Uptake and impact of a new live attenuated influenza vaccine programme in England: early results of a pilot in primary school-age children, 2013/14 influenza season

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As part of the introduction and roll-out of a universal childhood live-attenuated influenza vaccination programme, 4–11 year-olds were vaccinated in seven pilot areas in England in the 2013/14 influenza season. This paper presents the uptake and impact of the programme for a range of disease indicators. End-of-season uptake was defined as the number of children in the target population who received at least one dose of influenza vaccine. Between week 40 2013 and week 15 2014, cumulative disease incidence per 100,000 population (general practitioner consultations for influenza-like illness and laboratory-confirmed influenza hospitalisations), cumulative influenza swab positivity in primary and secondary care and cumulative proportion of emergency department respiratory attendances were calculated. Indicators were compared overall and by age group between pilot and non-pilot areas. Direct impact was defined as reduction in cumulative incidence based on residence in pilot relative to non-pilot areas in 4–11 year-olds. Indirect impact was reduction between pilot and non-pilot areas in <4 year-olds and >11 year-olds. Overall vaccine uptake of 52.5% (104,792/199,475) was achieved. Although influenza activity was low, a consistent, though not statistically significant, decrease in cumulative disease incidence and influenza positivity across different indicators was seen in pilot relative to non-pilot areas in both targeted and non-targeted age groups, except in older age groups, where no difference was observed for secondary care indicators.

Background

The United Kingdom (UK) has had a long-standing selective influenza vaccination programme that aims to directly protect populations at higher risk of severe disease due to influenza. This approach, as in many other countries in Europe, has been targeted at all those over 64 years of age and those less than 65 years in clinical risk groups, including pregnant women [1].

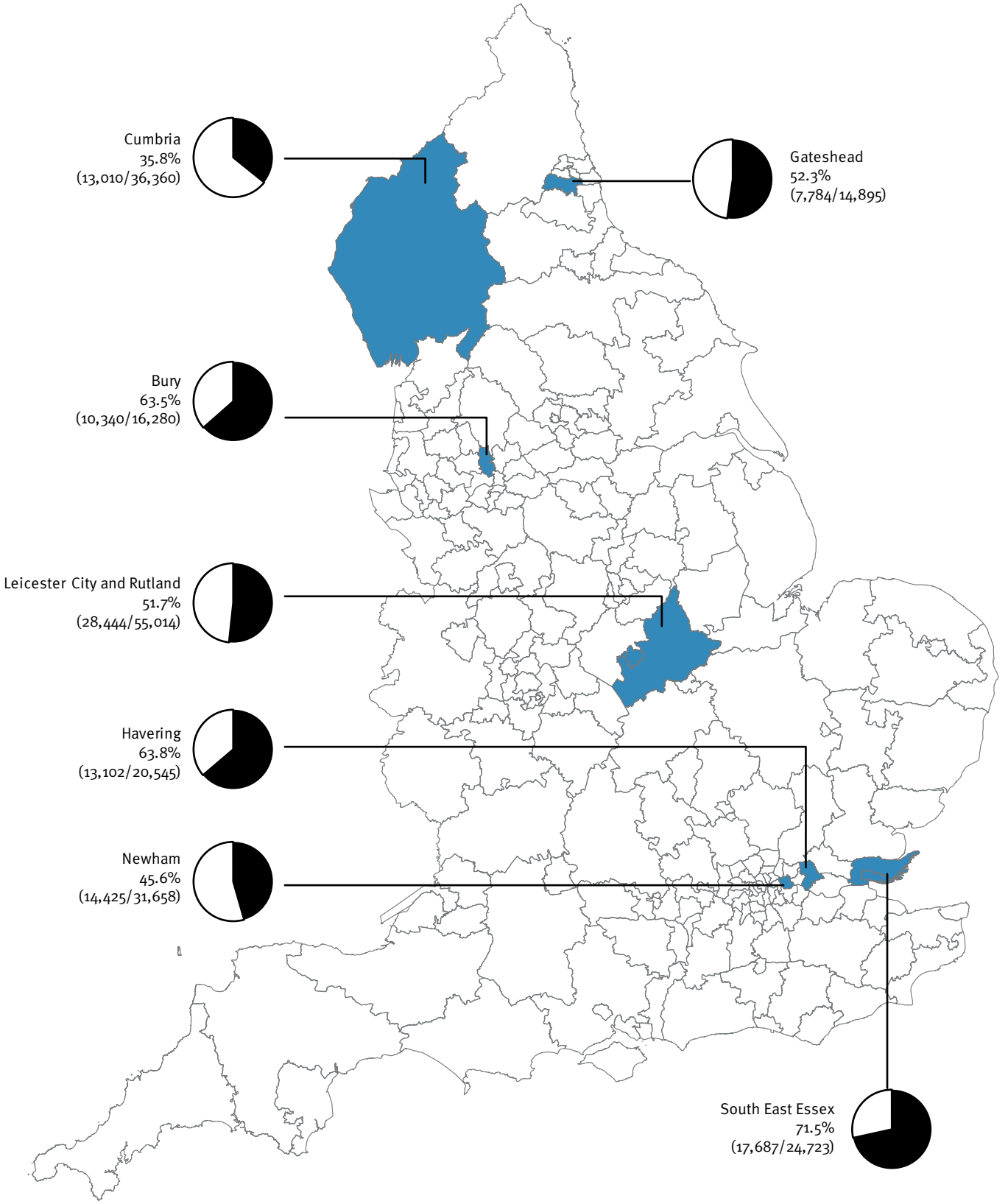
Although published work has demonstrated that the UK selective programme is cost-effective [2], it is apparent that there still remains a considerable burden of disease due to influenza in the population [3,4]. Children are recognised to play a key role in the transmission of influenza virus [5], with mathematical modelling predicting that targeting this group with influenza vaccine would not only reduce infection in immunised children themselves (direct programme impact) but also reduce influenza-related disease in other age groups, including elderly people, and individuals in high-risk groups (indirect programme impact) [6,7].

