MAJOR ARTICLE

Effectiveness of an Adjuvanted Monovalent Vaccine Against the 2009 Pandemic Strain of Influenza A(H1N1)v in Stockholm County, Sweden

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Background. Vaccination against the pandemic influenza A(H1N1)v was performed in many countries during 2009, but population-based data on vaccine effectiveness are lacking.

Methods. We conducted a prospective cohort study involving all inhabitants in Stockholm County (n = 2,019,183) who were offered a monovalent AS03-adjuvanted influenza A(H1N1)v vaccine (Pandemrix, GSK), between 12 October and 31 December 2009. Overall vaccine coverage was 52%. A Web-based register with data on all vaccinated was linked by unique personal identification number to mandatory reports of influenza A(H1N1)v diagnoses. Vaccine failure was defined as a diagnosis or admission to hospital because of influenza >14 days after vaccination. Risk factors associated with vaccine failure were investigated by conditional stepwise logistic regression in a nested case–control study. The weekly incidence rate ratio for being diagnosed with influenza among vaccinated versus nonvaccinated persons was calculated.

Results. Vaccine failure was seen in 25 patients, 11 children and 14 adults, of 2594 patients diagnosed with influenza A(H1N1)v. Compared with age-matched controls, patients with vaccine failure were more often immunocompromised (Hazard Ratio, 4.89; 95% confidence interval [CI], 2.19–10.89). During the 4 weeks with maximum influenza activity, the relative risk per week for an influenza A(H1N1)v diagnosis in the vaccinated population was .06 (95% CI .008–.41), .13 (95% CI .06–.27), .05 (95% CI .02–.12), and .07 (95% CI .03–.15), respectively, corresponding to a weekly vaccine effectiveness of 87–95%.

Conclusions. The monovalent AS03-adjuvanted influenza vaccine was highly effective in prevention of the pandemic influenza in Stockholm County. A single dose seemed to be sufficient in most, both children and adults, except in immunocompromised hosts.

Several new vaccines were developed against the novel influenza A(H1N1)v and recommended for use in the European Union during the 2009 pandemic [1]. The results concerning immunogenicity for both adjuvanted and nonadjuvanted vaccines have been promising in adults as well as children [2–8], and reports from studies on small or selected populations indicate that the pandemic vaccines were effective [9–15]. However, large population-based studies where high vaccine coverage was achieved prior to the peak of the pandemic are lacking.

Sweden used the AS03-adjuvanted monovalent vaccine from GSK (Pandemrix) for the vaccination campaign against the pandemic influenza. The first doses of vaccine were distributed in the middle of October 2009, which coincided with the beginning of the major peak of the epidemic.

In Stockholm County, with ~2 million inhabitants, nearly a third of the population was immunized within

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6–7 weeks, and half the population was immunized before the end of the year. By linking the Web-based vaccine register to the mandatory notifications for diagnoses of influenza A(H1N1)v, it was possible to prospectively study the effectiveness of the vaccine during the peak weeks of the influenza pandemic.

MATERIALS AND METHODS

Demographic Data

Stockholm County had 2,019,183 inhabitants in December 2009. The vaccination campaign against the pandemic influenza A(H1N1)v included all persons ≥6 months of age (n = 2,005,849 [Table 1]).

The National Board of Health defined the following groups as being especially at risk for developing severe influenza [16]: pregnant women, persons with certain chronic diseases (diabetes mellitus or pulmonary, heart, liver, renal, and immunocompromising disease), extreme obesity (body mass index [BMI] > 40) or neuromuscular disease affecting breathing capacity, and children with multiple dysfunctions/handicaps. The same groups, together with health-care workers, were given priority when the vaccination campaign started [17]. There were approximately 20,000 pregnant women during the vaccination period, based on the number of yearly births, and based on diagnoses from primary care and hospitals about 10% of the population were estimated to belong to another medical risk group.

Data Sources

Sminet. Influenza A(H1N1)v became a notifiable disease under the Swedish Communicable Diseases Act on 15 May 2009. Laboratory-verified cases had to be reported, using the patient's unique identification code, by the microbiological laboratory and the clinician responsible for the care of the patient. Cases with clinical suspicion of influenza were not reported. Reports were made to the regional county medical officer (CMO) and to the Swedish Institute for Infectious Disease Control (SMI) using a Web-based reporting system for notifiable diseases called "Sminet" [18].

