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INFLUENZA IN THE EMERGENCY DEPARTMENT: VACCINATION, DIAGNOSIS, AND TREATMENT: CLINICAL PRACTICE PAPER APPROVED BY AMERICAN ACADEMY OF EMERGENCY MEDICINE CLINICAL GUIDELINES COMMITTEE

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□ **Abstract—Background: Influenza is an acute respiratory virus that results in significant worldwide morbidity and mortality each year. As emergency physicians, we are often the first to encounter patients with seasonal influenza. It is therefore critical that we draw on the most recent and relevant research when we make clinical decisions regarding the diagnosis, treatment, and prophylaxis of this disease. Methods: A MEDLINE literature search from August 2009 to August 2015 was performed using the keywords *influenza vaccination efficacy* AND *systematic*, *influenza* AND *rapid antigen testing*, and *Oseltamivir* AND *systematic*, while limiting the search to human studies written in the English language. General review articles and case reports were omitted. Each of the selected articles then underwent a structured review. Results: We identified 163 articles through our literature search, of which 68 were found to be relevant to our clinical questions. These studies then underwent a rigorous review from which recommendations were given. Conclusions: Influenza vaccine efficacy continues to range between 40% and 80%. Vaccination has the potential to decrease disease severity and is recommended for individuals older than 6 months of age. If resources permit, vaccination can be offered to patients presenting to the emergency department. Rapid antigen detection for influenza is a simple bedside test with high specificity, but generally low sensitivity. If a patient presents with a syndrome consistent with influenza and has negative rapid antigen detection, they should either receive a confirmatory reverse transcriptase polymerase chain reaction or be treated as if they have influenza. Treatment with neuraminidase inhibitors can decrease the duration of influenza and is recommended in hospitalized patients, or in those with high risk of complications.**

□ **Keywords—influenza; rapid antigen testing; oseltamivir; antiviral; vaccination; efficacy; H1N1; H3N2**

INTRODUCTION

Influenza is an acute respiratory virus that is responsible for both epidemic and pandemic outbreaks of disease. Currently, there are three known types of influenza (A, B, and C) that are further subtyped based on their surface proteins: neuraminidase (N) and hemagglutinin (H) in type A and B, as well as hemagglutinin-esterase fusion in type C. The often more virulent influenza A has two predominant subtypes that are currently circulating in humans, including (H1/N1) and (H3/N2) (1). The annual global prevalence of seasonal influenza is estimated to be between 5% and 10% in adults and 20% and 30% in children. Worldwide, influenza is estimated to result in about 3 to 5 million cases of severe illness, and an estimated 250,000 to 500,000 deaths yearly (2). As emergency physicians, we are often the first providers to encounter

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seasonal influenza, leaving us to not only diagnose and treat this disease, but to also educate patients and family members on the potential benefits, strengths, and weaknesses of the yearly influenza vaccine. We conducted a structured systematic review of the literature to provide evidence-based recommendations for emergency department (ED) prevention, diagnosis, and treatment of the influenza virus.

METHODS

Three structured literature reviews were performed using MEDLINE and were all limited to studies that were published in the English language between August 2009 and August 2015. Search terms included *influenza vaccination efficacy* AND *systematic*, *influenza* AND, and *Oseltamivir* AND *systematic*. Two emergency physicians analyzed the abstract of each identified article to determine which ones should be pulled for more detailed review, based on the suspected relevance to the topic of interest. If either physician felt the study had relevance, the full article was pulled for review. Studies included for the final, detailed review for the *influenza vaccination efficacy* AND *systematic* and *influenza vaccination efficacy* AND *systematic* review, included large systematic reviews as well as meta-analyses. Studies for the *influenza* AND *rapid antigen testing* review included prospective trials, retrospective cohort trials, systematic reviews, and meta-analyses. General review articles and case reports were not included for formal review.