On the basis of this evidence and recommendations from the Joint Committee of Vaccination and Immunisation [8], the UK initiated a universal childhood immunisation programme with a newly licensed intranasally administered trivalent live attenuated influenza vaccine (LAIV) in the 2013/14 influenza season [9]. This programme is being rolled out over several seasons, with the ultimate intention of offering a single dose of LAIV to all healthy children aged 2–16 years annually. This is based upon published evidence that a second dose of LAIV provides only modest additional protection against laboratory-confirmed influenza infection (e.g. 60% versus 77% vaccine effectiveness for one and two doses, respectively) [11]. Influenza vaccine-naive children aged six months to less than nine years in clinical risk groups are offered two doses of vaccine, either LAIV or inactivated influenza vaccine for those in whom LAIV is contraindicated [10].

In this first season, the UK influenza vaccine programme targeted all children aged two and three years, reaching

Figure 1

Cumulative uptake of live attenuated influenza vaccine in primary school-age children[a] in pilot areas, England, 2013/14 influenza season



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

[a] Aged 4–11 years.

a provisional uptake of 42.6% (308,925/724,747) and 39.6% (285,616/722,048) respectively in England [12]. In addition, a series of geographically discrete pilots of LAIV vaccination for primary school-aged children (4–11 years) were organised in England. Local NHS England teams interested in running pilot immunisation programmes submitted business cases which were evaluated and sites selected by the national team. Different models of delivery (in particular, school- versus community-based) were evaluated in these pilots.

Despite recommendations for universal childhood influenza immunisation in several countries, only limited observational data have been published on the impact of such programmes [13-15]. The implementation of the new UK childhood influenza vaccine programme provides an opportunity to add to this evidence base. This paper presents early results from the primary school-age pilots of the direct and indirect impact of such a programme for a range of disease indicators during the 2013/14 influenza season (over and above vaccination of preschool age children). As seen elsewhere in Europe, the 2013/14 season was dominated by the circulation of influenza A(H1N1)pdm09 virus, with evidence of community transmission at low intensity from weeks 5 to 15 (27 January to 13 April) 2014 [12].

Methods

Uptake of live attenuated influenza vaccine

Seven geographically discrete pilot areas were selected in England. The target population was defined as children of primary school age (4 to 11 years-old) resident in seven pilot areas: Bury, Cumbria, Gateshead, Leicester City and Rutland, Havering and Newham boroughs (in London) and South East Essex (Figure 1), covering about 5% of the population of this age in England. End-of-season programme uptake was calculated based on number of children in the target population who received at least one dose of influenza vaccine during the campaign period (September 2013 to January 2014). Uptake data were reported weekly by each NHS England pilot area team during the season to PHE using a bespoke web-based portal.