Vaccinera. A Web-based register, "Vaccinera," was developed for the vaccination campaign. The register included the date of vaccination, batch number of the vaccine, the person's unique identification number, and if the person belonged to a medical risk group. "Vaccinera" had to be completed before the care giver could be reimbursed for performing the vaccination.

Common Health-Care Registers for Stockholm County Council (GVR). The diagnostic registers used by all acute care and geriatric hospitals in Stockholm County (called "GVR") can be accessed by the CMO in order to establish if a person with a notifiable disease, eg, influenza A(H1N1)v, has been admitted to the hospital.

Course of the Influenza A(H1N1)v Epidemic in Stockholm County

The first cases of influenza A(H1N1)v were diagnosed in May 2009. Initially, when there were mostly imported cases, a "search-and-contain" strategy was applied. In the beginning of July (Figure 1) this was changed to recommend testing only those who were severely ill or who belonged to a medical risk group, a strategy that was in place until the end of the epidemic. Around school start, in the second half of August, there was a small increase in the number of cases, but the main peak of the pandemic began in the second week of October (week 41), reached its highest point in the middle of November (weeks 46–47), and was over by the end of the year.

Vaccination

Vaccine Used. Sweden used Pandemrix® (GSK), a split-virion, inactivated, monovalent AS03-adjuvanted vaccine. A dose (.5 mL) contained 3.75 μg of an influenza A/California/7/2009 (H1N1)v–like strain and an adjuvant composed of squalene, DL-α-tocopherol, and polysorbate 80.

Vaccination Campaign. Initially (week 42), 2 doses of vaccine were recommended for all, .25 mL for children 3–12 years and .5 mL for persons ≥13 years of age. In children 6 months to 3 years of age, only those with chronic conditions were vaccinated initially, which was changed to a general recommendation from week 46.

Vaccine coverage by weeks 45 and 50 was ~50% and 80%, respectively, in pregnant women, and 50% and 100%, respectively, in persons with chronic diseases (Figure 2). Overall, patients belonging to medical risk groups constituted a large percentage of those vaccinated during the early part of the campaign, 74%, 72%, 60%, and 41%, respectively, during weeks 42–45. General vaccination of children >3 years of age started in week 45, followed by general vaccination of adults from weeks 48–49 (Figure 3). By the end of the year 52% of the population had received at least 1 dose of the vaccine, and 4% had also been given a second dose.

Diagnosis of Influenza A(H1N1)v

The diagnosis of influenza A(H1N1)v was established with a real-time polymerase chain reaction (RT-PCR) method at the microbiological laboratory at the Karolinska University Hospital. The basic method used for the detection of influenza A has been described earlier [19], and the type-specific RT-PCR for influenza A(H1N1)v was performed using a method developed at SMI using primers and probes distributed by the U.S. Centers for Disease Control and Prevention (Mia Brytting, personal communication).

Definitions and Statistics

According to the recommendations of the European Center for Disease Control, a person is considered to be protected 14 days

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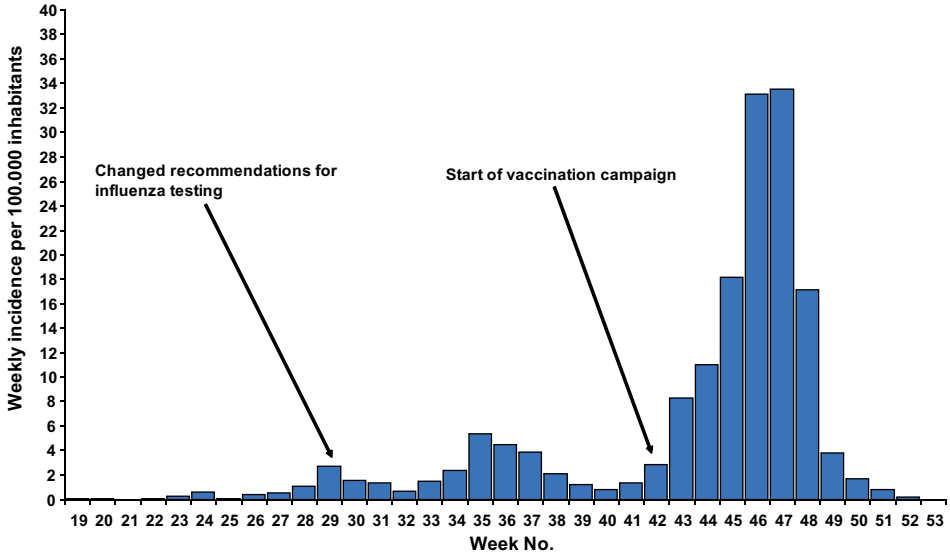

