www.medscape.com

Why Is Influenza So Difficult to Prevent and Treat?

Will We See Improvement Any Time Soon?

Linda Brookes, MSc, Andrew T. Pavia, MD, Gregory A. Poland, MD | January 23, 2015

Tough Questions About Influenza: Prevention and Treatment

When the Centers for Disease Control and Prevention (CDC) recently announced that this season's influenza vaccine was only 23% effective against the current predominant A strain (H3N2),[1] many people were unsurprised. Infectious diseases specialists were already aware that most of the A (H3N2) viruses currently circulating had drifted (mutated antigenically and genetically) from the A component selected for inclusion in the 2014-2015 seasonal vaccine.[2] Furthermore, for many members of the public who had been skeptical about the usefulness of any influenza vaccine, the announcement appeared to confirm their view that there was no benefit to being vaccinated. (The vaccine is even less effective in persons older than 50 years).

Despite the limited protection provided by this season's influenza vaccine, the CDC repeated its recommendation for vaccination of everyone aged ≥ 6 months. Because influenza was already widespread and the season is expected to be severe, the CDC also reiterated its earlier recommendation that as an adjunct to vaccination, all hospitalized patients and outpatients at high risk for serious influenza complications should be treated with an antiviral medication (neuraminidase inhibitor) as soon as possible after influenza is suspected, without waiting for laboratory confirmation of the diagnosis.[1,3] Antiviral treatment is also recommended as an option in non–high-risk individuals with suspected or confirmed influenza.

Regardless of the CDC's recommendations, many in the healthcare community have expressed doubts about the value of the current influenza vaccination program, given that the predominant strain is not included in the vaccine, and concerns have been raised about vaccine safety. Moreover, clinicians have been presented with conflicting evidence about the efficacy of antiviral drugs, and debate continues as to whether benefits of these agents outweigh the associated costs and risks.

To address these issues, Medscape spoke with two leaders in the field of influenza prevention and control to hear their views about the CDC's current recommendations; why the current approach appears to be so ineffective; and, of greatest importance, what can be done to improve the situation and prevent the spread of influenza, and possibly even a new pandemic, in the future. Andrew T. Pavia, MD, is George and Esther Gross Presidential Professor and chief of the Division of Pediatric Infectious Diseases at the University of Utah School of Medicine in Salt Lake City, Utah, and Gregory A. Poland, MD, is professor of medicine and director of the Vaccine Research Group, Mayo Clinic, Rochester, Minnesota. Both have expertise in vaccines and public health and have served on federal and state advisory committees on vaccine policy, biodefense, and pandemic influenza preparedness.

Why Didn't This Season's Flu Vaccine Provide Better Protection?

Dr Poland describes influenza, particularly H3N2, as "a promiscuous, ever-changing, constantly mutating, dynamic virus." He emphasized that the recommendations for the strains to be included in the vaccine are made in February or March of the preceding year and manufacturers begin the process of isolating and growing those viruses and creating vaccines no longer than a few months later, "but during that time, it is possible and often likely that the viruses, particularly the H3N2 strain, will drift, resulting in subtle variations from what we actually chose."

Although this way of selecting the vaccine components is the best possible method available with current technology, "it is inherently a game of chance and probability," Dr Poland admits. However, he also expresses some skepticism about the data published on "vaccine failure," even those from the CDC. "We tend to ascribe the failure of the vaccine to the inability of the antibody generated by it to kill the virus, but there be many other factors," he emphasizes. Injection of a vaccine that has been rendered ineffective by freezing or storing in the wrong place in the refrigerator, for example, should be called "failure to handle the vaccine properly" rather than "vaccine failure."

As evidence that this might be a widespread problem, Dr Poland cites a 2012 report from the Department of Health and Human Services Inspector General's office, which found that 76% of healthcare providers mishandled pertussis vaccine, diminishing its efficacy.[4] Similarly, Dr Poland says, "when you inject the vaccine into a frail, very elderly woman who has no capacity to respond with any reasonable degree of immunity, and she becomes infected, is that 'vaccine failure' or 'failure of that host's immune system to respond to the vaccine?' We need to be more sophisticated with respect to 'vaccine failure,' and about the differences between 'efficacy' and 'effectiveness' of vaccines." Dr Poland suggests.

