ORIGINAL ARTICLE

Safety of Influenza A (H1N1) Vaccine in Postmarketing Surveillance in China

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ABSTRACT

BACKGROUND

On September 21, 2009, China began administering vaccines, obtained from 10 different manufacturers, against 2009 pandemic influenza A (H1N1) virus infection in priority populations. We aimed to assess the safety of this vaccination program.

METHODS

We designed a plan for passive surveillance for adverse events after immunization with the influenza A (H1N1) vaccine. Physicians or vaccination providers were required to report the numbers of vaccinees and all adverse events to their local Center for Disease Control and Prevention (CDC), which then reported the data to the Chinese CDC through the online National Immunization Information System's National Adverse Event Following Immunization Surveillance System. Data were collected through March 21, 2010, and were verified and analyzed by the Chinese CDC.

RESULTS

A total of 89.6 million doses of vaccine were administered from September 21, 2009, through March 21, 2010, and 8067 vaccinees reported having an adverse event, for a rate of 90.0 per 1 million doses. The age-specific rates of adverse events ranged from 31.4 per 1 million doses among persons 60 years of age or older to 130.6 per 1 million doses among persons 9 years of age or younger, and the manufacturer-specific rates ranged from 4.6 to 185.4 per 1 million doses. A total of 6552 of the 8067 adverse events (81.2%; rate, 73.1 per 1 million doses) were verified as vaccine reactions; 1083 of the 8067 (13.4%; rate, 12.1 per 1 million doses) were rare and more serious (vs. common, minor events), most of which (1050) were allergic reactions. Eleven cases of the Guillain–Barré syndrome were reported, for a rate of 0.1 per 1 million doses, which is lower than the background rate in China.

CONCLUSIONS

No pattern of adverse events that would be of concern was observed after the administration of influenza A (H1N1) vaccine, nor was there evidence of an increased risk of the Guillain–Barré syndrome.

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Since the outbreak of the pandemic influenza A (H1N1) virus in 2009, nations around the world have produced a vaccine against this virus. During the summer of 2009, 10 Chinese vaccine manufacturers used the same reassortant strain X-179A (A/California/07/2009-A/PR/8/34) as the seed virus to produce various formulations of the vaccine.[1] Beginning in September 2009, the 10 manufacturers were licensed to produce the nonadjuvant, split-virion H1N1 vaccine by the State Food and Drug Administration of China[2] (and see the Supplementary Appendix, available with the full text of this article at NEJM.org). On September 21, 2009, China started to administer the vaccine to priority populations, followed by vaccination of any interested persons when vaccine supply became more abundant.

A vaccine against the "swine flu" virus during the 1976–1977 influenza season was associated with new cases of the Guillain–Barré syndrome in the United States,[3] and an association between seasonal influenza vaccination and the Guillain–Barré syndrome was noted in an analysis of data from the Vaccine Adverse Event Reporting System (VAERS) in the United States.[4] Since serious adverse vaccine reactions such as the Guillain–Barré syndrome are extremely rare, clinical trials may not be of sufficient size to detect their occurrence. Therefore, postmarketing surveillance for adverse events after immunization is required to evaluate the safety of the new influenza A (H1N1) vaccine.

METHODS

STUDY DESIGN

During the initial influenza A (H1N1) vaccination campaign, in which nearly 90 million persons in China were vaccinated from September 21, 2009, through March 21, 2010, passive surveillance for adverse events was conducted. The Chinese Center for Disease Control and Prevention (CDC) designed the study and gathered and analyzed the data. All the authors drafted the manuscript, made the decision to submit it for publication, and vouch for the accuracy and completeness of the data and the analysis.

VACCINATION AND ELIGIBILITY

In 2009, the Ministry of Health of China issued the Guideline for Vaccination against Pandemic (H1N1) Influenza.[5] The H1N1 vaccines used were nonadjuvant, split-virion vaccines. The priority population for vaccination included persons in frontline public services; students and teachers in preschools, elementary and middle schools, and high schools; persons with chronic conditions; and other populations at high risk for influenza A (H1N1) infection. All adults and children 3 years of age or older were eligible for one dose of vaccine containing 15 μg of hemagglutinin, whereas children 6 to 35 months of age were eligible for two doses of the vaccine, each with 7.5 μg of hemagglutinin. Contraindications for vaccination included a history of allergic reactions to eggs or their components (especially ovalbumin), gentamicin, formaldehyde, thimerosal, or any other trace elements in the vaccine; acute onset of a chronic or febrile disease; history of the Guillain–Barré syndrome; uncontrolled epilepsy or a progressive neurologic disorder; and other conditions identified as contraindications by the treating physicians.

