DOI:10.1111/j.1750-2659.2009.00070.x
www.blackwellpublishing.com/influenza

Original Article

Use of rapid tests and antiviral medications for influenza among primary care providers in the United States

Mark A. Katz,[a,b] Mark J. Lamias,[c] David K. Shay,[b] Timothy M. Uyeki[b]

[a]Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, GA, USA
[b]Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
[c]Office of Informatics, National Center for Preparedness, Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention and Science Applications International Corporation, Atlanta, GA, USA
Correspondence address: Mark Katz, MD, Centers for Disease Control and Prevention – Kenya, Mbagathi Road off Mbagathi Way, PO Box 606-00621, Village Market, Nairobi, Kenya. E-mail: mkatz@ke.cdc.gov

Accepted 23 November 2008. Published Online 12 February 2009.

Abstract

Limited data are available about how physicians diagnose and treat influenza. We conducted an internet-based survey of primary care and emergency physicians to evaluate the use of influenza testing and antiviral medications for diagnosis and treatment of influenza. In April 2005, an electronic link to a 33-question, web-based survey was emailed to members of the American College of Physicians, American Academy of Pediatrics, American Academy of Family Physicians, and American College of Emergency Physicians. Of the 157 674 physician members of the four medical societies, 2649 surveys were completed (1·7%). The majority of participants were internists (59%). Sixty percent of respondents reported using rapid tests to diagnose influenza. Factors associated with using rapid influenza tests included physician specialty, type of patient insurance, and practice setting. After controlling for insurance and community setting, emergency physicians and pediatricians were more likely to use rapid influenza tests than internists [odds ratio (OR) 3·7, confidence interval (CI): 2·3–6·1; and OR 1·7, CI: 1·4–2·1, respectively]. Eighty-six percent of respondents reported prescribing influenza antiviral medications. Reasons for not prescribing antivirals included: patients do not usually present for clinical care within 48 hours of symptom onset (53·0%), cost of antivirals (42·6%) and skepticism about antiviral drug effectiveness (21·7%). The use of rapid tests and antiviral medications for influenza varied by medical specialty. Educating physicians about the utility and limitations of rapid influenza tests and antivirals, and educating patients about seeking prompt medical care for influenza-like illness during influenza season could lead to more rapid diagnosis and improved management of influenza.

Keywords Antivirals, influenza, primary care, rapid tests.

Please cite this paper as: Katz *et al.* (2009) Use of rapid tests and antiviral medications for influenza among primary care providers in the United States. Influenza and Other Respiratory Viruses 3(1), 29–35.

Introduction

Influenza is a contagious, acute febrile respiratory illness associated with an estimated annual average of >200 000 hospitalizations and 36 000 deaths in the United States.[1,2] Despite this considerable burden of disease, limited data are available concerning how healthcare providers diagnose and treat influenza in clinical practice.

The accuracy of diagnosing influenza on clinical grounds alone is complicated by the co-circulation of other respiratory pathogens during influenza season that cause symptoms similar to those observed with influenza virus infection.[3,4] Rapid influenza diagnostic tests allow physicians to obtain prompt results on which to base their treatment decisions.[4] Few guidelines concerning the use of rapid influenza tests are available,[5,6] and while the number of commercially available rapid tests has increased, little is known about how often and when these tests are used by primary care physicians.

In the United States, four prescription antivirals in two medication classes are available for treatment of influenza:[5] the adamantanes (amantadine and rimantadine), and the neuraminidase inhibitors (oseltamivir and zanamivir). However, the Advisory Committee on Immunization Practices has recommended against the use of adamantanes beginning with the 2005–2006 influenza season because of high levels of adamantane resistance among circulating influenza A viruses.[7,8] Oseltamivir and zanamivir are

approved for treatment of influenza A and B in persons aged ≥1 year old and ≥7 years old, and for chemoprophylaxis of influenza in persons ≥1 year old and ≥5 years old, respectively. The efficacy of antivirals for treatment and chemoprophylaxis of influenza has been evaluated in published studies.[9–11] However, limited data exist regarding primary care physicians' use of antiviral medications for influenza. A cross-sectional study of 336 physicians in Texas and Massachusetts conducted during 2004 found that 61% of doctors had prescribed antivirals within the previous year;[12] a study of 738 primary care physicians in four states during the 2006–2007 influenza seasons found that 53·8% had prescribed antiviral agents.[13] We conducted an internet-based survey to evaluate influenza testing practices, including the use of rapid diagnostic tests, and antiviral prescription use for treatment and chemoprophylaxis of influenza among a large group of US primary care and emergency physicians.

