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Influenza antiviral prescribing practices during the 2007–08 and 2008–09 influenza seasons in the setting of increased resistance to oseltamivir among circulating influenza viruses☆

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ABSTRACT

Introduction: In December 2008, new interim guidelines on the use of influenza antiviral agents were released in response to a high prevalence of circulating oseltamivir-resistant seasonal influenza A(H1N1) and adamantane-resistant influenza A(H3N2) viruses. Zanamivir, oseltamivir +/− an adamantane, or oseltamivir was recommended, depending on virus type, subtype, and local surveillance data.
Materials and methods: Information about antiviral prescribing practices among IDSA Emerging Infections Network (EIN) members was obtained using two web-based questionnaires; one in January 2009 regarding the prior 2007–08 influenza season and one in April 2009 (prepandemic), regarding the concurrent 2008–09 season.
Results: In the 2007–08 survey, 646 (52%) of 1249 EIN members responded and in the 2008–09 season survey, 350 (27%) of 1281 responded. In 2008–09 vs. 2007–08: 59% vs. 69% prescribed or recommended antivirals for treatment ($p < .0001$); 48% vs. 80% prescribed oseltamivir alone and 39% vs. 10% prescribed zanamivir alone ($p < .0001$ for both). During 2008–09 28% reported treating fewer patients compared with 2007–08; 42% felt antivirals were less effective due to resistance and 40% felt patients had less severe illness. During 2008–09, 42% of respondents reported difficulty providing zanamivir to patients vs. 5% for oseltamivir ($p < .0001$). Only 11% of respondents could test for influenza A subtype. During both seasons, ~55% used local surveillance data to make treatment decisions.
Discussion: A mild winter influenza season, difficulty obtaining recommended agents, and lack of access to subtype diagnosis and surveillance data may have contributed to reduced antiviral use during 2008–09.

1. Introduction

Two classes of influenza antiviral agents are licensed for the treatment and chemoprophylaxis of influenza in the United States, the neuraminidase inhibitors (NAI) (oseltamivir and zanamivir), and the adamantanes (M2 channel inhibitors, amantadine and rimantadine) (Fiore et al., 2009). During the 2005–06 influenza season, the prevalence of resistance to adamantanes among circulating influenza A(H3N2) viruses increased to over 90%, prompting the Centers for Disease Control and Prevention (CDC) to recommend in January 2006 that only NAI be used for the treatment and chemoprophylaxis of influenza (CDC, 2006).

Resistance to oseltamivir was detected at a significant but low prevalence for the first time during the 2007–08 influenza season (CDC, 2008a). At the start of the 2008–09 influenza season, influenza surveillance data demonstrated that the prevalence of resistance to oseltamivir among circulating seasonal influenza A(H1N1) viruses had risen to >95%, most circulating influenza viruses were A(H1N1), and resistance to adamantanes was detected among 100% of circulating A(H3N2) viruses tested (CDC, 2008b). As a result, new interim guidelines on the use of influenza antiviral medications were released on December 19, 2008 (CDC Issues Interim Recommendations). These guidelines recommended that physicians review local influenza surveillance data to ascertain the

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virus types and influenza A virus subtypes circulating in their area and use available influenza diagnostic testing results on viral type to guide their choice of antiviral agent. If infection with influenza A virus was suspected, zanamivir or therapy with both oseltamivir and an adamantane was recommended; if infection with influenza B virus was suspected, oseltamivir or zanamivir monotherapy was recommended.

To understand whether the interim guidelines released in December 2008 were effectively communicated and could be implemented, we surveyed infectious disease physicians about their antiviral prescribing practices: in January 2009, regarding the prior 2007–08 influenza season, and again in April 2009, regarding the concurrent 2008–09 influenza season, prior to the circulation of pandemic influenza A(H1N1). During the 2007–08 season, 71% of 39,827 viruses identified by national surveillance were influenza A viruses and of the 29% that were subtyped, 26% were influenza A(H1N1) and 74% were influenza A(H3N2) viruses. Of the influenza A(H1N1) viruses tested for antiviral resistance, 11% were resistant to oseltamivir, none were resistant to zanamivir and 11% were resistant to the adamantanes. Of the influenza A(H3N2) viruses tested, all were susceptible to oseltamivir and zanamivir and 99.8% were resistant to the adamantanes (CDC, 2008a).