All adult vaccine recipients provided written informed consent, containing information about the vaccine, possible adverse effects, and medical care. For child recipients, a parent or guardian provided written informed consent. Vaccination was voluntary and free of charge for all recipients.

SURVEILLANCE SYSTEM

The National Immunization Information System's National Adverse Events Following Immunization (AEFI) Surveillance System was established in 2005 on the basis of World Health Organization (WHO) guidelines.[6] A pilot surveillance system was implemented in 10 provinces during 2005–2006. Subsequently, the system was strengthened with the creation of the online National AEFI Surveillance System (http://219.141.175.204) in 2008. By the end of 2008, a total of 29 provinces had reported adverse events using the online system.[7,8] All provinces participated in our study.

In the Guideline for Vaccination against Pandemic (H1N1) Influenza for China,[5] an adverse event is defined as the occurrence of any medical condition or event believed to be caused by the H1N1 vaccine. In our study, we defined serious adverse events, on the basis of WHO guidelines, as events involving hospitalization, death, life-threatening illness, or permanent disability.[6]

According to the Guideline for the Identification of Adverse Reaction after Immunization issued by the Chinese Ministry of Health in 2008,[9] each county, prefectural, and provincial CDC in

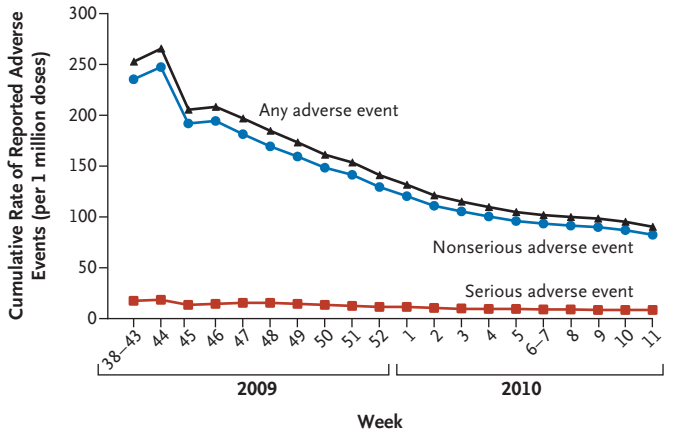

Figure 1. Estimated Cumulative Rates of Reported Adverse Events after Immunization with Influenza A (H1N1) Vaccine in China from September 21, 2009, to March 21, 2010.

The cumulative rate of reported adverse events was calculated by dividing the number of vaccinees who reported having an event by the number of vaccine doses administered from the beginning of the first week to the end of each week.

China must organize an expert panel to investigate adverse events and assess causality, using criteria based on Chinese Standard Procedures for Vaccination[10] and the Guideline for Vaccination against Pandemic (H1N1) Influenza.[5] The panels consist of physicians, epidemiologists, pharmacists, and other relevant experts. In general, prefectural or provincial expert panels investigate deaths, life-threatening illnesses, and permanent disabilities; county-level expert panels investigate other serious adverse events, and immunization-program managers or vaccination providers investigate common, minor adverse events. On the basis of the Guideline for Vaccination against Pandemic (H1N1) Influenza, adverse events are classified into one of five categories: vaccine reactions (common and minor to rare and more serious), program errors, coincidental illnesses, psychogenic reactions, and unclassifiable events.[6,10]

ADVERSE-EVENT REPORTING

Reporting by Vaccinees

At the time of vaccination, vaccinees were instructed to report any adverse event to physicians or vaccination providers. Adverse events that were fatal or that resulted in disability and clusters of events (i.e., notably high numbers of similar adverse events related to a certain vaccine) were required to be reported within 2 hours after their occurrence. The following adverse events were required to be reported within 2 days after their occurrence: anaphylaxis or other allergic reactions occurring within 24 hours after vaccination; fever (axillary temperature, >37.5°C), angioedema, or a local injection-site reaction (diameter, >2.5 cm) occurring within 5 days after vaccination; purpura, an Arthus reaction, febrile convulsion, seizure, or polyneuritis occurring within 15 days after vaccination; and the Guillain–Barré syndrome occurring within 3 months after vaccination. Other reactions that were common and minor (e.g., mild pain and fatigue) were not required to be reported (see the Supplementary Appendix).