Is Vaccination Worthwhile This Season?

Both Dr Poland and Dr Pavia support the CDC recommendation that everyone aged ≥ 6 months should be vaccinated. Although Dr Poland concedes that current vaccines are "not optimal" and Dr Pavia agrees that the benefit from them is "marginal," both emphasize that the cost of the vaccine is extremely low and it is associated with "essentially zero" risk.

They point to the reasons why vaccination is worthwhile in healthy as well as high-risk people. Vaccine protects against other strains of influenza, including the B viruses, which can cause severe disease and complications in infants, young children, and the elderly. The quadrivalent vaccine available this season contains two B viruses. "These two major lineages of influenza B vaccines are relatively stable, so when we choose the B strains, we are almost always right and the vaccine provides good protection against influenza B," says Dr Poland.

The vaccine also contains an H1N1 A virus and is likely to provide good protection against H1N1, because H1N1 has not demonstrated as much variability as the H3N2 strain after 2009. "So even if there is only 23% protection against H3N2, the protection against H1N1 and the B viruses are excellent," Dr Poland stresses, commenting that to date, only the H3N2 viruses have been problematic this season, which implies that the vaccine has been effective against the other viruses.

Dr Pavia points out that almost every year, a second wave of influenza occurs, caused by a different virus—typically influenza B, although sometimes H1N1. Usually the dominant strain (often an H3N2) accounts for about two thirds of all influenza cases and the other strains make up one third. "When we see this second wave, it will probably not be as severe or as intense as the present outbreak, but it is likely that it will be well matched to the second vaccine component, which will protect against it," Dr Pavia predicts, "That is a real benefit that we can count on."

Dr Pavia also suggests that when a vaccine is moderately to minimally effective against all medically attended disease, it often seems to mitigate the severity of the disease. "Although it may not protect you from getting flu, it may keep you out of the hospital or from getting a secondary complication," he says. "We have no evidence for this year's vaccine," he admits, "but studies from previous years show that the benefits of preventing hospitalization and pneumonia are probably stronger than the benefit of preventing medically attended influenza."[5,6]

Dr Poland points out that if everyone received the vaccine, it would also protect infants aged < 6 months and people who cannot be vaccinated (such as those who developed Guillain-Barré syndrome within 6 weeks of receipt of a prior dose of influenza vaccine) or those in whom vaccine efficacy is greatly diminished (the elderly or people who are immunocompromised). Egg allergy is no longer considered to be a contraindication to vaccination, because recombinant (RIV3) vaccine is now recommended for persons with an IgE-mediated egg allergy. "We prevent influenza from spreading to these individuals, and we reduce the overall burden of circulating influenza virus," he says.

Dr Poland also believes that with seven influenza vaccines currently available in the United States, a personalized approach to vaccines is now possible. "Although there is currently no optimal influenza vaccine, we have vaccines that most years are pretty good." he says. "You have the opportunity to administer the best vaccine for the patient in front of you, maximizing efficacy, safety, and acceptability. Let's understand these different vaccines, and use them," he urges.

Both Dr Pavia and Dr Poland compare influenza vaccination with wearing a seatbelt in a car: It may not protect from high-speed crashes all the time, but some protection is better than none. "Every year we have epidemics of

this virus, and although people argue about the exact numbers, it is clear that influenza kills people, and it leads to hospitalization and the requirement for medical care. It causes so-called presenteeism at work and school (diminishing decision-making and safety in the workplace, and making other people sick), as well as absenteeism, costing billions of dollars each year for time off work, over-the-counter medications, doctor visits, and hospital admissions," Dr Poland says.

How Can We Persuade the Public to Get Vaccinated?

