

SUMMARY
Centers for Disease Control and Prevention
Clinician Briefing
Antimicrobial Resistance; Influenza
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ANTIMICROBIAL RESISTANCE

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***Please note: Data and analysis discussed in these presentations were current when presented. Data collection and analysis are ongoing in many cases, therefore updates may be forthcoming elsewhere on this website, through publications such as [CDC's Morbidity and Mortality Weekly Report](#) or other venues. Presentations themselves will not be updated. Please bear this in mind when citing data from these presentations*

Trends in Resistance in Invasive Pneumococcal Disease: Disease Burden and Effect of Antibiotic Resistance on Clinical Outcome

- Resistance: two definitions
 - Functional definition: organisms become resistant to antibiotics, leading to treatment failures
 - Laboratory definition: organisms have elevated minimum inhibitory concentrations (MIC)
 - Definitions do not always match
- Evaluating role of resistance in treatment failures
 - With otitis media and meningitis, resistance is associated with treatment failures.
 - With other pneumococcal infections, e.g., bacteremia and pneumonia, data are less clear.
- Association between resistance and outcome is difficult to measure
 - People die from pneumococcal disease for many reasons. Resistance is just one of them.
 - Prospective outcome studies are difficult to perform
 - In retrospective studies, it's difficult to control for other factors related to poor outcome.
- Penicillin failures in pneumococcal pneumonia

- Penicillin resistance is not associated with poor outcome for pneumococcal pneumonia
- There is no documented relationship between penicillin resistance and the likelihood of death in invasive pneumococcal pneumonia.
- In summary, penicillin is not associated with bacteriologic failure in patients with pneumonia.
- Cephalosporin failures in pneumococcal pneumonia
 - There are few case reports of failures with cefazolin, cefuroxime, ceftazidime
 - Pharmacokinetic data suggest cefotaxime and ceftriaxone at appropriate doses should work up to MIC 2 µg/ml
 - Observational data are mixed on whether treatment failures occur with cefotaxime or ceftriaxone
- Summary of association of treatment failures and resistance in patients with pneumococcal pneumonia
 - Resistance is important for otitis media and meningitis
 - It is difficult to assess the relationship between resistance and outcome; more studies are needed
 - In spite of lack of evidence of treatment failures with penicillin, cefotaxime, ceftriaxone, and rare failures with newer fluoroquinolones, empiric therapy for severe pneumonia may require a combination of agents because of potential etiologies other than pneumococcus and because of resistance issues.
- Resistance to specific drug types
 - Penicillin and erythromycin: In *Streptococcus pneumoniae* in the United States, resistance is emerging rapidly. One in four infections was resistant as of 1999.
 - Macrolides: Similar in prevalence to penicillin resistance
 - Fluoroquinolones: resistance is uncommon in US
 - Levofloxacin: Fewer than 1% of strains are resistant
- New breakpoints for resistance for meningitis and non-meningitis
 - There are two sets of cutoffs: one for meningitis and one for non-meningitis for some beta-lactam agents.
 - We have to pay attention to the definitions used over time.
- Meningitis and non-meningitis resistance
 - Cefotaxime: 16% resistance for meningitis and 6% non-meningitis syndromes using different cut-offs..
- Pneumococcal conjugate vaccine in the United States
 - 7-valent vaccine (Prevnar™) was licensed in U. S. in 2000