Subsequent Reporting

After receiving a report of an adverse event in a vaccinee, the physician or vaccination provider was required to fill out a case-report form and submit it to the county CDC within 24 hours. A serious adverse event had to be reported within 2 hours by telephone to the county CDC and health bureau (which reported the cases to higher levels within 2 hours after that). The county CDC completed detailed case-investigation forms for all adverse events except for common, minor reactions. Information from both forms was reported to the Chinese CDC through the online National AEFI Surveillance System. All serious adverse events were investigated by expert panels of the county, prefectural, or provincial CDC immediately after receipt of reports. Prefectural and provincial CDCs checked the accuracy and completeness of the data within 1 week after adverse events were reported (see the Supplementary Appendix).

Reporting of Vaccine Doses

The aggregate number of vaccine doses administered was reported by immunization providers to the Chinese CDC during the campaign. Data on individual vaccinees were also required to be reported, through the online National Immunization Information System, for information about distribution of doses according to region, age, sex, and manufacturer (see the Supplementary Appendix).

OUTCOME MEASURES

The outcome measures in this study included the rate of reported adverse events and the proportions of various events. The rate of reported adverse events was calculated by dividing the number of vaccinees who reported having an event by the number of vaccine doses administered. The

Table 1. Reported Adverse Events after Immunization against the Influenza A (H1N1) Vaccine in China, September 21, 2009, through March 21, 2010.

Characteristic	No. of Doses Administered	Nonserious Events (N=7356)		Serious Events (N=711)		Total (N=8067)	
		no. of vaccinees (%)	*no./1 million doses*	*no. of vaccinees (%)*	*no./1 million doses*	*no. of vaccinees (%)*	*no./1 million doses*
Sex							
Male	47,244,025	3474 (47.2)	73.5	326 (45.9)	6.9	3800 (47.1)	80.4
Female	42,370,444	3882 (52.8)	91.6	385 (54.1)	9.1	4267 (52.9)	100.7
Age							
≤9 yr	12,780,590	1532 (20.8)	119.9	137 (19.3)	10.7	1669 (20.7)	130.6
10–19 yr	38,144,994	3143 (42.7)	82.4	293 (41.2)	7.7	3436 (42.6)	90.1
20–59 yr	36,361,455	2621 (35.6)	72.1	268 (37.7)	7.4	2889 (35.8)	79.5
≥60 yr	2,327,430	60 (0.8)	25.8	13 (1.8)	5.6	73 (0.9)	31.4
Region*							
Eastern	27,023,475	4214 (57.3)	155.9	267 (37.6)	9.9	4481 (55.5)	165.8
Middle	38,516,558	2582 (35.1)	67.0	289 (40.6)	7.5	2871 (35.6)	74.5
Western	24,074,436	560 (7.6)	23.3	155 (21.8)	6.4	715 (8.9)	29.7
Manufacturer							
A	6,581,777	1170 (15.9)	177.8	50 (7.0)	7.6	1220 (15.1)	185.4
B	5,011,561	846 (11.5)	168.8	30 (4.2)	6.0	876 (10.9)	174.8
C	12,802,806	1655 (22.5)	129.3	215 (30.2)	16.8	1870 (23.2)	146.1
D	6,352,951	728 (9.9)	114.6	50 (7.0)	7.9	778 (9.6)	122.5
E	7,287,768	612 (8.3)	84.0	46 (6.5)	6.3	658 (8.2)	90.3
F	12,080,652	929 (12.6)	76.9	69 (9.7)	5.7	998 (12.4)	82.6
G	30,533,377	1202 (16.3)	39.4	221 (31.1)	7.2	1423 (17.6)	46.6
H	7,276,897	207 (2.8)	28.4	28 (3.9)	3.8	235 (2.9)	32.3
I	171,327	2 (<0.1)	11.7	0	0.0	2 (<0.1)	11.7
J	1,515,353	5 (<0.1)	3.3	2 (0.3)	1.3	7 (0.1)	4.6
Total	89,614,469	7356 (100)	82.1	711 (100)	7.9	8067 (100)	90.0