Each of the selected articles underwent a grade of evidence review. Two or more of the study authors performed a detailed review of each selected article. The level of the evidence was assigned a grade using the definitions as noted in Table 1 and were based on reference focus, specific research design, and methodology.

All selected articles were also assigned a quality ranking based on quality of the design and methodology. This includes design consideration (e.g., focus, model structure, and presence of controls) and methodology consideration (i.e., actual methodology utilized). The definitions of the quality ranking scores are included in Table 2.

RESULTS

Through the influenza vaccination review, 44 abstracts were identified, of which 18 were thought to be relevant by the reviewers and were pulled for detailed formal review. The rapid antigen testing review identified 66 articles, with 29 articles being deemed relevant by reviewers. Finally, the oseltamivir review identified 53 total articles, of which 21 were deemed relevant.

Table 1. The Definitions of the Grades of Evidence of the Articles

Grade A	Randomized clinical trials or meta-analyses/systematic review (multiple clinical trials) or randomized clinical trials (smaller trials), directly addressing the review issue
Grade B	Randomized clinical trials or meta-analyses/systematic review (multiple clinical trials) or randomized clinical trials (smaller trials), indirectly addressing the review issue
Grade C	Prospective, controlled, nonrandomized, cohort studies, systematic review of cohort studies
Grade D	Retrospective, nonrandomized, cohort or case-control studies, systematic review of case–control studies
Grade E	Case series, animal/model scientific investigations, theoretical analyses, or case reports
Grade F	Rational conjecture, extrapolations, unreferenced opinion in literature, or common practice

The primary goal of this literature search was to determine the appropriate ED approach with regard to prevention, diagnosis, and treatment of the influenza virus. Specific focus was given to use of the seasonal influenza vaccine and its efficacy, what methods should be used in the ED to test for influenza and how these tests should be interpreted, and the clinical effectiveness of antiviral treatment for the treatment and prophylaxis of influenza. The final design and methodology scores are provided in Tables 3 and 4.

Question 1: What Is the Efficacy of the Seasonal Influenza Vaccine in Preventing Influenza and Disease-Related Morbidity?

Influenza vaccines are prepared annually and targeted at the most probable circulating strain. As a result, vaccine efficacy (VE) is closely linked to how well the vaccine is matched to circulating strains. Current studies demonstrate significant heterogeneity in quality, inclusion criteria, diagnosis of infection, and definition of endpoints. In 2012, Diaz Granados et al. published one of the largest meta-analyses to date, comprising 88,468 patients. Eligible patients included healthy children and nonelderly adults. The clinical endpoint was an occurrence of influenza-like symptoms combined with laboratory confirmation (e.g., polymerase chain reaction [PCR], culture) of disease. Diaz Granados et al. reported a summary VE of 65% against any strain, but slightly higher VE (78%) against matched strains (3). Other meta-analyses by Manzoli et al. in 2012 and Osteholm et al. in 2012 also reflected an overall VE of around 60% in healthy nonelderly adults (4,5). Similar efficacy has

Table 2. Definitions of the Quality Ranking Scores of the Articles

Ranking	Design Consideration Present	Methodology Consideration Present	Both Considerations Present
Outstanding	Appropriate	Appropriate	Yes, both present
Good	Appropriate	Appropriate	No, either present
Adequate	Adequate with possible bias	Adequate	No, either present
Poor	Limited or biased	Limited	No, either present
Unsatisfactory	Questionable/none	Questionable/none	No, either present

also been reported in children (6). This efficacy does not appear to be effected by previous wild-type infection or previous vaccines (7).

