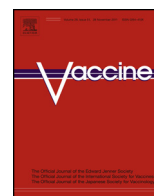




Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines: Reports to VAERS

Neal A. Halsey^{a,*}, Mari Griffioen^a, Stephen C. Dreskin^b, Cornelia L. Dekker^c, Robert Wood^d, Devindra Sharma^e, James F. Jones^f, Philip S. LaRussa^g, Jenny Garner^a, Melvin Berger^h, Tina Proveaux^a, Claudia Vellozzi^e, The Hypersensitivity Working Group of the Clinical Immunization Safety Assessment Network, Karen Broderⁱ, Rosanna Setse^j, Barbara Pahud^k, David Hrnčir^l, Howard Choi^j, Robert Sparks^m, Sarah Elizabeth Williams^m, Renata J. Engler^l, Jane Giduduⁱ, Roger Baxterⁿ, Nicola Kleinⁿ, Kathryn Edwards^m, Maria Canoⁱ, John M. Kelso^o

^a Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

^b Department of Medicine, University of Colorado, Denver, CO, USA

^c Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA

^d Department of Pediatrics, Division of Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

^e Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA, USA

^f Chronic Viral Diseases Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA

^g Department of Pediatrics, Division of Pediatric Infectious Diseases, Columbia University, New York, NY, USA

^h CSL Behring, King of Prussia, PA, USA

ⁱ Immunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA, USA

^j Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

^k Children's Mercy Hospital and Clinics, University of Missouri, Kansas City, MO, USA

^l Vaccine Healthcare Center Network, Military Vaccine Agency, U.S. Army Public Health Command, Walter Reed National Military Medical Center, Bethesda, MD, USA

^m Vanderbilt University School of Medicine, Nashville, TN, USA

ⁿ Kaiser Permanente Vaccine Study Center, Oakland, CA, USA

^o Division of Allergy, Asthma, and Immunology, Scripps Clinic, San Diego, CA, USA

ARTICLE INFO

Article history:

Received 1 July 2013

Received in revised form 29 August 2013

Accepted 10 September 2013

Available online xxx

Keywords:

Immunization
Influenza vaccine
Hypersensitivity
Anaphylaxis
Urticaria
Allergic reactions
H1N1 influenza vaccine

ABSTRACT

Background: Hypersensitivity disorders following vaccinations are a cause for concern.

Objective: To determine the type and rate by age, gender, and vaccine received for reported hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccines.

Design: A systematic review of reports to the Vaccine Adverse Event Reporting System (VAERS) following monovalent 2009 pandemic influenza A (H1N1) vaccines.

Setting/patients: US Civilian reports following vaccine received from October 1, 2009 through May 31, 2010.

Measurements: Age, gender, vaccines received, diagnoses, clinical signs, and treatment were reviewed by nurses and physicians with expertise in vaccine adverse events. A panel of experts, including seven allergists reviewed complex illnesses and those with conflicting evidence for classification of the event. **Results:** Of 1984 reports, 1286 were consistent with immediate hypersensitivity disorders and were attributed to anxiety reactions, syncope, or other illnesses. The female-to-male ratio was $\geq 4:1$ for persons 20-to-59 years of age, but approximately equal for children under 10. One hundred eleven reports met Brighton Collaboration criteria for anaphylaxis; only one-half received epinephrine for initial therapy. The overall rate of reported hypersensitivity reactions was 10.7 per million vaccine doses distributed, with a 2-fold higher rate for live vaccine.

Limitations: Underreporting, especially of mild events, would result in an underestimate of the true rate of immediate hypersensitivity reactions. Selective reporting of events in adult females could have resulted in higher rates than reported for males.

* Corresponding author at: Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Room w5041, Baltimore, MD 21205, USA. Tel.: +1 410 955 6964; fax: +1 410 502 6733.

E-mail address: nhalsey@jhsph.edu (N.A. Halsey).

