Emergency Department Visits for Antiviral Adverse Events During the 2009 H1N1 Influenza Pandemic

MARIBETH C. LOVEGROVE, MPH^a
NADINE SHEHAB, PHARM D, MPH^a
CRAIG M. HALES, MD, MPH^b
KATHY PONELEIT, MPH^c
ELIZABETH CRANE, PhD, MPH^c
DANIEL S. BUDNITZ, MD, MPH^a

ABSTRACT

The 2009 pandemic influenza A (H1N1) outbreak was associated with an increased use of antiviral agents and highlighted the role of population-based monitoring for related adverse drug events (ADEs). An ongoing, nationally representative emergency department-based surveillance system was used to identify and characterize ADEs during the pandemic. Active surveillance for ADEs successfully provided timely, population-based data during the pandemic. Increases in antiviral ADEs paralleled increases in prescribing. Type and severity of ADEs were similar across all seasons.

^aCenters for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases, Division of Healthcare Quality Promotion, Atlanta, GA

^bCenters for Disease Control and Prevention, Office of Surveillance, Epidemiology, and Laboratory Services, Atlanta, GA

^cSubstance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality (formerly the Office of Applied Studies), Division of Facility Surveys, Drug Abuse Warning Network, Rockville, MD

Address correspondence to: Daniel S. Budnitz, MD, MPH, Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion, 1600 Clifton Rd. NE, MS A-24, Atlanta, GA 30333; tel. 404-639-4096; fax 404-639-2647; e-mail <dbudnitz@cdc.gov>.

On April 26, 2009, the U.S. Department of Health and Human Services (HHS) declared a public health emergency for 2009 pandemic influenza A (H1N1) (hereafter, pH1N1).^{1,2} Influenza activity remained at higher-than-normal levels throughout the spring and summer, peaking in late October and early November 2009, and disproportionately affected younger people.³ The pH1N1 influenza virus was determined to be susceptible to the neuraminidase inhibitors (oseltamivir and zanamivir), which were recommended for treatment and chemoprophylaxis of pH1N1 infection.⁴ Given the pandemic spread and potential severity of infection with the pH1N1 virus, the Centers for Disease Control and Prevention (CDC) requested an Emergency Use Authorization to expand neuraminidase inhibitor use to include children younger than one year of age (oseltamivir) and patients of any age with severe disease (oseltamivir and zanamivir).⁵

Adverse events from medications are typically monitored through passive surveillance, primarily the U.S. Food and Drug Administration Adverse Event Reporting System (AERS), which relies on voluntary reporting of adverse drug events (ADEs) by health-care professionals and consumers and reporting by pharmaceutical manufacturers.⁶ Because the early stages of a novel influenza pandemic are associated with many unknowns, including possible delays in availability of vaccine, a 2008 Institute of Medicine report recommended that HHS consider options, in addition to AERS, for capturing antiviral adverse events, as use of antivirals, particularly among vulnerable populations, is likely to increase.⁷ We used data from an active, population-based surveillance system to monitor emergency department (ED) visits for antiviral ADEs during pH1N1 and compared these data with those from previous influenza seasons.

METHODS

The Drug Abuse Warning Network (DAWN) is an ongoing public health surveillance system administered by the Substance Abuse and Mental Health Services Administration (SAMHSA) that monitors drug-related hospital ED visits. DAWN uses a national probability sample of approximately 250 nonfederal, short-stay general hospitals that operate 24-hour EDs. On a regular basis, DAWN reporters at each facility actively review and record data from ED medical charts for the full spectrum of use, misuse, and abuse for any drug-related visit, including adverse reactions to drugs

and vaccines, as documented by the treating physician. Unweighted case data are available in near real time; national estimates are calculated annually. Direct patient identifiers are not collected.⁸

We defined a case as an ED visit made between January 1, 2006, and December 31, 2009, for an adverse event associated with an influenza antiviral (oseltamivir, zanamivir, amantadine, or rimantadine). We identified cases through a Web-based portal to near real-time DAWN data. We obtained additional narrative descriptions of ED visits from SAMHSA (Unpublished data, SAMHSA, Center for Behavioral Health Statistics and Quality, DAWN; unweighted ED data from DAWN, January 2006–December 2009) and coded them using the Medical Dictionary for Regulatory Activities version 9.1.⁹ Adverse events were categorized by implicated drug, patient demographics, disposition, and adverse event manifestation. We conducted analyses using SAS[®].¹⁰

