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ORIGINAL RESEARCH

Patient reported outcome data following influenza A (H1N1p) vaccination in the 2009–2010 season: web-based and telephone evaluation

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Background: There has been worldwide interest in the safety of the pandemic influenza A (H1N1p) vaccines, although limited data are available from the vaccine recipients' perspective. This evaluation was designed to collect data from people who had received an influenza vaccination during the 2009–2010 season using a web-based data collection tool supplemented by telephone reporting (*PROBE*).

Methods: People scheduled to receive the influenza A (H1N1p) or seasonal influenza vaccines were recruited through media advertising and campaigns throughout the West of Scotland. Vaccine recipients participated in the evaluation by answering demographic and side effect questions using *PROBE* methodology on the day of the immunization, after 3 days, 8 days, 6 weeks, 12 weeks, and 26 weeks.

Results: A total of 1103 vaccine recipients including 134 young children (0–4 years) participated in the evaluation; 694 (63%) received H1N1p vaccine only, 135 (12%) seasonal vaccine only, 224 (20%) both H1N1p and seasonal vaccines, and 50 (5%) received H1N1p or seasonal vaccine with a non-influenza vaccine (eg, travel or pneumococcal). Overall, 42% of recipients reported experiencing a side effect after their baseline vaccination; the most commonly reported were general and arm side effects (>20%). Injection site discomfort/pain and flu-like symptoms were reported by 57% and 24% of recipients, respectively. A significantly higher proportion of the 960 H1N1p vaccine recipients experienced a side effect (44% vs 27%, $P < 0.001$) or injection site discomfort/pain (61% vs 26%, $P < 0.001$) than those receiving seasonal influenza vaccines. Female sex and H1N1p vaccination were associated with a significantly higher risk of injection site discomfort/pain, whereas the 70+ age group was associated with a significantly lower risk. H1N1p vaccine was well tolerated by children under 5 years with side effects reported at a similar frequency to that found in the total population.

Conclusions: Safety and tolerability data from influenza vaccine recipients including young children (via parents/carers) can be effectively collected using an online questionnaire with a telephone option (*PROBE*). The influenza A (H1N1p) vaccine was well tolerated, but was associated with more local short-term reactions than the seasonal influenza vaccine.

Keywords: safety, influenza, vaccination, H1N1, patient reported outcomes, side effects

Introduction

The first outbreak of the influenza A (H1N1p) virus (swine flu) occurred in Mexico in April 2009. The first cases in the UK were confirmed shortly afterwards in late April 2009. As the virus spread worldwide, a global pandemic influenza (phase six) was declared by the World Health Organization (WHO) on 11 June 2009 and lasted until August 2010.[1,2] Most people infected with the H1N1p virus developed only a mild illness, which generally lasted for about 1 week. However, there was a risk of serious illness, developing complications

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such as acute respiratory distress syndrome caused by viral pneumonia and death with H1N1p infection.

A vaccine to prevent influenza A (H1N1p) was urgently required to protect people likely to be at greater risk of serious illness such as the very young, elderly, pregnant women, and those with underlying health problems. Two vaccines against the A (H1N1p) 2009 strain of the influenza virus were purchased by the UK government and used in the UK vaccination program for the 2009–2010 season. These were an $AS03_B$ adjuvanted split virion vaccine (Pandemrix®, GlaxoSmithKline Vaccines, Belgium)[3] and a non-adjuvanted whole virion vaccine (Celvapan®, Baxter Vaccines, Austria).[4] The vaccines were both approved under 'exceptional circumstances' by the European Medicines Agency (EMA) after they had been authorized initially as 'mock-up' vaccines and converted to influenza A (H1N1p) vaccines once the responsible strain of influenza had been identified. The European regulators evaluated their safety profiles by comparing the limited clinical trial data available with that of the extensive safety database for influenza vaccines, including data from 'mock up' vaccines containing H5N1 antigen.[5]

The public were educated about swine flu and the vaccination program through the UK health and public information bodies,[6] and all UK households were sent leaflets. The vaccination program focused on frontline health and social care workers and those groups of people at high risk of developing serious illness or complications (Table 1). The main differences to the seasonal flu target audience were the inclusion of all children aged 6 months to 5 years in the H1N1p campaign, and less emphasis on residential homes and carers of dependents.

Uptake rates for influenza A (H1N1p) vaccination were lower than expected. For example, in Scotland, the estimated cumulative uptake of the vaccine in the clinically at risk groups was 54.3% for the under 65 year group which included pregnant women, and 56.1% in the 65 and over (to end of February 2010).[7] Reasons given for non-immunization include possible side effects and concern about the adequacy of testing. The most common side effects with the vaccines were reported to be redness, pain, swelling, or hardness near the intramuscular injection site, muscular and joint pain, fever, fatigue, and headache.[3,4] Neurological disorders such as encephalomyelitis, neuritis, and Guillain–Barré syndrome have been reported very rarely (<1/10,000) during post-marketing surveillance.[3,4]

Table 1 UK vaccination program for the influenza A H1N1p virus

Phase 1 immunization commenced 21 October 2009
Frontline health care and social care workers
Clinical risk groups, in order of priority:
• Individuals aged 6 months and up to 65 years in the current seasonal flu vaccine clinical at-risk groups[a]
• Pregnant women
• Household contacts of immunocompromised individuals
• People aged 65 and over in the current seasonal flu vaccine clinical at-risk groups[a]
Phase 2 immunization commenced 20 November 2009
• Children over 6 months and under 5 years of age

Notes: [a]Clinical, at high risk groups include those with chronic respiratory, chronic heart, chronic renal, chronic liver or chronic neurological diseases, diabetes mellitus, and those who are immunosuppressed by disease or treatment.

There are significant risks associated with H1N1p infection. WHO figures show that 1%–10% of clinical cases of influenza A (H1N1p) needed hospitalization, with 10%–25% of those hospitalized requiring admission to intensive care units (ICUs).[8] A small proportion (2%–9%) of patients hospitalized with H1N1p infection die. Although, most cases of infection occurred in teenagers and young adults, the rates of hospitalization were highest in very young children.[8] In the UK, there have been 474 deaths due to the virus, to 30 September 2010.[9]

There has been enormous interest in the safety evaluation of pandemic A (H1N1p) 2009 vaccines. In order to monitor the vaccination programs, many existing national systems for signal detection, strength, verification, and confirmation have been improved and new systems instigated. For example, the US Food and Drug Administration has established a number of tools such as existing spontaneous reporting systems (Vaccine Adverse event reporting system [VAERs]), single database links (Vaccine safety datalink [VSD]), and separate database links (post licensure rapid immunization safety monitoring [PRISM]). The limited, publicly available, data to date indicate that the vaccines have a very positive benefit-risk profile with the benefits of reduced disease outweighing any safety risks of vaccination.