By early November 2014, only 40% of eligible people in the United States had received this season's influenza vaccine.[7] The Healthy People 2020 goal for influenza vaccination in the United States is 70%.[8] "We have a population that doesn't understand vaccines," Dr Poland admits. Dr Pavia believes that the attitude of "I have never had flu, I don't get flu, and I have done that without a vaccine, so why should I bother?" is very widespread. "That is just a misunderstanding; most people aren't going to get flu every year, and particularly if you don't have young children or work in a school, you won't get it every year."

There is also a misperception about side effects supposedly associated with the vaccine, the most common being that the vaccine causes influenza. "A common anecdote you hear people say is that they got the vaccine, then they got sick—not a month later, which very well might be because the vaccine didn't work, but two days later." Dr Pavia recalls. "The reasons for that are pretty clear-cut. We administer the vaccine between September and November, when colds are peaking, and some people will get a cold shortly after they received the flu vaccine, particularly if they stood in line at a clinic. But we tend to believe our experiences, so if someone gets a cold after receiving the vaccine, that must be cause and effect. That tends to have more weight than telling someone that it doesn't happen any more often than it does with a placebo."

According to a recent study,[9] 43% of people think that the flu vaccine will give them flu. "It just makes me want to tear my hair out," exclaims Dr Poland. The study also reported that correcting the misinformation did not lead people to change their opinion. Dr Poland explains that this is due to "belief-dependent realism," a theory that people make up their minds about something in the absence of any data and hence receiving data doesn't change their minds. "It is not a surprise that this occurs in the case of vaccines," Dr Poland says.

He also believes that clinicians have not communicated well with the public about vaccines. "We have been arrogant in that the way we educate people is using the preferred cognitive style of a physician, which tends to be highly analytic," he says. "The vaccine information sheets, for example, are designed by physicians and epidemiologists, and they are highly analytic—full of numbers. But a proportion of the population is innumerate, and those numbers mean nothing to them. Other people use very heuristic methods of making decisions."

Dr Poland and his daughter Caroline Poland, MA developed the Preferred Cognitive Styles and Decision-Making Model, and they say that it is incumbent on healthcare workers to understand the cognitive style of the patient and adapt their teaching to that style.[10]

Dr Pavia also believes that the flu expert community has failed to communicate the true message about influenza vaccination to the public. "It's a mediocre vaccine, it's 65% efficacious in an average year, and it doesn't work as well in children under age 2 years or in the elderly as it does in healthier patients. So although it is cheap and it is virtually free of side effects, it is not a great vaccine, and we have *not* always said that up front," he acknowledges. "The message should have been: It's partial protection, but it's cost-effective, it's easy, and at most it causes a sore arm for 24 hours, so why wouldn't we use it?"

Can We Improve Prediction of Next Season's Dominant Flu Virus?

The current way of predicting the dominant virus of the coming influenza season is outdated and should be improved, Dr Poland says. Dr Pavia suggests delaying the decision about the viruses to be included in the next vaccine until later in the year. "If we had picked the vaccine strain in May instead of February 2014, we would have picked the correct one," he believes. "By April or May, there was good evidence of the drifted A/Switzerland strain; it wasn't clear that it was going to be the dominant strain, but there was a pretty good hint and we probably would have chosen differently."

The element of chance in the selection of the vaccine strains gives rise to concern that an influenza pandemic like that of 1918-1919, which killed an estimated 50 million people worldwide, could not be predicted and thus no effective vaccine would be available. "The best we can do is a kind of backward approach," Dr Poland says. "For example, the 1918 influenza A H1N1 virus has been reconstructed,[11] so we can study it, and we now know that pieces of some of the proteins of the virus demonstrate unusual features that we don't see in viruses that aren't pandemic viruses. When we see a new variant virus, we can look at it and say that it has some but not all of those features, and know whether it is likely to have pandemic potential.

That is what happened in April 2009 with the first influenza pandemic of the 21st century, when a new H1N1 influenza virus was found in patients in Mexico and the United States.[12] "We are beginning to be able to look at the molecular structure of these viruses and predict by understanding more about them. We do not have an assay for that yet, but we are getting there."