Conclusions: Adult females may be at higher risk of hypersensitivity reactions after influenza vaccination than men. Although the risk of hypersensitivity reactions following 2009 pandemic influenza A (H1N1) vaccines was low, all clinics administering vaccines should be familiar with treatment guidelines for these adverse events, including the use of intramuscular epinephrine early in the course of serious hypersensitivity reactions.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

Vaccines, including influenza vaccines, can cause immediate hypersensitivity reactions. The rates of immediate hypersensitivity reactions vary by vaccine and age; anaphylaxis after vaccination occurs at a rate of approximately one per million doses administered [1,2]. Less severe reactions such as urticaria undoubtedly occur much more frequently.

The Vaccine Adverse Event Reporting System (VAERS), co-managed by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) [3], accepts reports from anyone with knowledge of an adverse event following vaccination, including healthcare providers, manufacturers and affected patients. We systematically reviewed all VAERS reports from the United States for possible immediate hypersensitivity reactions following monovalent 2009 pandemic influenza A (H1N1) vaccine (H1N1 vaccines) to determine factors associated with reported events, to assess the validity of diagnoses, and to determine if there were differences in reporting rates by vaccines produced by different manufacturer.

2. Methods

VAERS is a national spontaneous reporting system co-administered by the Centers for Disease Control and Prevention and the Food and Drug Administration that receives reports of adverse events that occur after vaccination [3]. Signs and symptoms of adverse events described on the VAERS form are coded, using the Medical Dictionary for Regulatory Activities (MedDRA) [4]. A report is classified as serious if one of the following events is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [5]. We identified possible VAERS reports of immediate hypersensitivity events following receipt of inactivated H1N1 vaccines (IV) or live attenuated influenza vaccine (LAIV) received from October 1, 2009 through May 31, 2010. Initially, during the H1N1 vaccine campaign, all serious adverse event reports reported to VAERS were reviewed for possible immediate hypersensitivity reactions as part of the Centers for Disease Control effort to detect unexpected serious adverse events from these new vaccines. In 2012, in order to detect all reports of hypersensitivity adverse events, a retrospective search of all VAERS reports for recipients of the H1N1 vaccine was conducted using the following MedDRA search terms: anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock, laryngeal edema, wheezing, allergic edema, face edema, tongue edema, laryngospasm, allergic respiratory symptom, respiratory distress, urticaria, urticaria generalized, urticaria papular, angioneurotic edema, idiopathic urticaria, cross sensitivity reaction, documented hypersensitivity to administered drug, drug hypersensitivity, hypersensitivity, type I hypersensitivity, urticaria thermal, urticaria vesiculosa, vaccination site hypersensitivity, lip swelling, swelling face, dyspnea, swollen tongue, allergy to vaccine, and throat tightness. These terms were chosen in order to capture all possible immediate hypersensitivity reactions, including those that may not have been properly diagnosed at the time of the report.

The retrospective search included reports of illness that had onset during days 0–2 following vaccination, and reports

without a time recorded. Reports from military personnel and those from outside the United States were excluded because the numbers of doses administered to these populations were not available for determination of reporting rates. Each report and available medical records were reviewed by two nurses and a physician (NAH) trained in reviewing VAERS reports. Additional information was obtained from medical records for reports from the persons who reported the adverse event and/or the healthcare providers when indicated to obtain information needed to verify the diagnosis and interviews were conducted with selected affected patients after the health care provider obtained consent from the patient. We classified reports into diagnostic categories based upon all the clinical evidence available. Patients with hives/urticaria who also had more severe symptoms (e.g. respiratory distress or angioedema) were classified in accordance with the most severe manifestation. Difficult to classify and/or unusual health events were reviewed by one or more allergists, and selected problem cases were reviewed with five to nine immunologists/allergists on conference calls conducted by the Clinical Immunization Safety Assessment (CISA) hypersensitivity working group [6,7]. The Brighton Collaboration case definition [8] was used to classify reports of anaphylaxis (Table 1). The number of doses of H1N1 vaccine distributed by manufacturer was obtained from the CDC. Immunization coverage rates by gender and age groups were estimated from the National Health Interview Survey (NHIS) [9].

This study was approved by the Institutional Review Board of the Johns Hopkins Bloomberg School of Public Health. Because VAERS is an ongoing surveillance program that does not meet the definition of research, it was determined that CDC IRB approval was not needed.