Influenza antiviral prescription data were obtained from CDC BioSense, which receives real-time data from RelayHealth[™] (www.relayhealth.com), an electronic prescriptions claims service provider for 20,000 to 30,000 pharmacies in all 50 states and Washington, D.C., as well as U.S. territories.¹¹

RESULTS

In the previous three influenza seasons, the number of ED visits for antiviral adverse events peaked in February. In 2009, however, following a peak in February, ED visits peaked again in June and November. The number of antiviral medication prescriptions followed a similar temporal pattern (Figure).

During the 2008–2009 influenza season (and through September 2009 to account for early pH1N1 activity), most adverse event visits were among females (59.4%) and people aged 18–44 years (41.0%) and were related to oseltamivir (71.3%). Most ED visits resulted in the patient being discharged home (77.8%). In comparison with previous influenza seasons, a higher proportion of adverse events involved children younger than 6 years of age during the extended 2008–2009 season and the first half of the 2009–2010 season (Table 1). In 2009, the most common adverse events associated with neuraminidase inhibitor use were gastrointestinal symptoms (48.1%), allergic reactions (31.3%), and central nervous system effects (19.9%). Compared with previous years, type and severity of ADEs were similar in 2009 (Table 2).

Figure. ED visits for influenza antiviral-related adverse events reported to DAWN and influenza antiviral prescriptions reported to BioSense, 2006–2007 to 2009–2010 influenza seasons^{a,b}

^aCase counts of ED visits are from DAWN, Substance Abuse and Mental Health Services Administration, 2006–2009. Numbers of influenza antiviral prescriptions are from BioSense, Centers for Disease Control and Prevention. Influenza antivirals include all formulations of amantadine, rimantadine, oseltamivir, and zanamivir. Includes reports through December 31, 2009.

^bIn response to the emergence of 2009 pandemic influenza A (H1N1), surveillance for adverse drug events during the 2008–2009 season extends beyond the typical influenza season and includes reports through September 30, 2009.

ED = emergency department

DAWN = Drug Abuse Warning Network

pH1N1 = 2009 pandemic influenza A (H1N1)

DISCUSSION

This article provides the first description of antiviral-related adverse events during the 2009 H1N1 influenza pandemic based on active, population-based surveillance. Antiviral safety monitoring using DAWN was conducted on an ongoing and regular basis throughout the pH1N1 outbreak and successfully contributed to response efforts by providing timely data to public health authorities on potential safety concerns resulting from widespread use of antiviral agents. We identified an increase in the number of ED visits for antiviral ADEs shortly after an emergency was declared for pH1N1,¹² and we identified another peak in visits with the second phase of the outbreak.¹³ The types of adverse events were consistent with the known safety profile of these agents and similar to data from previous seasons.^{14–16} These surveillance data reflected the nature of the pandemic and the antiviral recommendations for the 2009–2010 season in that a substantially higher propor-

tion of visits involved neuraminidase inhibitors than adamantanes and were made by people in younger age groups compared with previous seasons.⁵ Because the severity and types of adverse event manifestations were comparable to previous seasons, these data did not trigger further investigation.

Limitations

These data had a number of limitations. First, only adverse events that resulted in an ED visit were included. While the ED is an appropriate setting to identify many serious adverse events, rare, previously unreported ADEs or ADEs difficult to diagnose in the ED setting are less likely to be identified. Thus, these types of ADEs may have been underreported.¹⁷ Other types of adverse events may have been overreported. For example, in some cases, disease manifestations (e.g., underlying influenza infection) may have been confused with an antiviral adverse event. If more than

Table 1. ED visits for influenza antiviral-related adverse events reported to DAWN, by drug, patient characteristics, and disposition: 2006–2007 to 2009–2010 influenza seasons^a