There are many clinical questions regarding the influenza vaccine that remain unanswered. Specifically, there is a lack of quality evidence that investigates the morbidity and mortality benefits of the influenza vaccine (8). The current evidence on VE in the elderly, and the effect of VE on our ability to prevent influenza in this population, is too varied to make any conclusions (9,10). However, from a clinical standpoint, there is no debate on the potential for severe illness due to influenza infection in the elderly, therefore, vaccination in this age group should remain a priority (11). Similarly, severe illness and complications can arise in other at-risk groups, such as pregnant women and immunocompromised patients, and we must encourage their vaccination as well (12–16). Although side effects of the vaccine have been reported in certain groups, such as asthmatics, a recent Cochrane review found no significant increase in asthma exacerbations post vaccination (17). Emergency physicians are often in a position to educate patients and it is helpful to be familiar with the limitations of influenza vaccination, as well as the Centers for Disease Control and Prevention (CDC) guidelines for vaccinating eligible patients older than 6 months of age.

Recommendation: Emergency physicians should provide information on influenza vaccination for all patients older than 6 months of age. If an unvaccinated patient is encountered and the ED has the required resources, then an influenza vaccination should be offered. Otherwise, the patient should be referred to their primary physician or clinic to discuss vaccination.

Level of Recommendation: B.

Question 2: What Is the Most Effective Way to Test for Influenza in the ED Setting?

CDC recommends testing for influenza only when the results of the test will impact patient treatment. If testing is warranted, testing for influenza in the ED for influenza has traditionally relied on rapid antigen detection (RAD). Sensitivity depends heavily on the quality of the specimen, strain of influenza, viral titer (i.e., amount of virus being shed), duration of illness, and collection technique (18–20). Numerous studies have shown that sensitivity varies widely but generally falls within the 40% to 80% range for seasonal influenza and is even worse for H1N1 (40% to 60%) (21–32). It is imperative to recognize that a negative RAD does not exclude influenza, and if clinical suspicion exists, treatment should proceed as if the patient had tested positively (23,33–35).

Viral culture has long been considered the gold standard for diagnosis, but this process takes at least 48 h, which limits its utility in the ED. Nucleic acid detection (reverse transcriptase [RT]-PCR) has emerged in the past decade as the diagnostic test of choice for influenza and has been shown to have superior sensitivity and specificity when compared to viral culture and RAD (36–43). Sensitivity and specificity of RT-PCR approach 100% and are limited only by collection technique and viral titer (44). The RT-PCR can take approximately 1 to 6 h to yield results, however, so the clinical utility in the ED remains questionable. It may be prudent to send a confirmatory RT-PCR after a negative RAD if clinical suspicion is high, or the prevalence of influenza is high in the community (45–47).

Recommendation: Testing for influenza should only be performed if the results will change clinical management. If a RAD testing method is utilized, the provider should be aware of the limited sensitivity and the potential for false negatives. If clinical suspicion is moderate to high and RAD test is negative, one should consider sending a confirmatory RT-PCR or proceeding with empiric treatment for suspected influenza.

Level of Recommendation: Level B.

Question 3: What Is the Clinical Effectiveness of Antiviral Treatment on Treatment and Prophylaxis of Seasonal Influenza?

Currently, there are two classes of medication approved for seasonal influenza, amantadines and neuraminidase inhibitors (NI). It is commonly accepted that there is widespread resistance to amantadines and, therefore, treatment with NIs has been widely promoted as beneficial to patients, despite the fact that resistance to NIs are increasing as well (48). The largest collection of