3. Results

Of 1984 reports of suspected immediate hypersensitivity adverse events following H1N1 vaccines submitted to VAERS, medical records were obtained for 156 patients and 25 patients were contacted directly for supplemental information. Following review, 1286 reports were verified as hypersensitivity disorders. The remaining were attributed to anxiety reactions, syncope, or other conditions. Of the 1286 with hypersensitivity reactions, 140 were reported to have received other vaccines concurrently (100 of these received 2009–10 seasonal trivalent influenza vaccine); 190 were known to have received H1N1 vaccine only. For the remaining records no information regarding other vaccines was reported. The most common diagnosis assigned by the panel was hives/urticaria, followed by anaphylaxis and anxiety (Fig. 1). The gender distribution of reports with hypersensitivity diagnoses was approximately equal for young children, but after 9 years of age there was a predominance of females with the ratio of females to males greater than 4:1 for most age groups with a peak of 9.5:1 for 30–39 year olds, then decreasing to approximately equal distribution after 69 years of age (Fig. 2). This pattern was similar for reports from healthcare providers and self-reports from affected individuals or their family members (data not shown). Data from the National Health Interview Survey in May 2010 revealed slightly higher coverage rates for males than females for H1N1 vaccines in all age groups (Fig. 3). One hundred eleven of the immediate

Table 1

Brighton Collaboration major and minor criteria used in the case definition of anaphylaxis [8].

Organ system	Major	Minor
Dermatologic or mucosal	• Generalized urticaria (hives) or generalized erythema • Angioedema (not hereditary), localized or generalized • Generalized pruritus with skin rash	• Generalized pruritus without skin rash • Generalized prickle sensation • Localized injection site urticaria • Red and itchy eyes
Cardiovascular	• Measured hypotension • Clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following: ○ Tachycardia ○ Capillary refill time > 3 s ○ Reduced central pulse volume ○ Decreased level of consciousness	• Reduced peripheral circulation as indicated by the combination of at least 2 of: ○ Tachycardia and ○ Capillary refill time > 3 s without hypotension ○ Decreased level of consciousness
Respiratory	• Bilateral wheeze (bronchospasm) • Stridor • Upper airway swelling (lip, tongue, throat, uvula, or larynx) • Respiratory distress – 2 or more of the following: ○ Tachypnoea ○ Increased use of accessory respiratory muscles ○ Recession ○ Cyanosis ○ Grunting	• Persistent dry cough • Hoarse voice • Difficulty breathing without wheeze or stridor • Sensation of throat closure • Sneezing, rhinorrhea
Gastrointestinal		• Diarrhea • Abdominal pain • Nausea • Vomiting
Laboratory		• Mast cell tryptase elevation > upper normal limit

For all levels of diagnostic certainty: Anaphylaxis is a clinical syndrome characterized by

- sudden onset AND
- rapid progression of signs and symptoms AND
- involving multiple (≥ 2) organ systems, as follows.

Level 1 of diagnostic certainty:

- ≥ 1 major dermatological AND
- ≥ 1 major cardiovascular AND/OR ≥ 1 major respiratory criterion.

Level 2 of diagnostic certainty:

- ≥ 1 major cardiovascular AND ≥ 1 major respiratory criterion OR
- ≥ 1 major cardiovascular OR respiratory criterion AND
- ≥ 1 minor criterion involving ≥ 1 different system (*other than* cardiovascular or respiratory systems) OR
- (≥ 1 major dermatologic) AND (≥ 1 minor cardiovascular AND/OR minor respiratory criterion).

Level 3 of diagnostic certainty:

- ≥ 1 minor cardiovascular OR respiratory criterion AND
- ≥ 1 minor criterion from each of ≥ 2 different systems/categories.

hypersensitivity disorder reports met Brighton Collaboration criteria levels 1(38), 2(62), or 3(11) for anaphylaxis.

