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VOLUME 2 — ISSUE 2: TRANSCRIPT

Featured Cases: Infections—Pandemic & Seasonal Influenza

The featured Guest Author is Paul Auwaerter, Associate Professor of Medicine and Clinical Director, Divisions of Infectious Diseases and General Internal Medicine at the Johns Hopkins University School of Medicine. At the conclusion of this audio activity, participants should be able to:

- Identify which patients to suspect for influenza and describe how to diagnose influenza-like illness
- Describe how to treat influenza-like illnesses, as well as documented influenza infection in both ambulatory and hospitalized patients
- Addresses common patient concerns and questions regarding H1N1 influenza vaccination

This discussion, offered as a downloadable audio file and companion transcript, that covers the important issues related to pandemic and seasonal influenza in the format of case-study scenarios for the clinical practice. This program is a follow-up to the November 2009 eInfections Review newsletter, [Pandemic & Seasonal Influenza](#).

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Guest Faculty Disclosures

Paul G. Auwaerter, MD, has disclosed that he has served as a consultant for Adamas Pharmaceuticals, LifeCell, Schering-Plough and Wyeth. He has also disclosed that he is a stock shareholder for Johnson and Johnson, Merck, and Pfizer.

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MR. BOB BUSKER: Welcome to this eInfections Review podcast.

eInfections Review is presented by the Johns Hopkins University School of Medicine. This program is supported by an educational grant from AstraZeneca, Cubist Pharmaceuticals and ViroPharma.

Today's program is a follow-up to the November 2009 eInfections Review Newsletter, Pandemic & Seasonal Influenza.

Our guest is Dr. Paul Auwaerter from Johns Hopkins University.

This activity has been developed for primary care physicians, internists and infectious disease specialists caring for patients with infectious disease conditions. There are no fees or prerequisites for this activity.

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At the conclusion of this audio activity, participants should be able to:

- Identify which patients to suspect for influenza and describe how to diagnose influenza-like illness;
- Describe how to treat influenza-like illness, as well as documented influenza infection in both ambulatory and hospitalized patients; and
- Address common patient concerns and questions regarding H1N1 influenza vaccination.

I'm **BOB BUSKER**, Managing Editor of eInfections Review.

On the line with us we have this Newsletter's author. Dr. Paul Auwaerter is an Associate Professor of Medicine, as well as the Clinical Director, Division of Infectious Disease and General Internal Medicine at the Johns Hopkins University School of Medicine in Baltimore, Maryland.

Dr. Auwaerter has disclosed that he has the following relevant relationships with commercial supporters:

- He works or has worked as a consultant to Adamas Pharmaceuticals, Schering-Plough and Wyeth,
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His presentation today will not include discussions of off-label product uses.

Dr. Auwaerter, welcome to this eInfections Review podcast.

DR. PAUL AUWAERTER: Glad to be here.

MR. BUSKER: Now, to help address some of the concerns about both seasonal influenza and the current H1N1 pandemic, we've asked Dr. Auwaerter to present some scenarios that clinicians are likely to encounter in the exam room. So if you would, Dr. Auwaerter, please present our first case.

DR. AUWAERTER: I'd be happy to.

So, for example, let's say you're asked to see a 21-year-old woman who's been in excellent health, but she's had an abrupt onset of a fever, which she recorded as high as 101.8 degrees Fahrenheit, and also has a dry cough. She's been sick for about 24 hours and feels miserable, very achy, with lots of myalgia. She's been trying to take over-the-counter remedies with cough and cold type nostrums without any improvement. At this point, she called the physician's office to ask for advice and if she should be seen. So this is the kind of very typical clinical scenario that your nurse or your physicians may be faced with.

MR. BUSKER: Well, now, based on this case description, what is the likelihood that this presentation represents influenza illness?

DR. AUWAERTER: Well, you know, influenza, I think people have a certain clinical picture in their mind for a lot of practicing physicians. Typically, it might be the abrupt onset of a high fever, often over 101 degrees; intense muscle aches; and often accompanied by a severe headache and a dry cough. Now, that kind of prototypical influenza presentation, though, is probably a minority presentation. So one of the key questions that any clinician has to ask

themselves is how much influenza do they know is circulating in your community. Is it October or November of 2009, when you know there's lots of circulating pandemic influenza in the community; or is it, for example July, during a nonpandemic influenza season, when there is next to no influenza circulating? So first you have to understand the clinical context.