Nevertheless, many were anxious about the side effects associated with influenza vaccinations, particularly as these issues have been widely discussed in the media. The aim of this evaluation was to determine the real-life incidence of any side effects by collecting information directly from the recipients of pandemic A (H1N1p) vaccine and other influenza vaccines. The evaluation of side effects following the concurrent use of pandemic A (H1N1p) with seasonal influenza vaccine is of particular interest.

Methods

Study design

Patient Reported Outcomes Based Evaluation (*PROBE*) methodology, which consisted of a web-based system

supplemented by telephone reporting, was used to collect naturalistic data from patients who had received vaccination for H1N1p (swine flu) or seasonal influenza during the UK vaccination program for the 2009–2010 season.

Media advertising (newspaper, TV, and radio) and campaigns in public places such as libraries, children's nurseries, and GP surgeries, as well as workplaces where H1N1p vaccination was being implemented, were used to recruit people.

Patient reported outcomes based evaluation (*PROBE*)

Individuals who had received an influenza vaccination were asked to participate in the evaluation by logging onto a secure website (https://www.myflujag.com/) of Patients Direct, Glasgow, UK. Electronic consent was obtained before individuals were asked to complete a questionnaire, which took less than 5 minutes on the day of immunization, and was followed up at day 3, day 8, week 6, week 12, and week 26. The longer-term follow up was to try to capture rare events such as Guillain–Barré syndrome.

Respondents were questioned about demographic details, the vaccine they had received, and whether they had received a previous swine flu or seasonal flu vaccination. Unfortunately, the exact type of H1N1p vaccine received was not raised during questioning, and recorded. However, we know that the Medicines and Healthcare Products Regulatory Agency reports of adverse events attributed 99% to use of Pandemrix and 1% to Celvapan (where the vaccine was known). Additionally, the government purchase and recommendations were to use Pandemrix unless there was a contraindication such as egg allergy. It is therefore likely that >95% of recipients of the H1N1p vaccination had received the Pandemrix vaccine. The participants were asked directly whether they had experienced any pain or discomfort at the injection site and/or if they had experienced any side effects from the vaccination. The recording of a side effect led to a side effect cascade asking which body areas were associated with the side effects: general, head, chest, stomach, arm, leg, skin, bladder, sexual, emotional, and other, followed by specific side effects in each category such as headache, nausea, and vomiting. The action taken due to a reported side effect and its duration were also requested.

Individuals with no access to the Internet or who preferred to use the telephone could participate in the evaluation by using a Freephone number and speaking to a research nurse. The questions were given in the same structured format, with the research nurse entering the data directly into the web-based survey database. Alternatively, the research nurse provided telephone support on specific questions raised by the patient, and the patient completed the survey online.

Sample size and statistical methods

No formal sample size calculations were completed before the study. To illustrate the power of the study, given that of 143 individuals who did not receive the H1N1p vaccination at baseline, 25.9% experienced discomfort or pain, with 960 individuals receiving a H1N1p vaccination, there was 90% power to have detected an increase in the rate of discomfort or pain to 40%.

Data collected on the day of the immunization and after 3 and 8 days are summarized together as baseline data. Statistical analyses were performed using SPLUS for Windows (v 8.1; TIBCO Software Inc, Palo Alto, CA).

Fisher's exact test or Kruskal–Wallis test were used to test for significance of any differences between vaccines or vaccine combinations. Associations between discomfort or pain after the baseline vaccination and predictors (age, sex, chronic illness group, H1N1p vaccine, and seasonal flu vaccine) were determined using univariate and multivariate logistic regression. Odds ratios with 95% confidence intervals and *P* values are presented.

Results

Respondents

A total of 1103 vaccine recipients (448 males, 655 females) including 134 young children (0–4 years) through their parents or carers participated in the evaluation between 2 November 2009 and 31 May 2010 with 697 (63%) using the web-based mode and 406 (37%) using the telephone. Of the 1103 recipients, 694 (63%) received H1N1p vaccine only, 135 (12%) seasonal vaccine only, 224 (20%) both H1N1p and seasonal vaccines, and 50 (5%) received H1NI or seasonal vaccine along with a non-influenza vaccine such as a travel or pneumococcal vaccine at baseline (Table 2). Half (547/1103) of those vaccinated had a chronic illness. Overall, 960 respondents received the H1N1p influenza vaccine either alone (n = 694), in combination with a seasonal influenza vaccine (n = 224), or in combination with another vaccine (n = 42). Of the 960 H1N1p vaccine recipients, 501 (52%) had a chronic illness and 132 (14%) were in the 0–4 age group (Table 2).

The groups receiving the vaccines were significantly different at baseline for age and existing chronic illness (Table 3). The main age difference being the H1N1p-only group, with the highest proportion of under 5 year olds

Table 2 Demographic and clinical characteristics of respondents by combinations and types of influenza vaccines received at baseline