Figure 1. Weekly incidence of influenza A(H1N1)v during 2009 in Stockholm County. In total 3298 cases were diagnosed, 2594 during the period of the vaccination campaign, weeks 42–53.

after vaccination against influenza has been performed [20]. Because date of onset of illness was often lacking from the notification data, we defined vaccine failure as a diagnosis of influenza, or hospital admittance because of influenza, >14 days after the first vaccination, in both children and adults. Date of onset, in persons where this was reported, was on average 2 days prior to diagnosis/hospital admittance (data not shown). Data on patients diagnosed with influenza A(H1N1)v during the study period (weeks 42–53) were obtained from "Sminet" and linked by the person's unique personal ID number to "Vaccinera" and to "GVR."

To investigate the risk factors associated with vaccine failure a conditional univariate and stepwise logistic regression was used. As all the risk factors were of biologic importance, we included any variable whose univariate test demonstrated reasonable standard error estimates. The significance level for entering a variable into the model and removing a variable from the model was .05. Data were provided on 25 cases with a diagnosis of influenza A(H1N1)v and on 100 controls, not diagnosed with influenza, matched for the same age and the same day of vaccination (1:4 matching in a nested case-control design). The cases were also compared with patients who had been

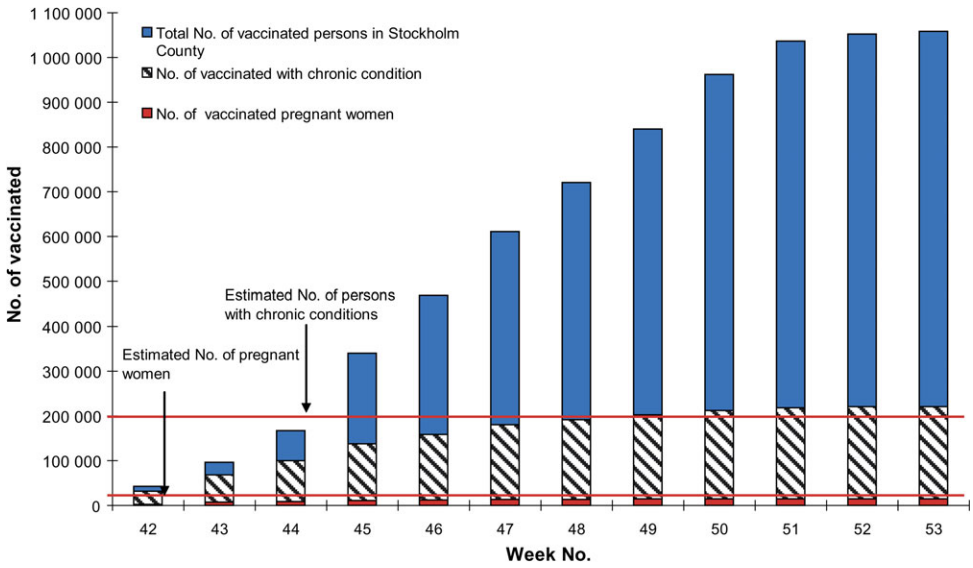

Figure 2. Cumulated no. of persons vaccinated per week, from the start of the vaccination campaign in week 42 until the end of 2009, in total and in persons given priority to vaccination, according to recommendations from the national board of health, due to pregnancy or chronic underlying conditions.

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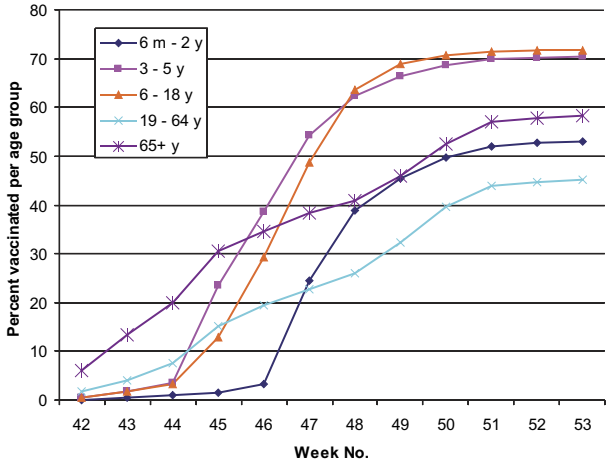

Figure 3. Cumulated percentage of the population, in different age groups, who had received at least 1 dose of vaccine against influenza A(H1N1)v per week, weeks 42–53, 2009.

vaccinated between one and 14 days before they were diagnosed with influenza. Here, the cases and controls were matched for the same day of vaccination (1: a varying number of controls in a nested case–control design).