The second key point, I would say, is that, interestingly, just the presence of fever over 101 degrees and a cough alone is about 70% accurate in whether someone may or may not have influenza, if it's occurring during the time frame that there is circulating influenza in your community. So for a physician, they would need to know the circulating issues, with regards to influenza, before making that clinical judgment. Now, we will in future cases deal a little more with the diagnostics, but that particular point is important.

Now, the third point I would make is that, interestingly, even though that 70% figure has been touted mainly for routine, seasonal influenza, during this pandemic 2009 influenza season many groups have examined intensely anyone presenting, for example, to either a physician's office or an emergency room setting. If someone has influenza-like illnesses, they subject them to very state-of-the-art diagnostics. And the interesting point here is this: That only about 25% of people presenting with fever, cough, and influenza-like symptoms actually has influenza. I think this is for several reasons, and the most likely one is because patients and physicians are so concerned about influenza that anyone with a more pedestrian viral illness, perhaps due to rhinovirus, coronavirus, bare influenza, gets evaluated. So the number of people seeking care, even for routine respiratory-tract infections that would have happened anyway, increases the numbers dramatically. So it actually turns out that that 70% figure is probably less accurate, at least in the context of all the media attention and all the other factors attendant to H1N1 influenza that occurred in this 2009 year.

So the concluding remark would be that you have to sort of still take it in context, but realize that there'll probably be less influenza per phone call when there's intense media scrutiny or public health concerns, because you're also picking up a lot of the routine pedestrian viral infections that may not have to called the office before.

MR. BUSKER: Based on those points, and here we do have a patient presenting with fever over 101 degrees, sudden-onset nonproductive cough, all right, she calls you. Do you tell her to come into the office? Do you tell her to go to the emergency room? How do you respond?

DR. AUWAERTER: Over the telephone, this kind of advice is depends a little bit on clinical judgment. There are a couple of factors that you would need to consider. This is a healthy patient, so typically if there aren't signs of respiratory distress, shortness of breath for example; signs of advanced illness, such as mental confusion--obviously, if there's the existence of cyanosis and these sorts of factors, usually we ask people to stay at home or certainly not come into the office or emergency room where they might actually spread the infection to other people. The reasons for this are that usually these sorts of influenza symptoms are self-limiting; they usually don't demand diagnosis or treatment because they will resolve on their own accord. So you usually can just offer supportive care.

Now, in a healthy person that does have shortness of breath, altered mental status or any other extreme signs of illness, they should be directed to the emergency room.

However, there are people with health conditions, such as severe heart or lung disease, for example, or perhaps they're immune suppressed because of medications or a malignancy and so on, that you may wish to either give empiric antiviral therapy, usually in the form of the oral medication oseltamivir, or direct them to your office or even an emergency room for diagnosis and treatment, especially if there's a concern that there actually might be a true pneumonia. And that would normally demand at least a chest X-ray and perhaps viral diagnostics.

You know, there is an old set of studies that pointed out whether you should refer someone to the emergency room or be concerned for pneumonia as opposed to bronchitis, which isn't exactly similar to influenza. However, I think it's true that if you're evaluating this person in the office, someone who has generally normal vital signs, meaning they're not tachycardic, they're not breathing over 26 times a minute, they're not hypotensive, they're not confused, and if your lung exam is otherwise unremarkable, there's really no reason to get a chest radiograph on that patient. So I think that still holds even for the

routine influenza patient, but if there are abnormal vital signs or any of the serious signs of problems, such as altered mental status, that may demand further attention.

MR. BUSKER: Well, now, let's assume you've got this patient in your office with these symptoms, how do you determine if this represents H1N1 influenza?

