Bacterial Co-infections and the 2009 H1N1 Influenza Pandemic

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Coordinator: Welcome and thank you for holding. At this time your lines are on listen-only until today's question and answer session. At that time to ask a question you may press star 1 on your phone. Today's call is being recorded, if you have any objections you may disconnect.

I would now like to turn the call over to Alycia Downs. Ma'am, you may begin.

Alycia Downs: Good morning and welcome to today's COCA conference call, Bacterial Coinfections and the 2009 H1N1 Influenza Pandemic. We are very excited to have CDC Subject Matter Experts present on this call. With us today we have Dr. Dianna Blau and Dr. Matthew Moore.

We will not be using a PowerPoint presentation and there will be no Continuing Education credits or contact hours available for this call.

I will now turn the call over to Dr. Dianna Blau.

Dianna Blau: Thank you Alycia and thanks to all the callers for allowing us to speak with you today. As Alycia mentioned we're going to discuss bacterial coinfections in the context of the current influenza pandemic. These findings come from

evaluation of autopsy specimens from fatal cases of 2009 pandemic influenza A H1N1 infections.

The Infectious Diseases Pathology Branch, or IDPB, at CDC routinely receives biopsy and autopsy specimens for evaluation from a variety of infectious diseases.

These specimens are submitted for confirmation of an etiologic agent or for identification of an unknown agent in which an infectious disease process is highly suspected.

Prior to April of this year on average in the past three influenza seasons, that is from October 2005 to April 2009, IDPB would receive about 48 suspect or confirmed influenza cases a season.

Since influenza-associated pediatric deaths became nationally notifiable in 2004 the majority of these cases received in the past three seasons were pediatric cases but the age range was 28 days to 81 years.

During the early part of this current pandemic updated guidance for the submission of tissue specimens for the pathologic evaluation of influenza virus infections were posted on the CDC H1N1 Website.

These specimens were requested and sent in for evaluation in order to gain a better understanding of the pathogenesis and how this virus behaves. Autopsy or lung biopsy specimens were submitted by local hospitals, medical examiners and coroners and local and state health departments.

These came from patients previously confirmed to have pandemic H1N1 infection or from patients in which testing was negative or not performed but did have autopsy pathologic findings suggesting respiratory viral infections.

All of the cases that will be described from here were confirmed to have 2009 pandemic influenza A H1N1 virus infection by RPTCR analysis of respiratory specimens.

These were either a nasal pharyngeal swab, bronchial alveolar lavage fluid or lung tissue. From April 29 to August 20 of this year IDPB received specimens from over 200 cases for evaluation of influenza virus infection.

Of these cases 77 that were from confirmed fatal and resided in the US and that had adequate tissue specimens were fully evaluated. This extensive evaluation included (asbase) to detect bacterial coinfection.

Before we discuss the bacterial coinfections in these cases I would like to provide a brief summary of the demographic of these 77 cases. There was no difference with respect to gender with males constituting 53% of the patients.

The median age was 39 years with the youngest patient being two months and the oldest 84 years. Eight-one percent of these patients though fell within the 20-59 year age group. The youngest patients in the series had a date of death in the first two months of May and June while the oldest patients had a date of death in the latter June and July.

These patients came from all across the United States as well as Puerto Rico. The majority were submitted from the Northeast. Of these 77 patients where previous medical history was available 90% had at least one underlying medical condition with obesity defined as BMI equal or greater to 30 being

noted in 49% of the patients, morbid obesity with a BMI equal or greater that 40 was noted in 19%.

Hypertension or cardiovascular disease was documented in 30% of the patients followed by asthma in 24%. Ten percent of the patients were recorded to have diabetes and 6% were HIV positive. Three patients in this series were pregnant. All were in their last trimester.

The duration of illness in these 77 patients was eight days with the range of 1 to 44 days. The clinical symptoms were known for 72% of these patients. Fever, cough and shortness of breath were the most common at 80%, 68% and 61% respectively.