The reported onset of symptoms was within 15 min after vaccine receipt in 212 (17%) of the 1286 with hypersensitivity disorders; 188 (15%) were 16–60 min, 234 (18%) were between 1 and 4 h, 607 (47%) were 5–48 h, 22 (2%) were more than 2 days after vaccine administration, and for 23 (2%) the time interval could not be precisely determined. Most of the reports with onset more than 4 h were hives/urticaria or other rashes, 56 were facial swelling, and one patient had a serum sickness-like illness. Treatment

information was available for 912 reports (Table 2). The most common therapy administered for all conditions was diphenhydramine. Fifty-two (51%) of 102 patients with anaphylaxis for whom treatment data were available received epinephrine, the recommended therapy for severe immediate hypersensitivity reactions [10,11].

Vaccine distribution information revealed that 127,075,320 doses of monovalent influenza vaccine were distributed in the U.S. during 2009 and 2010 (Table 3). The reporting rate of hypersensitivity was 10.1 per million doses of monovalent vaccine distributed.

Table 2
Treatment of 912 patients with suspected hypersensitivity reactions reported to VAERS by diagnosis.

Diagnosis (N)	Epinephrine	Diphenhydramine	Steroids	H2 antagonists	Inhaler/nebulizer
Hives/urticaria (394)	17 (4%)	359 (91%)	122 (31%)	34 (9%)	7 (2%)
Anaphylaxis (102)	52 (51%)	87 (85%)	74 (73%)	31 (30%)	15 (15%)
Anxiety (63)	15 (24%)	48 (76%)	21 (33%)	4 (6%)	11 (17%)
Angioedema (76)	8 (11%)	66 (87%)	40 (53%)	10 (13%)	5 (7%)
Respiratory hypersensitivity (70)	22 (31%)	40 (57%)	33 (47%)	8 (11%)	42 (60%)
Rash, other (46)	3 (7%)	34 (74%)	23 (50%)	2 (4%)	2 (4%)
Sensation of throat closure (43)	15 (35%)	37 (86%)	19 (44%)	5 (12%)	4 (9%)
Pruritus without rash (21)	2 (10%)	21 (100%)	8 (38%)	2 (10%)	1 (5%)
Other (56)	2 (4%)	22 (39%)	24 (43%)	4 (7%)	24 (43%)
Vasovagal response (12)	6 (50%)	9 (75%)	5 (42%)	1 (8%)	0 (0%)
Serum sickness (2)	0 (0%)	1 (50%)	1 (50%)	0 (0%)	0 (0%)
Facial swelling $\geq$ 4 h after vaccine (27)	4 (15%)	22 (81%)	12 (44%)	2 (7%)	2 (7%)

Table 3
1286 hypersensitivity reactions by H1N1 vaccine manufacturer.

H1N1 vaccine manufacturer	Hypersensitivity ^a reports	Doses distributed	Rate per million doses distributed
CSL	27	3,451,900	7.8
Novartis	298	37,778,800	7.9
Sanofi pasteur	554	64,089,420	8.6
Medimmune ^b	256	21,755,200	11.8
Unknown	151		
All influenza vaccines	1286	127,075,320	10.1

H1N1 vaccines = monovalent 2009 pandemic influenza A (H1N1) vaccine.

^a Hypersensitivity only; anxiety, vasovagal and other were removed.^b Live Medimmune vs Novartis $p < .001$, vs Sanofi pasteur $p < .001$, and vs. CSL $p = .05$.

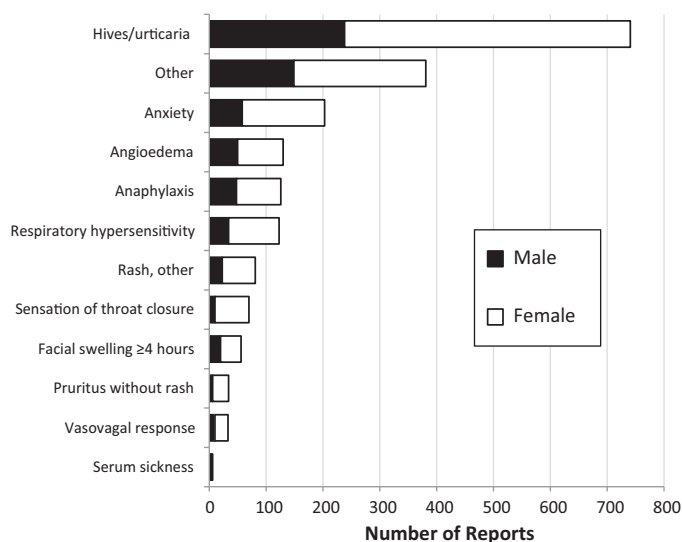
Although the reporting rates were all in the same general range, the rate for the live vaccine was significantly higher than for each of the inactivated vaccines (Table 3). The rate of anaphylaxis was 0.8 per million doses, with no significant differences by manufacturer.