	Number (% of total) of respondents							
	H1N1p only	Seasonal only	H1N1p and seasonal	H1N1p/seasonal and other	Overall	H1N1p[1]	Seasonal[1]	Other[1]
Respondents	694 (62.9%)	135 (12.2%)	224 (20.3%)	50 (4.5%)	1103	960 (87.0%)	382 (34.6%)	50 (4.5%)
Data collection method								
Web	395 (56.7%)	83 (11.9%)	185 (26.5%)	34 (4.9%)	697	607 (87.1%)	289 (41.5%)	34 (4.9%)
Phone	299 (73.6%)	52 (12.8%)	39 (9.6%)	16 (3.9%)	406	353 (86.9%)	93 (22.9%)	16 (3.9%)
Sex								
Male	287 (64.1%)	60 (13.4%)	81 (18.1%)	20 (4.5%)	448	386 (86.2%)	153 (34.2%)	20 (4.5%)
Female	407 (62.1%)	75 (11.5%)	143 (21.8%)	30 (4.6%)	655	574 (87.6%)	229 (35.0%)	30 (4.6%)
Age (years)								
0–4	123 (91.8%)	2 (1.5%)	7 (5.2%)	2 (1.5%)	134	132 (98.5%)	9 (6.7%)	2 (1.5%)
5–29	42 (58.3%)	9 (12.5%)	18 (25.0%)	3 (4.2%)	72	63 (87.5%)	28 (38.9%)	3 (4.2%)
30–49	111 (47.8%)	31 (13.4%)	77 (33.2%)	13 (5.6%)	232	200 (86.2%)	115 (49.6%)	13 (5.6%)
50–69	229 (54.1%)	65 (15.4%)	101 (23.9%)	28 (6.6%)	423	352 (83.2%)	180 (42.6%)	28 (6.6%)
70+	189 (78.1%)	28 (11.6%)	21 (8.7%)	4 (1.7%)	242	213 (88.0%)	50 (20.7%)	4 (1.7%)
Chronic illness	321 (58.7%)	43 (7.9%)	154 (28.2%)	29 (5.3%)	547	501 (91.6%)	212 (38.8%)	29 (5.3%)
Previous H1N1p flu vaccination	13 (37.1%)	13 (37.1%)	4 (11.4%)	5 (14.3%)	35	20 (57.1%)	20 (57.1%)	5 (14.3%)
Previous seasonal flu vaccination	433 (96.2%)	2 (0.4%)	1 (0.2%)	14 (3.1%)	450	447 (99.3%)	4 (0.9%)	14 (3.1%)

Note: [1]Caution – numbers do not total to sample size due to all counts included.

(123 out of 134 recruited). The main outcomes have been run by different age splits (eg, <5 vs 5+, <18 vs 18+) and the sub group results mirror the overall group with no change to the conclusions (Tables A6 and A7).

The groups were similar for sex split. The percentage who received a previous vaccination was expected to be different, because the H1N1p vaccine was introduced after the start of the seasonal flu vaccination program and therefore many had already received this vaccination. Previous vaccination was not a predictor of pain/discomfort as seen in Table 7.

Table 3 Demographic and clinical characteristics of respondents by combinations and types of influenza vaccines received at baseline (within group)

	H1N1 only	Seasonal only	H1N1 and seasonal	*P* value[a]
N	694	135	224	
Sex				
Male	287 (41.4%)	60 (44.4%)	81 (36.2%)	= 0.247
Female	407 (58.6%)	75 (55.6%)	143 (63.8%)	
Age				
0–4	123 (17.7%)	2 (1.5%)	7 (3.1%)	<0.001
5–29	42 (6.1%)	9 (6.7%)	18 (8.0%)	
30–49	111 (16.0%)	31 (23.0%)	77 (34.4%)	
50–69	229 (33.0%)	65 (48.1%)	101 (45.1%)	
70+	189 (27.2%)	28 (20.7%)	21 (9.4%)	
Chronic illness	321 (46.3%)	43 (31.9%)	154 (68.8%)	<0.001
Prev H1N1 vaccination	13 (1.9%)	13 (9.6%)	4 (1.8%)	<0.001
Prev seasonal vaccination	433 (62.4%)	2 (1.5%)	1 (0.4%)	<0.001

Note: [a]*P* value from Fisher exact test.

Twenty-six week follow-up data were obtained from more than half of the respondents (577, 52%; see Table A1 for follow-up rates).

Side effects

Overall, 42% of respondents reported experiencing a side effect after their baseline vaccination. There was a significant difference between the H1N1p influenza vaccine and seasonal vaccine recipients. Of the 960 recipients of an H1N1p influenza vaccine, a significantly higher proportion (425, 44%) experienced a side effect compared with those who received only the seasonal influenza vaccine (38/143, 27%, $P < 0.001$; Table 4). Greater numbers of side effects were also reported by respondents who had received H1N1p, compared with those who had not ($P < 0.001$; Table 4). The most commonly reported side effects were muscle wasting and headache (>9%).

Muscle weakness and joint pain were reported by a significantly higher proportion of respondents receiving the combination of H1N1p and seasonal influenza vaccines than H1N1p or seasonal influenza vaccination alone (Table 4).

Flu-like symptoms were reported by 24% (195/824) of all recipients responding to this question with 2% (17/824) having to take time off work due to their symptoms. However,

Table 4 Number (%) of respondents recording any side effects after baseline influenza vaccination

Side effects	H1N1p only	Seasonal only	H1N1p and seasonal	H1N1p/ seasonal and other	Overall	*P* value[d]	H1N1p total	Not H1N1p total	*P* value[e]
N ($N_{MISSING}$)	694 (0)	135 (0)	224 (0)	50 (0)	1103 (0)		960 (0)	143 (0)	
Any[a]	314 (45.2%)	35 (25.9%)	94 (42.0%)	20 (40.0%)	463 (42.0%)	0.001	425 (44.3%)	38 (26.6%)	<0.001
Any (including pain/discomfort)[b]	511 (73.6%)	61 (45.2%)	167 (74.6%)	33 (66.0%)	772 (70.0%)	<0.001	708 (73.8%)	64 (44.8%)	<0.001
N side effects (including pain/ discomfort)/ respondent	2.0 (2.8)	0.9 (2.0)	2.4 (3.7)	2.5 (4.5)	2.0 (3.0)	<0.001	2.1 (3.1)	1.0 (2.1)	<0.001
Side effect[c]									
N ($N_{MISSING}$)	688 (6)	131 (4)	220 (4)	49 (1)	1088 (15)				
Muscle wasting	70 (10.2%)	12 (9.2%)	21 (9.5%)	5 (10.2%)	108 (9.9%)	0.985			
Headache	76 (11.0%)	7 (5.3%)	26 (11.8%)	2 (4.1%)	101 (9.3%)	0.090			
Lethargy/tiredness	58 (8.4%)	7 (5.3%)	26 (11.8%)	6 (12.2%)	97 (8.9%)	0.148			
Sleeping problems	49 (7.1%)	4 (3.1%)	16 (7.3%)	3 (6.1%)	72 (6.6%)	0.352			
Fever	35 (5.1%)	4 (3.1%)	13 (5.9%)	2 (4.1%)	54 (5.0%)	0.701			
Loss of appetite	39 (5.7%)	3 (2.3%)	10 (4.5%)	2 (4.12%)	54 (5.0%)	0.462			
Muscle weakness	24 (3.5%)	5 (3.8%)	20 (9.1%)	4 (8.2%)	53 (4.9%)	0.005			
Shaking/tingling	28 (4.1%)	2 (1.5%)	13 (5.9%)	3 (6.1%)	46 (4.2%)	0.172			
Nausea	29 (4.2%)	2 (1.5%)	8 (3.6%)	3 (6.1%)	42 (3.9%)	0.366			
Dizziness	16 (2.3%)	4 (3.1%)	12 (5.5%)	2 (4.1%)	34 (3.1%)	0.114			
Cough	17 (2.5%)	2 (1.5%)	12 (5.5%)	2 (4.1%)	33 (3.1%)	0.100			
Joint pain	14 (2.0%)	1 (0.8%)	14 (6.4%)	2 (4.1%)	31 (2.8%)	0.006			