Vomiting and diarrhea were reported in 23% and 13% of these patients respectively. Hospitalization information was known for 67% of these patients with 69% of the patients being hospitalized. Fifteen percent died in the ER and the remaining either died at home or unknown.

Eighty-one percent of these patients where the information was available required assisted ventilation. Sixty-three percent received or were prescribed antivirals while 89% received antibiotics.

Thirty-nine percent of the patients had an ante mortem diagnosis of pneumonia. Forty-seven percent of these patients were diagnosed with H1N1 infection by post mortem evaluation.

In other words if an autopsy had not been performed in almost half of these patients there would not have been a diagnosis of pandemic influenza A H1N1 virus infection. This serves as a reminder that medical examiners and coroners can have an important role in public health and clinical medicine.

The respiratory tissues of these 77 cases were evaluated for the presence of bacterial organisms by several methods. Histopathologic examination of HNE, (hemotloxin) (unintelligible) stained sections, special histochemical stains including tissue gram stain and Warthin Starry silver stain and immunohistochemical staining with antibody specific against the following four bacteria, streptococcus pneumoniae, Group A streptococcus, staphylococcus aureus and haemophilus influenzae.

These are common causes of bacterial pneumonia and were major causes of morbidity and mortality in the previous influenza pandemics both before and after the advent and use of antibiotics.

DNA from these patients was also extracted from formalin fixed paraffin embedded sections of lung tissue and used as a template for wide-range PCR assay targeting (panubacterial) 16SR DNA genes.

In cases where there was histochemical positive staining for a particular bacterial organism these results were also confirmed by (CC)-specific PCR assays using the DNA extracted from formalin fixed paraffin embedded tissue sections.

Of these 77 patients 22 or 29% of them had evidence of at least one bacterial species. Of these 22 case patients 10 had evidence of streptococcus pneumoniae, seven with staphylococcus aureus, six with Group A streptococcus or streptococcus pyogenes, two with streptococcus mitis and one with haemophilus influenzae. Four of these cases had evidence of more than one bacterial species.

The median age of these 22 case patients that had bacterial coinfections was slightly lower than the overall case theories at 31 years. The range was two months to 56 years. Half of them were male.

The duration of illness of these 22 was also statistically shorter when compared to the cases in the series that did not have a bacterial coinfection. Seventy-eight percent of these cases sought medical care although only 44% of these case patients were hospitalized before death. And all required mechanical ventilation.

Seventy-eight percent of these patients where information was available received antibiotic treatments. Seventy-six percent of these case patients with bacterial coinfection had underlying medical conditions known to increase the risk of influenza-associated complications or were indications for vaccination with 23 pneumococcal polysaccharide vaccines.

Since the most common bacterial organism found in these case patients with pneumococcus and 76% had indication for vaccinations pneumococcal vaccine this raises questions about the use of vaccine in this current pandemic.

I will now turn it over to Dr. Matt Moore who will discuss this issue further. Thank you.

Matthew Moore: Thanks, Dianna . I just wanted to make a few brief comments to try to put these really important findings into context and then we'll open it up for questions.

During the early part of this pandemic the evidence of bacterial coinfections was pretty much absent among 30 hospitalized cases of confirmed H1N1 in

California and among ten confirmed cases among patients admitted to intensive care units in Michigan.

These reports may have led to the perception that bacterial coinfections play only a limited or maybe even no role in this current pandemic. But there are some important things to keep in mind about diagnostic tests that are used in routine clinical practice.

Most important is that we think the yield of routine clinical tests for the detection of bacteria among patients with pneumonia is quite low; less than 10% of patients who are hospitalized with pneumonia have positive blood cultures.

Testing of lung tissue on the other hand especially using the PCR and immunohistochemistry methods that Dianna just discussed is likely to be more sensitive than testing of routinely collected clinical specimens ante mortem.

During previous influenza pandemics bacterial pneumonia caused by streptococcus pneumoniae, H influenza, staff aureus and Group A strep contributed to influenza associated morbidity and possibly even the majority of influenza associated deaths according to some reports published just within the last year.