- Vaccine includes 7 common pediatric serotypes: (4, 6B, 9V, 14, 18C, 19F, 23F). Five of these types cause most resistant infections.
- Vaccine is recommended for all children < 2 years and children 2-4 years with certain chronic illnesses/immunocompromising conditions
- Why conjugate vaccine may help reduce resistance
 - There is a close relationship between serotype and resistance
 - 80% of infections are caused by resistant organisms that are serotypes in the 7-valent vaccine
 - With the introduction of the vaccine in 2000, penicillin resistance in *S. pneumoniae* in the U. S. has declined
- Rates of invasive disease among children <2 years have been declining since their peak in 1999.
 - One in 5 strains is now resistant to penicillin compared with 1 in 4 in 1999.
 - Pneumococcal conjugate vaccine is reducing the prevalence of resistance.
- Summary of magnitude of the problem
 - For pneumonia patients, few (<2%) strains have MICs high enough to cause failure resulting from resistance when treated with penicillin, cefotaxime, ceftriaxone, or newer fluoroquinolones. A substantial proportion of strains have MICs high enough to fail therapy with macrolides.
 - Beta-lactam resistance of high enough levels to result in treatment failures for otitis media and meningitis patients is more common.
 - There was an increase in the number of infections caused by resistant strains in the 1990s, but conjugate vaccine is now reducing disease caused by resistant strains.
 - How long this reduction in disease caused by resistant strains will continue and how far resistant disease will drop is unknown.
- Take-home messages
 - Resistance matters. There is evidence for treatment failures for otitis media and meningitis and at higher MIC levels, for pneumonia.
 - Resistance levels increased to high levels during the 1990s for many common agents but now may be decreasing somewhat because of the conjugate vaccine.
 - Appropriate antibiotic uses is critical for maintaining the benefits of the vaccine.

Patricia Cook
Program Director - Get Smart: Know When Antibiotics Work
Division of Bacterial and Mycotic Diseases
National Center for Infectious Diseases

- The Get Smart program is designed to promote appropriate antibiotic use in the community.
- Campaign aims to reduce the spread of antibiotic resistance by:
 - Promoting appropriate prescribing guidelines among providers
 - Decreasing demand for antibiotics for viral upper respiratory infections among healthy adults and parents of young children
 - Increasing adherence to prescribed antibiotics for upper respiratory infections
- Appropriate antibiotic use:
 - Only prescribe antibiotic therapy when beneficial
 - Use an appropriate (targeted) agent
 - Use the appropriate dose and duration
- Reasons for antibiotic overuse: conclusions from eight focus groups
 - Patient concerns
 - Want clear explanation
 - Green nasal discharge
 - Need to return to work
 - Provider concerns
 - Patient expects antibiotic
 - Diagnostic uncertainty
 - Time pressure
- Get Smart medical curriculum in medical schools
 - Prototype developed
 - Piloted at 6 medical schools
 - University of Pittsburgh School of Medicine
 - University of New York Upstate Medical University
 - Oregon Health and Science University
 - Tulane University
 - Indian University School of Medicine
 - Association of American Medical Colleges
 - Nationwide launch in 2004
- Related activities
 - Otitis media curriculum
 - Intended for pediatric and family medicine residents
 - Focus on proper diagnosis of acute otitis media
 - Residency medical curriculum
 - For pediatric, family medicine, and internal medicine residents
 - Appropriate antibiotic prescribing curriculum
 - Based on medical school project/curriculum

- What clinicians can do
 - Read CDC guidelines
 - Train office staff
 - Display materials in your office
 - Promote open dialog with patients
 - Discard inappropriate antibiotic samples
 - Join local efforts

- CDC partners in Get Smart campaign
 - Professional associations
 - Medical schools
 - State and local health departments
 - Managed care organizations
 - Pharmacy benefit management companies
 - Pharmaceutical companies
 - Health-care purchasers

- Reasons to partner with CDC
 - Be part of a national campaign that will have national recognition
 - Scientific and programmatic expertise of CDC
 - Access to large network of national partners and intervention programs
 - Prepared educational tools, academic detailing sheets, and media
 - Funding to health departments for development and implementation of appropriate use programs
 - Formal recognition of partnership with CDC

QUESTIONS AND ANSWERS

Dr. Marquerite Neal
 Infectious Diseases Society of America

I'm wondering, if in the campaign you're going to use professional societies as a pipeline for the communication network?

Patricia Cook
 Yes, absolutely.

Dr. Neal
 Because I didn't hear that in the list.

Ms. Cook
 Yes, professional organizations we definitely want. In fact, that's one of the things we're trying to get right now. We have AAP; we have nurses' associations. In fact, I was looking at the list of the people that we have. We already have the American Academy of Family Physicians, nurse practitioners. So we have several of your organizations

already involved, but we can use every one of you there in our campaign. And if you're interested in partnering with us, my e-mail is pcook@cdc.gov and I can get you all the information to partner with us.

Dr. Neal

Might I suggest a couple of other organizations?

Ms. Cook

Yes, please.