Notes: [a]Patients responding yes to the question: 'Do you consider that you have had any side effects from this vaccination.' Response options were yes or no; [b]any side effects defined from the side effect cascade plus reports of pain or discomfort; [c]patients responding to the question: 'The unusual symptom affecting me was...": (tick all that apply) – Reports for 3% and above (+ significant findings). [d]*P* value from Fisher's exact test or Kruskal–Wallis test on the difference between the 4 vaccine groups. [e]*P* value from Fisher's exact test or Kruskal–Wallis test on the difference between respondents receiving H1N1p vaccine and those receiving vaccines other than H1N1p (seasonal/seasonal + other).

there were no significant differences in the incidence of flu-like symptoms, absenteeism, or duration of time taken off due to flu-like symptoms between the H1N1p and seasonal vaccine or between the different vaccine combinations (Table 5). Vaccine recipients were specifically asked whether they had any pain or discomfort at the injection site and 57% reported that they had some discomfort or some pain after the baseline vaccination. A significantly higher proportion of H1N1p than seasonal influenza vaccine recipients reported local discomfort/pain (61% vs 26%, $P < 0.001$). The duration

Table 5 Number (%) of respondents recording specific side effects after baseline influenza vaccination

Side effects	H1N1p only	Seasonal only	H1N1p and seasonal	H1N1p/ seasonal and other	Total	*P* value[b]	H1N1p total	Not H1N1p total	*P* value[c]
N ($N_{MISSING}$)	534 (160)	106 (29)	149 (75)	35 (15)	824 (279)		714 (246)	110 (33)	
Flu-like symptoms[a]	128 (24.0%)	18 (17.0%)	38 (25.5%)	11 (31.4%)	195 (23.7%)	0.233	175 (24.5%)	20 (18.2%)	0.184
Absenteeism due to flu-like symptoms	9 (1.7%)	2 (1.9%)	5 (3.4%)	1 (2.9%)	17 (2.1%)	0.486	15 (2.1%)	2 (1.8%)	1.000
Time off due to flu-like symptoms									
None	525 (98.3%)	104 (98.1%)	144 (96.6%)	34 (97.1%)	807 (97.9%)		699 (97.9%)	108 (98.2%)	
One day	1 (0.2%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	2 (0.2%)		1 (0.1%)	1 (0.9%)	
1–3 days	5 (0.9%)	1 (0.9%)	1 (0.7%)	1 (2.9%)	8 (1.0%)	0.198	7 (1.0%)	1 (0.9%)	0.339
>3 days	(0.6%)	(0.0%)	4 (2.7%)	0 (0.0%)	7 (0.8%)		7 (1.0%)	0 (0.0%)	
N ($N_{MISSING}$)	688 (6)	131 (4)	220 (4)	49 (1)	1088 (15)		949 (11)	139 (4)	
Muscular side effects	131 (19.0%)	11 (8.4%)	48 (21.8%)	11 (22.4%)	201 (18.5%)	0.006	190 (20.0%)	11 (7.9%)	<0.001
Narcolepsy/seizure	42 (6.1%)	3 (2.3%)	15 (6.8%)	3 (6.1%)	63 (5.8%)	0.273	60 (6.3%)	3 (2.2%)	0.051

Notes: [a]Patients who had responded that they were 'generally' affected were asked to give more details of these side effects. Options were flu-like symptom; fever; tingling; disturbed sleep; loss of appetite; muscle weakness; muscle pain; shaking; dizziness; sleep problems; liver problems; weight gain; general lethargy/tiredness; feelings of extreme cold; sweating; allergic reaction; other. All options which applied could be ticked. Number (%) of respondents ticking flu-like symptoms are displayed with number (%) recording that they took any time off due to flu-like symptoms; [b]*P* value from Fisher exact test on the difference between the four vaccine groups; [c]*P* value from Fisher exact test on the difference between respondents receiving H1N1p vaccine and those receiving vaccines other than H1N1p (seasonal/seasonal + other).

of discomfort/pain experienced following H1N1p influenza vaccination was also significantly longer compared with seasonal influenza vaccination only ($P < 0.001$; Table 6).

A similar incidence of side effects and local discomfort/pain was seen after concurrent administration of the H1N1p influenza vaccine with the seasonal vaccine as with the H1N1p vaccine alone (combination vs H1N1p only, any side effect: 42% vs 45%, Table 4; discomfort/pain: 145/224, 65% vs 416/694, 60%).

Because the events of side effects and discomfort/pain were recorded in response to separate questions, a post hoc sensitivity analysis was undertaken to compare any side effects measured from the side effect cascade (specific events selected for area of side effect) plus reports of discomfort/pain. These results are included in Table 4. (See Tables A2–A4 for side effect data summarized by reporting method.)

Multivariate logistic regression analyses showed that the female sex and influenza A (H1N1p) vaccination were associated with a significantly higher risk of having pain or discomfort, whereas the 70+ age group was associated with a significantly lower risk (Table 7). Influenza A (H1N1p) vaccination and female sex were also predictive factors in a vaccine recipient experiencing pain or discomfort lasting more than 3 days, along with the 30–49 and 50–69 age groups.