DR. AUWAERTER: This is a common question that patients actually ask nowadays more than healthcare providers. You know, at the first and early signs of the H1N1 pandemic there was a real thought you had to diagnose everybody with influenza, or not, for lots of reasons that might be due to quarantine and other factors. But those have really fallen by the wayside. And it's important to note that the rapid diagnostic tests that have been developed for seasonal influenza, which were at most 70% sensitive, perform much more poorly for this pandemic H1N1 strain of influenza. So these have generally been discarded. If you do perform one and it's positive, at least in the fall of 2009, you could probably take that as evidence that the person likely has H1N1 influenza. But I think most clinicians and knowledgeable people about influenza are not recommending that these be performed. The real decision point is whether you're going to administer an antiviral such as oseltamivir or not. So ultimately, you would not choose to perform any diagnostic tests on a healthy person in this case unless you were concerned they were severely ill enough for you to refer them to the hospital, in which case additional testing would be performed.

MR. BUSKER: In your opinion, Dr. Auwaerter, should this patient receive antiviral therapy for influenza?

DR. AUWAERTER: For a healthy patient without any concerning signs of severe illness, the recommendation now is to not use antiviral therapy. The choices for antiviral therapy include the oral drug oseltamivir and also the inhaled powder zanamivir. Either of these, if administered within 48 hours of the onset of influenza symptoms, might diminish the overall duration of illness by about a day. So many people don't feel that it gives a lot of bang for the buck.

So one of the concerns has been, especially when there were many cases of influenza, which if everyone gave the drug to people that may have the infection that it may lead to an easier or faster emergence of

resistance. And the second point is that there might be shortages of oseltamivir that would prevent someone that was truly deserving of the drug from receiving it. So although the drug is certainly FDA approved for someone that you might suspect has influenza, at least in this case, where someone does not have severe illness, the usual recommendation is to not give the drug.

But I would have to say on the other point; there have definitely been cases of previously healthy people, perhaps a third of the population of people that have had severe influenza illness, or even fatality, due to influenza that had no risk factors. And the point is if you're going to try to prevent those problems, how should you apportion or make decisions about giving oseltamivir? Honestly, we don't have an easy answer. We don't know why some healthy people go on and have severe illness despite not having risk factors. We don't know if it's host issues or if it's the virus. So for the moment, those are hard situations to understand, and I also wouldn't fault someone for giving an antiviral drug, even to healthy people, as long as they were doing it in that context. But this is a very small percentage. How many? Perhaps 1 in 10,000 cases. So it gets hard to understand whether you should really administer so much drug to so many people to try to help prevent the truly severe cases. This remains a very difficult clinical conundrum.

MR. BUSKER: There's been a lot of press, both popular press and in the medical literature, about resistance to these antivirals. Can you clarify the current evidence for us?

DR. AUWAERTER: At the moment there is actually less than one percent of viral isolates. In fact, the latest is that 0.3% of viral isolates might have resistance to oseltamivir, the most commonly used antiviral compound. So I don't think it's really a clinical important issue at the moment.

That said, one of the interesting stories from this summer came from an MMWR report centered on two camps — these were camps for children — where the administrators of the camp decided to give wholesale chemoprophylaxis to prevent influenza in these camps. It's very interesting that resistant virus emerged from those camps in the setting of widespread use of oseltamivir. So I think it's a legitimate concern, and something many people have wondered. Should be using combination drug

therapy or other strategies to help prevent the emergence of resistance in this case. But for the moment it is not clinically important for most cases.

MR. BUSKER: Thank you, Dr. Auwaerter. Now, if you would, take us to another typical scenario.

DR. AUWAERTER: Okay. So here's a different scenario.

This is a 43-year-old man that had a renal transplant six years ago, has been in very stable health but is on immune-suppressant drugs. And he's developed, over three days, respiratory difficulties with cough, shortness of breath and fever. His physician recommended that he travel to the hospital for admission. In the emergency department it was noted that he was hypoxemic on room air with an oxygen saturation of 86%. That improved on 4 liters of nasal cannula. A chest radiograph suggested hazy infiltrates that were patchy in distribution in both lower lobes.

MR. BUSKER: What is the role of viral diagnostics in patients like this who present to the emergency department?