The findings that Dianna just described indicate that bacterial pneumonia may be contributing to pandemic influenza associated mortality in a manner similar to that of previous pandemics. However there are some important limitations that we need to acknowledge.

First of all we really can't use these results to estimate the prevalence of bacterial pneumonia among pandemic H1N1 deaths. For example Dianna told us that 29% of the cases that she described had evidence of bacterial infections. That does not mean that 29% of all H1N1 deaths are necessarily associated with bacterial complications.

That may be because the sample of cases that had tissues submitted to CDC was not chosen systematically and might be representative of all pandemic H1N1 deaths or even all pandemic H1N1 deaths that are associated with bacterial pneumonia; we just don't know.

Second we also don’t know all of the factors that might have led to submission of some specimens and not others. It may be that certain centers or clinicians have particular questions about individual patients and again therefore these results may not be representative of all pandemic H1N1 deaths.

Thirdly, not all potential bacterial pathogens were evaluated just those that have been associated with previous pandemics. For example some pathogens like legionella were not evaluated and that particular pathogen was not even known during any of the three previous pandemics so we don't know whether there's any association between legionella and pandemic influenza infection.

However the most common bacterial organism seen among the case patients described by Dianna was streptococcus pneumoniae or pneumoccocus. And this is really important because unlike all of the three influenza pandemics that occurred in the 20th Century we now have two pneumococcal vaccines that may help to reduce morbidity and mortality related to influenza.

Sixteen of the case patients that Dianna described had ACIP indications for pneumococcal vaccination. Almost all of those were individuals between the ages of 2 and 64 years.

Although we don't know the vaccination status of those individual patients we do know that only about 16% of people between the ages of 18 and 64 who actually have indications for pneumococcal polysaccharide vaccine have actually received the vaccine.

Let me just say that again, only 16% of people between 18 and 64 years of age who are supposed to receive pneumococcal polysaccharide vaccine have actually received it.

Persons at increased risk for invasive pneumococcal disease include young children, the elderly and persons of any age with certain comorbidities including chronic lung or cardiovascular disease and immunosuppressive conditions.

All children under the age of five years of age should receive pneumococcal conjugate vaccine according to current recommendations. In addition the 23 valent polysaccharide vaccine is routinely recommended for all persons 2-64 who have those high risk conditions and everyone 65 years of age and older.

If you add up all of the people in the United States who should have received pneumococcal polysaccharide vaccine but have not yet received it that total is about 70 million individuals. So we have a terrific opportunity to prevent additional pneumococcal disease and potentially pneumococcal disease associated with the current pandemic.

So during this pandemic we're recommending that providers should encourage high risk persons especially those aged 2-64 years of age to receive pneumococcal polysaccharide vaccine because of the low coverage in that group and because higher rates of influenza illness and death are occurring in that same age group.

So these findings of bacterial coinfections among fatal cases of H1N1 kind of serve to remind us as healthcare providers that management of patients with community-acquired pneumonia and influenza should include the use of empiric antibacterial therapy and antiviral medications.

For public health departments and clinicians we really want to emphasize the use of seasonal and pandemic influenza vaccines when the pandemic vaccine becomes available as well as vaccines to prevent pneumococcal disease.

So with that this concludes the formal part of our presentation and we would be happy to entertain any questions we might have.

Coordinator: Thank you. We will now begin the question and answer session. If you would like to ask a question please press star 1. Please un mute your phone and record your name clearly when prompted. Your name is required to introduce your question. To withdraw your question press star 2. One moment please for the first question.

Again as a reminder please press star 1 on your phone and record your name if you have a question. One moment please. All right our first question, sir, you now have an open line.

Question: Thank you very much. Thank you for this very important update. Could you please repeat for me what percentage of the patients received the

pneumococcal vaccine in the 77 cohort of patients and then specifically those that had secondary bacterial infection. I missed that.