Table 6 Number (%) of respondents with local side effects of discomfort and/or pain and their duration after baseline influenza vaccination

Discomfort/pain	H1N1p total	Not H1N1p total	Overall	*P* value[b]
Presence				
N ($N_{MISSING}$)	960 (0)	143 (0)	1103 (0)	
Discomfort[a]	377 (39.3%)	26 (18.2%)	403 (36.5%)	<0.001
Pain[a]	212 (22.1%)	11 (7.7%)	223 (20.2%)	<0.001
Discomfort/pain[a]	589 (61.4%)	37 (25.9%)	626 (56.8%)	<0.001
None	371 (38.4%)	106 (74.1%)	477 (43.2%)	
Duration				
N ($N_{MISSING}$)	901 (59)	138 (5)	1039 (64)	
<5 min	32 (3.6%)	2 (1.4%)	34 (3.3%)	
>5 min, <1 h	18 (2.0%)	1 (0.7%)	19 (1.8%)	<0.001
>1 h, <1 day	47 (5.2%)	5 (3.6%)	52 (5.0%)	
>1 day, <3 days	278 (30.9%)	16 (11.6%)	294 (28.3%)	
>3 days	155 (17.2%)	8 (5.8%)	163 (15.7%)	

Notes: [a]Patients responding some discomfort or some pain (as applicable) to the question: 'Did you have any pain or discomfort at the injection site.' Response options were some discomfort, some pain or none. Number (%) of respondents selecting some discomfort, some pain and some discomfort or some pain are displayed; [b]*P* value from Fisher exact test on the difference in presence of symptoms and duration responses between respondents receiving H1N1p vaccine and those receiving vaccines other than H1N1p (seasonal/seasonal + other).

Children

Of the 134 vaccine recipients aged under 5 years, 132 received H1N1p vaccine (123 alone, seven in combination with seasonal vaccine, and two with other vaccines). In children under 5 years, and in those under 18 years, any side effects and local discomfort/pain after H1N1p vaccination were reported at a similar frequency to that found in the total population. (See Tables A5 and A6 for age group data.) Meaningful comparisons between children under 5 receiving or not receiving H1N1p vaccine cannot be made as only two vaccine recipients in the under 5 age group did not receive H1N1p. Two children in this age group were hospitalized after receiving the H1N1p vaccine: a 3-year old female with muscle pain, chest, leg, skin, and emotional side effects and a 1-year old female with general side effects.

Hospitalization

Most respondents experienced side effects that needed no action (16%) or were self-treated (20%, Table 8). However, eight vaccine recipients reported side effects leading to a hospital visit during the evaluation: seven after the baseline vaccination, and one at the 26-week follow up. The seven respondents reported 14 side effects after the baseline vaccination. (Table 8; see Table A7 for further details of vaccine recipients requiring hospital action due to a side effect.)

Side effects of special interest

The adverse events of narcolepsy and seizure are of special interest and there was a trend towards a higher proportion of H1N1p vaccine recipients reporting narcolepsy/seizures than with seasonal vaccine recipients (6.3% vs 2.2%, $P = 0.051$; Table 5).

One of the vaccine recipients attending hospital experienced narcolepsy. This was a 59-year-old female who received both H1N1p and seasonal influenza vaccine due to chronic disease. She also experienced general side effects (fever, tingling, disturbed sleep, loss of appetite, lethargy/tiredness), head-related side effects (headache), chest-related side effects (chest tightness, palpitations), and emotional side effects (difficulty concentrating and increased irritability), leading to a visit to an accident and emergency department. The respondent was given advice only, no formal diagnosis, and did not require treatment or hospital admission. Only one other recipient of the H1N1p influenza vaccine required treatment from a doctor for narcolepsy/seizures. This was a 3.5 year-old male, who experienced seizures/fits 12 weeks after being vaccinated against influenza A (H1N1p), who was treated by his doctor. Further investigation indicates that it is

Table 7 Multivariate regression analyses for vaccine recipients having pain or discomfort after baseline vaccination

Predictor	Level	Odds ratio (95% CI), *P* value	Overall *P* value
Pain or discomfort			
Age	0–4	–	$P < 0.001$
	5–29	1.06 (0.55, 2.06), $P = 0.862$	
	30–49	1.21 (0.71, 2.07), $P = 0.481$	
	50–69	0.59 (0.35, 1.00), $P = 0.049$	
	70+	0.24 (0.13, 0.43), $P < 0.001$	
Sex	Female	2.12 (1.62, 2.77), $P < 0.001$	
Chronic illness special group	Yes	1.21 (0.90, 1.62), $P = 0.203$	
H1N1p flu vaccination	Yes	4.69 (2.85, 7.71), $P < 0.001$	
Seasonal flu vaccination	Yes	1.06 (0.68, 1.66), $P = 0.794$	
Previous H1N1p vaccination	Yes	1.34 (0.63, 2.85), $P = 0.447$	
Previous seasonal flu vaccination	Yes	1.28 (0.82, 1.98), $P = 0.276$	
Pain or discomfort lasting >3 days			
Age	0–4	–	$P = 0.002$
	5–29	2.26 (0.89, 5.74), $P = 0.085$	
	30–49	3.44 (1.58, 7.47), $P = 0.002$	
	50–69	2.18 (0.99, 4.80), $P = 0.054$	
	70+	1.40 (0.58, 3.40), $P = 0.458$	
Sex	Female	1.90 (1.29, 2.79), $P = 0.001$	
Chronic illness special group	Yes	1.02 (0.70, 1.50), $P = 0.914$	
H1N1p flu vaccination	Yes	4.19 (1.88, 9.35), $P < 0.001$	
Seasonal flu vaccination	Yes	1.21 (0.72, 2.05), $P = 0.473$	
Previous H1N1p vaccination	Yes	1.13 (0.38, 3.39), $P = 0.823$	
Previous seasonal flu vaccination	Yes	0.95 (0.56, 1.63), $P = 0.858$	

likely that this attendance was due to the child's underlying health condition and not due to the vaccine.

No other side effects of special interest required treatment from a doctor or a visit to hospital.

Discussion

The *PROBE* methodology of an online questionnaire with a telephone option available for respondents provided an effective way of collecting safety data from a large number of vaccine recipients (n = 1103) during the 2009–2010 season. Using a simple questionnaire, which took about 5 minutes to complete, vaccine recipients gave demographic details including age and sex, confirmed the presence or absence of chronic illness, and provided vaccine and side effect information including duration and action taken due to the side effect.