	Influenza season			
	2006–2007	2007–2008	2008–2009 ^b	2009–2010
	Cases N (percent)	Cases N (percent)	Cases N (percent)	Cases N (percent)
Drug				
Adamantanes				
Amantadine	27 (35.1)	36 (27.7)	66 (25.3)	11 (2.7)
Rimantadine	1 (1.3)	1 (0.8)	1 (0.4)	1 (0.2)
Neuraminidase inhibitors				
Oseltamivir	49 (63.6)	93 (71.5)	186 (71.3)	397 (96.6)
Zanamivir	0 (0.0)	0 (0.0)	8 (3.1)	2 (0.5)
Gender				
Female	38 (49.4)	73 (56.2)	155 (59.4)	255 (62.0)
Male	39 (50.6)	57 (43.8)	106 (40.6)	156 (38.0)
Age (in years)				
<6	7 (9.1)	11 (8.5)	29 (11.1)	92 (22.4)
6–11	15 (19.5)	7 (5.4)	29 (11.1)	52 (12.7)
12–17	6 (7.8)	3 (2.3)	15 (5.7)	34 (8.3)
18–44	17 (22.1)	57 (43.8)	107 (41.0)	151 (36.7)
45–64	21 (27.3)	31 (23.8)	48 (18.4)	61 (14.8)
≥65	11 (14.3)	21 (16.2)	33 (12.6)	21 (5.1)
Disposition				
Discharged to home	61 (79.2)	104 (80.0)	203 (77.8)	368 (89.5)
Admitted to intensive care unit/critical care/surgery	3 (3.9)	2 (1.5)	5 (1.9)	3 (0.7)
Admitted to psychiatric unit	2 (2.6)	2 (1.5)	8 (3.1)	0 (0.0)
Admitted to other inpatient unit	11 (14.3)	18 (13.8)	38 (14.6)	33 (8.0)
Transferred	0 (0.0)	2 (1.5)	2 (0.8)	4 (1.0)
Left against medical advice	0 (0.0)	1 (0.8)	2 (0.8)	0 (0.0)
Other or not documented	0 (0.0)	1 (0.8)	3 (1.1)	3 (0.7)
Total ^c	77 (100.0)	130 (100.0)	261 (100.0)	411 (100.0)

^aCase counts of ED visits are from DAWN, Substance Abuse and Mental Health Services Administration, 2006–2009. Includes reports through December 31, 2009.

^bIn response to the emergence of 2009 pandemic influenza A (H1N1), surveillance for adverse drug events during the 2008–2009 season extends beyond the typical influenza season and includes reports through September 30, 2009.

^cThe total reflects drug reports (more than one antiviral can be implicated in a single ED visit).

ED = emergency department

DAWN = Drug Abuse Warning Network

one medication was reported, drugs other than influenza antivirals may have contributed to the adverse event. None of these limitations, however, would be expected to affect trends over time.

Second, the number of hospitals reporting to DAWN varies over the years; however, this variation would not account for the substantial increase in the number of cases reported in 2009 compared with previous years and should not have affected the types of ADEs reported. Third, BioSense antiviral use data represent prescriptions approved by third-party payers (e.g., private insurance, Medicare, or Medicaid) and do not

include prescriptions that were paid for out-of-pocket, denied coverage, or ordered from online pharmacies. However, RelayHealth estimates that CDC receives data for approximately 50% of anti-infective prescription transactions in the U.S.

CONCLUSION

Surveillance using DAWN data successfully complemented passive surveillance by providing timely, population-based data for the detection and characterization of ADEs associated with influenza antivirals during a

Table 2. ED visits for neuraminidase inhibitor-related adverse events reported to DAWN, by adverse event manifestation, 2006–2009^a

Adverse event manifestation ^b	2006–2008	2009
	Cases N (percent)	Cases N (percent)
Gastrointestinal	75 (42.4)	281 (48.1)
Nausea, vomiting, diarrhea, and related effects	70 (39.5)	253 (43.3)
Other gastrointestinal effects	15 (8.5)	69 (11.8)
Central nervous system	30 (16.9)	116 (19.9)
Neuropsychiatric	14 (7.9)	36 (6.2)
Altered mental status	6 (3.4)	15 (2.6)
Other central nervous system effects	20 (11.3)	90 (15.4)
Allergic	68 (38.4)	183 (31.3)
Moderate/severe ^c	22 (12.4)	36 (6.2)
Mild/not documented ^d	62 (35.0)	178 (30.5)
Respiratory	10 (5.6)	45 (7.7)
Musculoskeletal	10 (5.6)	26 (4.5)
Other manifestation	37 (20.9)	103 (17.6)
Inconsistent with influenza antiviral adverse drug event ^e	12 (6.8)	27 (4.6)
None documented	2 (1.1)	0 (0.0)

^aCase counts of ED visits are from DAWN, Substance Abuse and Mental Health Services Administration, 2006–2009. Includes reports through December 31, 2009. Neuraminidase inhibitors include all formulations of oseltamivir and zanamivir.