Table 3. Grade and Quality of Literature

Reference No.	First Author	Year	Grade	Quality Ranking	Design
(1)	CDC	2012	E	Adequate	Consensus statement
(2)	Cortes-Penfield	2014	B	Good	Systematic review
(3)	Diaz Granados	2012	A	Outstanding	Meta-analysis
(4)	Manzoli	2012	A	Good	Review of meta-analyses
(5)	Osterholm	2012	B	Good	Systematic review and meta-analysis
(6)	Gonzalez de Dios	2013	E	Adequate	General review
(7)	Belshe	2010	A	Good	Systematic review
(8)	Michiels	2011	B	Good	Systematic review
(9)	Jefferson	2010	A	Outstanding	Systematic review
(10)	Thomas	2010	A	Outstanding	Systematic review
(11)	Beyer	2013	B	Good	Systematic review
(12)	Yuen	2014	D	Adequate	Systematic review
(13)	Shehata	2014	D	Adequate	Systematic Review
(14)	Chan	2014	B	Good	Meta-analysis
(15)	Manske	2014	E	Poor	Systematic review
(16)	Johnston	2013	E	Adequate	Systematic review
(17)	Cates	2013	A	Outstanding	Systematic review
(18)	Duman	2013	C	Adequate	Prospective cohort
(19)	Landry	2011	E	Poor	General review
(20)	Apisarnthanarak	2010	B	Adequate	Randomized trial
(21)	Peaper	2014	E	Poor	Referenced editorial
(22)	Dale	2010	E	Poor	Referenced editorial
(23)	Marzoratti	2012	E	Adequate	General review
(24)	Bruning	2014	C	Good	Clinical trial
(25)	Sutter	2012	C	Good	Clinical trial
(26)	Cho	2013	C	Good	Clinical trial
(27)	Self	2012	C	Good	Clinical trail
(28)	Kumar	2012	E	Adequate	Referenced editorial
(29)	De Witte	2012	C	Good	Clinical trial
(30)	Biggs	2010	C	Good	Clinical trial
(31)	Herzum	2010	C	Good	Clinical trial
(32)	Vasoo	2009	C	Good	Clinical trial
(33)	de la Tabla	2010	C	Good	Clinical trial
(34)	Lucas	2011	C	Good	Clinical trial
(35)	Talbot	2010	E	Adequate	General review
(36)	DiMaio	2012	C	Good	Clinical trial
(37)	Park	2011	D	Adequate	Retrospective review
(38)	Mahony	2011	E	Adequate	General review
(39)	Al Johani	2011	C	Poor	Clinical trial
(40)	Papillard-Marechal	2011	C	Good	Clinical trial
(41)	Coleman	2011	C	Adequate	Clinical trial
(42)	Ciblak	2010	C	Adequate	Clinical trial
(43)	Talbot	2010	C	Good	Prospective cohort
(44)	Jernigan	2011	D	Adequate	Retrospective review
(45)	CDC	2014	E	Adequate	Consensus statement
(46)	Boku	2013	C	Adequate	Clinical trial
(47)	Balish	2013	C	Good	Clinical trial
(48)	Thorlund	2011	B	Good	Systematic review
(49)	Jefferson	2014	A	Outstanding	Systematic review
(50)	Hsu	2012	A	Good	Systematic review and meta-analysis
(51)	Shun-Shin	2009	A	Good	Systematic review and meta-analysis
(52)	Burch	2009	A	Good	Meta-analysis
(53)	Ebell	2013	A	Good	Meta-analysis
(54)	Michiels	2013	C	Adequate	Systematic review
(55)	Hernan	2011	A	Good	Meta-analysis
(56)	Jefferson	2010	A	Outstanding	Systematic review
(57)	Jefferson	2009	A	Outstanding	Systematic review
(58)	Flannery	2014	B	Adequate	Systematic review
(59)	Jefferson	2014	A	Outstanding	Systematic review
(60)	Rainwater	2014	C	Good	Systematic review
(61)	Wang	2012	A	Good	Systematic review
(62)	Wang	2012	A	Good	Systematic review
(63)	Jackson	2011	B	Adequate	Systematic review
(64)	Jefferson	2012	A	Outstanding	Systematic review

(*Continued*)

Table 3. Continued

Reference No.	First Author	Year	Grade	Quality Ranking	Design
(65)	Santesso	2013	D	Adequate	Meta-analysis
(66)	Khazeni	2009	B	Good	Systematic review
(67)	Fiore	2011	E	Adequate	Consensus statement
(68)	Yates	2010	C	Good	Prospective cohort