Logistic regression analyses showed that H1N1p influenza vaccination and female sex were both predictive factors in a vaccine recipient reporting a side effect of pain or discomfort, and of these side effects lasting for more than 3 days. The association of the influenza A (H1N1p) vaccine with a higher incidence of local side effects was in line with data from previously reported studies, and none had a serious outcome. Clinical studies in children have shown that the influenza A (H1N1p) adjuvanted split virion vaccine was more reactogenic than the whole virion vaccine seasonal vaccine.[10] A previous study has also shown that injection site reactions were reported more frequently for recipients of H1N1p vaccine adjuvanted with ASO3A than without adjuvant, but these reactions were generally transient.[11] Mild side effects such as local discomfort/pain in the arm after vaccination with Pandremix have been reported in the manufacturer's clinical trials, and are to be expected given the nature of the adjuvant used in the vaccine to stimulate a strong immune response.

Chronic illness may also be an important risk factor associated with injection site pain or discomfort. Interestingly, the analyses also showed that old age (over 70 years) was the main risk factor associated with a decreased likelihood of reporting injection site pain or discomfort after vaccination. Whether this is due to greater tolerance of pain or discomfort, or a reduction in local reactions in this age group, is unclear.

Recent reports of an increased risk of narcolepsy and other neurological events cannot be confirmed from this evaluation. There were no reported cases of Guillain–Barré syndrome, but with a coincident background disease rate of 21.5 cases of 10 million individuals within 6 weeks,[12] this was hardly unexpected.

Table 8 Number (%) of respondents recording action taken due to a side effect following baseline vaccination, with type of side effect requiring hospital use

Action taken due to a side effect	H1N1p total	Not H1N1p total	Overall
N ($N_{MISSING}$)[a]	949 (11)	139 (4)	1088 (15)
No event	535 (56.4%)	105 (75.5%)	640 (58.8%)
Nothing	165 (17.4%)	14 (10.1%)	179 (16.5%)
Self-treated	199 (21.0%)	16 (11.5%)	215 (19.8%)
Doctor advice	27 (2.8%)	1 (0.7%)	28 (2.6%)
Doctor treatment	17 (1.8%)	2 (1.4%)	19 (1.7%)
Hospital	6 (0.6%)	1 (0.7%)	7 (0.6%)
P value[b]	0.002		
Health service use	50 (5.3%)	4 (2.9%)	54 (5.0%)
P value[b]	0.296		
Number of side effects requiring hospital use of type reported			
Total	13	1	14
General	4	0	4
Muscular	1	0	1
Head	1	0	1
Chest	2	0	2
Stomach	0	1	1
Leg	1	0	1
Skin	1	0	1
Emotional	2	0	2
Narcolepsy/seizure	1	0	1

Notes: [a]Patients responding to the question 'What did you do about your side effect.' Options were: I did nothing; I treated it myself; I went to the doctor and was given advice; I went to the doctor and was given treatment; I was taken to hospital; [b]*P* value from Fisher exact test on the difference in responses between respondents receiving H1N1p vaccine and those receiving vaccines other than H1N1p (seasonal/seasonal + other).

In this evaluation, the proportion of respondents reporting any side effect, pain, or discomfort after vaccination with pandemic H1N1p vaccine was similar to that in those receiving concurrent administration of the vaccine with the seasonal vaccine. These results differ from those of a recently reported, randomized study comparing the safety and immunogenicity of participants receiving an H1N1p vaccine (Fluval®) or the H1N1p and seasonal whole-virion non-adjuvanted vaccines. That study showed that adverse events and pain at the injection site were reported by more recipients of both vaccines than by those who received the H1N1p vaccine only (any 18% vs 10%, pain 10% vs 4%).[13]

Strengths and limitations of the study

The strengths of using the methodology outlined in this paper are that it allowed patient-reported outcome data from a large number of vaccine recipients to be collected simply and quickly. When required, the respondents could be contacted again by email or telephone to provide longitudinal follow-up data, with 26-week data collected from more than half of the respondents in this evaluation. The option of telephone reporting supported by trained staff, in addition to web-based data collection, is important as it widens participation and enables evaluation of a study population that is more representative of the target population, thus reducing bias.

Most of the methods employed by the regulatory authorities in Europe or the US for monitoring adverse events still rely on spontaneous reporting. In contrast to spontaneous reporting systems, the *PROBE* methodology should result in less underreporting (as participants are already part of the process), should be less affected by media reporting or physician prejudices, and be able to calculate a numerator (number of events) and denominator (number of people exposed/vaccinated). Additionally, the databases interrogated by the regulatory authorities need to pre-specify the events of interest or be limited to generic headings which often do not capture the detail required. The *PROBE* methodology can also assess overall benefit:risk by obtaining quality of life data at the same time as adverse event and impact on work/education data (absenteeism/presenteeism measure).

A limitation of the methodology, however, is that despite including data collected using a Freephone service, the population studied may not fully represent the views of the general population. There may also be some disadvantages from grouping together the two different modes of reporting and this study showed that there were differences in the characteristics and responses of telephone and Internet participants. There were also differences in the baseline characteristics of the populations receiving each vaccine, which could have contributed to the findings.

Participants were trusted to answer the questions honestly, particularly as they may have been influenced by negative publicity surrounding the use of the H1N1p influenza vaccine in the UK. Including questions regarding pregnancy and type of vaccine received, would have been useful, in order to provide further data. A comparison of the two novel vaccines used in the UK vaccination program for influenza A (H1N1p) may have been of interest, although respondents may not have been aware of which vaccine they had received.

Finally, we gathered information on absenteeism from work but presenteeism is gaining recognition as being a more useful indicator of 'impact on work' and we could have used a suitable questionnaire to assess this.

Conclusions

Safety and tolerability data from influenza vaccine recipients including young children (via parents/carers) can be effectively collected using an online questionnaire with a telephone option (*PROBE*). The influenza A (H1N1p)

vaccine was well tolerated, but was associated with more local short-term reactions than the seasonal influenza vaccine.

Authors' contributions

AW was involved in the conception, design, set up, acquisition of data, analysis and interpretation of data, reviewing drafts of the manuscript, and approval of final version.

GC was involved in the conception, design, set up, acquisition of data, analysis and interpretation of data, reviewing drafts of the manuscript, and approval of final version.

NP was involved in acquisition of data, data verification, designing data reports, analysis and interpretation of data, designing the manuscript content, reviewing drafts of the manuscript, and approval of final version.