The specific allergens that might have been responsible for the hypersensitivity disorders in these patients and allergy histories were not available for most reports. Four patients reported a history of egg allergy, but two of these reported eating eggs regularly without problems and one other patient was negative to skin tests with egg protein. One of the 4 patients developed anaphylaxis (Brighton level 1) 30 min after vaccination and reported a history of allergy to peanuts, tree nuts, and possible egg allergy prior to vaccination. Two of these four patients had respiratory hypersensitivity only, and one had sensation of throat closure. One additional

1-year-old patient developed hives 2 days after vaccination and 1 day after eating eggs but did not report a history of egg allergy prior to vaccination; allergy testing revealed allergy to eggs.

4. Discussion

The overall rate of anaphylaxis reports to VAERS following receipt of 2009 pandemic influenza A (H1N1) vaccines was low, and consistent with other reports of anaphylaxis following immunizations in populations where all health outcomes were identified and linked to immunization records [2,12]. Less severe hypersensitivity reactions were reported at a higher rate than anaphylaxis, consistent with the recognized more frequent occurrence of milder hypersensitivity reactions from vaccines and other causes [2]. These rates most likely underestimate the true rate because of the recognized underreporting of mild or moderate adverse events in passive surveillance systems such as VAERS [3]. The higher rate of reports in adult females cannot be explained by differences in immunization coverage since males had slightly higher coverage rates. The higher reported rate in adult females could be explained by higher rates of reporting adverse events by females or by a true higher rate of immediate hypersensitivity reactions in females. Since the gender ratios were similar for reports from different sources, we do not believe that this pattern can be attributed to selective reporting by females. The pattern of equal rates in children under 10 years of age, increasing female-to-male ratios by age with a peak in 20–39 year olds and then reverting to approximately equal in older individuals suggests a biological effect possibly associated with reproductive hormones. Other reports of patients treated in emergency rooms and hospitals suggest that adult females may be at higher risk than males of developing hypersensitivity reactions following exposure to different allergens [13–19]. There may be biologic mechanisms that could explain the apparent higher rate of hypersensitivity reactions among females following a variety of allergen exposures. Females have reported higher rates of other adverse events than males in clinical trials of rubella and anthrax vaccines [20–22]. Studies of hypersensitivity reactions following other products should include analyses of gender ratios by age to

**Fig. 1.** Diagnoses for 1984 reports to VAERS of suspected hypersensitivity following H1N1 vaccines by gender. VAERS = Vaccine Adverse Event Reporting System. H1N1 vaccines = monovalent 2009 pandemic influenza A (H1N1) vaccine.