Methods

The Centers for Disease Control and Prevention's Influenza Division partnered with four major medical professional organizations to assess utilization of influenza testing and influenza antiviral medication prescribing practices during the 2004–2005 influenza season. The American College of Physicians (ACP), the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Emergency Physicians (ACEP), all agreed to electronically send information about our web-based survey to their physician members. In April 2005, each society requested that their members with email addresses on file complete our survey. Recruitment strategies differed among the four medical associations. The ACP sent out a description of the survey along with a hyperlink to the survey website in an electronic mail to its non-student, non-resident members. The AAP sent out a description of the survey with a hyperlink to the web survey as part of an electronic, breaking-news summary that is periodically distributed to members. The ACEP included a description of the survey with a uniform resource locator (URL) to the survey in its biweekly electronic newsletter. The AAFP described the survey and placed the link in its weekly electronic newsletter and posted the URL on its members-only website. Invitation letters informed potential respondents that their names and other identifying information would remain confidential and that their response would only be reported in aggregate form.

The web-based survey instrument was developed and deployed using the mrInterview V2.2 software (SPSS Inc., Chicago, IL, USA). The survey website was deployed on a CDC web server running Windows Internet Information Service 5.0 (Microsoft, Redmond, WA, USA). Respondents accessed the web site via the URL provided in their emailed invitation or from a referring URL on one of the partner organization's web sites. Upon clicking the URL, users were connected to the survey over a 128-bit Secure Sockets Layer connection. All data collected via the web-based survey were stored in a secure relational SQL Server 2000 database at CDC (Microsoft).

The instrument asked respondents to answer 33 questions across several screens about demographics, use of rapid influenza tests, and use of antiviral medications. Survey respondents could answer all questions in total; however, some respondents could have answered fewer questions because the survey contained conditional skip patterns or 'routing' that directed respondents only to relevant questions based upon answers to previous questions.

Upon closing the survey, respondent data were exported to an analytical dataset, transformed, and analyzed using SAS 9.13 (SAS Institute Inc., Cary, NC, USA, 2005) and Epi-Info 6 (Centers for Disease Control, Atlanta, GA, USA, 2000). Data analysis was performed using descriptive statistics, categorical data analysis techniques, and multivariable logistic regression. A chi-squared test was used to generate two-sided *P*-values; *P*-values of 0·05 or less were considered statistically significant. Partially completed surveys were excluded from the analyses.

The study was determined to be exempt from CDC institutional review board review because no personal identifiers were collected. All four participating medical professional societies approved the study.

Results

Of the 157 674 members of the professional medical organizations who were informed electronically about the survey, 3573 (2·3%) completed at least part of the survey. Of those, 924 (26%) began the survey, but failed to complete it entirely, and were excluded from further analysis. Seventy-four percent (2649) of respondents (or 1·7% of the total number of physicians who were informed about the survey) completed the survey. Demographic information was similar among physicians who completed any portion of the survey compared with physicians who completed the entire survey. Survey participation by specialty was as follows: internists, 6·5% (1563/23 960); pediatricians, 1·5% (888/60 000); emergency physicians, 0·7% (116/17 000); and family practitioners, 0·1% (80/56 000). Thirty-six respondents identified 'medicine/pediatrics' as their primary specialty, and 27 respondents did not identify a primary specialty. Because the survey was voluntary and anonymous, no information was available about non-respondents. However, the mean age (48 years) of participating internists, a group that comprised the majority of respondents, was relatively similar to those of all eligible

ACP members (mean age = 52 years) (American College of Physicians, unpublished data). Of internists that completed the survey, 65% were male, compared to 73% of all ACP members.