DR. AUWAERTER: Unlike in the office setting, I think for patients seen in the emergency department with the potential to be admitted to the hospital, viral diagnostics are highly important. And this is really for two reasons. The first is to understand exactly why the patient is so ill as to require hospitalization. So trying to see if this influenza or another infection is highly important. The second key point is to prevent nosocomial transmission of infection, specifically influenza. So those viral diagnostics are very important, and many hospitals have tried to develop strategies for H1N1 influenza, which might include direct fluorescent antigen tests, shell-vial cultures or even some fancier PCR-based technologies, to try to get to rapid and clear diagnosis of whether someone has influenza or not. And until that point, often patients with influenza-like illnesses and respiratory problems are put on isolation. So it's not only for therapeutic decisions but also for infection-control measures.

MR. BUSKER: Now, without a definitive influenza diagnosis, should this patient receive antiviral therapy empirically?

DR. AUWAERTER: If there's not an alternative diagnosis for someone with a respiratory illness that's severe enough to warrant hospitalization, all those patients, in the context of a known circulating influenza strain, should receive influenza treatment. And this should be regardless of the 48-hour rule.

So here are some important points. The first—and the Center for Disease Control has emphasized this—is that anyone who's an influenza suspect with severe illness would benefit from empiric antiviral therapy for influenza. This should be started as soon as anybody would start antibiotics, for example, for community-acquired pneumonia. So it's that same kind of idea that earlier treatment in severe illness does offer benefit.

Another point to make is that patients, even if they are beyond the first 48-hour illnesses, in the setting of severe illness, there is growing information that antiviral therapies improve. And it's important to note that although oseltamivir has gotten all the press as an oral compound, there are two other drugs that are available for clinicians. Zanamivir is an inhaled powder and often is not used in the hospital setting because for people who are very ill this powder might make their respiratory status worsen. But it is another alternative. The third is an emergency authorization for a parenteral form of a neuraminidase inhibitor similar to oseltamivir called peramivir. Peramivir is now available for patients who are intolerant of oral therapy, oseltamivir, or who may be considered a treatment failure with oseltamivir with severe influenza.

So there are a number of options there, and the key points are that for influenza-like illness, start empiric antiviral therapy early and regardless of the amount of time that they've been ill.

MR. BUSKER: Looking at this patient specifically, yes, there's a concern about influenza, but should this patient be treated for Staph aureus?

DR. AUWAERTER: One of the interesting aspects that we've already learned from this influenza season is that a quarter or more of patients with severe influenza may have bacterial superinfection. So, certainly, we know influenza can cause a severe viral illness, and that alone can cause a severe pneumonia and respiratory problem. But it's also been known for years, even with earlier influenza pandemics, that

certain bacterial superinfections occur. *Staph aureus* is the most famous, but interestingly, with the application to autopsy cases of so-called 16S ribosomal sequencing technology, it looks like *Streptococcus pneumoniae* or the pneumococcus is really one of the most common superinfections that complicate severe influenza.

My recommendation would be if you have someone with a severe respiratory illness and it would otherwise be called community-acquired pneumonia, of course consider influenza, but I would also consider treatment for community-acquired pneumonia with the knowledge that the pneumococcus is one of the main offending bacterial superinfections, especially if someone's been ill for more than several days.

Now, you might ask, well, *Staph aureus* is one of the more lethal infections if it actually gets into the lung, and that's true. And historically we've been more concerned when we've seen evidence of necrotizing pneumonitis, often with cavitation and so on, when people have had so-called community-acquired *Staph aureus* MRSA infection of the foot or lung. And this has happened in both pediatric populations and adults.

So, certainly, if someone is more ill or heading to the intensive care unit in this setting, I would also recommend *Staph aureus* treatment. And that could be in the form of vancomycin therapy. Some advocate for linezolid, based on enhanced pharmacokinetics. But certainly either of those would well cover community-acquired MRSA in the critically ill patient.

MR. BUSKER: And we'll return in a moment with Dr. Paul Auwaerter from Johns Hopkins.