CDC = Centers for Disease Control and Prevention
Definitions of the grades of evidence provided in Table 1. Definitions of the quality ranking scores provided in Table 2.

data is from the Cochrane collaboration. The recently published review from Jefferson et al. utilized study reports of all randomized controlled trials both published and unpublished (49). These data were obtained directly from the pharmaceutical industry in their supported trials. The authors evaluated 53 studies and found a large amount of attrition, reporting, and attention biases. However, based on these data, they concluded that oseltamivir and zanamivir decreased time to the alleviation of first symptoms by 16 h and 12 h, respectively (49). Additional meta-analyses and systematic reviews have found similar benefits with regard to disease duration with treatment compared with placebo (50–52). Jefferson et al. found that neither drug reduced the rate of hospitalization in adults or healthy children (49). Additionally, although there are some studies that suggest otherwise, there is no conclusive evidence that oseltamivir or zanamivir decrease influenza complications (53–57). A recent review by Flannery et al. found that there was no significant difference in outcomes when one compared high-dose oseltamivir with standard-dose oseltamivir in critically ill patients (58).

We identified several articles that investigated the effectiveness of prophylactic antiviral use on transmission of influenza. The data show that prophylaxis does prevent transmission of disease with a number needed to treat for benefit of 33 and 51 for oseltamivir and zanamivir, respectively (49,59). Chemoprophylaxis appears to be particularly beneficial in those patients who reside in long-term care facilities (60). Although additional studies are needed, children appear to derive a benefit from prophylactic therapy as well (61,62). The use of NI, mainly oseltamivir, does have some adverse effects that should be considered when prescribing the medications. Oseltamivir is associated with higher rates of nausea, vomiting, and headaches (49,54,63–66). In summary, use of NI provides marginal benefit in decreasing during of symptoms and reduction in transmission of disease (67,68).

Recommendation: We recommend that clinicians continue to follow CDC guidelines that state NIs should be used for patients that are hospitalized; are at higher risk for complications; and have severe, complicated, or progressive illness.

Level of Recommendation: B.

Limitations

The review of the clinical question addressed in this article is limited by the quantity and quality of publications on this topic. Also, the structure and search parameters of this literature review may have resulted in information being omitted. The treatment and vaccine searches were limited to systematic reviews and meta-analyses and, therefore, might have omitted relevant single studies from review.

CONCLUSIONS

Influenza is a complex virus with studies that suggest vaccination is far from 100% efficacious, and that treatment with NIs is expensive yet offers marginal benefit

Table 4. Supportive Evidence (Reference Numbers)

Quality/Grade	A	B	C	D	E	F
Outstanding	(3), (9), (10), (17), (49), (56), (57), (59), (64)					
Good	(4), (7), (50), (51–53), (55), (61), (62)	(2), (5), (8), (11), (14), (48), (66)	(24–27), (29), (30–34), (36), (40), (43), (47), (60), (68)			
Adequate		(20), (58), (63)	(18), (41), (42), (46), (54)	(12), (13), (37), (44), (65)	(1), (6), (16), (23), (28), (35), (38), (45), (67)	
Poor			(39)		(15), (19), (21), (22)	
Unsatisfactory						

Definitions of the quality ranking scores provided in Table 2. Definitions of the grades of evidence provided in Table 1.

to patients. In addition, testing in most EDs relies on the rapid antigen test, which has poor sensitivity. However, there is little question that influenza poses a significant annual health threat to an at-risk population (e.g., elderly, immunocompromised, and very young) and the drawbacks of vaccination and aggressive treatment are minimal, other than cost to the health care system.