The cumulative incidence rate ratios, per week, for being diagnosed with influenza among vaccinated versus nonvaccinated persons were calculated starting from 2 weeks after the vaccination campaign began until the end of the year. For a given week the rate of persons who developed influenza >14 days after being vaccinated out of the cumulated number of persons who had been vaccinated up until 2 weeks before was compared with the rate of persons with an influenza diagnosis out of all nonvaccinated persons, excluding persons who had had a previous influenza diagnosis. The χ^2test was used for the comparison of rates and, where appropriate, to calculate relative risks with 95% confidence interval (CI). Statistical significance was set at the .05 level with 2-sided P values. All statistical analyses were performed with GraphPad Instat v. 3.10, GraphPad Software Inc., or SAS System 9.1, SAS Institute Inc.

RESULTS

Influenza A(H1N1)v Diagnoses

During the study period (weeks 42–53, 2009) a total of 1,051,316 persons received at least 1 dose of vaccine. During the same period, 2594 patients older than 6 months of age were diagnosed with influenza A(H1N1)v, 285 (11%) were hospitalized, and 11 persons (.4%) died. The highest incidence was seen in children (Table 1).

In 188 of 2594 (7%) patients, 141 outpatients and 47 inpatients, the influenza diagnosis was established after a person had been vaccinated. None of the patients who died had been vaccinated. Twenty-five of 188 patients, 17 outpatients and 8 inpatients, filled the criteria for vaccine failure (Figure 4 and Table 2). All children but one had received a single dose of vaccine. Immunocompromising conditions (n = 10) and chronic pulmonary disease (n = 8) were the most common underlying conditions among patients with vaccine failure. Five of 8 patients who required hospital treatment were severely immunocompromised, having stem cell transplants [2], hematologic malignancies [2], or rheumatoid arthritis [1].

Underlying chronic conditions, and especially immunocompromising conditions (Hazard Ratio (HR), 4.89; 95% CI, 2.19, 10.89), were significantly more common among the 25 patients with vaccine failure than in controls (Table 3). A comparison of possible risk factors was also made between cases with vaccine failure and patients who had been diagnosed with influenza A(H1N1)v within 1–14 days after being vaccinated (n = 73). The 2 groups had similar age and sex distributions, but the presence of an immunocompromising condition was significantly

Table 1. Age and Sex Distribution of the Population 6 Months of Age or Older in Stockholm County in December 2009 (Statistics Sweden) and Cumulative Incidence per 100,000 Inhabitants of a Diagnosis of Influenza A(H1N1)v and Hospital Treatment Because of Influenza A(H1N1)v During Weeks 42–53, 2009

	No. of persons in Stockholm County		Cumulative incidence of influenza A(H1N1)v diagnosis		Cumulative incidence of influenza A(H1N1)v hospitalizations	
Age group	Males	Females	Males	Females	Males	Females
6 months–2 years	36,062	34,050	397	364	77.7	58.7
3–5 years	40,307	38,451	372	322	24.8	23.4
6–12 years	79,330	75,627	430	353	21.4	15.9
13–18 years	75,118	71,026	193	196	14.6	14.1
19–29 years	147,156	147,502	92	154	7.5	20.3
30–39 years	157,642	154,612	72	151	3.8	14.9
40–49 years	151,108	147,026	78	97	11.3	17.1
50–64 years	176,393	178,488	39	57	11.9	13.4
≥65 years	127,755	168,197	5	10	1.7	4.8