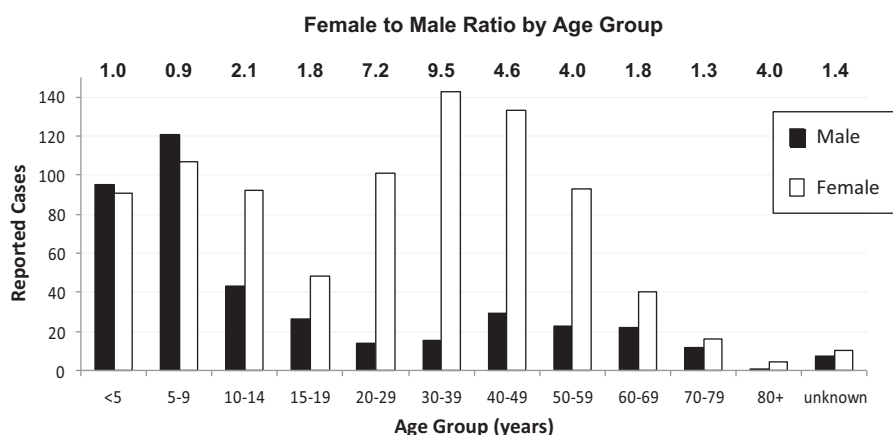


Fig. 2. 1286 reports of verified hypersensitivity adverse events submitted to VAERS following H1N1 vaccines by age and gender. VAERS = Vaccine Adverse Event Reporting System. H1N1 vaccines = monovalent 2009 pandemic influenza A (H1N1) vaccine.

see if there is a pattern similar to what was observed in this study. Also, a better understanding of the role of hormones and genetics in the pathogenesis of hypersensitivity reactions would help explain the observed differences in rates by gender.

Since all vaccine doses distributed are not administered, the rates by manufacturer slightly underestimate the rates of reported reactions. The reporting rate was higher for the live vaccine than for any of the inactivated vaccines. Possible explanations for these differences could include increased awareness or concern about respiratory symptoms following the live vaccine, differences in components, or the route of administration.

In spite of the known therapeutic advantage of the early use of intramuscular epinephrine during an immediate hypersensitivity reaction, epinephrine was administered to only 51% of patients with anaphylaxis and 9% of patients with angioedema [10,11]. Treatment with epinephrine is safe and establishing standard protocols for management of anaphylaxis can improve the utilization rates for epinephrine and other essential medications [23]. Delays in initiating treatment with epinephrine can be associated with severe complications, need for hospitalization, and death [24,25]. Most patients received diphenhydramine and many received combinations of therapy. Standard guidelines for management of serious allergic reactions have been developed and all clinics where vaccines are administered should have staff trained in recognizing the early signs of severe immediate hypersensitivity and initiating proper therapy [21,26,27].

Patients who have had an immediate hypersensitivity reaction following a vaccine require careful investigation to determine the advisability of administering any additional doses of the vaccine,

usually under the guidance of a specialist. CISA has developed an algorithm approach to assist with evaluating and managing these patients [28].

As with most hypersensitivity reactions to vaccines, the specific allergens responsible for the reactions have not been determined for most of the affected individuals. All of the 2009 influenza vaccines were produced in eggs and contained residual small amounts of egg protein as well as some other potential allergens (polymyxin, neomycin, or gentamicin) and some contained polysorbate 80 which can cause anaphylactoid reactions [29–31]. The risk of serious immediate hypersensitivity reactions to influenza vaccines among egg allergic patients is very low and most egg allergic patients can safely receive influenza vaccines because of the reduced levels of residual egg protein in vaccines produced in recent years [26,32]. However, serious hypersensitivity reactions can occur as noted in the patient in this series who developed anaphylaxis and the two patients with respiratory hypersensitivity. Thus, patients with a history of more serious reactions to egg need to be evaluated by a specialist to determine the advisability of administering any additional doses of the vaccine [26,30].

Most vaccines can cause hypersensitivity reactions [33]. Careful review of reported hypersensitivity reactions can help determine factors associated with these reactions and help differentiate true hypersensitivity reactions from syncope, anxiety reactions and other disorders.

Role of the funding source

This study was supported by the Clinical Immunization Safety Assessment Network through a subcontract with America's Health Insurance Plans under contract 200-2002-00732 from the Centers for Disease Control and Prevention (CDC). CDC personnel were involved in the collection, and interpretation of the data.