Disease indicators

LAIV programme impact was measured for a range of clinical and virological respiratory end points in primary and secondary care from week 40 2013 to week 15 (30 September 2013 to 13 April 2014), the end of notable community transmission of influenza [12]. To ensure appropriate surveillance coverage for each sentinel surveillance scheme (in primary care, hospital emergency departments and general hospital admissions), additional participating sites were recruited in each pilot area where required.

Surveillance in primary care was undertaken through monitoring the weekly influenza-like illness (ILI) consultation rates through the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) sentinel general practitioner (GP) network, with nine practices participating in pilot areas and 78 in non-pilot areas. Sentinel practices, in conjunction with practices from the Sentinel Microbiology Network (SMN) scheme, undertook respiratory swabbing and testing with influenza virus polymerase chain reaction (PCR) assays for a proportion of patients presenting with ILI, including all patients under 17 years of age. Influenza swab positivity rates and GP consultation rates in pilot and non-pilot areas were compared by age group.

The Emergency Department Sentinel Surveillance System (EDSSS) monitors routine syndromic surveillance data, in real-time, using anonymised emergency department attendances, across a sentinel network of emergency departments [16]. Attendances monitored included those for acute respiratory illness (two emergency departments in pilot and 30 in non-pilot areas). The proportion of all EDSSS admissions coded as 'respiratory' in pilot and non-pilot areas was compared by age group.

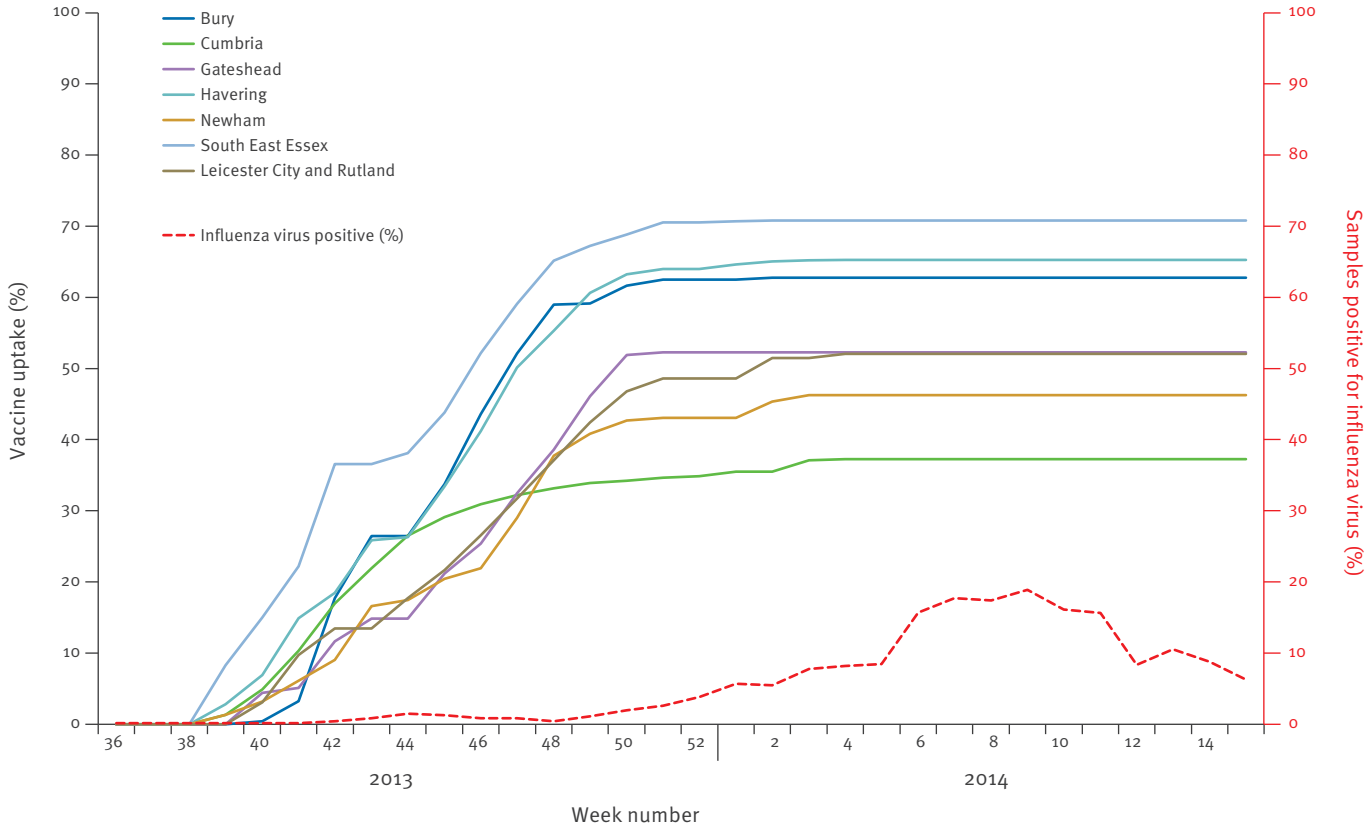
The UK Severe Influenza Sentinel Surveillance System (USISS) [17] consists of a network of 35 National Health Service (NHS) hospital trusts (nine in pilot areas and 26 in non-pilot areas) that report the number of laboratory-confirmed hospital and intensive-care unit (ICU) weekly admissions due to influenza. As routine USISS data were not in the LAIV target age groupings, influenza hospitalisation rates by age group for primary school-age children and non-targeted age groups were calculated for pilot and non-pilot areas using estimated hospital catchment populations [18]. As the age groups of hospital catchment populations did not match our targeted and non-targeted age groups, population estimates were adjusted in line with Office for National Statistics age-specific population proportions from mid-2012 population estimates [19].