And your point out recommending appropriate use of the pneumococcal vaccine is very important so could you repeat that please?

Matthew Moore: Sure Dr. Powell. This is Matt Moore. So we don't know the vaccination status of any of these cases. We got relatively limited clinical information on them and we have no information about whether any of them were vaccinated.

Question cont'd: Oh okay.

Matthew Moore: The 16% number that I was quoting is sort of national coverage estimates from various surveys that have been done to assess pneumococcal vaccine coverage among people who have indications to receive it.

Question cont'd: Right but I thought you said that - and maybe I misheard this but that of the patients in the cohort there was 16 that had ACIP indications for the vaccine and obviously you don't know how many of those were vaccinated. But was I hearing you correctly because I would have thought it would have been a higher number.

Dianna Blau: Hi, it was 16 of the 22 that had bacterial coinfection.

Question cont'd: Oh okay, very good. So that - okay.

Matthew Moore: Yes.

Question cont'd: I appreciate that clarification.

Matthew Moore: And, you know, I guess this would be a good time to interject now that you've asked this question Dr. (Powell), that we are preparing a report for the morbidity and mortality weekly report.

We don't have an official publication date on that yet but it's with the MMWR editor right now and we are getting it out as quickly as we possibly can so all of the information that we've discussed today will come out in that written report.

Question cont'd: Thanks for the clarification.

Matthew Moore: Sure.

Coordinator: All right, our next question, sir you now have an open line.

Question: Yes, a question, on the seven staff aureus isolates were you able to probe them for the (mec) gene to see if they were MRSA strains?

Dianna Blau: Yes, three of those were - actually four - five of those was MRSA, two of them had coinfections and then two of them was methicillin susceptible or negative of the (mec) gene.

Question cont'd: Yes, I was going to say presence or absence of the (mec) gene.

Dianna Blau: Correct.

Question cont'd: Because you don't have the isolate to test.

Dianna Blau: Right.

Matthew Moore: That's correct.

Dianna Blau: Correct.

Question cont'd: Thank you.

Coordinator: All right our next question. Sir, you now have an open line.

Question: I'm working in the emergency department and looking at a large number of folks coming in and trying to identify those who have lung disease as opposed to the typical novel H1N1 upper tract disease. Obviously we can't get chest x-rays nor should we on all of them.

Are there any clinical clues to identify those who are at higher risk for complications such as hypoxemia and pulse oximetry or any other things that we can do in a rapid way given the fact that we're going to see large volumes of patients?

Matthew Moore: To distinguish between those who have influenza alone versus those who have influenza plus a bacterial complication?

Question cont'd: Yes.

Matthew Moore: I'm not aware of any Dr. (Prod) and I'm going to defer to Dr. Tim Uyeki who is an expert in the Influenza Division to join us on this question. But, you know, ever study I've ever read on etiologies of community acquired pneumonia has said that you really cannot reliably distinguish between people who have viruses and bacteria on the basis of for example a chest x-ray alone or any other factors that are present at the initial visit.

Tim, do you have any thoughts on this?

Tim Uyeki: Yes, thanks, Matt. This is Tim Uyeki from the Influenza Division at CDC. That's a great question but unfortunately as Matt is alluding to there really aren't good data to guide us on that. Clearly you're targeting on the right patient population which is those who have maybe underlying comorbidities, chronic lung disease and so forth that suggests that they may be at much higher risk for complications of pandemic H1N1 virus infection.

But whether or not you could distinguish between pandemic H1N1 virus infection versus coinfection with an invasive bacterial pathogen versus some other etiology and there are other co-circulating respiratory viruses to worry about as well.

So I think it would be very, very difficult to do that - but - based upon any data that we're aware of. But I think clearly you're focusing on those that may be at high risk; people with chronic lung disease and other comorbidities.

Certainly the pregnant woman population is a population that has been disproportionately affected with severe disease and fatal outcomes. And there are others.

Matthew Moore: Thank you.

Coordinator: Okay thank you...