^bA single ED visit can be associated with more than one adverse event manifestation.

^cIncludes anaphylactic reaction/shock, angioedema, erythema multiforme, eye/face/lip/mouth/pharyngeal/tongue/vulval edema, and Stevens-Johnson syndrome

^dIncludes dermatitis, drug eruption/hypersensitivity, edema, erythema, erythematous/generalized/papular/pruritic rash, flushing, generalized/oral pruritus, palmar erythema, peripheral edema, purpura, throat tightness, and urticaria

^eIncludes cases where neither the case description nor the diagnosis was consistent with a possible influenza antiviral-related adverse event

ED = emergency department

DAWN = Drug Abuse Warning Network

pandemic. Continuing these surveillance efforts would be useful for future influenza seasons.

The authors thank Victor Johnson, Northrop Grumman, contractor for the Centers for Disease Control and Prevention, and Inga Allred of RTI International for assistance with programming; and Kathy Ghanouni, PharmD, for assistance with data collection. No individuals named herein received compensation for their contributions.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the funding agencies.

REFERENCES

1. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009;360:2605-15.
2. Department of Health and Human Services (US). Determination that a public health emergency exists. April 2009 [cited 2009 Dec 23]. Available from: URL: http://www.hhs.gov/secretary/phe_swh1n1_april_2009.html
3. Update: influenza activity—United States, August 30, 2009–March 27, 2010, and composition of the 2010–11 influenza vaccine. *MMWR Morb Mortal Wkly Rep* 2010;59(14):423-30.
4. Update: influenza activity—United States, August 30–October 31, 2009. *MMWR Morb Mortal Wkly Rep* 2009;58(44):1236-41.
5. Centers for Disease Control and Prevention (US). Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season [cited 2009 Dec 23]. Available from: URL: <http://www.cdc.gov/H1N1flu/recommendations.htm>
6. Food and Drug Administration (US). Adverse Event Reporting System (AERS) [cited 2009 Dec 23]. Available from: URL: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>
7. Institute of Medicine. Antivirals for pandemic influenza: guidance on developing a distribution and dispensing program. Washington: National Academies Press; 2008.
8. Substance Abuse and Mental Health Services Administration, Office of Applied Studies (US). Drug Abuse Warning Network, 2006: national estimates of drug-related emergency department visits. DAWN Series D-30, DHHS Publication No. (SMA) 08-4339. Rockville (MD): SAMHSA; 2008.
9. Bousquet C, Lagier G, Lillo-Le Louët A, Le Beller C, Venot A, Jaulent MC. Appraisal of the MedDRA conceptual structure for describing and grouping adverse drug reactions. *Drug Saf* 2005;28:19-34.
10. SAS Institute, Inc. SAS®: Version 9.2 for Windows. Cary (NC): SAS Institute, Inc.; 2008.

11. CDC (US). BioSense [cited 2009 Dec 23]. Available from: URL: <http://www.cdc.gov/biosense/index.html>
12. Update: influenza activity—United States, April–August 2009. *MMWR Morb Mortal Wkly Rep* 2009;58(36):1009-12.
13. CDC (US). Fluviv: a weekly influenza surveillance report prepared by the Influenza Division [cited 2009 Dec 23]. Available from: URL: <http://www.cdc.gov/flu/weekly/weeklyarchives2009-2010/weekly50.htm>
14. Khazeni N, Bravata DM, Holty JE, Uyeki TM, Stave CD, Gould MK. Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. *Ann Intern Med* 2009;151:464-73.
15. Jefferson T, Jones M, Doshi P, Del Mar C. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. *BMJ* 2009;339:b5106. doi: 10.1136/bmj.b5106.
16. Matheson NJ, Harnden AR, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. *Cochrane Database Syst Rev* 2007;(1):CD002744.
17. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. *JAMA* 2006;296:1858-66.