Dr Pavia is less sanguine, however, about our ability to make predictions. "One thing that you can predict about flu is that all predictions are wrong," he says. "It is a frustratingly unpredictable disease, and the time between pandemics can be as short as 10 and as long as 50 years." Although he believes that a far worse scenario than 1918, for example—an H5N1 disease (avian influenza) pandemic—is unlikely, "the challenge is to get people enthusiastic about preparing for something with that much uncertainty."

Can We Develop Better Flu Vaccines?

Cell-based influenza vaccines and vaccines containing adjuvants could expand the capacity to produce influenza vaccines within a few years. The vaccines that use adjuvants tolerate some moderately poor matching, Dr Pavia explains. One of these vaccines, a monovalent H1N1 influenza vaccine, was used in the United Kingdom and parts of Europe during the 2009 pandemic. However, one type of adjuvanted monovalent H1N1 vaccine was associated with rare cases of narcolepsy and has not been used since that time.

Although enthusiasm for this type of vaccine has waned, and no adjuvanted influenza vaccine has ever been licensed in the United States to date, Dr Pavia suggests that with an adjuvanted vaccine, "we probably could have made the mistake we made this year and instead of efficacy declining from 65% to 23%, it might have only declined to 40%-50%."

Further into the future, such new technologies as recombinant DNA techniques should allow production of vaccine candidates to be generated as soon as the genetic sequence of the influenza virus is known. This approach would eliminate the need for viruses grown in eggs or cells. These technologies are still mostly in early stages of development but may eventually substantially reduce production timelines.

Dr Poland and Dr Pavia agree that the "holy grail" is to have a vaccine that generates immunity against parts of the virus that cannot change, so that no matter how the virus mutates, the effectiveness of the vaccine is not affected. This would be the so-called universal vaccine, and it is hoped that it would not only be effective against all strains, but also induce a longer-lasting immunity, perhaps for 5-10 years. "There is promising evidence in the test tube and in the mouse," Dr Poland notes, "but we are not very close to putting that in the arms of volunteers, and we are several years away from trying out a universal vaccine."

Cost may be another complication with a universal vaccine. As Dr Pavia points out, "We will be looking to replace a commodity vaccine that can be produced at a cost of $10-$15 per dose and sold at a profit at $20-$25 with something that is going to cost tens of millions of dollars to develop and that will be harder to produce." He admits to worrying about how willing individuals, countries, and insurance agencies will be to shift to $120 or $200 vaccines. "If it is 100% effective and the effect lasts for 5 years, it will be highly cost-effective; but if we only go from 65% to 85% effectiveness and we have to give it every 2 years, then it requires some very tricky economic calculations," he cautions.

Who Should Receive Antiviral Drugs?

Dr Poland acknowledges the controversy about the benefits of treatment with currently available antiviral agents

(neuraminidase inhibitors), particularly in otherwise healthy people, in whom the principal effect appears to be shortening of symptoms by a day. However, in general, people have much less skepticism about pills than they do vaccines. "People are more willing to take risks when they are sick and want to get well than to prevent future illness," he suggests. The currently available antiviral agents "absolutely can be life-saving," he says, "but they are associated with similar problems, although not of the same magnitude, as antibiotics, in that when they are used widely, we begin to apply a selective pressure that causes mutations that reduce their effectiveness."

Dr Pavia agrees. "Treatment with antivirals requires much more careful thought. Their cost is not trivial—about $100 per dose in the United States, although peramivir, the newest injectable drug, costs about $900 per dose. Oseltamivir is relatively well tolerated, but it causes vomiting in about 10% of people, so unlike flu vaccine, which falls under what in the United States would be called 'the chicken soup principle' (in other words, it can't hurt), you need justification to use antivirals," he stresses. He believes that the data on antivirals are "quite good," despite the widely publicized criticism from Tom Jefferson, MD, of the Cochrane Institute and *BMJ* associate editor Peter Doshi, PhD, of the University of Maryland School of Pharmacy.[13-15]

"A false controversy has been created by a very strict dogmatic interpretation of the data," Dr Pavia says. He comments that the Cochrane Collaboration analyzed the data on the basis of intention to treat, whereas only 30%-40% of the people in the study had influenza. Their main finding was that the size of the benefit for previously healthy people who went to the doctor with a flu-like illness and were treated (not people with laboratory-confirmed influenza) was modest—less than 1 day, on average, of reduced symptoms. "That is a rather small benefit for which to purchase and take a drug."