AMcC was involved in the data extraction, data cleaning, designing data reports, analysis and statistical interpretation of data, reviewing drafts of the manuscript, and approval of final version.

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Disclosures

AW has no competing interests. He is a director of the company Patients Direct. GC has no competing interests. He is a director of the company Patients Direct. NP has no competing interests. He is an employee of the company Patients Direct. AMcC has no competing interests.

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Appendix 1

Description of data: statistical summaries of follow-up data at 6, 12 and 26 weeks, respondents recording any side effects and discomfort/pain split by reporting method and age groups (<5 and ≥5, <18, and ≥18 years), and individual patient data for patients with a side effect leading to hospitalization (Tables A1 to A7).

Table A1 Follow-up rates by combinations of vaccines received at baseline, all patients

	N	H1N1 only	Seasonal only	H1N1 and seasonal	H1N1/seasonal and other	*P* value[a]
6 weeks						
N ($N_{MISSING}$)	1103 (0)	694 (0)	135 (0)	224 (0)	50 (0)	
No	390 (35.4%)	229 (33.0%)	43 (31.9%)	98 (43.8%)	20 (40.0%)	
Yes	713 (64.6%)	465 (67.0%)	92 (68.1%)	126 (56.2%)	30 (60.0%)	0.020
12 weeks						
N ($N_{MISSING}$)	1103 (0)	694 (0)	135 (0)	224 (0)	50 (0)	
No	457 (41.4%)	271 (39.0%)	52 (38.5%)	113 (50.4%)	21 (42.0%)	
Yes	646 (58.6%)	423 (61.0%)	83 (61.5%)	111 (49.6%)	29 (58.0%)	0.023
26 weeks						
N ($N_{MISSING}$)	1103 (0)	694 (0)	135 (0)	224 (0)	50 (0)	
No	526 (47.7%)	307 (44.2%)	61 (45.2%)	130 (58.0%)	28 (56.0%)	0.003
Yes	577 (52.3%)	387 (55.8%)	74 (54.8%)	94 (42.0%)	22 (44.0%)	

Note: [a]*P* value from Fisher's exact test.

Table A2 Number (%) of respondents recording side effects following baseline influenza vaccination, by contact method

Side effects	H1N1 only	Seasonal only	H1N1 and seasonal	H1N1/ seasonal and other	*P* value[a]	Overall	H1N1 total	Not H1N1 total	*P* value[b]
Web									
N ($N_{MISSING}$)	395 (0)	83 (0)	185 (0)	34 (0)		697 (0)	607 (0)	90 (0)	
Any side effects	163 (41.3%)	22 (26.5%)	72 (38.9%)	10 (29.4%)	0.055	267 (38.3%)	243 (40.0%)	24 (26.7%)	0.015
Discomfort or pain	257 (65.1%)	29 (34.9%)	125 (67.6%)	18 (52.9%)	<0.001	429 (61.5%)			
Any (including pain/discomfort)[c]	291 (73.7%)	43 (51.8%)	140 (75.7%)	19 (55.9%)	<0.001	493 (70.7%)	448 (73.8%)	45 (50.0%)	<0.001
Telephone									
N ($N_{MISSING}$)	299 (0)	52 (0)	39 (0)	16 (0)		406 (0)	353 (0)	53 (0)	
Any side effects	151 (50.5%)	13 (25.0%)	22 (56.4%)	10 (62.5%)	0.002	196 (48.3%)	182 (51.6%)	14 (26.4%)	0.001
Discomfort or pain	159 (53.2%)	7 (13.5%)	20 (51.3%)	11 (68.8%)	<0.001	197 (48.5%)			
Any (including pain/discomfort)[c]	220 (73.6%)	18 (34.6%)	27 (69.2%)	14 (87.5%)	<0.001	279 (68.7%)	260 (73.7%)	19 (35.8%)	<0.001

Notes: [a]*P* value from Fisher's exact test on the difference between the four vaccine groups; [b]*P* value from Fisher's exact test on the difference between respondents receiving H1N1 vaccine and those receiving vaccines other than H1N1 (seasonal/seasonal + other); [c]any side effects defined from the side effect cascade plus reports of pain or discomfort.

Table A3 Number (%) recording side effects following baseline influenza vaccination, by age group, and contact method

Side effects	N	Age at baseline (years)		Age at baseline (years)		Contact method	
		<18	≥18	<5	≥5	Telephone	Web
N ($N_{MISSING}$)	1103 (0)	157 (0)	946 (0)	132 (0)	971 (0)	406 (0)	697 (0)
Any side effects[a]	463 (42.0%)	74 (47.1%)	389 (41.1%)	61 (46.2%)	402 (41.4%)	196 (48.3%)	267 (38.3%)
	P value[b]	0.163		*P* = 0.302		0.001	
Discomfort or pain	626 (56.8%)	101 (64.3%)	525 (55.5%)	85 (64.4%)	541 (55.7%)	197 (48.5%)	429 (61.5%)
	P value[b]	0.045		*P* = 0.062		<0.001	

Notes: [a]Any side effects defined from the side effect cascade plus reports of pain or discomfort; [b]*P* value from Fisher's exact test.

Table A4 Number (%) recording side effects following baseline H1N1 influenza vaccination, by age, and contact method

Side effects	N	Age at baseline (years)		Age at baseline (years)		Contact method	
		<18	≥18	<5	≥5	Telephone	Web
Received H1N1 flu vaccine							
N ($N_{MISSING}$)	960 (0)	153 (0)	807 (0)	130 (0)	830 (0)	353 (0)	607 (0)
Any side effects[a]	425 (44.3%)	73 (47.7%)	352 (43.6%)	60 (46.2%)	365 (44.0%)	182 (51.6%)	243 (40.0%)
P value[b]		0.375		0.704		0.001	
Discomfort or pain	589 (61.4%)	100 (65.4%)	489 (60.6%)	85 (65.4%)	504 (60.7%)	190 (53.8%)	399 (65.7%)
P value[b]		0.279		0.334		<0.001	
Did not receive H1N1 flu vaccine							
N ($N_{MISSING}$)	143 (0)	4 (0)	139 (0)	2 (0)	141 (0)	53 (0)	90 (0)
Any side effects[a]	38 (26.6%)	1 (25.0%)	37 (26.6%)	1 (50.0%)	37 (26.2%)	14 (26.4%)	24 (26.7%)
P value[b]		1.000		0.462		1.000	
Discomfort or pain	37 (25.9%)	1 (25.0%)	36 (25.9%)	0 (0.0%)	37 (26.2%)	7 (13.2%)	30 (33.3%)
P value[b]		1.000		1.000		0.010	

Notes: [a]Any side effects defined from the side effect cascade plus reports of pain or discomfort; [b]*P* value from Fisher's exact test.