REFERENCES

1. Centers for Disease Control and Prevention. Severe influenza among children and young adults with neurologic and neurodevelopmental conditions—Ohio, 2011. MMWR Morb Mortal Wkly Rep 2012;60:1729–33.
2. Cortes-Penfield N. Mandatory influenza vaccination for health care workers as the new standard of care: a matter of patient safety and nonmaleficent practice. Am J Public Health 2014;104:2060–5.
3. Diaz Granados CA, Denis M, Plotkin S. Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials. Vaccine 2012;31:49–57.
4. Manzoli L, Loannidis JP, Flacco ME, et al. Effectiveness and harm of seasonal and pandemic influenza vaccines in children, adults, and the elderly. Hum Vaccine Immunother 2012;8:851–62.
5. Osterholm MT, Kelley NS, Sommer A, Belongia E. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis 2012;12:36–44.
6. Gonzalez de Dios J, Rodrigo Gonzalo de Liria C, Piedra PA, Corretger Rauet JM, Moreno-Pérez D. Universal immunisation against influenza in paediatrics, yes or no? An Pediatr (Barc) 2013;79:261.e1–26111.
7. Belshe RB, Toback SL, Yi T, et al. Efficacy of live attenuated influenza vaccine in children 6 months to 17 years of age. Influenza Other Respir Viruses 2010;4:141–5.
8. Michiels B, Govaerts F, Remmen R, Vermeire E, Coenen S. A systematic review of the evidence on the effectiveness and risks of inactivated influenza vaccines in different target groups. Vaccine 2011;29:9159–70.
9. Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev 2010;CD004876.
10. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. Cochrane Database Syst Rev 2010;CD005187.
11. Beyer WE, McElhaney J, Smith DJ, et al. Cochrane re-arranged: support for policies to vaccinate elderly people against influenza. Vaccine 2013;31:6030–3.
12. Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women—a systematic review. Vaccine 2014;32:4602–13.
13. Shehata MA, Karim NA. Influenza vaccination in cancer patients undergoing systemic therapy. Clin Med Insights Oncol 2014;8:57–64.
14. Chan TC, Fan-Ngai HI, Ka-Hay LJ, Chu LW, Hon-Wai Chan F. Effectiveness of influenza vaccination in institutionalized older adults: a systematic review. J Am Med Dir Assoc 2014;15:226.e1–6.
15. Manske JM. Efficacy and effectiveness of maternal influenza vaccination during pregnancy: a review of the evidence. Matern Child Health J 2014;18:1599–609.
16. Johnston JA, Tincher LB, Lowe DK. Booster and higher antigen doses of inactivated influenza vaccine in HIV-infected patients. Ann Pharmacother 2013;47:1712–6.
17. Cates CJ, Rowe BH. Vaccines for preventing influenza in people with asthma. Cochrane Database Syst Rev 2013;2:CD000364.
18. Duman M, Gencpinar P, Ozbek OA, et al. Value of rapid antigen test for pandemic influenza A (H1N1) 2009 in the pediatric emergency department. Pediatr Emerg Care 2013;29:612–6.
19. Landry ML. Diagnostic tests for influenza infection. Curr Opin Pediatr 2011;23:91–7.
20. Apisarnthanarak A, Mundy LM. Rapid testing for pandemic influenza A (H1N1): diagnostic test utility and specimen source. Infect Control Hosp Epidemiol 2010;31:663–4.
21. Peaper DR, Landry ML. Rapid diagnosis of influenza: state of the art. Clin Lab Med 2014;34:365–85.
22. Dale SE. The role of rapid antigen testing for influenza in the era of molecular diagnostics. Mol Diagn Ther 2010;14:205–14.
23. Marzoratti L, Iannella HA, Gómez VF, Figueroa SB. Recent advances in the diagnosis and treatment of influenza pneumonia. Curr Infect Dis Resp 2012;14:275–83.