Conflicts of interest statement

N.H. has as a member of the Clinical Immunization and Safety Assessment (CISA) Network, received compensation for serving on Safety Monitoring Committees for Novartis and Merck, has provided expert legal advice in patent lawsuits for GlaxoSmithKline and has received research funding from NIH. S.D. has served as a consultant for the Clinical Immunization and Safety Assessment (CISA) Network and is a member of a Medical Expert Panel for the Division of Vaccine Injury Compensation (DVIC) for the Department of Health and Human Services and a member of an External Data Monitoring Committee at Pfizer, Inc. C.D. has received research

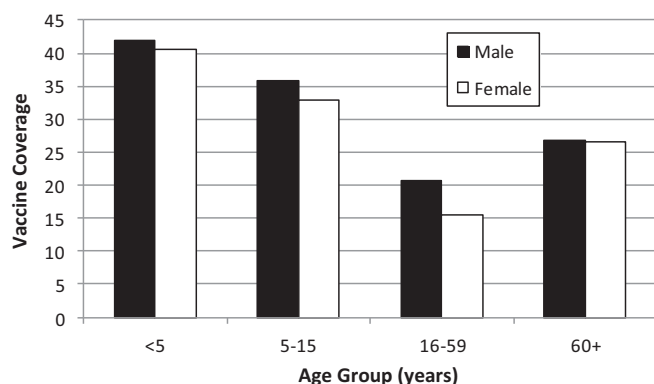


Fig. 3. H1N1 immunization coverage by age and gender – as of May 2010. H1N1 vaccines = monovalent 2009 pandemic influenza A (H1N1) vaccine.

support from NIH, EMMES Corp. (NIH prime) and CDC and is compensated as a member of the HIV Vaccine Trial Network Safety Monitoring Board and is a member of the External Data Monitoring Committee for Study Drug ACC-001 (vanutide cridificar) a joint development project for an Alzheimer's disease vaccine between Pfizer and Janssen and her husband is CEO of Dynavax Technologies, Inc. and owns stock in the company. R.W. is a consultant for the Asthma and Allergy Foundation of America, serves on the Medial Advisory Board for Food Allergy Research and Education and has received research funding from NIH. P.L. has served on a Data Safety Monitoring Committee for a Novartis meningococcal vaccine. M.B. is a salaried employee for CSL Behring. N.K. has received research grants from sanofi pasteur, GSK, Merck, Novartis, Pfizer and Protein Sciences. No other author has a conflict to declare.

Acknowledgements

We thank Elaine Miller and Oidda Museru for their assistance in obtaining reports from the Vaccine Adverse Event Reporting System. This study was supported by the Clinical Immunization Safety Assessment Network and Vaccine Safety Datalink through a subcontract with America's Health Insurance Plans under contract 200-2002-00732 from the Centers for Disease Control and Prevention (CDC).