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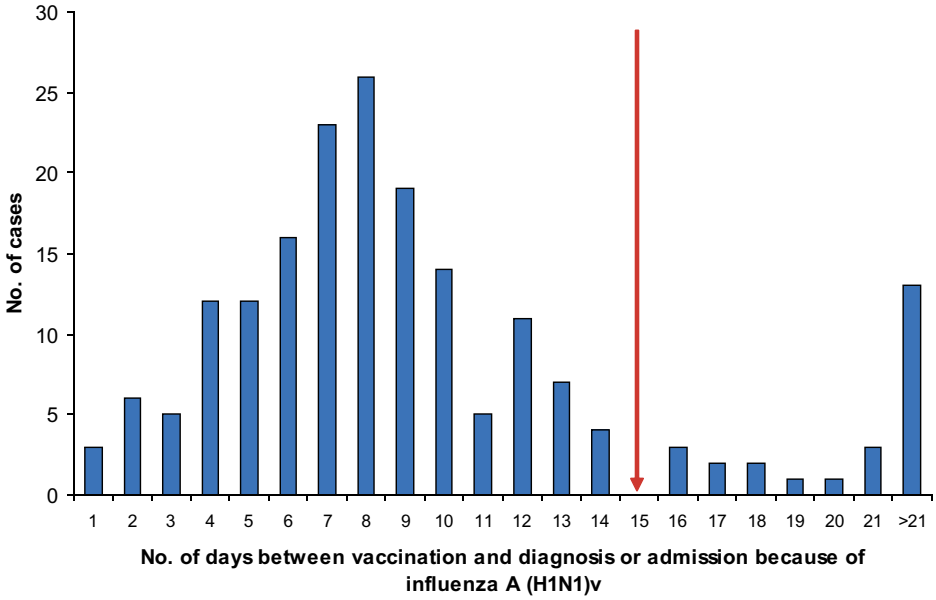

Figure 4. Interval (no. of days) from vaccination to diagnosis of, or admission because of, influenza A(H1N1)v in 188 vaccinated persons. The red arrow marks that a vaccinated person was considered to have had a protective immune response from day 15 after the vaccination against influenza was performed.

more prevalent among cases than in controls (HR, 8.45; 95% CI, 2.19–32.61).

Effectiveness of Vaccination

The weekly risk for being diagnosed with influenza A(H1N1)v >14 days after vaccination was significantly lower in the vaccinated than in the nonvaccinated population (Table 4). During the 4 weeks with maximum influenza activity (weeks 45–48) the relative risk per week for the vaccinated population was .05–.13, corresponding to an effectiveness of the vaccine of 87–95%. During the peak weeks, the estimated vaccine effectiveness was 89–92% in children 6 months–12 years and 69–89% in adults 30–64 years of age (Table 5).

If persons were to be considered protected after >7 days after vaccination, the number of failures rose to 101. However, there was still a significantly lower incidence of influenza in the vaccinated than in the nonvaccinated group during weeks 45–51, with estimated weekly effectiveness (95% CI) of 68% (28–86), 50% (27–65), 76% (65–84), 78% (66–85), 81% (56–92), 69% (10–89), and 90% (24–98), respectively (data not shown).

DISCUSSION

This prospective population-based cohort study, including ~1 million vaccinated and 1 million nonvaccinated persons above 6 months of age, clearly indicates that the monovalent AS03-adjuvanted influenza vaccine was highly effective in prevention of the pandemic influenza A(H1N1)v in Stockholm County. In total, there were only 25 vaccine failures, corresponding to a weekly effectiveness of 87%–95% during the peak of the epidemic.

Our findings confirm the results from previous studies on selected populations, of which 3 used the same adjuvanted vaccine as we did in Stockholm [9–11]. A German study, with a vaccine uptake of 7%, indicated a vaccine effectiveness (VE) of 96.8% in persons 14–59 years of age and of 83.3% in persons ≥60 years of age [9]. In a Scottish cohort study comparing the rate of influenza positivity in vaccinated vs unvaccinated cases, with a vaccine uptake of 12%, the VE was 95% [10]. In the third, a Canadian case–control study of children <10 years of age, VE was 100% [11]. In addition, there are some studies where other or several vaccines have been used. In a Chinese cohort study of a monovalent, nonadjuvanted vaccine, comparing laboratory-positive cases in vaccinated versus unvaccinated persons, VE 14 days after vaccination was 87% [15]. However, the study population consisted of >80% students, who had to be of a certain height and to be physical fit. Three case-control studies using the test-negative design, based either on sentinel practitioner surveillance networks [13, 14] or on hospitalized patients [12], showed VEs of 60%, 72%, and 90%, respectively. In all 3, more than 1 vaccine was used, and vaccinations were started at, or after, the peak of the epidemic.