During the 2008–09 season, prior to the circulation of pandemic influenza A(H1N1) viruses, 67% of 24,793 viruses identified were influenza A viruses and of the 40% subtyped, 90% were influenza A(H1N1) viruses and 10% were influenza A(H3N2) viruses. Of the influenza A(H1N1) viruses tested for antiviral resistance, 99% were resistant to oseltamivir, none were resistant to zanamivir and 0.4% were resistant to the adamantanes. Of the influenza A(H3N2) viruses tested, all were susceptible to oseltamivir and zanamivir and all were resistant to the adamanatanes. In both seasons, all influenza B viruses were susceptible to oseltamivir and zanamivir; adamantanes are not effective against influenza B viruses (CDC, 2009).

2. Materials and methods

The Infectious Diseases Society of America (IDSA) Emerging Infections Network (EIN) is a provider-based sentinel network that was established in 1995 as part of a Cooperative Agreement Program award from the Centers for Disease Control and Prevention (CDC) (Executive Committee of the Infectious Diseases Society of America Emerging Infections Network, 1997). The EIN conducts surveys among its members on topics of clinical importance to rapidly assess the impact of specific public health concerns.

Two web-based questionnaires were distributed by e-mail and facsimile to 1249 infectious diseases consultants who were members of EIN in January 2009, regarding the 2007–08 influenza season, and 1281 EIN members in April 2009, regarding the 2008–09 influenza season. Typically, two reminders to encourage survey completion are sent within several weeks after the first mailing. The 2007–08 season survey was re-sent twice; however, repeat mailings of the 2008–09 season survey were not done due to the 2009 pandemic influenza A(H1N1) outbreak and accompanying declaration of a public health emergency (Pandemic (H1N1), 2009).

The January survey, sent before wide-spread influenza activity was reported for that year in any state, queried physicians on the following about the 2007–08 influenza season: antiviral prescribing practices; available influenza diagnostic testing and turnaround time for results; educational resources used to guide their clinical treatment and/or chemoprophylaxis decisions; and whether the interim guidelines on antiviral use released on December 19, 2008 were accessible, clear and comprehensive. In April, after most states had experienced wide-spread seasonal influenza activity and before pandemic influenza A(H1N1) viruses began to circulate, the 2008–09 season survey was sent to assess whether antiviral prescribing practices had changed during the 2008–09 influenza season as a result of the new guidance or other factors, and to assess which resources were most useful when treating patients during the 2008–09 influenza season. Not all questions were repeated in both surveys. Influenza was defined to include both laboratory-confirmed and clinically suspected influenza.

Data were collected and tabulated by the EIN coordinating center in Iowa City, IA. Frequency analyses and cross-tabulations were performed using SAS 9.1 (Cary, NC). Additional analyses were performed at CDC also using SAS 9.1 (Cary, NC). Proportions were compared using Chi-square tests; p-values <.05 were considered statistically significant.

3. Results

From January 15 to February 10, 2009, 646 (52%) of 1249 EIN members responded to the 2007–08 survey emailed three times in January. From April 21 to May 7, 2009, 350 (27%) of 1281 EIN members responded to the 2008–09 season survey emailed once in April. Of those that responded to the April survey, 302 (86%) reported they had also responded to the January survey. Respondents to the January survey were more likely to have had <15 years of experience compared with respondents to the April survey (57% vs. 47%, p-value = .007). There were no other differences in characteristics of respondents to the two surveys including: type of practice (adult, pediatric or both), type of employer, region of practice, number of hospitals in which the member practiced, whether the member practiced adult infectious diseases, pediatric infectious diseases, general internal medicine or general pediatrics, and whether the member was involved in teaching or research.