Dr. Neal

I would be thinking, in terms of... there are a number of surgical subspecialties. For example, the ENT group is one, and then the Infectious Disease Society of America, obviously, has felt like they sing to the church choir, but we'd certainly be happy to keep showcasing this.

Ms. Cook

IDSA is a partner with us already, but we haven't thought about the emergency medical technicians, and thank you for that.

INFLUENZA

Dr. Scott Harper

Medical Officer

Division of Viral and Rickettsial Diseases

National Center for Infectious Diseases

Current Status of Influenza Outbreak and CDC Recommendations

- The 2003-2004 season began early, in October, and is the earliest since the mid 1970s with activity first reported in Texas.
- The fact that the season began early does not predict its length or its severity.
- The predominant viruses circulating at this point come from the influenza A, H3N2 family. These strains have predominated in past seasons that have been relatively mild.
- Although we will not have quantitative data for a while on deaths and hospitalizations, anecdotally, it looks so far as though we are having a more severe season.
- The current H3N2 viruses that are predominantly circulating are Fujian-like viruses. About 75% of the isolates that CDC has antigenically characterized have been Fujian-like and about 25% are H3N2 Panama-like viruses (the H3N2 component of this year's vaccine).
- At this time there is no indication that the Fujian variant is any more potent than the Panama viruses or other influenza A, H3N2 viruses.
- There has been a lot of media attention focused on childhood deaths. We know that influenza kills children; however, we also know that the vast majority of

- people that die secondary to influenza this year will be persons over the age of 65 and those of any age with underlying high-risk conditions.
- CDC is gearing up to determine at the end of the season whether this was a more severe influenza season for children. More testing for influenza is being done this year compared to previous years, will make it difficult to compare this year's outbreak to previous years.
 - CDC has combined all its influenza websites into one, which is www.cdc.gov/flu.
 - An MMWR from last Friday, December 12, ("Update: Influenza Activity-- United States, 2003-04 Season" (MMWR December 12, 2003 / 52(49);1197-1202) <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5249a1.htm>) provides an influenza update. This includes descriptions of pediatric cases and an outbreak of influenza in pregnancy, etc.
 - This MMWR also includes interim supplemental vaccine recommendations. In light of the current vaccine situation, emphasis is being placed on targeting trivalent, inactivated vaccine to people who are at high risk for complications from influenza:
 - adults age 65 and older
 - pregnant women in their second or third trimester
 - anyone over the age of six months who has chronic underlying medical conditions that predispose them to complications
 - people who are institutionalized
 - In addition, healthy children aged 6 to 23 months should be vaccinated since they have higher rates of hospitalizations than children in other age groups.
 - Information will be posted on the CDC website today on interim chemoprophylaxis and treatment guidelines, that is, the use of antivirals. This will include a discussion of general considerations as well as situations in which antivirals should be used and situations in which they should be considered for use (<http://www.cdc.gov/flu/professionals/antiviralguid.htm>).
 - Interim vaccine recommendations are presented in "Update: Influenza Activity-- United States, 2003-04 Season" (MMWR December 12, 2003 / 52(49);1197-1202) <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5249a1.htm>
 - The same infection control guidelines apply as in the past:
 - Droplet precautions should remain in effect for hospitalized influenza patients, including giving them a private room, cohorting patients, use of surgical masks within three feet of patients, etc..
 - Airborne precautions are not recommended for influenza.
 - Attention should be paid to hand hygiene, use of gowns and gloves if there's anticipated contact with secretions, etc.
 - Vaccination for healthcare workers continues to be recommended.
 - The MMWR previously mentioned (<http://www.cdc.gov/flu/professionals/antiviralguid.htm>) includes supplemental antiviral recommendations as they pertain to healthcare workers.

- The new CDC website (www.cdc.gov/flu) also includes information on laboratory diagnosis, use of commercial rapid tests versus direct fluorescent antibody and viral culture, etc..