"If one looks at data from people who had influenza (the only group who could benefit), there was a 1.25- to 1.5-day difference in median time to symptom improvement and somewhat greater benefit in ability to return to work. Another meta-analysis showed a reduction in the number of lower respiratory tract infections treated with antibiotics."[16] Dr Pavia points out that the main weakness is that clinical trials did not address antiviral use in people who were at high risk of having more severe disease, and no large clinical trials have enrolled patients with heart disease, diabetes, or other high-risk criteria, or looked exclusively at children younger than 2 years or adults older than 65 years.

"We have observational studies—many of them extremely well done, some not quite so good, and some of them horrible," Dr Pavia acknowledges. Several meta-analyses of the observational data, also done by strict methodological criteria, showed more impressive results.[17-19] Among patients who were treated in the hospital, there was a reduction in risk of requiring admission to the intensive care unit (ICU) and a reduction in the risk for death. Among high-risk patients treated early, there was a reduction in risk of being hospitalized or developing pneumonia. "This is the basis of the CDC recommendation that I am involved with," Dr Pavia stated.

"We are very lukewarm about the use of antiviral drugs for otherwise healthy people; it is a discretionary choice. But for patients who are at high risk for complications—those with underlying medical illnesses, extremes of age, pregnant women (a particularly important group), and those who are severely ill or who are sick enough to be in hospital with flu—we are now talking about medically important benefit. Those are the settings where we should use the drugs, as the CDC recommends."

How Should Antiviral Drugs Be Used in Flu?

We need to give antiviral agents as early as possible, Dr Pavia says. "We know that if you start the drug within 48 hours of onset of symptoms, you will see an improvement of about 30 hours in time to getting better, but if you start the drug after 48 hours, there is no discernible benefit," he stresses. "In patients with moderate disease in whom the symptoms aren't going to last long anyway, you must start treatment within 48 hours of onset of symptoms, or you will be wasting your time. At this time of year, if I had a fever of 103°F with massive muscle aches and a cough, I would prescribe the drug for myself if it was within 48 hours rather than sending off for a test. But if I have low-grade fever and I feel just a bit poorly, I don't think the drug should be prescribed."

The studies on treatment of hospitalized patients were different, in that they showed that treating these patients more than 48 hours after onset of symptoms still provides some benefit.[20] "As the CDC guidelines indicate, for

someone who is sick enough to be in the hospital and perhaps in the ICU, using the 48-hour cut-off for treatment is not appropriate," Dr Pavia confirms. "However, it is still important to start treatment as early as possible, because when the results were compared in people who were treated at 24 hours vs 48, 72, or 96 hours, there was a corresponding effect on the magnitude of the reduction in ICU admission or death." Almost all of the data accumulated in hospitalized patients are with oseltamivir, Dr Pavia mentions, "so we can't extrapolate to zanamivir, and we don't have any adequate clinical trial data with peramivir other than in acute uncomplicated influenza."

Should Antibiotics Ever Be Given for Influenza?

A recent CDC study[21] that examined clinician treatment practices for outpatients with influenza during the 2012-2013 season showed that only 16% of patients with laboratory-confirmed influenza were prescribed oseltamivir or zanamivir, whereas as many as 30% were prescribed one of three common antibiotics. "Unfortunately, we know from several observational studies that if you go into an emergency department in the United States or Canada with influenza, you are more likely to leave with a prescription for antibiotics that you don't need than for an antiviral that might do you some good. That is a big problem," Dr Pavia says.

"Don't prescribe antibiotics unless there is a medical reason," Dr Poland stresses. "This is why we have a major crisis in antibacterial resistance."