During both years most respondents reported caring for patients with influenza (Table 1). In the 2007–08 season survey, 58% of respondents reported that the majority or all of the treated patients with influenza were inpatients. A greater proportion of respondents reported prescribing or recommending influenza antiviral medications for treatment and chemoprophylaxis during the 2007–08 season compared to the 2008–09 season (69% vs. 59% for treatment, p-value < .0001; 34% vs. 23% for chemoprophylaxis, p-value < .0001). In addition, during 2007–08 only 5% reported treating none of their patients with antiviral medications while during 2008–09 24% reported treating none (p-value < .0001).

During the 2007–08 influenza season, 80% of respondents who prescribed antiviral agents for their patients with influenza prescribed oseltamivir alone for treatment and 10% prescribed zanamivir alone (Table 1). During 2008–09, 66% prescribed oseltamivir plus an adamantane, 39% prescribed zanamivir alone and 48% prescribed oseltamivir alone. Medications prescribed for chemoprophylaxis were similar (data not shown).

In the 2007–08 survey, we asked physicians which factors they considered when deciding to treat patients with influenza with antiviral medications. Among 369 respondents, the following factors were reported: laboratory confirmation by a diagnostic test (80%), time from illness onset to presentation (79%), underlying medical conditions of the patient (79%), severity of clinical symptoms (74%), local influenza surveillance data (56%), efficacy data from published studies (43%), whether it was “flu season” (40%), and national influenza surveillance data (21%). In the 2008–09 survey, we asked physicians which factors helped them decide which antiviral agents to use. Among 210 respondents reporting on the 2008–09 influenza season, 62% reported using influenza rapid test results that distinguish influenza type A from type B to help them decide on treatment, and 54% reported using local

Table 1
Use of influenza antiviral agents, 2007–08 and 2008–09.

	2007–08 influenza season# (%)	2008–2009 influenza season# (%)	*p*
Respondents[a]	*N* = 646	*N* = 350	
Number taking care of patients with influenza	513 (79)	294 (84)	.08
Prescribed or recommended influenza antiviral medications	*N* = 509	*N* = 350	
Treatment			
Yes	351 (69)	172 (59)	<.0001
No	156 (31)	122 (42)	
Prophylaxis			<.0001
Yes	174 (34)	67 (23)	
No	334 (66)	227 (77)	
Proportion of patients with influenza that were treated with antiviral medications	*N* = 371	*N* = 228	
None	20 (5)	55 (24)	<.0001
1–24%	131 (35)	65 (29)	.05
25–49%	50 (13)	23 (10)	.18
50–74%	57 (15)	26 (11)	.14
75–99%	55 (15)	27 (12)	.26
All	33 (9)	22 (10)	.82
Agents prescribed/recommended for treatment	*N* = 347	*N* = 171	
Oseltamivir[b]	278 (80)	81 (48)	<.0001
Zanamivir[b]	34 (10)	66 (39)	<.0001
Amantadine[c]	13 (4)	16 (9)	.0091
Rimantadine[c]	23 (7)	20 (12)	.05
Combination therapy, not specified	22 (6)	Not asked	
Combination therapy with oseltamivir[b] and amantadine[c]	Not asked	41 (24)	
Combination therapy with oseltamivir[b] and rimantadine[c]	Not asked	72 (42)	

[a] Respondents to the January survey were significantly more likely than non-respondents to have pediatric practices (*p*-value = .04), practice in the East South Central region (*p*-value = .008) and have at least 15 years of ID experience (*p*-value = .04). Respondents to the April survey were significantly more likely than non-respondents to have at least 15 years of ID experience (*p*-value < .0001) and to have teaching responsibilities (*p*-value < .0001).
[b] Neuraminidase inhibitor.
[c] Adamantane.

surveillance data on types and influenza A subtypes of circulating influenza viruses; 15% reported that they did not have enough information on which to make treatment decisions. Of the 39 (19%) who reported using "other" sources, 27 (69%) used national or CDC data/recommendations.

The most common reasons respondents did not prescribe antiviral agents to patients with influenza during the 2007–08 influenza season were that the patient presented >2 days after onset of illness (73%) or that the patient had mild illness (46%) (Table 2). In April, when asked whether, in addition to modifying the antiviral agents they prescribed, the current circulation of antiviral resistant seasonal influenza viruses changed their prescribing practices during the 2008–09 influenza season, 141 (67%) responded that they treated the same proportion of patients with influenza, 58 (28%) reported treating a smaller proportion and 10 (5%) reported treating a larger proportion. Of the 58 that treated a smaller proportion, 50 indicated why: 42% felt the agents were less effective, 40% had more patients with mild illness, 22% were unwilling to subject their patients to the side effects of antiviral medications and 24% reported "other" (unspecified).