Raymond A. Strikas, M.D.
Director
Smallpox Preparedness and Response Activity
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Influenza and Influenza Vaccine

Overall Key Messages

- **Influenza seasons can vary substantially in terms of timing and pattern of onset, peaking, decline, and overall severity.** In the United States, the 2003--04 influenza season began unusually early, with community activity first reported in early October, followed by continued spread of influenza activity during the weeks ending October 4--December 6. National activity levels have not yet peaked, and neither the duration of activity nor the season's eventual magnitude is known.
- **Influenza seasons dominated by A (H3N2) viruses (e.g., those in 1996--97, 1997--98, and 1998--99) typically are associated with high levels of severe illness and deaths.** No evidence exists to indicate that the A/Fujian-like viruses in circulation are more virulent than other influenza A (H3N2) viruses. However, reports of severe pediatric illnesses and deaths underscore the severe consequences that influenza infections can cause in children.
- **So far this season, influenza A/Fujian/411/2002-like viruses are predominating in the United States.** This strain differs from the influenza A (H3N2) virus contained in the 2003--04 vaccine (i.e., A/Panama/2007/99). Current influenza vaccines should provide some protection against A/Fujian-like viruses. However, the level of protection remains uncertain until vaccine effectiveness studies are completed. The vaccine also contains A/New Caledonia/20/99 (H1N1)-like and B/Hong Kong/330/2001-like viruses and should protect persons who are vaccinated against these viruses if they circulate more widely later in the season.
- **More Americans appear to have gotten vaccinations against flu this year than ever before.** We're pleased about the strong response and high consumer demand for influenza vaccine. We want everyone who wants a flu shot to be able to get one, especially those people who are at high risk for complications.
- **It looks like the demand for influenza vaccine this season may exceed the demand seen in previous flu seasons.** Some health care providers have used -- or may use -- all of their supplies of influenza vaccine. It's not easy to predict (months in advance) how many people will get an influenza vaccination. In past years, supply has generally been sufficient to meet demand, but this year, a strong demand has continued for longer than usual into the month of December. At a time when flu vaccination clinics are typically winding down, people are still seeking flu shots.

- **Three companies produce flu vaccine for the United States, two of these companies produce only inactivated injectable flu vaccine (i.e., flu shots).** The two companies that produce flu shots for the U. S. together made about 82 million doses of the injectable vaccine, which ordinarily would be enough to exceed U. S. demand. The third company makes a live attenuated influenza vaccine which is given as a nasal spray.
- **In a typical year, millions of doses of flu vaccine are discarded.** Typically, fewer than half the 185 million people for whom CDC recommends a flu shot actually get one. This year, more people than usual have sought flu vaccination. Public health officials hope this trend — growing numbers of people, particularly those at risk of complications getting a flu shot will continue each year, matched by increasing supplies of vaccine.
- **Substantial numbers of influenza cases in children, including severe or unusual complications and deaths, have been reported in a number of states.** At this point, it is unclear whether influenza is impacting children more severely this season than in other years or if a heightened awareness of severe influenza disease in children has led to increased testing and reporting of pediatric cases. We are investigating these issues.
- **CDC has received reports of severe complications of influenza occurring in young infants, school-age children, and adolescents.** Complications have included encephalopathy, seizures, dehydration with severe hypotension, respiratory failure requiring mechanical ventilation, and secondary bacterial pneumonia, including necrotizing pneumonia with community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Three deaths (an infant aged 20 months with underlying reactive airways disease, a previously healthy infant aged 22 months, and a previously healthy child aged 16 years) have been associated with secondary pneumonia caused by CA-MRSA. Other influenza-related deaths not related to CA-MRSA in children have occurred. Fatal cases reported to CDC are being investigated by local and state health authorities. The vaccination status of the majority of the deceased children has not been determined.

Projections/Predictions Regarding the Influenza Season

- Influenza activity nationwide currently is moderate to severe and is expected to increase during the coming weeks.
- We cannot predict how long this flu season will last nor how many people will develop life-threatening complications or die.
- A characteristic of the epidemiology of influenza is that influenza seasons can vary substantially from year to year in terms of timing and pattern, predominant viruses and severity.