The exact date for onset of disease was unknown for many of our patients. We therefore used >14 days from vaccination to the laboratory diagnosis, or hospital admittance, as the definition of a vaccine failure. When known, the date of onset was on average 2 days prior to the diagnosis or admission, which may have led to a slight underestimation of the vaccine effectiveness. On the other hand, we, in accordance with others [10–13],

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Table 2. Demographic Data of Patients ($n = 25$) With Vaccine Failure, That Is, With a Diagnosis of Influenza A(H1N1)v >14 Days After Vaccination

Age (years)	Sex	Week of diagnosis	No. of vaccine doses received	No. of days from vaccination to diagnosis or admission to hospital	Chronic pulmonary disease	Immuno-compromised	Other chronic diseases[a]	Pregnancy[b]	Hospitalized
1	F	50	2	25 and 8, respectively	N	N	N	NA[c]	N
4	M	47	1	17	N	N	N	NA	N
4	F	47	1	26	N	Y	N	NA	Y
5	M	47	1	19	Y	N	N	NA	N
5	M	48	1	17	N	N	N	NA	N
6	M	46	1	22	Y	N	N	NA	N
6	M	48	1	18	N	N	N	NA	N
7	F	46	1	29	N	Y	N	NA	N
8	F	46	1	20	N	N	N	NA	N
8	F	50	1	16	N	N	N	NA	N
9	F	48	1	35	Y	N	N	NA	N
34	F	46	1	16	N	N	N	Y, w 28	N
35	F	46	1	18	N	N	N	Y, w 17	N
35	F	49	1	29	N	Y	N	N	Y
36	M	51	1	15	N	N	N	NA	Y
38	F	49	1	46	N	Y	Renal/hepatic	N	N
39	F	46	2	21 and 1, respectively	N	Y	N	N	N
40	M	48	1	28	Y	Y	Heart	NA	N
49	M	47	1	31	N	Y	N	NA	Y
50	F	48	1	28	Y	N	N	N	Y
50	M	48	1	38	N	N	N	NA	N
52	M	47	1	24	Y	N	Obese	NA	Y
56	F	46	1	21	Y	Y	N	NA	N
57	F	45	1	24	Y	Y	N	NA	Y
67	F	49	1	25	N	Y	Renal/hepatic, diabetes	NA	Y

[a] Chronic diseases defined as risk factors according to Swedish National Board of Health (see Methods): extreme obesity (BMI >40) or neuromuscular disease affecting breathing capacity, chronic heart disease, chronic liver or renal failure, diabetes mellitus where a severe febrile disease could lead to metabolic complications, and children with multiple dysfunctions/handicaps.

[b] Gestation week of pregnancy at vaccination.

[c] Not applicable.

Table 3. Hazard Ratios for Possible Risk Factors Associated With Vaccine Failure in Cases ($n = 25$), That Is, Persons With a Diagnosis of Influenza A(H1N1)v >14 Days After Vaccination, Compared With Controls ($n = 100$) Who Were of the Same Age and Vaccinated on the Same Day but Were Not Diagnosed With Influenza

Variable	Cases	Controls	*P*	HR (95% CI)
Sex				
Female	14	56	.75	1.14 (.51, 2.54)
Male	11	44		
Any chronic disease	15	36	.06	2.18 (.98, 4.84)
Chronic lung disease	8	20	.25	1.63 (.70, 3.78)
Chronic heart disease	2	6	.74	1.27 (.30, 5.39)
Immunocompromised	10	5	.0001	4.89 (2.19, 10.89)
Obesity (BMI >40)	1	3	.82	1.26 (.17, 9.32)
Neuromuscular disease	0	1	.99	NA
Chronic renal or hepatic disease	2	0	.02	5.35 (1.26, 22.68)
Diabetes	1	7	.63	.61 (.08, 4.50)
Children with multiple dysfunctions/handicaps	0	3	.99	NA
Pregnancy	2	4	.46	1.73 (.41, 7.32)

NOTE. For each case the first 4 persons of the same age vaccinated on the same day, irrespective of vaccination site, were chosen as controls. NA, not applicable.