Table 2
Reasons for not treating patients with influenza with antiviral agents during the 2007–08 influenza season.

	2007–08 influenza season *N* = 501 %
Patient presented >2 days after onset of illness	73
Patient had mild illness	46
Did not see patients with influenza	19
Patient did not want to take medication	13
Patient too young to take antiviral	13
Contraindications	9
Patient could not afford the medication	9
Concern for side effects of antivirals	8
Patient could not take PO or inhaled	3
Patients had received influenza vaccination	3
Did not feel influenza antiviral agents are effective	2

During both influenza seasons, respondents reported more difficulty obtaining zanamivir than oseltamivir (Fig. 1: (a) 2007–08 season and (b) 2008–09 season). Excluding those that reported never prescribing the drug, in 2008–09, 41 (42%) of 98 respondents reported it was difficult or very difficult to provide zanamivir to their patients, compared with 7 (5%) of 147 reporting the same for oseltamivir ($p < .0001$). Respondents reported that both amantadine and rimantadine were difficult or very difficult to provide during 2008–09 (amantadine: 14%, rimantadine: 30%) (Fig. 1b); very few respondents reported prescribing the adamantanes during 2007–08 (Fig. 1a). Respondents who reported difficulty obtaining antiviral agents reported that the medications were not available from outpatient pharmacies (36%), inpatient pharmacies (21%) or from both inpatient and outpatient pharmacies (33%).

We asked about influenza diagnostic testing capacity in the 2007–08 survey only; 25 (5%) reported never testing for influenza. Of those that reported testing for influenza, 90% reported being able to test for viral type and 79% reported that test results were available within <24 h. However, only 11% reported being able to test for influenza A virus subtype, and of those, 9% had subtype results available in <24 h, 49% in 1–3 days, 23% in 4–7 days and 12% had to wait longer than 1 week to receive subtype results.

During both seasons, the majority of respondents reported that they received information on influenza from multiple sources, including the new CDC Health Advisory "Interim Recommendations for the Use of Influenza Antiviral Medications" (CDC Issues Interim Recommendations) (Table 3). In response to the two mailings of the 2007–08 survey, approximately 4–7 weeks after the new recommendations were released, 436 (90%) of 484 respondents reported being aware of the new recommendations. Of 448 respondents, 390 (87%) reported that the recommendations were easy to understand and 384 (87%) of 443 respondents reported that they provided enough information.