* The eastern region includes Beijing, Tianjin, Shanghai, Jiangsu, Zhejiang, Fujian, Shandong, Guangdong, and Hainan provinces. The middle region includes Shanxi, Hebei, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, Hubei, Hunan, Liaoning, and Guangxi provinces. The western region includes Sichuan, Chongqing, Guizhou, Yunnan, Inner Mongolia, Tibet, Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang provinces.

cumulative rate of reported adverse events was calculated by dividing the number of vaccinees who reported having an event by the number of vaccine doses administered from the beginning of the first week to the end of each week.

RESULTS

REPORTED ADVERSE EVENTS

Between September 21, 2009, and March 21, 2010, a total of 89.6 million doses of the H1N1 vaccine were administered, and 8067 vaccinees reported having an adverse event. The overall rate of reported adverse events was 90.0 per 1 million vaccine doses, with the weekly cumulative rate ranging from 90.0 to 265.0 per 1 million doses (Fig. 1).

A total of 3800 male vaccinees had an adverse event (47.1% of the total number; rate per 1 million vaccine doses, 80.4), and 4267 female vaccinees had an adverse event (52.9%; rate, 100.7 per 1 million doses) (Table 1). The age-specific rates of adverse events ranged from 31.4, among vaccinees 60 years of age or older, to 130.6 among those 9 years of age or younger. Cases were reported from all provinces of China. The rates of reported adverse events were 165.8 per 1 million

doses in the eastern region, 74.5 per 1 million in the middle region, and 29.7 per 1 million in the western region. The rate ranged from 4.6 to 185.4 per 1 million doses among the 10 manufacturers. Among all 8067 vaccinees with an adverse event, 711 (8.8%; rate per 1 million doses, 7.9) had a serious event, and 7356 (91.2%; rate, 82.1 per 1 million) had a nonserious event.

TYPES OF EVENTS

Of the 8067 vaccinees with an adverse event, 6552 (81.2%; rate per 1 million doses, 73.1) had

Table 2. Reported Adverse Events.

Adverse Event	Cases (N=8067)	Rate
	no. of vaccinees (%)	*no./1 million doses*
Common, minor vaccine reaction*		
Fever		
37.1–37.5°C	404 (5.0)	4.5
37.6–38.5°C	1770 (21.9)	19.8
≥38.6°C	1323 (16.4)	14.8
Diameter of area of redness and swelling		
≤2.5 cm	239 (3.0)	2.7
2.6–5.0 cm	67 (0.8)	0.7
>5.0 cm	33 (0.4)	0.4
Diameter of area of induration		
≤2.5 cm	0	0.0
2.6–5.0 cm	0	0.0
>5.0 cm	30 (0.4)	0.3
Other	1773 (22.0)	19.8
Total	5469 (67.8)	61.0
Rare, more serious vaccine reaction		
Urticaria	838 (10.4)	9.4
Henoch–Schönlein purpura	75 (0.9)	0.8
Anaphylaxis	49 (0.6)	0.5
Angioedema	37 (0.5)	0.4
Anaphylactic laryngeal edema	30 (0.4)	0.3
Arthus reaction	11 (0.1)	0.1
Atopic dermatitis	3 (<0.1)	0.03
Thrombocytopenic purpura	3 (<0.1)	0.03
Other allergic reaction	4 (<0.1)	0.04
Febrile convulsion	11 (0.1)	0.1
Guillain–Barré syndrome	8 (0.1)	0.1
Brachial neuritis	5 (0.1)	0.1
Acute disseminated encephalomyelitis	2 (<0.1)	0.02
Encephalopathy	1 (<0.1)	0.01
Polyneuritis	1 (<0.1)	0.01
Seizure	1 (<0.1)	0.01
Lymphangiitis and lymphadenitis	2 (<0.1)	0.02
Thrombocytopenia	1 (<0.1)	0.01
Erythema multiforme	1 (<0.1)	0.01
Total	1083 (13.4)	12.1

Table 2. (Continued.)