Respondents included physicians practicing in all 50 states as well as the District of Columbia, Puerto Rico, Guam and the US Virgin Islands. Fifty-nine percent were male (Table 1). The median age was 47 years (range: 26–90 years). The majority of the respondents were internists (59·0%). Only six respondents (0·2%) indicated that they were not currently practicing medicine. Most respondents practiced in an outpatient primary care setting (87·2%), and 37·6% treated patients with private insurance, while 36·2% cared for patients covered by Medicaid and Medicare. Nearly half (44%) of those who completed the survey were affiliated with an academic institution.

Physicians reported ordering rapid influenza tests much more often than other tests for influenza. Eighty-four percent of respondents reported using at least one of five testing methods to diagnose influenza; 60·2% used rapid tests, and fewer ordered other tests including immunoflouorescence (17·4%), viral culture (14·6%), serology (4·8%) or RT-PCR (2·5%). Among physicians who used rapid tests, more tests were performed in the office (45·9%) than at an affiliated laboratory at their practice site (31·7%) or an outside laboratory (22·4%). Half (49·9%) reported receiving rapid test results in <30 minutes. The most common reasons cited for not ordering rapid tests included the high costs (34·1%), a belief that rapid tests were not helpful with clinical management (30·0%) and lack of test availability (18·3%).

Use of influenza tests varied significantly by specialty: 53·5% of internists reported using rapid diagnostic tests compared with 66·7% of family practitioners, 69·2% of pediatricians, and 80·2% of emergency medicine physicians. Physicians who treated mostly privately insured patients were more likely to order rapid tests than physicians who treated predominantly uninsured patients (68·3% versus 33·9%, $P < 0·001$). Physicians who practiced in suburban and rural settings were more likely to use rapid tests than those who practiced in urban areas [odds ratio (OR) 1·8, 95% confidence interval (CI): 1·5–2·1; and OR 3·5, 95% CI: 2·7–4·5, respectively]. Frequency of rapid test use did not vary significantly by physician age. After controlling for type of insurance and community setting, emergency physi-

Table 1. Characteristics of survey respondents

Demographic information	Number of respondents (percentage)
Male	1554 (59·4)
Age	Mean = 47·1; median = 47; mode = 48
Medical specialty	
Internal medicine	1563 (59·0)
Pediatrics	888 (33·5)
Family practice	80 (3·0)
Medicine/Pediatrics	36 (1·4)
Emergency medicine	116 (4·4)
Primary practice site	
Outpatient office or clinic	2297 (87·2)
Inpatient hospital setting	172 (6·5)
Emergency room	127 (4·8)
Nursing home or other residential institution	39 (1·5)
Affiliation with an academic institution	1156 (43·9)
Community type	
Urban	1044 (39·7)
Suburban	1175 (44·6)
Rural	413 (15·7)
Most common insurance plan among patients	
Private insurance	987 (37·6)
HMO	466 (17·8)
Medicaid and medicare	950 (36·2)
Uninsured	116 (4·4)

HMO, Health Maintenance Organization.

Table 2. Use of rapid tests and antiviral medications for influenza by specialty

Specialty	Number answering 'yes' (%)	Odds ratio	95% Confidence intervals
Do you order rapid influenza tests to diagnose influenza?*			
Internal medicine	821 (53·5)	Reference group	
Pediatrics	597 (69·2)	1·7	1·4–2·1
Family practice	48 (66·7)	1·2	0·7–2·1
Medicine/Pediatrics	24 (68·6)	1·9	0·9–4·0
Emergency medicine	93 (80·2)	3·7	2·3–6·1
When you suspect a patient has influenza, do you ever prescribe antiviral medications?**			
Internal medicine	1359 (88·9)	Reference group	
Pediatrics	668 (77·5)	0·3	0·2–0·3
Family practice	70 (98·6)	6·8	0·9–49·9
Medicine/Pediatrics	33 (94·3)	1·7	0·4–7·5
Emergency medicine	105 (91·3)	1·0	0·5–2·1

*Predominant type of patient insurance and community included in logistic regression models.
**Predominant type of patient insurance, community, and use of rapid tests for influenza were included in the logistic regression model.

cians and pediatricians remained more likely to use rapid tests than internists (Table 2).