Influenza Vaccine Manufacturing and Supplies

- **Manufacturers of the flu vaccine, like manufacturers of consumer goods, use past history of consumer demand to determine how much product to produce.** This year demand exceeded their projections (i.e., about 82 million doses of the injectable vaccine). Flu vaccine manufacturers absorb significant financial losses when they have to discard unused vaccine. In fact, this year one company is no longer producing flu vaccine.
- **At the start of this flu season, vaccine supply was plentiful (i.e., enough to meet typical demand) There are at least three major reasons why manufacturers of flu shots have sold all of their supplies.**
 - Early Influenza season: Earlier than usual outbreaks of influenza fueled a surge of vaccine orders later in the season than usual. In past seasons, manufacturers of flu vaccine have received relatively few orders in late November and December.
 - Highly visible public awareness campaigns: Many public and private health providers have made increasing efforts to educate the public, particularly those people at high risk for serious complications from influenza, to get a flu vaccination.
 - Extensive news coverage: The early flu season generated news stories about the potential for this year's flu season to be one of the most severe in the past few years. Much news coverage devoted to influenza-related deaths in children this year, has generated increased concern about influenza. In an average, year flu kills about 36,000 people in the United States. The news coverage may have motivated people who otherwise would not have to get flu shots and in sustaining interest in flu shots in December.

Influenza Vaccine Production

- **Making vaccine is a year-long process, involving several steps.** Once vaccine strains are selected, it can take more than four months to produce enough vaccine for the U. S. That is why the manufacturing process begins so early each year.
- **(Since it can take more than four months to produce influenza vaccine) The companies cannot make more vaccine in time for this flu season.** In addition, producing more vaccine now would jeopardize production capacity for next year.
- **Federal agencies are actively working with public and private sector partners to develop effective policies for vaccine purchase, distribution, and delivery.**

Guidance on Use of Available (Injectable) Vaccine

- **Vaccination**

- Emphasis should be placed on targeting trivalent inactivated vaccine to persons at high risk for complications from influenza: all children aged 6-23 months; adults aged ≥ 65 years; pregnant women in their second or third trimester during influenza season; and persons aged ≥ 2 years with underlying chronic conditions.
- Persons at high risk should be encouraged to search locally for vaccine if their usual health-care provider no longer has vaccine available.
- All children at high risk, including those aged 6-23 months, who report for vaccination should be vaccinated with a first or second dose, depending on vaccination status. Doses should not be held in reserve to ensure that two doses will be available.
- Next priority should be given to vaccinating those persons at greatest risk for transmission of disease to persons at high risk, including household contacts and health-care workers.
- Healthy persons aged 5-49 years should be encouraged to be vaccinated with intranasally administered live, attenuated influenza vaccine.
- Decisions about vaccinating healthy persons, including adults aged 50-64 years, with inactivated influenza vaccine should be made on a case-by-case basis, depending on local disease activity and vaccine supply.
- Health departments and health-care providers should work together to reallocate influenza vaccine to health-care providers in need when possible.

Hygiene

- Good respiratory hygiene and cough etiquette should be encouraged, including cleaning of hands, and staying at home when symptomatic with fever and respiratory illness.

Medication

- Antiviral medications with specific activity against influenza A viruses are available. These should be considered either for treatment or chemoprophylaxis for influenza A, especially in persons at high risk for complications from influenza.

Other Protective Actions that Can Be Taken

Aside from getting vaccinated, people can take several, simple steps to protect themselves and their loved ones from influenza:

- Wash your hands frequently with soap and warm water. Teach children the same healthy habits.
- Cover your nose and mouth when you cough and sneeze, preferably with a facial tissue or your arm, not your hands. Promptly discard used facial tissues.

- If you are sick with cough and fever, stay home from work or school until you recover.
- Contact your medical provider if you are experiencing severe symptoms that you believe require medical attention.

Those who have already received the flu should remember the following:

If you develop the flu, it is advisable to get plenty of rest, drink a lot of liquids, and avoid using alcohol and tobacco. Also, you can take medications to relieve the symptoms of flu (but *never* give aspirin to children or teenagers who have flu-like symptoms – and particularly fever – without first speaking to your doctor.)

- If, however, your flu symptoms are unusually severe (for example, if you are having trouble breathing), you should consult your health-care provider right away.
- If you are at special risk from complication of flu, you should consult your health-care provider when your flu symptoms begin. This includes people **65 years or older**, people with **chronic medical conditions**, **pregnant women**, or **children**. Your doctor may choose to use certain antiviral drugs to treat the flu.