The Respiratory DataMart scheme (RDMS) [20] reports all influenza virus PCR respiratory swab results from a network of PHE and NHS laboratories, with the majority of samples (>68%) [20] taken from patients in secondary care. Postcode of patients' residence was used to allocate patients to pilot and non-pilot areas. Influenza swab positivity rates in pilot and non-pilot areas were compared by age group.

Weekly excess mortality due to all causes and to respiratory illness was estimated in pilot and non-pilot areas based upon place of residence. The EuroMOMO (European monitoring of excess mortality for public health action) standard algorithm was used to calculate number of deaths expected for a given week in the year [21]. The number of observed deaths (corrected for reporting delay) was compared with the modelled number expected each week to determine if statistically significant excess mortality was seen in pilot and non-pilot areas.

Figure 2

Estimated weekly proportion of uptake of live attenuated influenza vaccine in primary school-age children[a] by pilot area and weekly proportion of samples positive for influenza virus[b], England, 2013/14 influenza season[c]



[a] Aged 4–11 years.

[b] Through the Respiratory DataMart scheme (RDMS).

[c] Week 36 2013 to week 15 2014 (2 September 2013 to 13 April 2014).

Measuring impact of the live attenuated influenza vaccine programme

Cumulative disease incidence rates per 100,000 population were calculated by summing the number of disease episodes each week from week 40 2013 to week 15 2014 relative to the population at risk. Cumulative influenza swab positivity was calculated by summing the number of positive samples and the number of samples tested each week from week 40 2013 to week 15 2014, with a similar calculation done for EDSSS respiratory attendances.

As a sample of primary and secondary care centres were recruited, sampling based statistical methods were used. Cumulative indicators were statistically compared overall and by age group between pilot and non-pilot areas for different indicators. Direct impact was defined as reduction in cumulative disease incidence based on residence in pilot and non-pilot areas in the target age group (4–11 year-olds). Indirect impact was defined as reduction in cumulative disease incidence over the same period between pilot and non-pilot areas in non-target age-groups (<4 years of age and >11 years of age). Cumulative incidence rates were compared between pilot and non-pilot areas by calculating risk ratios with 95% confidence intervals. Negative binomial regression was used to account for extra-Poisson variability between GPs or NHS hospital trusts within pilot and non-pilot areas. The cumulative proportion of samples positive for influenza virus and EDSSS admissions coded as respiratory were compared between the areas using logistic regression (giving odds ratios) with adjustment for overdispersion.

Results

Vaccine uptake

The total target population for the pilot study was estimated to be 199,475 children aged 4–11 years of age. Six of the seven pilot areas chose to deliver the programme through a school-based approach, while Cumbria delivered through community pharmacies and primary care. A total of 104,792 primary school-age children received at least one dose of LAIV or inactivated vaccine during the study period, an uptake of 52.5%. This ranged from 35.8% (Cumbria) to 71.5% (South

East Essex) at pilot level (Figure 1), with final uptake in all pilot areas reached when there was evidence of community influenza transmission from week 5 2014 onwards (Figure 2). Uptake by school year decreased from 56.1% (16,727/29,826) in reception class children (aged 4–5 years) to 49.7% (12,859/ 25,864) in children in year 6 (aged 10–11 years), with a steady decline in uptake with increasing age (chi squared test for trend p<0.0001).