Overall 85·6% of participants reported having prescribed antiviral medications when they suspected that a patient has influenza. The percentage varied by specialty, from a low among pediatricians (77·5%) to a high among family practitioners (98·6%) ($P < 0·001$). After controlling for predominant type of patient insurance, practice community, and use of rapid tests, pediatricians remained less likely than internists to use antivirals (Table 2). There were no statistically significant differences in antiviral use between internists and family practitioners, emergency physicians, or medicine/pediatrics physicians.

Physicians who reported using rapid influenza tests were more likely to report prescribing antivirals than those who did not use rapid tests (OR 2·9, 95% CI: 2·3–3·6). Among those who reported using antivirals for treatment, oseltamivir was prescribed most often (69·9%), followed by amantadine (21·2%), rimantadine (8·0%), and zanamivir (0·9%). Overall, 46·0% percent of physicians said they 'always' prescribe antiviral medications for treatment of influenza when a patient presents with influenza symptoms within 48 hours from illness onset, compared to 41·8% of physicians who reported doing so 'sometimes', and 12·2% who reported prescribing antivirals 'rarely' in this setting. Physicians cited the fact that patients do not usually present for clinical care within 48 hours of symptom onset (53·0%), the high cost of antivirals (42·6%), and skepticism about the effectiveness of antivirals (21·7%) as the most common reasons they did not prescribe these medications.

Over half of physicians (57·5%) said they had prescribed antivirals for chemoprophylaxis of influenza. Among these respondents, oseltamivir was prescribed most often (55·3%) followed by amantadine (30·8%), rimantadine (13·1%), and zanamivir (0·8%). Physicians who used rapid tests were more likely to prescribe antivirals for influenza chemoprophylaxis than non-rapid test users (OR 2·58, 95% CIs: 2·2–3·1).

Discussion

Our survey is the first to address testing and prescribing patterns for influenza among a nationwide cohort of primary care physicians from four specialties (internal medicine, pediatrics, family practice, and emergency medicine). While only a small percentage of physicians eligible to participate completed the survey, the absolute number of responses was high, especially among internists.

Sixty percent of primary care physicians reported ordering rapid influenza tests. These findings are similar to results from a cross-sectional study conducted at the end of the 2003–2004 influenza season, in which 62% of 336 physicians from Texas and Massachusetts reported using rapid influenza tests,[12] and a more recent study of 730 primary care physicians in four states during the 2006–2007 influenza season, in which 61% of physicians reported ordering rapid influenza antigen tests.[13] Thirty percent of participants reported not using rapid influenza tests because clinical diagnosis of influenza was considered adequate and because rapid tests were viewed as not helpful for clinical management. Several studies suggest that rapid tests can be a useful aid in diagnosing influenza virus infection, especially when the prevalence of influenza in a community is moderate,[14–17] although the use of these tests appears to be of limited use when the prevalence of influenza is <10%.[18] The positive predictive value of rapid tests is lowest during periods of low influenza activity,[4] and the World Health Organization recommends that during these periods of low influenza activity positive results be interpreted with caution and confirmed by immunofluorescence, viral culture or RT-PCR.[19] Additionally, during periods of high influenza activity, the negative predictive value of rapid tests is relatively low, and therefore specimens that test negative by rapid test should be retested by confirmatory tests such as viral culture or RT-PCR.[4,18]

Thirty-four percent of respondents cited high costs as a reason for not ordering rapid influenza tests. Rapid diagnostic tests have been shown to reduce additional diagnostic testing, inappropriate prescribing of antibiotics, and overall hospital costs.[4,20,21] Thus, ultimately increased use of rapid influenza tests to diagnose influenza could lead to increased cost savings.

In our survey, 4·8% of physicians reported ordering serology to diagnose influenza. Reliable influenza serological testing is not widely available, and requires collection of paired acute and convalescent sera. Therefore, serological testing results cannot inform clinical management of the acutely ill patient.