References

- [1] Erlewyn-Lajeunesse M, Hunt LP, Heath PT, Erlewyn-Lajeunesse M, Hunt LP, Heath PT, et al. Anaphylaxis as an adverse event following immunisation in the UK and Ireland. *Arch Dis Child* 2012;93(1):974–5.
- [2] Bohlke K, Davis RL, Marcy SM, Braun MM, DeStefano F, Black SB, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003;112(4):815–20.
- [3] Varrichio F, Iskander J, DeStefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004;23(4):287–94.
- [4] International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). Medical dictionary for regulatory activities (MedDRA). <http://www.meddra.org/> [accessed 29.08.13].
- [5] Food and Drug Administration. 21 CFR Part 600.80. Postmarketing reporting of adverse experiences. Federal Register 1997;62:52252–3. <http://www.gpo.gov/fdsys/granule/CFR-2009-title21-vol7/CFR-2009-title21-vol7-sec600-80/content-detail.html> [accessed 29.08.13].
- [6] Williams SE, Klein NP, Halsey N, Dekker CL, Baxter RP, Marchant CD, et al. Overview of the Clinical Consult Case Review of adverse events following immunization: Clinical Immunization Safety Assessment (CISA) network 2004–2009. *Vaccine* 2011;29(40):6920–7.
- [7] LaRossa PS, Edwards KM, Dekker CL, Klein NP, Halsey NA, Marchant C, et al. Understanding the role of human variation in vaccine adverse events: the Clinical Immunization Safety Assessment Network. *Pediatrics* 2011;127(Suppl. 1):S65–73.
- [8] Rüggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5675–84.
- [9] CDC. National Health Interview Survey. Questionnaires, Datasets, and Related Documentation. www.cdc.gov/nchs/nhis/nhis.questionnaires.htm [accessed 29.08.2013].
- [10] Simons FE. Anaphylaxis pathogenesis and treatment. *Allergy* 2011;66(Suppl. 95):31–4.
- [11] Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;126(3):477–80. Erratum in: *J Allergy Clin Immunol* 2010;126(6):1104.
- [12] Lee GM, Greene SK, Weintraub ES, Baggs J, Kulldorff M, Fireman BH, et al. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. *Am J Prev Med* 2011;41(2):121–8.
- [13] Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol* 2001;108(5):861–6.
- [14] Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007;120(4):878–84.
- [15] Namork E, Fæste CK, Stensby BA, Egaas E, Løvik M. Severe allergic reactions to food in Norway: a ten year survey of cases reported to the food allergy register. *Int J Environ Res Public Health* 2011;8(8):3144–55.
- [16] Sole D, Ivancevich JC, Borges MS, Coelho MA, Rosario NA, Arduoso LR, et al. Anaphylaxis in Latin America: a report of the online Latin American survey on anaphylaxis (OLASA). *Clinics (Sao Paulo)* 2011;66(6):943–7.
- [17] Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol* 2008;122(6):1161–5.
- [18] Kurt E, Demir AU, Cadirci O, Yildirim H, Pinar Eser T. Immediate-type drug hypersensitivity and associated factors in a general population. *Allergol Immunopathol (Madr)* 2011;39(1):27–31.
- [19] Sheikh A, Alves B. Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data. *Clin Exp Allergy* 2001;31(10):1571–6.
- [20] Weibel RE, Stokes Jr J, Buynak EB, Hilleman MR. Influence of age on clinical response to HPV-77 duck rubella vaccine. *JAMA* 1972;222(7):805–7.
- [21] Swartz TA, Klingberg W, Goldwasser RA, Klingberg MA, Goldblum N, Hilleman MR. Clinical manifestations, according to age, among females given HPV-77 duck rubella vaccine. *Am J Epidemiol* 1971;94(3):246–51.
- [22] Marano N, Plikaytis BD, Martin SW, Rose C, Semenova VA, Martin SK, et al. Effects of a reduced dose schedule and intramuscular administration of anthrax vaccine adsorbed on immunogenicity and safety at 7 months: a randomized trial. *JAMA* 2008;300(13):1532–43. Erratum in: *JAMA* 2008;300(19):2252.
- [23] Arroabarren E, Lasa EM, Olaciregui I, Sarasqueta C, Muñoz JA, Pérez-Yarza EG. Improving anaphylaxis management in a pediatric emergency department. *Pediatr Allergy Immunol* 2011;22(7):708–14.
- [24] Cox L, Nelson H, Lockett R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol* 2011;127(1 Suppl.):S1–55.
- [25] American College of Allergy, Asthma, & Immunology. Food allergy: a practice parameter. *Ann Allergy Asthma Immunol* 2006;96(3 Suppl. 2):S1–68.
- [26] Simons FER. Pharmacologic treatment of anaphylaxis: can the evidence base be strengthened? *Curr Opin Allergy Clin Immunol* 2010;10:384–93.
- [27] Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2011;60(2):1–61.
- [28] Wood RA, Berger M, Dreskin SC, Setse R, Engler RJ, Dekker CL, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. *Pediatrics* 2008;122(3):e771–7.
- [29] Kelso JM. Administration of influenza vaccines to patients with egg allergy: update for the 2010–2011 season. *J Allergy Clin Immunol* 2010;126(6):1302–4.
- [30] Institute for Vaccine Safety. Allergens table. <http://vaccinesafety.edu/components-Allergens.htm> [updated 21.02.13; accessed 29.08.2013].
- [31] Coors EA, Seybold H, Merk HF, Mahler V. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. *Ann Allergy Asthma Immunol* 2005;95(6):593–9.
- [32] Centers for Disease Control and Prevention (CDC). Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2011;60(33):1128–32.
- [33] Committee to Review Adverse Effects of Vaccines, Institute of Medicine. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press; 2012. www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx [accessed 29.08.2013].