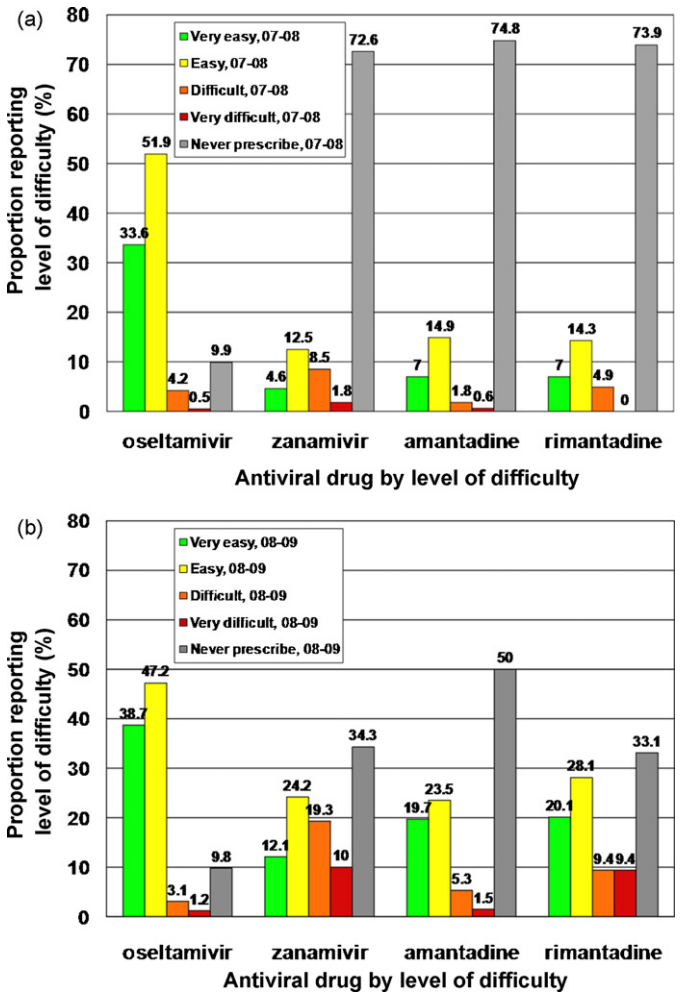

Fig. 1. Level of difficulty reported by physicians in providing antiviral agents to their patients, 2007–08 and 2008–09. Of 58 respondents to the April survey reporting that it was difficult or very difficult to provide antiviral agents to their patients during 2008–09, 21 (36%) reported the medication was not available from an outpatient pharmacy, 12 (21%) reported the medication was not available from an inpatient pharmacy and 19 (33%) reported the medication was not available from both inpatient and outpatient pharmacies. Other responses included: non-formulary at the Veterans Administration ($n = 2$), unable to find the specific inhaler for zanamivir ($n = 1$), problems with insurance coverage ($n = 1$), difficult to administer ($n = 1$), had to be ordered ($n = 1$). (a) 2007–08 and (b) 2008–09.

4. Discussion

During the 2008–09 influenza season, the majority of EIN survey respondents reported that they received the interim guidelines on antiviral use released via Health Alert in December 2008 and at that time felt they were easy to understand and contained sufficient information. However, fewer physicians reported prescribing antiviral agents during the 2008–09 influenza season compared with the 2007–08 influenza season. Several factors might have contributed to this difference, including concerns about antiviral effectiveness, milder illness during the 2008–09 season due to the limited circulation of influenza A(H3N2) viruses, or differences in characteristics of respondents to the two surveys. In addition, the new interim guidelines may have been difficult for physicians to implement due to limited availability of zanamivir, rimantadine and amantadine. Only half of the EIN survey respondents used local surveillance data to guide treatment decisions and laboratory testing results on influenza A virus subtype were not commonly available. Finally, about one-fifth of respondents reported that they did not want to subject their patients to the potential side effects of two antiviral agents.

Before December 2008, zanamivir was not widely used in clinical practice (CDC, 2008c; Dharan et al., 2009; Katz et al., 2009). However, in 2008–09, zanamivir was the only agent recommended for empiric monotherapy of influenza and 39% of respondents that reported prescribing antiviral agents used zanamivir. It is possible that the proportion prescribing zanamivir would have been greater if availability was not limited. During 2008–09, adamantanes were also difficult to obtain. The adamantanes had not been recommended for use from January 2006, due to high proportions of resistant A(H3N2) viruses (CDC, 2006), to December 2008 (CDC Issues Interim Recommendations) when they were recommended only in combination with oseltamivir. It is possible that there was not enough time between early December 2008 and the 2008–09 influenza season to allow pharmacies to stock these agents. However, it is also possible that pharmacists were not aware of the guidelines or that the guidelines did not influence which drugs were stocked in pharmacies. Importantly, many respondents reported that these agents were difficult to obtain from inpatient pharmacies, suggesting that antiviral agents were hard to provide to even the most severely ill patients with influenza.

Most clinicians reported using commercially available rapid antigen tests, as has been reported elsewhere (CDC, 2008c; Katz et al., 2009; Rothberg et al., 2006). However, only a very small proportion (11%) of respondents reported having the capacity to determine influenza A virus subtype. Only 9% of those who could

Table 3
Sources of information on influenza[a], 2007–08 and 2008–09.