Adverse Event	Cases (N=8067)	Rate
	no. of vaccinees (%)	*no./1 million doses*
Coincidental illness†		
Guillain–Barré syndrome	1 (<0.1)	0.01
Other	1063 (13.2)	11.9
Total	1064 (13.2)	11.9
Psychogenic reaction‡		
Hysteria	134 (1.7)	1.5
Fainting	119 (1.5)	1.3
Other	156 (1.9)	1.7
Total	409 (5.1)	4.6
Unclassifiable§		
Guillain–Barré syndrome	2 (<0.1)	0.02
Other	40 (0.5)	0.4
Total	42 (0.5)	0.5

* Some common, minor vaccine reactions were not required to be reported: fever that was under 37.6°C, area of redness and swelling or induration of 2.5 cm or less in diameter, and "other" reactions (e.g., irritability, malaise, paleness, headache, muscle pain, and loss of appetite).

† The "other" category of coincidental illness includes diarrhea, gastritis, and gastroenteritis; upper respiratory infection and fever; Henoch–Schönlein purpura; acute lymphoblastic leukemia; the myelodysplastic syndrome; polyneuritis; multiple sclerosis; acute demyelinating disease; acute myelitis; brachial neuritis; viral encephalitis; encephalopathy; seizure; myocarditis; acute myocardial infarction; hypertension; nephrotic syndrome; diabetes; deafness; keratitis; and abortion.

‡ The "other" category of psychogenic reaction includes light-headedness, dizziness, tingling, breath-holding, vomiting, and screaming, all as a result of anxiety about the immunization.

§ The "other" category of unclassifiable reaction includes Henoch–Schönlein purpura, thrombocytopenic purpura, seizure, febrile convulsion, polyneuritis, brachial neuritis, peripheral neuropathy, acute myelitis, acute demyelinating myelopathy, meningismus, systemic lupus erythematosus, hypertension, deafness, optic neuritis, and facial paralysis, all of unknown origin.

events classified as vaccine reactions (Table 2). A total of 5469 of the vaccinees with a vaccine reaction (67.8% of the 8067 with adverse events; rate per 1 million doses, 61.0) had common, minor reactions (typical local and systemic reactions), and the remaining 1083 vaccinees with a vaccine reaction (13.4% of all with adverse events; rate per 1 million doses, 12.1) had rare, more serious reactions. A total of 1050 of the vaccinees with more serious reactions (13.0% of vaccinees with adverse events; rate per 1 million doses, 11.7) had allergic reactions, including 838 with urticaria, 75 with Henoch–Schönlein purpura, 49 with anaphylaxis, 37 with angioedema, 30 with anaphylactic laryngeal edema, 11 with an Arthus reaction, 3 with atopic dermatitis, 3 with thrombocytopenic purpura, and 4 with other allergic reactions. A total of 29 vaccinees with more serious vaccine reactions (0.4% of all those with adverse events; rate per 1 million doses, 0.3) had neurologic reactions, including 8 cases with Guillain–Barré syndrome.

Of the 8067 vaccinees with adverse events reported, 1064 (13.2%; rate per 1 million doses, 11.9) had events classified as coincidental illnesses; 409 (5.1%; rate per 1 million doses, 4.6) had events classified as psychogenic reactions; and 42 (0.5%; rate per 1 million doses, 0.5) had events considered to be unclassifiable.

The majority of the vaccine reactions occurred within 1 day after vaccination, and all cases of anaphylaxis occurred on the day of vaccination (Table 3). The median interval from vaccination to the onset of the adverse event was 10 minutes (range, 2 to 90).

DEATHS

Ten sudden deaths (rate per 1 million doses, 0.1) occurred after vaccination, 5 among male vaccinees and 5 among female vaccinees. The age range of vaccinees who died was 11 to 61 years. The interval between vaccination and death was 0 to 9 days. Autopsy, performed in 4 of the 10 vaccinees who died, revealed a preexisting heart

Table 3. Interval from Vaccination to Onset of Selected Adverse Events.