24. Bruning AH, Van Dijk K, Van Eijk HW, et al. Evaluation of a rapid antigen detection point-of-care test for respiratory syncytial virus and influenza in a pediatric hospitalized population in the Netherlands. Diagn Microbiol Infect Dis 2014;80:292–3.
25. Sutter DE, Worthy SA, Hensley DM, et al. Performance of five FDA-approved rapid antigen tests in the detection of 2009 H1N1 influenza A virus. J Med Virol 2012;84:1699–702.
26. Cho CH, Woo MK, Kim JY, et al. Evaluation of five rapid diagnostic kits for influenza A/B virus. J Virol Methods 2013;187:51–6.
27. Self WH, McNaughton CD, Grijalva CG, et al. Diagnostic performance of the BinaxNow Influenza A&B rapid antigen test in ED patients. Am J Emerg Med 2012;30:1955–61.
28. Kumar S, Henrickson KJ. Update on influenza diagnostics: lessons from the novel H1N1 influenza A pandemic. Clin Microbiol Rev 2012;25:344–61.
29. De Witte E, Goossens H, Ieven M. Evaluation of the ESPLINE(R) Influenza A & B-N assay for the detection of influenza A and B in nasopharyngeal aspirates. Eur J Clin Microbiol Infect Dis 2012;31:761–6.
30. Biggs C, Walsh P, Overmyer CL, et al. Performance of influenza rapid antigen testing in influenza in emergency department patients. Emerg Med J 2010;27:5–7.
31. Herzum I, Lutz T, Koch F, et al. Diagnostic performance of rapid influenza antigen assays in patients infected with the new influenza A (H1N1) virus. Clin Chem Lab Med 2010;48:53–6.
32. Vasoo S, Stevens J, Singh K. Rapid antigen tests for diagnosis of pandemic (Swine) influenza A/H1N1. Clin Infect Dis 2009;49:1090–3.
33. de la Tabla VO, Antequera P, Masia M, et al. Clinical evaluation of rapid point-of-care testing for detection of novel influenza A (H1N1) virus in a population-based study in Spain. Clin Microbiol Infect 2010;16:1358–61.
34. Lucas PM, Morgan OW, Gibbons TF, et al. Diagnosis of 2009 pandemic influenza A (pH1N1) and seasonal influenza using rapid influenza antigen tests, San Antonio, Texas, April-June 2009. Clin Infect Dis 2011;52(Suppl. 1):S116–22.
35. Talbot HK, Falsey AR. The diagnosis of viral respiratory disease in older adults. Clin Infect Dis 2010;50:747–51.
36. DiMaio MA, Sahoo MK, Waggoner J, et al. Comparison of Xpert Flu rapid nucleic acid testing with rapid antigen testing for the diagnosis of influenza A and B. J Virol Methods 2012;186:137–40.
37. Park YJ, Jin JY, Yang HJ, et al. Clinical characteristics of 2009 pandemic influenza A (H1N1) infection in children and the performance of rapid antigen test. Korean J Pediatr 2011;54:405–8.
38. Mahony JB, Petrich A, Smieja M. Molecular diagnosis of respiratory virus infections. Crit Rev Clin Lab Sci 2011;48:217–49.
39. Al Johani SM, Al Balawi M, Al Alwan B, et al. Validity of two rapid point of care influenza tests and direct fluorecence assay in comparison of real time PCR for swine of origin Influenza virus. J Infect Public Health 2011;4:7–11.
40. Papillard-Marechal S, Enouf V, Schnuriger A, et al. Monitoring epidemic viral respiratory infections using one-step real-time triplex RT-PCR targeting influenza A and B viruses and respiratory syncytial virus. J Med Virol 2011;83:695–701.
41. Coleman LA, Kieke B, Irving S, et al. Comparison of influenza vaccine effectiveness using different methods of case detection: clinician-ordered rapid antigen tests vs. active surveillance and testing with real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). Vaccine 2011;29:387–90.