Dr Pavia believes that the problem might be a consequence of a lack of familiarity with antivirals and confusion over when to use and when not to use them. Also, there is a "deeply ingrained tendency" to prescribe antibiotics for sick patients because they need something or because of the perception that patients are going to be happier.

Another very important reason is that clinicians "don't want to risk missing anything," he adds. "Even if they know that out of 99 influenza cases, fewer than one will have a bacterial superinfection, physicians don't want to have not treated that one person who develops bacterial pneumonia as a complication of flu. It is true that flu predisposes to bacterial pneumonia, but it is not true that giving an antibiotic will prevent it, because the patient is likely to be infected with a different bacterium from the one targeted by the antibiotic," he emphasizes. "And if you treat 100 patients who don't need an antibiotic for every one who does, you are probably going to send one to the hospital with a rash. If several develop diarrhea—including potentially severe diarrhea—you will do far more harm than good."

What Can We Expect in the Future?

Dr Pavia cited a report of the 2009 H1N1 influenza epidemic written by Harvey Fineberg, MD, PhD, formerly head of the Institute of Medicine,[22] that concluded that the world is poorly prepared to face another influenza pandemic or a similar worldwide epidemic. "Dr Fineberg has said that the Ebola experience is proof of our lack of preparation," Dr Pavia added.

Dr Pavia believes that to some degree, "we need to think about pandemic influenza more broadly—not about whether we have the right flu tools, but whether we have a coordinated worldwide response to any major infectious disease emergency." That helps justify investment in influenza, he believes, "because we may never see another Ebola outbreak in a city again, we may never see SARS (severe acute respiratory syndrome) again, but the one infectious disease emergency that we can be sure will happen—and we don't know when it will happen—will be pandemic flu," he warns.

"Putting it in perspective, however, the benefits of vaccinating patients right now with influenza vaccine are modest, and if patients are resistant, it is probably not the greatest investment of time," Dr Pavia admits. "On the other hand, identifying high-risk patients, those with fragile states of health and multiple risk factors, during this fairly severe H3N2 outbreak, and knowing how you are going to start them on antivirals early if they get influenza will make a very large difference; of the two recommendations, that one is much more important," he says.

Dr Poland is not very optimistic about how soon new vaccines may become available. "As much of a proponent as I am for vaccines, I have also been the hardest on the industry in saying that we need better vaccines," he says. "As good as airplane safety is now, no one is satisfied with it. We want it to be even better, and the same is true for the

safety and efficacy of influenza and other vaccines. I have talked to companies and pushed them to consider various new methodologies."

"However, there is a lack of incentive for the pharmaceutical industry to develop new vaccines. Remember that the influenza vaccine is generally not much of a money-maker," he continues. "It is a very difficult vaccine to make, and it is extremely labor-intensive." Nonetheless, influenza vaccines are less complex to produce than HIV, malaria, or tuberculosis vaccines, none of which have been successfully produced to date, so Dr Poland does expect to see advances in influenza vaccines in the future, although not soon.

Dr Pavia expressed similar reservations about future antivirals. "Having talked about why we should use the current antiviral drugs, we should admit that they are not perfect," he acknowledges. "Resistance to oseltamivir has been a big problem in some years; we haven't seen it in a big way since 2008, but we all anticipate that resistance to oseltamivir will be a big issue again. Furthermore, we don't yet have anything that works extremely well in critically ill patients to whom we must administer drugs intravenously."

"We need better drugs," he continues. Flu kills 20,000-40,000 people annually, so even if a drug is not cost-effective for you and me to take it to avoid 3 days in bed, it will have a significant health impact. If new and better drugs could be developed, we would be willing to purchase them. The problem has been that drug companies don't see it as highly profitable, even with all the income that oseltamivir has generated in the past few years; thus, few resources have been devoted to developing better drugs."