Programme impact

The cumulative all-age ILI GP consultation rate was higher in non-pilot (64.5/100,000 population) than in pilot areas (17.7/100,000), with a similar pattern for all three age groups (Figure 3). The overall risk difference of pilot relative to non-pilot cumulative incidence was –46.8/100,000. Using data from RCGP, the risk ratio was 0.34 (an estimated impact of vaccination of 66%), though this was not statistically significant (Table).

The overall cumulative influenza swab positivity rate in primary care in pilot areas was 8.5% (15/176) compared with 16.2% (265/1,634) in non-pilot areas, with a consistent pattern for all three age groups (Figure 3). Derived from RCGP/SMN influenza virus positivity data, the odds ratios for pilot relative to non-pilot areas for children aged ≥12 years and all ages, with values of 0.54 and 0.53 respectively, were not statistically significant (Table).

Through EDSSS, the overall cumulative proportion of emergency department attendances coded as respiratory was 5.5% (2,804/51,413) in pilot compared to 8.7% (83,224/954,225) in non-pilot areas (Table), with a consistently lower cumulative proportion in children <4 years and aged 4 to <12 years, but no apparent difference in people older than 12 years. The overall odds ratio was 0.60 (estimated impact of 40%), which was not statistically significant, as was the case for age-specific estimates.

The cumulative all-age incidence of laboratory-confirmed influenza hospitalisations reported through the USISS sentinel scheme was 5.5 per 100,000 population in pilot compared with 7.0 per 100,000 in non-pilot areas (Table). The cumulative incidence of hospitalisations in <4 year old and 4–11 year old was higher in non-pilot compared with pilot areas; however, it was very similar for people aged 12 years or more (Figure 3). The overall risk difference of pilot vs non-pilot areas was –1.5/100,000 and risk ratio was 0.76 (an estimated impact of 24%), which was not statistically significant.

Through RDMS, overall cumulative influenza swab positivity was similar in pilot and non-pilot areas (Table). Similar age-specific cumulative positivity was seen for each age group (Figure 3), although time to cumulative peak positivity was shorter in non-pilot compared with pilot areas for 4–11 year-olds. The overall odds ratio (0.99) showed that there was little difference in pilot relative to non-pilot areas.

No significant excess all-cause or all-respiratory mortality was observed in pilot or non-pilot areas in children aged <4 years, 4–11 years or people aged ≥12 years.