Adverse Event	Total No.	Immunization Day	Days after Immunization			
			Day 1	Days 2–5	Days 6–15	>Day 15
			number of vaccinees (percent)			
Common, minor vaccine reaction						
Fever	3497	1711 (48.9)	1198 (34.3)	523 (15.0)	58 (1.7)	7 (0.2)
Redness and swelling	339	209 (61.7)	89 (26.3)	36 (10.6)	4 (1.2)	1 (0.3)
Induration	30	14 (46.7)	8 (26.7)	7 (23.3)	0	1 (3.3)
Rare, more serious vaccine reaction						
Urticaria	838	462 (55.1)	241 (28.8)	113 (13.5)	19 (2.3)	3 (0.4)
Henoch–Schönlein purpura	75	13 (17.3)	23 (30.7)	33 (44.0)	5 (6.7)	1 (1.3)
Anaphylaxis	49	49 (100.0)	0	0	0	0
Angioedema	37	25 (67.6)	7 (18.9)	4 (10.8)	1 (2.7)	0
Anaphylactic laryngeal edema	30	26 (86.7)	4 (13.3)	0	0	0
Arthus reaction	11	8 (72.7)	1 (9.1)	2 (18.2)	0	0
Atopic dermatitis	3	2 (66.7)	1 (33.3)	0	0	0
Thrombocytopenic purpura	3	2 (66.7)	1 (33.3)	0	0	0
Other allergic reaction	4	3 (75.0)	0	1 (25.0)	0	0
Febrile convulsion	11	8 (72.7)	2 (18.2)	1 (9.1)	0	0
Guillain–Barré syndrome	8	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)	4 (50.0)
Brachial neuritis	5	4 (80.0)	0	1 (20.0)	0	0
Acute disseminated encephalomyelitis	2	0	0	1 (50.0)	1 (50.0)	0
Encephalopathy	1	0	1 (100)	0	0	0
Polyneuritis	1	0	1 (100)	0	0	0
Seizure	1	1 (100.0)	0	0	0	0
Lymphangiitis and lymphadenitis	2	0	1 (50.0)	1 (50.0)	0	0
Thrombocytopenia	1	0	0	1 (100)	0	0
Erythema multiforme	1	1 (100.0)	0	0	0	0
Unclassifiable						
Henoch–Schönlein purpura	8	2 (25.0)	3 (37.5)	1 (12.5)	2 (25.0)	0
Thrombocytopenic purpura	2	1 (50.0)	0	1 (50.0)	0	0
Seizure	4	2 (50.0)	1 (25.0)	1 (25.0)	0	0
Febrile convulsion	1	0	1 (100)	0	0	0
Polyneuritis	4	2 (50.0)	0	0	1 (25.0)	1 (25.0)
Guillain–Barré syndrome	2	0	0	0	2 (100)	0
Brachial neuritis	2	0	1 (50.0)	0	0	1 (50.0)
Peripheral neuropathy	2	0	1 (50.0)	0	1 (50.0)	0
Acute myelitis	2	0	0	0	0	2 (100)
Acute demyelinating myelopathy	1	0	0	0	0	1 (100)
Meningismus	1	1 (100.0)	0	0	0	0
Systemic lupus erythematosus	1	0	0	0	1 (100)	0
Hypertension	1	1 (100.0)	0	0	0	0
Deafness	7	0	3 (42.9)	1 (14.3)	2 (28.6)	1 (14.3)
Optic neuritis	3	1 (33.3)	1 (33.3)	0	1 (33.3)	0
Facial paralysis	1	0	0	1 (100)	0	0

condition in 3 and skeletal malformation due to rachiterata mutation and thoracic and renal malformations in 1. Of the 6 vaccinees for whom autopsy results were not available, 2 had preexisting heart conditions, 1 had an aortic aneurysm, 1 had decompensated hepatic cirrhosis and liver failure, 1 had a stroke followed by cerebral herniation, and 1, who died 43 hours after vaccination, had no history of medical conditions.