"If in 2016 we have another major pandemic or one like those of 1956 or 2009 that were not terribly severe, or if we see a pandemic that is oseltamivir-resistant, we will have a much more severe disease and more deaths than if we had a drug that worked. Right now, we don't have drugs that we could speed through the pipeline to be ready in 12 months. I just hope that within the next 8-10 years, the next time we have a mismatch, we have learned lessons and will have developed really good flu vaccines, and we will have the next generation of antiviral drugs that are more effective. But I am not totally confident that we will get there," Dr Pavia concludes.

References

1. Flannery B, Clippard J, Zimmerman RK, et al. Early estimates of seasonal influenza vaccine effectiveness—United States, January 2015. MMWR Morb Mortal Wkly Rep. 2015;64:10-15. Abstract

2. Grohskopf LA, Olsen SJ, Sokolow LZ, et al; Centers for Disease Control and Prevention. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2014-15 influenza season. MMWR Morb Mortal Wkly Rep. 2014;63:691-697. Abstract

3. Centers for Disease Control and Prevention. CDC health update regarding treatment of patients with influenza with antiviral medications. January 9, 2015. http://emergency.cdc.gov/HAN/han00375.asp Accessed January 18, 2015.

4. Levinson DR. Vaccines for Children Program: vulnerabilities in vaccine management. Washington, DC: Department of Health and Human Services, Office of the Inspector General; 2012. https://oig.hhs.gov/oei/reports/oei-04-10-00430.asp Accessed January 19, 2015.

5. Talbot HK, Zhu Y, Chen Q, Williams JV, Thompson MG, Griffin MR. Effectiveness of influenza vaccine for preventing laboratory-confirmed influenza hospitalizations in adults, 2011-2012 influenza season. Clin Infect Dis. 2013;56:1774-1777. Abstract

6. Fry AM, Kim IK, Reed C, et al. Modeling the effect of different vaccine effectiveness estimates on the number of vaccine-prevented influenza-associated hospitalizations in older adults. Clin Infect Dis. 2014;59:406-409. Abstract

7. Centers for Disease Control and Prevention. National early season flu vaccination coverage, United States, November 2014. http://www.cdc.gov/flu/fluvaxview/nifs-estimates-nov2014.htm Accessed January 18, 2015.

8. US Department of Health and Human Services. Healthy People 2020: immunization and infectious diseases. http://www.healthypeople.gov/2020/topics-objectives/topic/immunization-and-infectious-diseases Accessed January 21, 2015.

9. Nyhana B, Reiflerba J. Does correcting myths about the flu vaccine work? An experimental evaluation of the effects of corrective information. Vaccine. 2015;33:459-464. Abstract

10. Poland CM, Poland GA. Vaccine education spectrum disorder: the importance of incorporating psychological and cognitive models into vaccine education. Vaccine. 2011;29:6145-6148. Abstract

11. Tumpey TM, Basler CF, Patricia V, et al. Characterization of the reconstructed 1918 Spanish influenza pandemic virus. Science. 2005:310:77-80. Abstract

12. World Health Organization. 2009. World now at the start of 2009 influenza pandemic. http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/print.html Accessed January 17, 2015.

13. 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.

14. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545.

15. Jefferson T, Doshi P. Multisystem failure: the story of anti-influenza drugs. BMJ. 2014;348:g2263.

16. 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;53:277-279. Abstract

17. Muthuri S, Venkatesan S, Myles P, et al; PRIDE Consortium Investigators, Nguyen-Van-Tam JS. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. 2014;2:395-404.

18. Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis. 2013;207:553-563. Abstract

19. 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;156:512-524. Abstract

20. McGeer A, Green KA, Plevneshi A, et al; Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis. 2007;45:1568-1575. Abstract

21. Havers F, Thaker S, Clippard J, et al. Use of influenza antiviral agents by ambulatory care clinicians during the 2012-2013 influenza season. Clin Infect Dis. 2014;59:774-782. Abstract

22. Fineberg HV. Pandemic preparedness and response—lessons from the H1N1 influenza of 2009. N Engl J Med. 2014;370:1335-1342. Abstract

Cite this article: Why Is Influenza So Difficult to Prevent and Treat? *Medscape*. Jan 23, 2015.