We found that 86% of respondents reported prescribing antiviral medications for influenza treatment. This proportion is substantially higher than the reported 61% of physicians that prescribed antivirals during the 2003–2004 influenza season and the reported 54% of physicians that prescribed antivirals during the 2006–2007 seasons in two smaller studies.[12,13] The differences between the studies may reflect the fact that our survey was conducted at the end of an influenza season characterized by a highly publicized influenza vaccine shortage. It may also reflect a volunteer bias; clinicians who had a high interest in influenza management may have been more likely to use rapid influenza tests and antiviral medications and to participate in the on-line survey than those who did not respond to the survey, or those who participated in other studies.

In addition, because of the anticipated influenza vaccine shortage for the 2004–2005 season, CDC issued specific guidelines on the use of antivirals in October 2004, encour-

aging the use of the adamantanes for chemoprophylaxis of influenza A and the use of neuraminidase inhibitors for influenza treatment.[22] Seventy-one percent of respondents indicated that they were familiar with these guidelines; this awareness may have increased the proportion of respondents who reported using antivirals.

Twenty-two percent of respondents said they do not prescribe antivirals because they were 'not convinced (antivirals) work'. When administered within 2 days of illness onset, all four antiviral agents have been shown to reduce the duration of uncomplicated influenza illness due to infection with susceptible viruses by approximately 1 day, and may reduce complications and hospitalizations,[5,23–26] although they may not decrease viral shedding.[27] Thus, more education of physicians about the utility of antivirals may lead to increased and appropriate use of these drugs.

Recent reports of antiviral resistance complicate the issue of antiviral use. In 2005, CDC identified widespread resistance to adamantanes among circulating influenza virus strains in the United States, and issued a health advisory recommending against using amantadine or rimantidine for treatment or chemoprophylaxis of influenza A for the 2005–2006 influenza season,[7] a recommendation that remained in place through the 2007–2008 influenza season.[5] A review of global influenza surveillance from the 2005–2006 season described nearly universal resistance to amantadine among H3N2 viruses and 15·5% resistance among H1N1 isolates.[28] Despite CDC recommendations and these recent surveillance data showing high adamantine resistance among influenza viruses, a recent study found that 26% of primary care physicians prescribed adamantanes for influenza during the 2006–2007 influenza season.[13] Although a low prevalence of influenza virus resistance to oseltamivir in recent seasons has been reported,[29–31] influenza surveillance in Europe from November 2007 to January 2008 showed 14% of H1N1 viruses were resistant to oseltamivir.[32] Continued global virological surveillance for emergence of resistant influenza virus strains and better physician education about surveillance data and treatment guidelines are therefore critical.

We used mrInterview software to design a questionnaire and distribute it electronically to a large number of clinicians, all in a short amount of time. This software allowed us to collect and analyze data rapidly. Such an approach could be helpful during future influenza seasons if events occur such as the unexpectedly high prevalence of influenza A resistance to adamantanes in the 2005–2006 season; the effect of sudden changes in practice guidelines due to unforeseen events could be evaluated in a timely way to facilitate rapid development and issuance of revised guidelines.

Real-time, web-based data collection eliminates the need for entering data into computer databases as well as the costs associated with distribution of the survey (e.g., postal costs, paper, envelopes, copying, etc.). Quality of collected data is also improved as web-based forms can perform data validation as survey responses are entered. Unlike the traditional paper-based surveys, web-based surveys can make use of validation rules that provide error messages to respondents in real-time if data entry errors are made, allowing correction prior to survey submission, and thereby improving data quality.

Our study has a number of limitations. The survey was limited to physicians who were members of the four medical professional societies with email addresses on file. Therefore, the responses may not be representative of the views of all members or the clinical practice of non-member physicians and may not be generalizable to all members of the four participating organizations. For example, the percentage of physicians who reported having an academic affiliation in our survey (44%) was substantially higher than the percentage of physician members of the ACP and the ACEP who report academic affiliations (9% and 23%, respectively) (American College of Physicians, American College of Emergency Physicians, Unpublished Data); no data were available from the AAFP or AAP. Due in part to differences in recruitment of survey respondents by each of the organizations, response varied by specialty. The overall proportion of survey respondents among eligible physician members was <2%, and the absolute numbers of participating emergency physicians and family practitioners was quite low. This may reflect the fact that many physicians are very busy and overburdened with electronic communication. Additionally, despite the large absolute number of survey respondents, it is likely that some volunteer bias was present. For example, only physicians who had internet access and actively checked their email accounts could have completed our survey. Due to privacy concerns, we were unable to obtain demographic data on non-respondents and therefore, a true non-response bias analysis could not be completed. However, despite the low frequency of eligible participants, the absolute number of respondents was high among internists and pediatricians, and our survey is the largest to date to address the use of testing and antivirals for influenza among physicians, and the only one to do so in a nationwide cohort.