Discussion

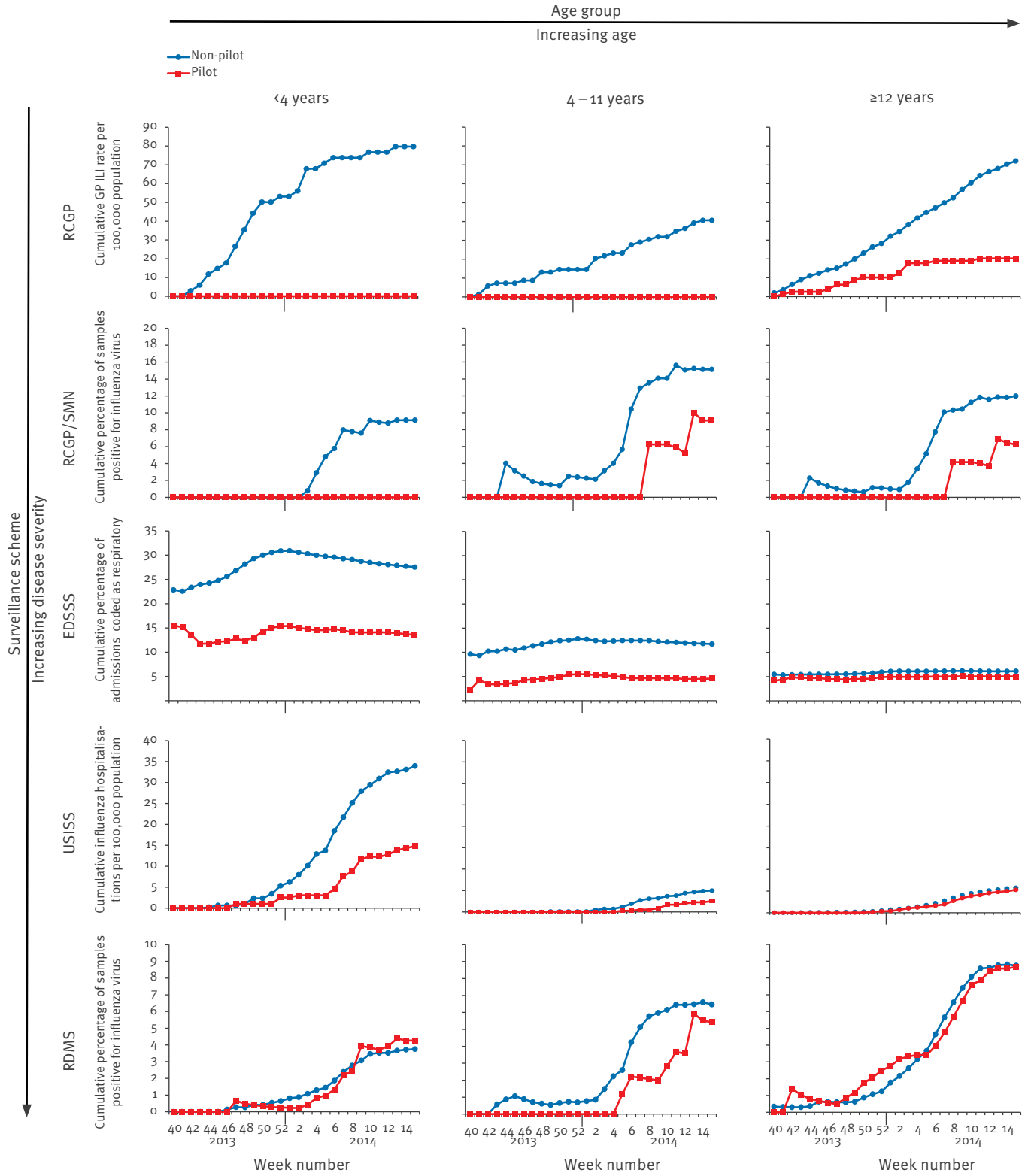
This pilot universal paediatric influenza vaccination programme achieved an overall uptake of 53% (ranging from 36 to 72% in individual pilot areas) in primary school-age children in the first year of implementation in England. Although the results were not statistically significant, the cumulative disease incidence was lower in pilot relative to non-pilot areas in both targeted and non-targeted age groups for a range of influenza indicators – both laboratory-confirmed and syndromic. These observed differences were smaller for more severe disease end-points.

The LAIV programme delivered in primary school settings (in six of the seven pilot areas) achieved a relatively good uptake in the target population, although there was variation in coverage by pilot area. The lowest uptake was observed in the one pilot area where delivery was through a community pharmacy/primary care setting. There was also significant variation in uptake by year group, with coverage levels highest among the youngest, with a steady decline with increasing age. These levels compare favourably with those achieved in the United States, where LAIV has been recommended for all children for several years. Implementation has been varied in the United States [14], with uptake of 41% reported in children 5–12 years of age from one study in 2011/12 [22]. The modelling work of Baguelin et al. suggests that reaching levels of 30% vaccine coverage in children would already start to produce substantial benefits [6]. Thus, the overall high uptake achieved in our target population in the first year, particularly with a school-based delivery model, augers well for the future. Further evaluation into factors that might explain local variation in uptake is under way and will inform future programme implementation.

These early results suggest a direct programme impact, with reductions in incidence seen for a wide range of influenza indicators including primary care consultations, swab positivity, hospitalisation of laboratory-confirmed cases and percentage of respiratory-coded emergency department attendances in pilot vs non-pilot areas for 4–11 year-olds. A direct impact among the immunised group of at least 25–30% would be expected, based on the observed uptake of 53% with a moderately effective vaccine (with a vaccine effectiveness of 50–60%). No evidence of a reduction, however, in swab positivity from RDMS data, which relate mainly to samples taken in secondary care settings, was seen in pilot compared with non-pilot areas for the same age group. Direct impact of such school-based programmes has previously been demonstrated in North America for end points such as emergency department

Figure 3

Cumulative disease indicators in pilot vs non-pilot areas by age group across surveillance schemes, England, 2013/14 influenza season[a]



EDSSS: Emergency Department Sentinel Surveillance System; GP: general practitioner: ILI: influenza-like illness; RCGP: Royal College of General Practitioners; SMN: Sentinel Microbiology Network; USISS: UK Severe Influenza Sentinel Surveillance System; UK: United Kingdom.

[a] Week 40 2013 to week 15 2014 (30 September 2013 to 13 April 2014).