DR. JOHN BARTLETT: Hello. I'm John Bartlett from the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. I'm one of the Program Directors for eInfections Review. eInfections Review is a combination newsletter and podcast program delivered via e-mail to subscribers. Newsletters are published every other month. Each issue reviews current literature in areas of importance to infectious diseases specialists, to primary care physicians and clinicians caring for all kinds of infectious diseases. These podcasts, which are available as downloadable transcripts, provide case-based scenarios to help bring new information into practice in the exam room and at the bedside.

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MR. BUSKER: Welcome back to our December 2009 eInfections Review podcast. Our topic is pandemic and seasonal influenza. I'm Bob Busker, Managing Editor of eInfections Review, and our guest is Dr. Paul Auwaerter, Associate Professor of Medicine and Clinical Director, Divisions of Infectious Diseases and General Internal Medicine, at the Johns Hopkins University School of Medicine in Baltimore.

Now, we've been bringing the information presented in our November newsletter into clinical practice via case-study scenarios. Dr. Auwaerter, we've just discussed two interesting cases. Would you present us with another one, please?

DR. AUWAERTER: Well, I think one of the more frequent questions that I've been asked, really, is regarding influenza immunization.

So the case I would just posit is a simple one of a healthy 23-year-old, otherwise in good health. His family and friends have given him conflicting advice about whether he should get the H1N1 vaccination, and he doesn't know what to do; he's asking his physician for recommendations because he's heard a lot of issues that perhaps this vaccine has not been well tested; that it was rushed to production and may have adverse consequences.

MR. BUSKER: I think we can assume that this is a fairly common question that many physicians are hearing. So I guess the first thing we want to address is does this patient fall into an identified risk category for pandemic H1N1?

DR. AUWAERTER: This patient technically does fall into it on the basis of age, being in his early twenties. And the initial emphasis for influenza pandemic immunization has really targeted several populations: pregnant women, caretakers of infants under six months of age who can't otherwise get the influenza vaccine, also children, young adults, and then adults over their mid-twenties who may have comorbidities,

such as heart disease, lung disease, immune suppression, and so forth.

Now, those have been the initial target groups, in part because we've not seen a lot of influenza in older populations. And the thought is that H1N1 actually circulated prior to 1957, so there may be some cross-immunity with this new pandemic strain amongst people who lived in this earlier era. So that's why that has been targeted for that reason. And so even a healthy person who says they've never had influenza, the recommendations are to go ahead and get the vaccine.

MR. BUSKER: Another common question I think clinicians may hear from patients like this would be about thimerosal or other vaccine components. Now, the concern would be, is there something in the vaccine that can place them at risk for an untoward reaction. What kind of advice would you give in response to those kinds of questions?

DR. AUWAERTER: Many people are leery of vaccines, and there are probably two reasons for that. The first is so-called adjuvants. It's important to note that none of the influenza vaccine supply in the United States has any immune adjuvant in it. Some European manufacturers directed for non-U.S. markets have used adjuvants such as squalene. But there are no adjuvants in the U.S. supply. So there is clearly a fair amount of misunderstood information that people are using as a reason or excuse for not undergoing influenza immunization. Thimerosal, which is an antimicrobial meant to try to help prevent bacterial growth in multi-dose vaccine vials, also especially for adult population, seems to have no impact. The amount of mercury—this is a mercury-based compound—is miniscule. And interestingly, even though it has pretty much vanished from the pediatric vaccine supply, from all vaccines, all comers, there's been no diminishment in rates of autism, which was really why thimerosal was thought to get such a bad press initially, along with other neurological conditions.

I think, that all being said, people who have looked very hard at thimerosal or even immune adjuvants have been unable to come up with any health concerns. So the way I always phrase it is that the risk of severe influenza far outweighs any theoretical risk of either an adjuvant or something like thimerosal that could be present in the vaccine.

MR. BUSKER: In 1976 the swine flu vaccination was linked to *Guillain-Barré* syndrome. What are the risks, neurologic and otherwise, associated with the current vaccine?