Rapid influenza tests can be a useful tool for prompt diagnosis of influenza,[14–17] and early antiviral treatment can effectively reduce the duration of illness and may reduce complications from infection with susceptible viruses.[5,23,24,26] Our results show considerable variation in the use of these two tools by physicians. These findings are consistent with a previous cross-sectional study that demonstrated considerable variability in prescribing of antiviral medications.[33] Focused investigation of these differences in practice patterns among primary care physicians could help

identify ways in which primary care specialties could be better informed about the use of rapid testing and antivirals for influenza. Educating physicians about the utility (as well as limitations) of rapid influenza tests and the effectiveness and efficacy of antiviral medications could improve the diagnosis and treatment of influenza and might reduce unnecessary antibiotic use and other diagnostic tests,[34–36] lessen the duration of patient time in the emergency room or clinic, and result in reduction of healthcare costs.[20] Guidelines for use of rapid influenza tests, and wider circulation of current guidelines for use of antiviral medications for influenza[6,37,38] – especially in light of the current high prevalence of adamantane-resistant influenza A virus strains and oseltamivir-resistant influenza A(H1N1) virus strains– could offer important direction for primary care physicians in their approach to clinical management of suspected influenza patients.

Acknowledgements

The authors would like to acknowledge the American College of Physicians, the American Academy of Pediatricians, the American College of Emergency Physicians, and American Academy of Family Practitioners for their collaboration on this survey.

References

1 Thompson WW, Shay DK, Weintraub E *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003; 289: 179–186.

2 Thompson WW, Shay DK, Weintraub E *et al.* Influenza-associated hospitalizations in the United States. JAMA 2004; 292: 1333–1340.

3 Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with use of a clinical case definition. Clin Infect Dis 2000; 31: 1166–1169.

4 Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. Pediatr Infect Dis J 2003; 22: 164–177.

5 Fiore AE, Shay DK, Haber P *et al.* Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2007; 56: 1–54.

6 American Academy of Pediatrics Committee on Infectious Diseases. Antiviral therapy and prophylaxis for influenza in children. Pediatrics 2007; 119: 852–860.

7 CDC. High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents – United States, 2005–06 influenza season. MMWR Morb Mortal Wkly Rep 2006; 55: 44–46.

8 Bright RA, Shay DK, Shu B, Cox NJ, Klimov AI. Adamantane resistance among influenza A viruses isolated early during the 2005–2006 influenza season in the United States. JAMA 2006; 295: 891–894.

9 Demicheli V, Jefferson T, Rivetti D, Deeks J. Prevention and early treatment of influenza in healthy adults. Vaccine 2000; 18: 957–1030.

10 Hayden FG, Atmar RL, Schilling M *et al.* Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. N Engl J Med 1999; 341: 1336–1343.

11 Treanor JJ, Hayden FG, Vrooman PS *et al.* Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. JAMA 2000; 283: 1016–1024.

12 Rothberg MB, Bonner AB, Rajab MH, Kim HS, Stechenberg BW, Rose DN. Effects of local variation, specialty, and beliefs on antiviral prescribing for influenza. Clin Infect Dis 2006; 42: 95–99.

13 CDC. Influenza-testing and antiviral-agent prescribing practices – Connecticut, Minnesota, New Mexico, and New York, 2006–07 influenza season. MMWR Morb Mortal Wkly Rep 2008; 57: 61–65.

14 Rothberg MB, Fisher D, Kelly B, Rose DN. Management of influenza symptoms in healthy children: cost-effectiveness of rapid testing and antiviral therapy. Arch Pediatr Adolesc Med 2005; 159: 1055–1062.