GUILLAIN–BARRÉ SYNDROME

Eleven confirmed cases of the Guillain–Barré syndrome (rate per 1 million doses, 0.1) occurred after vaccination. The affected patients were 8 to 67 years of age; 6 were males and 5 were females. The median interval between vaccination and onset of the Guillain–Barré syndrome was 13 days (range, 0 to 80). In 8 of the 11 cases, there was no evidence of a cause other than vaccination; these cases were therefore classified as vaccine reactions (Table 2 and Table 3). One of the 11 cases occurred in a patient with a history of infection and was therefore classified as a coincidental illness; the other 2 cases were considered to be unclassifiable. Of the 8 cases that were a vaccine reaction, 4 occurred within 15 days after vaccination, and 4 occurred more than 15 days after vaccination (Table 3).

According to the Chinese Acute Flaccid Paralysis Surveillance System, during the H1N1 vaccination campaign, from September 2009 to March 2010, the monthly average number of reported cases of the Guillain–Barré syndrome among children under 15 years of age was 74 (range, 37 to 109; incidence, 1.9 cases per 1 million persons; 95% confidence interval [CI], 1.5 to 2.4) (Fig. 2). The number was higher in the previous corresponding interval, September 2008 to March 2009, during which there were 105 cases (range, 81 to 138; incidence, 2.7 per 1 million; 95% CI, 2.2 to 3.3).

DISCUSSION

We have summarized the results of adverse-event surveillance after 89.6 million doses of the influenza A (H1N1) vaccine were administered in China. The rate of reported adverse events was approximately 90 per 1 million doses. The majority of events were nonserious; the rate of reported serious adverse events was about 8 per 1 million doses. The rates are similar to those associated

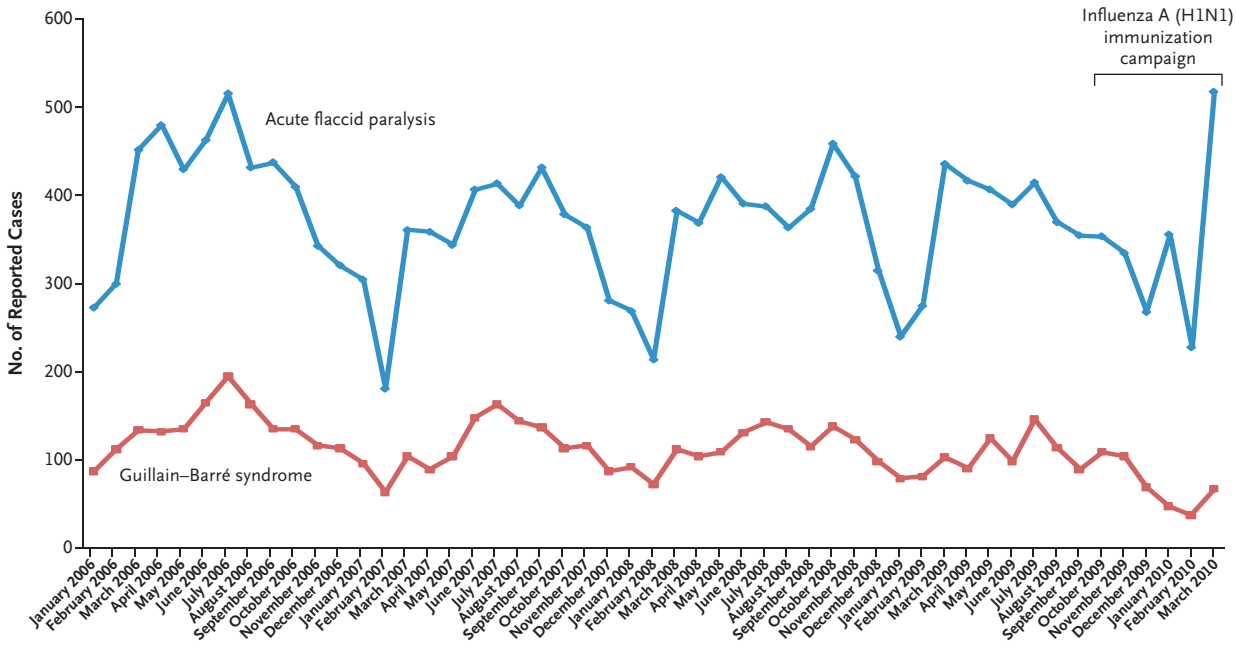

Figure 2. Numbers of Reported Cases of Acute Flaccid Paralysis and Guillain–Barré Syndrome in Children under 15 Years of Age in China from January 2006 through March 2010.