	2007–08 influenza season$N = 501$# (%)	2008–09 influenza season$N = 288$# (%)
MMWR (including Influenza Updates)	433 (86)	200 (69)
CDC influenza website (FluView)	342 (68)	128 (44)
State health department	311 (62)	Not asked
State or local health advisories	Not asked	127 (44)
Media (television, newspaper, or internet site not listed above)	98 (20)	Not asked
Communication from professional organization[b]	98 (20)	Not asked
WHO influenza website	33 (7)	Not asked
CDC Health Advisory from 12/19/08	N/A	243 (84)
IDSA influenza treatment guidelines released 3/12/09	N/A	95 (33)
AAP influenza treatment guidelines	Not asked	26 (9)
Other[c]	72 (14)	8 (3)

[a] In January, EIN members were asked "where did you get your information on influenza"; in April, EIN members were asked "what sources of information on influenza were most useful to you".
[b] IDSA ($n = 65$), AAP ($n = 9$), EIN ($n = 8$), PIDS ($n = 6$).
[c] 2007–08: Institutional or local virology lab ($n = 23$), local/city/county health dept ($n = 16$), local epidemiologists/infection control ($n = 8$), colleagues/ID conferences ($n = 6$), FluSTAR ($n = 2$), FluWatch (Public health agency of Canada) or CCDR ($n = 2$), PHAC ($n = 2$), ProMED ($n = 3$). 2008–2009: Institutional/local lab data ($n = 3$), ID conferences ($n = 1$), Kaiser flu summary ($n = 1$), Infectious Disease News ($n = 1$), EIN listserv ($n = 1$).

determine subtype, less than one percent of respondents, reported being able to receive the results in less than 24 h. Lastly, only half of respondents reported using local influenza surveillance data during the 2007–08 and 2008–09 influenza season, suggesting that subtype data from either source might not have been readily available or that physicians were unaware of them. However, influenza diagnostic testing practices, including availability of subtyping and reliance on rapid influenza diagnostic tests, may have changed after these surveys were conducted with the emergence of 2009 pandemic influenza A(H1N1) in the U.S.

This study had the following limitations. The physicians responding to our survey are members of the Infectious Disease Society of America and the majority has subspecialty training in Infectious Diseases. Therefore, their responses regarding influenza diagnostic capacity and awareness of the interim guidelines on antiviral agent use are likely not generalizable to all physicians. In addition, only half of EIN members responded to our January survey, though this proportion is similar to other EIN surveys previously published (Ortiz et al., 2006; Podewils et al., 2005). Lastly, we limited our mailings of the April survey due to the 2009 pandemic influenza A(H1N1) outbreak and accompanying public health emergency that was declared on April 26, 2009. As a result, physician responses regarding the 2008–09 influenza season may have been biased since physicians had only one opportunity to respond to the survey and the response rate was low (only 27% of EIN members responded).

The 2008–09 influenza season was the first time that the most common circulating influenza A virus subtype was also resistant to the most commonly used antiviral medication (oseltamivir). The lack of an available test that could determine influenza A subtype or antiviral susceptibility in a timely manner to inform treatment decisions in suspected influenza patients required that new and complex antiviral guidance for empiric treatment be issued at the beginning of the season. The circulation of the 2009 pandemic influenza A(H1N1) virus that emerged during April 2009 and continued to circulate during the 2009 Southern Hemisphere and 2009–10 Northern Hemisphere influenza seasons has required additional changes in guidance and recommendations for the use of antiviral agents. Since April 2009, 64 oseltamivir-resistant 2009 pandemic influenza A(H1N1) viruses have been identified in the United States and 81% of these had documented exposure to oseltamivir (CDC, 2010). Antiviral guidelines may continue to be revised as surveillance data on influenza viruses in circulation [A(H1N1), A(H3N2), 2009 A(H1N1) and B] are obtained. It is important that physicians continue to monitor for changes in the guidance at http://www.cdc.gov/H1N1flu/recommendations.htm and that medical organizations and states alert their members/residents of any changes. New guidance should consider the responses from this survey, especially regarding lack of availability of prompt subtype testing results, and limited access to surveillance data. Lastly, efforts to ensure that adequate drug supplies are available at the local level throughout the upcoming influenza season are important.

Conflict of interest

None of the authors have any association that might pose a conflict of interest.

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