DR. AUWAERTER: This is a still somewhat controversial point, but I think one many patients are leery of: that somehow a healthy person gets a vaccine and then develops a neurological problem thereafter. Most famously, this was highlighted during this so-called 1976 swine influenza vaccination program. So the way how I phrase it to people is as follows. The risk of *Guillain-Barré*, which is a paralytic illness, is about 1 in 100,000 for anyone in the United States. There are about 3,000 cases a year. So 1 in 100,000. The best we can tell from vaccine adverse event reporting systems is that the risk of influenza precipitating *Guillain-Barré* syndrome is about one in 1 million. Now, the risk of severe influenza afflicting a healthy person and causing death is somewhere between 1 in 10,000 to 1 in 100,000, perhaps lower.

So that said, overall the theoretical risks of *Guillain-Barré*, which is generally an illness that you can get over with good support, is really far less common than would be the consequences of severe illness from influenza, or even the routine *Guillain-Barré* that might occur even if you didn't have a vaccine. The analogy I sometimes give patients is that if we painted everyone's toenails in the country, the next day there would be heart attacks, there would be *Guillain-Barré* syndrome, and there would be all sorts of things. But we don't think it's because we painted toenails. So it's the same thing when you have a mass program like influenza where you're immunizing so many people. It's sometimes confusing to understand what baseline rates are occurring. So that said, there's at least a 10- or a 100-fold less likely consequence of influenza causing *Guillain-Barré* syndrome.

So that's the sort of context. And, again, when you have an unknown, people are often much more fearful. You know, we always say people are more afraid to fly than drive; it's because they don't usually fly but they always drive. It's the same thing here with the vaccine. You don't customarily get immunized, and especially a healthy person; this may be new to them. So there's more concern and fear of the unknown that might occur as a consequence.

MR. BUSKER: Let me ask you about another common office scenario. Let's say this patient was offered a live attenuated vaccine but has heard that this is more dangerous than the inactivated IM influenza vaccine. Again, your advice in this situation?

DR. AUWAERTER: The live attenuated influenza vaccine has been around for a few years but clearly is newer than the inactivated influenza vaccine, the so-called flu shot. As far as any studies that have been performed, the amount of adverse effects are about the same, except there's a little more respiratory consequence, meaning sniffles, so on, that might last for a day or two after influenza. But none of these are significantly important or severe. So I think many people feel, because it's new, that there's less knowledge of it, there's less safety, so they're more inclined to wait for the shot. However, I would tell you that the live virus tends to actually engender better antibody protection, especially in younger patients such as children. So, for example, my own children have gotten the FluMist, and I feel it's exactly as safe and don't have any genuine health concerns with them receiving that vaccine as opposed to the standard inactivated flu shot.

MR. BUSKER: Well, you mentioned younger patients. There's been some press about not giving the live attenuated vaccine to the elderly. Your comments?

DR. AUWAERTER: The live attenuated influenza virus is only FDA approved up to the age of 49. And this was done in part, I believe, because of initial vaccine trials. So generally, it's not viewed that there's any safety or health concern, but the vaccine has not been well studied in older populations. The usual advice is to not receive FluMist if you're 50 or older. That said, other reasons might be that people that have been heavily and previously exposed to influenza may not mount as strong an antibody response to the nasal vaccine spray as opposed to the injection.

Future studies might show that this is indeed a good product. And it's of some interest, I know some institutions early in the pandemic H1N1 influenza, when there was only FluMist available--that's the brand name of the live attenuated influenza vaccine--that did give the vaccine to people over 49 because the thought was something is better than nothing in terms of protection, especially for healthcare workers. So nothing's set in stone, but I would say, in general, my

advice would be for patients over 50 to only get the inactivated influenza vaccine.

MR. BUSKER: Dr. Paul Auwaerter from the Johns Hopkins University School of Medicine, thank you for participating in this eInfections Review podcast.

DR. AUWAERTER: Bob, I'm very happy to have helped out today, and thanks so much.

MR. BUSKER: This podcast is presented in conjunction with the eInfections Review Newsletter, a peer-reviewed, CME-accredited literature review e-mailed bi-monthly to clinicians treating patients with infectious diseases. These podcasts are presented in alternate months as follow-up to the e-newsletter content.

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