Table A5 Number (%) recording side effects following baseline influenza vaccination, by age group (<18, ≥18 years)

Side effects	H1N1 only	Seasonal only	H1N1 and seasonal	H1N1/seasonal and other	*P* value[a]	Overall	H1N1 total	Not H1N1 total	*P* value[b]
Aged <18 years									
N ($N_{MISSING}$)	138 (0)	4 (0)	12 (0)	3 (0)		157 (0)	153 (0)	4 (0)	
Any	–	–	–	–		74 (47.1%)	73 (47.7%)	1 (25.0%)	0.623
Discomfort/pain	90 (65.2%)	1 (25.0%)	8 (66.7%)	2 (66.7%)	0.428	101 (64.3%)	–	–	
Any (including pain/discomfort)[c]	109 (79.0%)	2 (50.0%)	10 (83.3%)	2 (66.7%)	0.352	123 (78.3%)	121 (79.1%)	2 (50.0%)	0.205
N ($N_{MISSING}$)	138 (0)	4 (0)	12 (0)	3 (0)		157 (0)	153 (0)	4 (0)	
Narcolepsy/ seizures	17 (12.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.719	17 (10.8%)	17 (11.1%)	0 (0.0%)	1.000
Aged ≥18 years									
N ($N_{MISSING}$)	556 (0)	131 (0)	212 (0)	47 (0)		946 (0)	807 (0)	139 (0)	
Any	–	–	–	–		389 (41.1%)	352 (43.6%)	37 (26.6%)	<0.001
Discomfort/pain	326 (58.6%)	35 (26.7%)	137 (64.6%)	27 (57.4%)	<0.001	525 (55.5%)	–	–	
Any (including pain/discomfort)[c]	402 (72.3%)	59 (45.0%)	157 (74.1%)	31 (66.0%)	<0.001	649 (68.6%)	587 (72.7%)	62 (44.6%)	<0.001
N ($N_{MISSING}$)	550 (6)	127 (4)	208 (4)	46 (1)		931 (15)	796 (11)	135 (4)	
Narcolepsy/ seizures	25 (4.5%)	3 (2.4%)	15 (7.2%)	3 (6.5%)	0.185	46 (4.9%)	43 (5.4%)	3 (2.2%)	0.135

Notes: [a]*P* value from Fisher's exact test on the difference between the four vaccine groups; [b]*P* value from Fisher's exact test on the difference between respondents receiving H1N1 vaccine and those receiving vaccines other than H1N1 (seasonal/seasonal + other); [c]any side effects defined from the side effect cascade plus reports of pain or discomfort.

Table A6 Number (%) recording side effects following baseline influenza vaccination, by age group (<5, ≥5 years)

Side effects	H1N1 only	Seasonal only	H1N1 and seasonal	H1N1/seasonal and other	*P* value[a]	Overall	H1N1 total	Not H1N1 total	*P* value[b]
Aged <5 years									
N ($N_{MISSING}$)	123 (0)	2 (0)	5 (0)	2 (0)		132 (0)	130 (0)	2 (0)	
Any	–	–	–	–		61 (46.2%)	60 (46.2%)	1 (50.0%)	1.000
Discomfort/pain	81 (65.9%)	0 (0.0%)	3 (60.0%)	1 (50.0%)	0.294	85 (64.4%)	–	–	
Any (including pain/discomfort)[c]	97 (78.9%)	1 (50.0%)	4 (80.0%)	1 (50.0%)	0.365	103 (78.0%)	102 (78.5%)	1 (50.0%)	0.392
Aged ≥5 years									
N ($N_{MISSING}$)	571 (0)	133 (0)	219 (0)	48 (0)		971 (0)	830 (0)	141 (0)	
Any	–	–	–	–		402 (41.4%)	365 (44.0%)	37 (26.2%)	<0.001
Discomfort/pain	335 (58.7%)	36 (27.1%)	142 (64.8%)	28 (58.3%)	<0.001	541 (55.7%)	–	–	
Any (including pain/discomfort)[c]	414 (72.5%)	60 (45.1%)	163 (74.4%)	32 (66.7%)	<0.001	669 (68.9%)	606 (73.0%)	63 (44.7%)	<0.001

Notes: [a]*P* value from Fisher's exact test on the difference between the four vaccine groups; [b]*P* value from Fisher's exact test on the difference between respondents receiving H1N1 vaccine and those receiving vaccines other than H1N1 (seasonal/seasonal + other); [c]any side effects defined from the side effect cascade plus reports of pain or discomfort.

Table A7 Patients with a side effect leading to hospitalization

Subject	Age (years)/sex	Influenza vaccine history	Influenza vaccine received at baseline	Reason given for hospitalization	Survey time	Subsequent vaccinations	Co-existing conditions
347	58/female	None	Seasonal only	Stomach	Baseline	No subsequent vaccinations (up to week 12)	None known
376	3/female	Prior seasonal	H1N1 only	Muscle Chest Legs Skin Emotional	Baseline	No subsequent data	Cerebral Palsy
419	42/male	None	H1N1 and seasonal	Legs	Baseline	H1N1 at 6 weeks No subsequent vaccinations (up to week 12)	Multiple sclerosis
493	61/female	Prior seasonal	H1N1 only	Chest	26 weeks	No subsequent vaccinations (up to week 26)	None known
585	59/female	None	H1N1 and seasonal	General Head Chest Emotional Narcolepsy/seizures	Baseline	No subsequent vaccinations (up to week 26)	Chronic disease group Asthma
743[a]	55/female	Prior seasonal	H1N1 only	General	Baseline	No subsequent vaccinations (up to week 26)	
984[a]	1/female	Prior H1N1	H1N1 only	General	Baseline	No subsequent vaccinations (up to week 26)	
1124	45/female	Prior seasonal	H1N1 only	General	Baseline	No subsequent data	None known

Note: [a]Follow-up contact reports have indicated that patients 743 and 984 did not attend hospital in relation to their vaccine and may be classified as 'incorrect reports'.