Table

Cumulative primary care consultations, hospitalisations, influenza positivity and emergency department attendances in children (<4, 4–11 years) and ≥12 year-olds in pilot and non-pilot areas, England, 2013/14 influenza season[a]

Surveillance scheme	Disease indicator	Age group (years)	Pilot areas	Non-pilot areas	Ratio[b] (95% CI)	p value
RCGP	**Number of sentinel GPs**		**9**	**78**		
	Cumulative GP ILI consultation rate per 100,000 population[c]	<4	0.0	73.6	0 (0–1.47)	0.170
			(0/3,641)	(27/36,672)		
		4–11	0.0	37.9	0 (0–1.33)	0.110
			(0/7,809)	(28/73,957)		
		≥12	20.3	66.8	0.38 (0.08–1.86)	0.232
			(16/78,953)	(483/723,075)		
		Total	17.7	64.5	0.34 (0.07–1.72)	0.194
			(16/90,403)	(538/833,704)		
RCGP/SMN	**Number of swabbing GPs**		**10**	**76**		
	Cumulative proportion (%) of swabs positive for influenza (n/N)[d]	<4	NA	9.1	1 (0–4.58)	1.000
			(0/9)	(17/186)		
		4–11	9.1	15.1	0.49 (0.07–3.26)	0.462
			(2/22)	(23/152)		
		≥12	9.1	17.3	0.54 (0.28–1.04)	0.067
			(13/143)	(221/1,276)		
		Total	8.5	16.2	0.53 (0.28–1.01)	0.055
			(15/176)	(265/1,634)		
EDSSS	**Number of sentinel emergency departments**		**2**	**30**		
	Cumulative percentage of emergency department admissions coded as respiratory (n/N)[d]	<4	13.6	27.5	0.42 (0.16–1.09)	0.075
			(361/2,658)	(26,645/96,747)		
		4–11	4.6	11.7	0.36 (0.10–1.33)	0.127
			(141/3,080)	(8,950/76,471)		
		≥12	5.0	6.1	0.81 (0.38–1.72)	0.583
			(2,302/45,675)	(47,629/781,007)		
		Total	5.5	8.7	0.60 (0.30–1.19)	0.146
			(2,804/51,413)	(83,224/954,225)		
USISS	**Number of sentinel NHS hospital trusts**		**9**	**26**		
	Cumulative incidence of laboratory-confirmed influenza hospitalisations per 100,000 population[c]	<4	14.8	31.4	0.37 (0.11–1.25)	0.111
			(29/195,379)	(146/465,442)		
		4–11	2.6	5.0	0.28 (0.13–1.56)	0.203
			(9/352,911)	(42/840,722)		
		≥12	5.3	5.8	0.93 (0.43–2.04)	0.858
			(174/3,293,487)	(452/7,845,918)		
		Total	5.5	7.0	0.76 (0.33–1.75)	0.516
			(212/3,841,777)	(640/9,152,082)		
RDMS	Cumulative percentage of swabs positive for influenza virus (n/N)[d]	<4	4.3	3.7	1.13 (0.30–4.26)	0.858
			(31/727)	(262/6,991)		
		4–11	5.4	6.5	0.79 (0.21–3.05)	0.735
			(7/129)	(98/1,514)		
		≥12	8.7	8.7	1.02 (0.39–2.66)	0.966
			(91/1,050)	(1,110/12,704)		
		Total	6.8	6.9	0.99 (0.35–2.80)	0.988
			(129/1,885)	(1,432/20,820)		

CI: confidence interval; EDSSS: Emergency Department Sentinel Surveillance System; GP: general practitioner: ILI: influenza-like illness; n/N: number positive/number tested; RCGP: Royal College of General Practitioners; SMN: Sentinel Microbiology Network; USISS: UK Severe Influenza Sentinel Surveillance System; UK: United Kingdom.

[a] Week 40 2013 to week 15 2014 (30 September 2013 to 13 April 2014).

[b] When the numerator was zero in the pilot area, ratio confidence intervals were calculated using Fisher's exact test.

[c] Risk ratio calculated with negative binomial regression.

[d] Odds ratio calculated with logistic regression, correcting for overdispersion.

consultations and school absenteeism [13,14], but, as in this study not for other more severe disease end points [15].