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Table 4. Cumulative Incidence of Influenza A(H1N1)v in Vaccinated Versus Nonvaccinated Population, 6 Months of Age and Older (n = 2,004,919), by Week, From Start of the Vaccination Campaign (Week 42) Until the End of 2009

Variable	Week												
	Before 42	42	43	44	45	46	47	48	49	50	51	52	
Vaccinated population													
No. of influenza cases[a]	NA	0	0	0	1	7	5	6	3	2	1	0	
Total no. vaccinated[b]				43,154	95,517	166,337	338,888	467,820	608,307	717,160	835,290	956,008	
Not vaccinated population													
No. of influenza cases	760	66	167	226	379	657	601	355	75	25	14	4	
Total no. not vaccinated[c]				1,960,772	1,908,273	183,7073	1,663,858	1,534,323	1,393,476	1,284,547	1,166,390	1,045,658	
P, rate of influenza in vaccinated vs not vaccinated	NA	NA	NA	.0454	<.0001	<.0001	<.0001	<.0001	<.0001	.04	.013	.16	
Relative Risk (RR) (95% CI)				0	.06 (.008–.41)	.13 (.06–.27)	.05 (.02–.12)	.07 (.03–.15)	.13 (.04–.38)	.21 (.01–.78)	.16 (.02–1.1)	0	

NOTE. Week 53 is not included because there were no influenza A(H1N1)v positive cases this week in either the vaccinated or the nonvaccinated group. NA, not applicable.

[a] Number of persons with a diagnosis of influenza A(H1N1)v >14 days after having been vaccinated.

[b] Cumulative number of persons who had been vaccinated >2 weeks earlier, minus the number of persons previously diagnosed with influenza A(H1N1)v up to the current week.

[c] Number of persons in population not vaccinated with pandemic vaccine, excluding those who had already been diagnosed with influenza A(H1N1)v.

found the vaccine to be protective, albeit to a lower degree, already when >7 days had passed since vaccination.

We found a high weekly effectiveness in children, despite the fact that most had only received a single vaccine dose. However, 6 of 11 children with vaccine failure were previously healthy, which in contrast to the Canadian study [11] indicates that 2 doses may be required for protection in some individuals. Further, although 1 dose of 1.875 μg of AS03-adjuvanted formulations in young children results in high seroconversion and seroprotection rates [8, 21], it can be questioned to what extent this can be translated into protection against clinical disease.

The weekly effectiveness among adults was somewhat lower, 69%–93%, which may be explained by the fact that 12 of 14 patients with failure had underlying medical risk factors, of which 8 were severely immunocompromised. An immunocompromising condition was the most significant risk factor for a vaccine failure, according to the nested case-control study. Since only one of these 8 patients had received 2 doses of vaccine, the potential benefit of a second vaccine dose cannot be evaluated.

No vaccine failures were seen in persons 10–33 years of age. A possible reason could be that a single vaccine dose provides an even better immune stimulation and protection in older children and young adults than in young children. Another reason could be that chronic underlying diseases are less prevalent among these age groups than among older adults. A third reason, applicable only to persons 19–33 years of age, is that they had the lowest vaccine coverage. In addition, the start of the general vaccination for this age group was so late (around weeks 48–49) that very few had had time to seroconvert until the epidemic was over.

Our study has several strengths. The vaccination campaign started well before the peak of influenza epidemic, and it was prospective, was population-based, and included 2 million persons of which about half were vaccinated. The registers used for notification of influenza A(H1N1)v, for recording vaccinations, and for diagnoses made in hospitals were all mandatory and could be linked by the Swedish unique personal identification number. Also, the propensity for vaccination was very high among risk groups, and they accounted for a majority of persons who were evaluable for effectiveness during the peak of the epidemic (weeks 45–48).

There are also limitations. First, we could not adjust for medical risk factors, since these were not available for the nonvaccinated half of the population. However, since vaccine coverage among the estimated risk group population was 50% after 3 weeks and 100% after 8 weeks of the campaign, it is unlikely that adjustments for such covariates would have lowered the effectiveness found in the crude analysis. Instead, our findings are likely to be an underestimation of the true effectiveness of the vaccine in the general population.