The most common symptoms of the flu include:

Influenza, also known as the flu, is a contagious disease that is caused by the influenza virus. It attacks the respiratory tract in humans (nose, throat, and lungs). The flu is different from a cold. Influenza usually comes on suddenly and may include these symptoms:

- Severe (usually high) fever
- Headache
- Tiredness (can be extreme)
- Dry cough
- Sore throat
- Nasal congestion
- Body aches

QUESTIONS AND ANSWERS

Dr. Marguerite Neal

Hello, Ray. Great job to everyone. I'll just jump in with both feet. Can you give us perspective and commentary on discussions related to more actively promulgating widespread use of the live-attenuated in the settings in which many of us have absolutely no vaccine available?

Dr. Strikas

Yes. You remind me of something I omitted to say, and then I'll ask Dr. Harper to comment as well. I didn't say what's being done in terms of addressing the issue with

vaccine supply, and that's very important. CDC has been able to identify some sources of inactivated vaccine and 250,000 doses, in allotments of 100,000 and 150,000, are being shipped to state health departments, either now or in the next few weeks.

An additional 375,000 doses inactivated vaccine will get to the state health departments in mid-January, and CDC has a contract with WYETH Medimmune for the FluMist live-attenuated vaccine, of which we are told there are over three million doses still available, to allow state and local health departments to purchase that product, if they so desire, at a cost of \$20.00 a dose.

I do think that product, although it has a limited licensure for persons between 5 and 49 years of age, offers an alternative that we recommend - I think Scott said this - people seek, if they are in that age group and don't have high-risk medical conditions and wish to be vaccinated. Because, as far as anyone knows, it's an excellent vaccine, which is why it's licensed and they should take advantage of it.

The limitation - and I don't know if you were referring to this - that some are concerned about, is that it's not the preferred vaccine for people in close contact with persons with immuno-compromising conditions, because of the concern about shedding of the attenuated virus that could conceivably cause, although it's never even documented to cause, significant illness in such people.

I don't know that we have a clear answer, except to get more data, about the duration of time in which this vaccine virus is shed from vaccinated persons and see if it could be transmitted to susceptible other people. Scott, did you want to add to that?

Dr. Harper

Yes. I guess another issue with the live-attenuated virus is, as you mentioned, it's labeled for persons 5 to 49 who are healthy, and the reason that it's not less than five is because there were some potential safety considerations, and it's not licensed above the age of 50, because of some efficacy effectiveness issues, just needing more data.

So that's all to say that above and beyond the use in potential contacts of immuno-suppressed persons, the issue of using that vaccine off label in these persons who either have high-risk health conditions or are outside of that age range would require significant intervention, certainly within and outside of CDC, because of the current restrictions on use and the current labeling.

So I can say that there have been preliminary discussions; just this topic has come up, and we have been talking about it here in meetings, but that's about all. That's as far as it's gone. There are no specifics that I can really relay right now, mainly because of my own personal ignorance on it. But I can tell you that that is a topic, which has been actively discussed over the last couple of days.

Dr. Strikas

Have we addressed your questions?

Dr. Neal

Yes, and I would just reiterate it is a hot topic of discussion on the ground, in the trenches. There are possible populations that are a fit. Schoolteachers kind of come to mind, in terms of potentially skirting some of the concerns for healthcare workers. I don't want to bog down the line. I have a second question, but I'll get back in line.

Dr. Neal

Another question that I have relates to whether we have any data on using a neurometadase inhibitor, concurrently with a person who is vaccinated with the live-attenuated vaccine?

The question that I have relates to whether we have any data on using a neuraminidase inhibitor, concurrently with a person who is vaccinated with the live-attenuated vaccine?

Dr. Harper

This is Scott Harper. So there are recommendations about that, limited data. The implication for this is that if you have, for instance, a healthcare worker, who is in an institutional setting where there's an outbreak, and they have not been previously vaccinated, the healthcare worker, typically with an inactivated vaccine, you would vaccinate them and then you would give them chemoprophylaxis for two weeks, until they had enough time to build an antibody response from the vaccine.

That cannot be accomplished with the live-attenuated influenza vaccine, because of issues with, mainly, in vitro data of inhibiting the virus' ability to replicate and then cause an antibody response if you do administer antivirals. So the current recommendations state that if somebody gets a live-attenuated influenza vaccine, they cannot get chemoprophylaxis for two weeks afterwards.