A recent systematic review identified some evidence that vaccinating children can provide indirect benefits particularly against milder endpoints, but highlighted that larger scale studies were required against a range of endpoints in different settings [22]. Our study starts to address that need. The findings in this article are also encouraging in the light of observations in the US in 2015/16, where observational studies indicated that LAIV has had little or no effect among children [11]. This

is in contrast to findings of moderate VE in other geographical settings such as the UK, Canada and Finland [23]. The reasons for these observations remain under investigation, though preliminary work has suggested impaired replicability of the A/California-like LAIV strain A/Bolivia (H1N1)pdm09 in 2015/16 [24]. This strain has since been updated in the vaccine, so it will be important to evaluate the direct and indirect population impact of this new LAIV vaccine virus.

The reductions we observed occurred in a season in which new genetic subgroups in influenza A(H1N1)pdm09 viruses emerged (6B.1 and 6B.2) and circulated as the predominant strains. These factors raised some concerns about possible vaccine mismatch, together with the end of season LAIV VE findings of 58% (overall) and of 42% against A(H1N1)pdm09 in children 2–17 years of age [5]. Our results suggest that average uptake levels of 58% among all primary school-age children compared with the rest of the country – where only primary school-age children in school years 1 and 2 were offered vaccine, will result in reduction in influenza transmission in the local population. This is evidenced by observation of both direct and indirect impacts for a range of indicators in primary and (to a lesser extent) secondary care in these local areas.

Although there were reductions in a range of clinical endpoints in pilot compared with non-pilot areas in young adults, the differences were non-significant and became less for more severe indicators and the older age groups. The lesser effects observed could be related to how children interact with vulnerable groups such as the elderly particularly in settings such as care homes; other studies have also not been able to determine a significant difference [10]. Further research is planned to look at these differences, as this is where much of the health economic benefits of a school-age influenza vaccination programme were projected to be derived [4].

This study builds upon methodology developed in the first two seasons of the recently established childhood LAIV programme in order to evaluate its uptake and impact. The use of population-level data sources is a strength of this study, as we were able to compare our findings, in relation to vaccine uptake, with earlier published research [6,7] and assess their impact across a range of indicators when primary school children were targeted. Examination of historical data suggests some caution is needed in interpretation, however, as there are pre-vaccine era programme differences in regard to primary care ILLI consultation rates between pilot and non-pilot areas. The practices in pilot areas are more likely to have been newly recruited, which may explain pre-vaccination differences in reporting practice. The apparent effect sizes of this particular indicator should thus not be overestimated, with the majority of them non-significant in the models, which also take into account clustering at the reporting unit level. The ongoing roll-out of the national programme to increasing

age cohorts of school children (in 2016/17, the programme additionally included children aged 3 and 7 years and in 2017/18 to children aged 8 years) will result in less notable differences in vaccine uptake between pilot and non-pilot areas; and thus the opportunity to undertake such comparative observational studies between geographical areas is, therefore, diminishing. Finally, the size of the pilot areas is relatively small, so results should be interpreted with caution as we had limited power to detect significant differences, particularly for more severe endpoints.

The differential roll-out of the LAIV programme across the countries of the UK, with Scotland and Northern Ireland vaccinating primary school-age children and Wales secondary school-age children in 2015/16 has shown some early encouraging signs in relation to reductions in primary care consultations for those countries vaccinating primary school-age children [3]. This study in England provides further important opportunities to understand the population level impacts of the universal paediatric influenza vaccination programme.

Conclusion

In conclusion, our findings support the on-going roll out of the national LAIV programme for children of primary school age. Further work will need to be undertaken to evaluate the impact of the LAIV programme against a range of endpoints, in particular, the more severe ones such as those against mortality and to investigate the discordance observed between the UK and US paediatric programmes.

Acknowledgements

The authors would like to acknowledge all the patients involved; the PHE and NHS staff in each of the vaccine pilot sites who were responsible for planning and delivering the LAIV -school age programme; Mariya Hriskova, Filipa Ferreira, Ana Costa and David Mullet of the University of Surrey; all the participating general practices of the RCGP Research and Surveillance Centre Unit sentinel scheme; all participating emergency departments in the Emergency Department Syndromic Surveillance System and the Royal College of Emergency Medicine; Nisha Oppilamany, Sophia Steinberger and Bersabeh Sile of PHE and all the participants of the UK Severe Influenza Surveillance Scheme; and Praveen Sebastian Pillai and the staff of the PHE Respiratory Virus Unit, Paul Loveridge of the PHE Real-time Syndromic Surveillance Team and contributing PHE and NHS laboratories. This work was supported by Public Health England as part of an ongoing evaluation of the introduction of the new childhood influenza vaccination programme. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 634446.

Conflict of interest

None declared.

Authors' contributions

RP led the design of the study and study group; all (MS, FW, NA, NB, HZ, IY, JE, ET, MD, AE, HH, SP, RB, GS, SL and MZ) were members of the study group and involved in data collection, management and analyses; MS, FW, NA and RP led the data analysis; MS undertook the summary analyses; HZ was responsible for the RDMS system, data management and analysis; NB was responsible for the USISS system, data management and analysis; HH, AE and GS were responsible for the EDSSS data system management and analysis; IY worked directly with the practices and RB, SP and SdeL were responsible for the RCGP data system management and analysis; JE, MD and MZ were responsible for virological testing schemes; ET was responsible for monitoring of vaccine uptake in the pilot sites; RP drafted the initial manuscript; all co-authors reviewed and commented including approval of the final version.

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