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Table 5. Cumulative Incidence of Influenza A(H1N1)v in Vaccinated Versus Nonvaccinated Population, by Week, in Children 6 Months–12 Years of Age (n = 303,973) and Adults 30–64 Years of Age (n = 964,186), Weeks 44–52

	Week 44		Week 45		Week 46		Week 47		Week 48		Week 49		Week 50		Week 51		Week 52	
Variable	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults	Children	Adults
Vaccinated population																		
No. of influenza cases[a]	0	0	0	1	3	4	3	2	3	3	0	2	1	0	0	1	0	0
Total no. vaccinated[b]	1,534	20,242	4,484	43,298	8,837	76,143	43,837	159,140	87,481	203,618	150,709	237,950	192,012	270,210	207,208	334,619	214,741	408,280
Not vaccinated population																		
No. of influenza cases	71	63	111	85	246	151	205	147	96	104	12	21	5	7	2	5	0	3
Total no. not vaccinated[c]	301, 012	943,881	297,951	920,739	293,349	887,739	258,151	804,593	214,398	760,008	151,158	725,653	109,149	693,386	94,651	628,971	87,118	555,307
P, rate of influenza in vaccinated vs nonvaccinated	.36	.47	.37	.22	.16	.02	<.0001	<.0001	<.0001	<.0001	.0015	.12	.048	.22	.18	.62	NA	.37
RR (95% CI)	0	0	0	.25 (.04–1.80)	.41 (.13–1.27)	.31 (.11–.83)	.09 (.03–.27)	.07 (.02–.28)	.08 (.02–.24)	.11 (.03–.34)	0	.29 (.07–1.24)	.11 (.01–.97)	0	0	.38 (.04–3.22)	0	0

NOTE. Week 53 is not included in the table because there were no influenza A(H1N1)v positive cases this week in either the vaccinated or the nonvaccinated group in any age group. NA, not applicable.

[a] Number of persons with a diagnosis of influenza A(H1N1)v >14 days after having been vaccinated.

[b] Cumulative number of persons who had been vaccinated >2 weeks earlier, minus the number of persons previously diagnosed with influenza A(H1N1)v up to the current week.

[c] Number of persons in population not vaccinated with pandemic vaccine, excluding those who had already been diagnosed with influenza A(H1N1)v.

Second, the sampling for an influenza diagnosis was not made systematically but in routine medical care. During the time of the vaccination campaign persons with an influenza-like illness (ILI) were recommended to seek medical care if they were severely ill, had an underlying illness, or were pregnant. However, it is not known if vaccinated persons with ILI were more or less prone than nonvaccinated persons to seek medical care. Neither do we know if physicians were more or less prone to sample vaccinated persons with ILI. We believe that patients with chronic diseases were more likely to contact their doctors if they became ill, despite being vaccinated, than healthy nonvaccinated persons. In that case, the diagnostic sampling would lead to an underestimation of vaccine effectiveness.

A third limitation is that we do not know if persons who earlier in the season had had an undiagnosed influenza A(H1N1)v were included in the vaccinated or in the nonvaccinated group. However, the percentage of nondiagnosed influenza patients was probably low at the beginning of the epidemic since all persons with ILI were recommended sampling for influenza and contact tracing was performed. Further, SMI has estimated that <10% of the Swedish population became infected during the pandemic [22], which is consistent with some [23] but slightly lower than other countries [24, 25]. Since the main peak of the epidemic with 80% of all diagnoses was during the time of the vaccination campaign, it is unlikely that undiagnosed cases prior to the campaign had a major influence on our results.

Vaccinations may have had some effect on the magnitude or duration of the epidemic in Stockholm County. The incidence of diagnoses, hospitalizations, and case fatality rates because of influenza A(H1N1)v were of the same magnitude as [26–29], or higher than [23], those described from other countries. However, the epidemic in Stockholm County had a flat and short peak, while in several countries where vaccinations were not performed the epidemic outbreaks had sharper peaks and/or were of much longer duration [30–33]. It is possible that the 20–25% of the Stockholm population who had seroconverted after vaccination by weeks 47–48 contributed to halting the spread of influenza in the community.

In conclusion, the monovalent AS03-adjuvanted influenza A(H1N1)v vaccine was very effective in preventing the pandemic influenza in Stockholm County. A single dose gave adequate protection in most adults, including persons belonging to medical risk groups with the exception of those who had an immunocompromising disease and/or treatment. Although the effectiveness was high, vaccine failures seen also in healthy children may indicate the need for a second dose in the youngest age groups.

Acknowledgments

Ethics committee approval: The Department of Communicable Diseases Control and Prevention is a regional authority, and the county medical officer has the right by law to access registers and to follow up preventive actions

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concerning diseases included in the Swedish Act of Notifiable Diseases. Therefore no approval was needed from the Regional Ethical Committee.

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Potential conflicts of interest. All authors: no conflicts.

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