Data are from the Chinese Acute Flaccid Paralysis Surveillance System.

with seasonal and pandemic influenza A (H1N1) vaccines in the United States.[11,12] In our study, the rate of reported adverse events in Shanghai, China (the locale with the most complete data), was 385 per 1 million doses of the 2009 H1N1 vaccine, as compared with 425 per 1 million for the 2009 trivalent seasonal influenza vaccine.

We studied nearly 90 million administered doses of the influenza A (H1N1) vaccine, providing sufficient power to detect rare adverse events. In addition, we conducted investigations to verify every serious reported adverse event and to assess causal association.

The influenza A (H1N1) vaccine recipients included higher proportions of students, teachers, and health care providers than the proportions in the general population. These groups tend to be healthier and have greater access to health care. Also, since the vaccine studied was new, the recipients may have been more likely to report adverse events, especially soon after vaccination. Concern about vaccine safety tends to diminish over the period of vaccine use, as reflected by the decline in the rate of nonserious adverse events reported over the study period; however, the rate of reported serious events remained relatively stable. The overall rate of reported adverse events in this study is similar to the rate reported in the United States after 82.4 million doses of the influenza A (H1N1) vaccine were administered.[12]

In this study, reporting of nonserious reactions such as low-grade fever or mild local reactions was not mandatory; therefore, the rate was most likely underreported. Nonserious vaccine reactions accounted for more than 90% of all adverse events reported in vaccinees. These results are similar to the findings from clinical trials in China and other countries and from postmarketing surveillance of other influenza vaccines,[11-16] and are also similar to background data on seasonal influenza vaccine, the combined diphtheria–tetanus–pertussis vaccine, and measles and hepatitis B vaccines from WHO reports.[17]

Only a small fraction of vaccinees with reported adverse events had serious vaccine reactions. Also, most vaccine reactions occurred within 1 day after vaccination; few cases occurred more than 5 days after vaccination. Most cases of life-threatening anaphylaxis and laryngeal edema occurred within 30 minutes after vaccination. Such allergic reactions may be caused by ovalbumin, formaldehyde, thimerosal, or other ingredients of the vaccine. These findings are similar to those of postmarketing surveillance of H1N1 vaccines in other countries.[18-20] Our study also showed that the rate of reported adverse events varied among vaccines produced by different manufacturers. This variation might be due to differences in manufacturing techniques.

Although an association between the influenza vaccine and the Guillain–Barré syndrome was observed in 1976,[3] studies of subsequent influenza vaccines have not confirmed this finding.[21,22] During our surveillance period, 11 cases of the Guillain–Barré syndrome were reported, 3 of them in patients under 15 years of age, with a rate of 0.1 cases per 1 million doses. This rate is lower than the baseline incidence rate of 1.9 cases per 1 million population among children under 15 years of age in China, according to the Acute Flaccid Paralysis Surveillance System during the same period; our H1N1 vaccination campaign was not associated with an increase in cases of acute flaccid paralysis or the Guillain–Barré syndrome. Also, the rate of the Guillain–Barré syndrome in our study did not exceed the baseline incidence rate of 0.6 to 1.9 cases per 1 million population in European countries or the estimated risk of 1 case per 1 million doses of seasonal influenza vaccines given in the United States.[4,22]

Our study has two important limitations. First, the vaccination data based on sex, manufacturer, and age were estimated. Second, the Chinese National AEFI Surveillance System is passive and therefore dependent on vaccine recipients' health care–seeking behavior and health care providers' vigilance — making underreporting likely, as is shown by the higher rate of reported adverse events in the economically well-developed eastern regions of China than in the underdeveloped central and western regions.

In conclusion, these findings suggest that the H1N1 vaccine has a reasonable safety profile, and there is no evidence that the vaccine is associated with an increased risk of the Guillain–Barré syndrome.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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