15 Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? JAMA 2005; 293: 987–997.

16 Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. Am J Med 2002; 113: 300–307.

17 Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. Ann Intern Med 2003; 139: 321–329.

18 Grijalva CG, Poehling KA, Edwards KM *et al.* Accuracy and interpretation of rapid influenza tests in children. Pediatrics 2007; 119: e6–e11.

19 WHO. WHO recommendations on the use of rapid testing for influenza diagnosis, http://www.who.int/csr/disease/avian_influenza/guidelines/RapidTestInfluenza_web.pdf, 2005.

20 Bonner AB, Monroe KW, Talley LI, Klasner AE, Kimberlin DW. Impact of the rapid diagnosis of influenza on physician decision-making and patient management in the pediatric emergency department: results of a randomized, prospective, controlled trial. Pediatrics 2003; 112: 363–367.

21 Bhavnani D, Phatinawin L, Chantra S, Olsen SJ, Simmerman JM. The influence of rapid influenza diagnostic testing on antibiotic prescribing patterns in rural Thailand. Int J Infect Dis 2007; 11: 355–359.

22 Control CfD. CDC Health Advisory: Influenza Antiviral Medications: 2004–2005 Interim Chemoprophylaxis and Treatment Guidelines. Atlanta, GA: Centers for Disease Control, 2004.

23 Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 2003; 163: 1667–1672.

24 McGeer A, Green KA, Plevneshi A *et al.* Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis 2007; 45: 1568–1575.

25 Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med 2005; 353: 1363–1373.

26 Whitley RJ, Hayden FG, Reisinger KS *et al.* Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001; 20: 127–133.

27 Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006; 367: 303–313.

28 Deyde VM, Xu X, Bright RA *et al.* Surveillance of resistance to adamantanes among influenza A(H3N2) and A(H1N1) viruses isolated worldwide. J Infect Dis 2007; 196: 249–257.

29 Hatakeyama S, Sugaya N, Ito M *et al.* Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. JAMA 2007; 297: 1435–1442.

30 Sugaya N, Mitamura K, Yamazaki M *et al.* Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. Clin Infect Dis 2007; 44: 197–202.
31 Kiso M, Mitamura K, Sakai-Tagawa Y *et al.* Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004; 364: 759–765.
32 Lackenby A, Hungnes O, Dudman S *et al.* Emergence of resistance to oseltamivir among influenza A (H1N1) viruses in Europe. Euro Surveill 2008 Jan 31; 13 (5). pii: 8026.
33 Linder JA, Bates DW, Platt R. Antivirals and antibiotics for influenza in the United States, 1995–2002. Pharmacoepidemiol Drug Saf 2005; 14: 531–536.
34 Sharma V, Dowd MD, Slaughter AJ, Simon SD. Effect of rapid diagnosis of influenza virus type A on the emergency department management of febrile infants and toddlers. Arch Pediatr Adolesc Med 2002; 156: 41–43.
35 Poehling KA, Zhu Y, Tang YW, Edwards K. Accuracy and impact of a point-of-care rapid influenza test in young children with respiratory illnesses. Arch Pediatr Adolesc Med 2006; 160: 713–718.
36 Iyer SB, Gerber MA, Pomerantz WJ, Mortensen JE, Ruddy RM. Effect of point-of-care influenza testing on management of febrile children. Acad Emerg Med 2006; 13: 1259–1268.
37 Harper S. Seasonal influenza – diagnosis, chemoprophylaxis, treatment, and institutional outbreak management: clinical practice guidelines by the Infectious Diseases Society of America (IDSA). Seasonal and Pandemic Influenza Meeting. Washington, DC, 2007.
38 CDC. CDC Health Advisory: CDC Issues Interim Recommendations for the Use of Influenza Antiviral Medications in the Setting of Oseltamivir Resistance among Circulating Influenza A (H!N!) Viruses, 2008-09 Influenza Season, Dec. 19, 2008. Available at http://www2a.cdc.gov/HAN/ArchiveSys/ViewMsgV.asp?/AlertNum=00279.