42. Ciblak MA, Kanturvardar M, Asar S, et al. Sensitivity of rapid influenza antigen tests in the diagnosis of pandemic (H1N1) 2009 compared with the standard rRT-PCR technique during the 2009 pandemic in Turkey. Scand J Infect Dis 2010;42:902–5.
43. Talbot HK, Williams JV, Zhu Y, et al. Failure of routine diagnostic methods to detect influenza in hospitalized older adults. Infect Control Hosp Epidemiol 2010;31:683–8.
44. Jernigan DB, Lindstrom SL, Johnson JR, et al. Detecting pandemic 2009 influenza A (H1N1) virus infection: availability of diagnostic testing led to rapid pandemic response. Clin Infect Dis 2011; 52(Suppl. 1):S36–43.
45. Centers for Disease Control and Prevention. Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests. 2014. Available at: http://www.cdc.gov/flu/professionals/diagnosis/clinician_guidance_ridt.htm. Accessed June 15, 2015.
46. Boku S, Naito T, Murai K, et al. Near point-of-care administration by the attending physician of the rapid influenza antigen detection immunochromatography test and the fully automated respiratory virus nucleic acid test: contribution to patient management. Diagn Microbiol Infect Dis 2013;76:445–9.
47. Balish A, Garten R, Klimov A, et al. Analytical detection of influenza A(H3N2)v and other A variant viruses from the USA by rapid influenza diagnostic tests. Influenza Other Respir Viruses 2013;7:491–6.
48. Thorlund K, Awad T, Boivin G, et al. Systematic review of influenza resistance to the neuraminidase inhibitors. BMC Infect Dis 2011; 11:134.
49. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev 2014;4:CD008965.
50. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012;156:512–24.
51. Shun-Shin M, Thompson M, Heneghan C, et al. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. BMJ 2009;339:b3172.
52. Burch J, Corbett M, Stock C, et al. Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis. Lancet Infect Dis 2009;9:537–45.
53. Ebell MH, Call M, Shinholser J. Effectiveness of oseltamivir in adults: a meta-analysis of published and unpublished clinical trials. Fam Pract 2013;30:125–33.
54. Michiels B, Van Puyenbroeck K, Verhoeven V, et al. The value of neuraminidase inhibitors for the prevention and treatment of seasonal influenza: a systematic review of systematic reviews. PLoS One 2013;8:e60348.
55. Hernan MA, Lipsitch M. Oseltamivir and risk of lower respiratory tract complications in patients with flu symptoms: a meta-analysis of eleven randomized clinical trials. Clin Infect Dis 2011;53:277–9.
56. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev 2010;CD001265.
57. Jefferson T, Jones M, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults: systematic review and meta-analysis. BMJ 2009;339:b5106.
58. Flannery AH, Thompson Bastin ML. Oseltamivir dosing in critically ill patients with severe influenza. Ann Pharmacother 2014; 48:1011–8.
59. Jefferson T, Jones M, Doshi P, et al. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ 2014;348:g2545.
60. Rainwater K, Chun K, Lessler J. Influenza outbreak control practices and the effectiveness of interventions in long-term care facilities: a systematic review. Influenza Other Respir Viruses 2014;8: 74–82.
61. Wang K, Shun-Shin M, Gill P, et al. Neuraminidase inhibitors for preventing and treating influenza in children (published trials only). Cochrane Database Syst Rev 2012;4:CD002744.
62. Wang K, Shun-Shin M, Gill P, et al. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane Database Syst Rev 2012;1:CD002744.
63. Jackson RJ, Cooper KL, Tappenden P, et al. Oseltamivir, zanamivir and amantadine in the prevention of influenza: a systematic review. J Infect 2011;62:14–25.
64. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. Cochrane Database Syst Rev 2012;1:CD008965.
65. Santesso N, Hsu J, Mustafa R, et al. Antivirals for influenza: a summary of a systematic review and meta-analysis of observational studies. Influenza Other Respir Viruses 2013;7(Suppl. 2):76–81.
66. Khazeni N, Bravata DM, Holty JE, et al. Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza. Ann Intern Med 2009; 151:464–73.
67. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1–24.
68. Yates L, Pierce M, Stephens S, et al. Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant. Health Technol Assess 2010;14:109–82.