There was also a suggestion of an indirect impact of the programme, which was an important contributor to the estimated cost-effectiveness of the new universal childhood influenza vaccine programme in the earlier modelling work [6]. Reductions, albeit non-significant, in GP ILI consultation rate and proportion of respiratory swabs positive for influenza in primary care for non-targeted age groups, particularly in children under 4 years and also to some extent in people older than 11 years were seen. Such indirect effects have been seen previously for less severe end points in the United States [15]. Little evidence of indirect impact, however, was seen in our study for influenza hospitalisations, swab influenza positivity rate (from RDMS), emergency department admissions coded as respiratory and excess mortality in older people. Some potential explanations for this are outlined below. Further work is required to understand these differences between schemes and disease severity.

There are several potential limitations to this study. Firstly, the 2013/14 influenza season in the UK was characterised by influenza A(H1N1)pdm09 virus circulation, the novel pandemic strain that first emerged in 2009: across surveillance schemes, only moderate influenza activity was seen predominately in the hospital-based surveillance systems and mainly in younger adults. There was little signal of influenza activity either in primary care or from syndromic surveillance, nor was there evidence of excess mortality in elderly people. Along with the small geographical coverage of the pilot areas, this will have limited the ability of the school-age pilot programme to detect evidence of direct and indirect impact. Secondly, older people, who are typically susceptible to severe disease following influenza virus infection, are recognised to have background immunity to influenza A(H1N1)pdm09 [23], hence the lack of impact in relation to excess mortality among elderly people and why so few lives are likely to have been saved by the LAIV programme in the 2013/14 influenza season. Thirdly, the potential indirect effects of the programme (through reduction in transmission) would be diluted through opportunities for populations (e.g. adult unvaccinated groups) to move back and forth into pilot areas, thus reducing the potential herd effects of vaccinated paediatric groups. This may also explain why the time to peak positivity was shorter for non-pilot compared with pilot areas for some indicators. Fourthly, we were very aware of the possibility of cluster effects, with the data being at the GP or hospital trust level. For this reason, we carefully examined each outcome indicator for evidence of overdispersion and as a consequence employed the more conservative negative binomial regression (rather than Poisson regression). Fifthly, a sample of GP practices and hospitals were newly recruited to surveillance schemes in pilot areas raising the possibility of differential reporting.

These early, first season findings, which are consistent across a range of surveillance indicators, highlight the apparent value of vaccinating primary school children. The encouraging uptake levels achieved in most pilot areas demonstrate the feasibility of delivering such a programme in this population. While the estimates of programme impact were not statistically significant, it is encouraging that both direct and indirect impact (higher estimates in non-pilot relative to pilot areas) was seen across a range of surveillance schemes in primary care. The results were more nuanced for severe end points, where an impact was observed in children aged under 11 years (both targeted and non-targeted), but not in older age groups, which is an important contributor to the cost-effectiveness of the programme. These findings highlight the importance of further evaluation of data from the 2013/14 season. In 2014/15, pilot areas will continue to administer LAIV in primary school, with additional pilots in secondary school-age children (age 11–13 years) [24]. It will be important to continue the surveillance started in 2013/14, to determine if the observations presented here are repeatable and further quantify them to inform optimal roll-out.

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The authors would like to acknowledge all the PHE and NHS staff in each of the seven pilot sites (Bury, Cumbria, Gateshead, Havering, Leicester City, East Leicestershire and Rutland, Newham and South East Essex) who were responsible for planning and delivering the LAIV primary school-age programme; all the participating GPs of the RCGP Research and Surveillance Unit sentinel scheme; all the participants of the UK Severe Influenza Surveillance Scheme; all participating EDs in the Emergency Department Syndromic Surveillance System; and the staff of the PHE Respiratory Virus Unit and contributing PHE and NHS laboratories. The authors would like to thank Helen Hughes from the PHE Real-time Syndromic Surveillance Team for her comments. The authors are also grateful to James Lewis from the Microbial Risk Assessment team in the Emergency Response Department, Public Health England, for producing the pilot site uptake map.

Conflict of interest

None declared.

Authors' contributions

RP led the design of the study and study group; all co-authors were members of the study group and involved in data collection, management and analyses; HG, NA and RP led the data analysis; HG 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; ZB, AE and GES were responsible for the EDSSS data system management and analysis; HD and SL were responsible for the RCGP data system management and analysis; JE, MD and MZ were responsible for virological testing schemes; NS, AS and LL were responsible for monitoring of vaccine uptake in the pilot sites; RP drafted

the initial manuscript with HG; all co-authors reviewed and commented including approval of the final version.

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