Tim Uyeki: And I guess my one comment would be that in - as you are probably aware our CDC guidance in terms of antiviral treatment is really focused on, number one, early antiviral treatment of any hospitalized patient.

And in your patients who are coming in for presentation in the emergency room our recommendations are certainly out patient early antiviral treatment with a neuraminidase inhibitor, Oseltamivir or Zanamivir in patients who have - who are in high risk groups for complications of influenza.

And that would include persons who have underlying comorbidities particularly chronic lung disease. It would also include a number of other chronic comorbid conditions as well as pregnant women and very young children especially those less than two years of age.

So I think what you're getting at is decisions - clinical decisions on whether, one, to admit a patient or, number two, whether to initiate both antiviral and/or - and antibiotic therapy. And I think that those are clinical decisions that you need to rely on clinical judgment.

But from the influenza perspective certainly earlier antiviral treatment even in patients who are not going to be - who are stable enough and don't need hospital admission would benefit from earlier treatment than later treatment. Thanks.

Coordinator: All right our next question comes from with the Mid Atlantic Renal Coalition. Ma'am, you now have an open line.

Question: Thank you. My question has been answered by previous questions. Hello?

Coordinator: All right, our next question comes from - I'm sorry sir, I can't pronounce your name but you now have an open line.

Matthew Moore: Maybe he doesn't know that he has an open line.

Coordinator: I'm going to go ahead and try and announce his name in...

Question: (Unintelligible). Hi, good morning, my question also has been answered already.

Coordinator: Did we have another question from...

Matthew Moore: It sounds like his question was answered, is there anyone else in the...

Coordinator: All right I guess our next question, your now have an open line.

Question: Hi, thank you for the call. I have a question on comorbidities. You described - you gave us a list of comorbidities and the frequency associated with them. But if you can clarify what were the comorbidities amongst pediatric cases for example, was obesity one of them?

And for adults was there generally more than one such as obesity, hypertension and diabetes? In other words just to get a better sense of what the combinations of comorbidities were? Thanks.

Matthew Moore: So I'm going have Dianna answer that question. I do want to just cautious you again that this is a relatively small series and we're trying to be very careful not to generalize the findings from this series to all patients. But go ahead, Dianna.

Dianna Blau: Yes and the answer I'm going to give you is just about the cases that had the bacterial coinfections. So of those the pediatric cases the majority did not have underlying medical conditions but the ones that did were obesity and there was a Downs Syndrome patient.

With the adults with respect to your question about if there was more than one comorbidity, yes, in the majority of those patients there was at least one comorbidity but in most times it was more than one or more than two.

Question cont'd: Okay thank you.

Tim Uyeki: This is Tim Uyeki, just a brief comment. So as Dianna and Matt were getting at to be cautious that these are just fatal cases in particular these are cases with bacterial invasive coinfection. But clearly the fatal outcomes are just one part of it and those with bacterial infection are just one part of it. Clearly there are many people that have been hospitalized with complications that fortunately have not had fatal outcomes.

And we know that there are sort of a lot of different comorbidities that have been associated with a higher risk for severe complications of influenza that would require hospital admission. And so I think the whole picture that has to be taken into account is not just those for fatal outcomes but those that underlying comorbidities that do increase the risk of hospitalization for complications.

And a lot of those are very similar to what has been described for many years for complications of seasonal influenza. But in addition what we're seeing - what my colleagues have mentioned is that obesity and morbid obesity and then in terms of what I mentioned, pregnant women, these are other high risk groups that had not been - they're recognized at least pregnant women recognized for complications of seasonal influenza but we're seeing a particular disproportionate impact on this pandemic. Thanks.

Coordinator: We do have a few more questions on the line. We have a question. Ma'am, you now have an open line.

Question: Thank you. Not so much a question as a plea. We're with the state health department and we'd love to get this information out to stakeholders but the quality of the information is right now dependent on our rapidly scrawled handwritten notes so the sooner you guys can get this in writing so that we can really evaluate it thoughtfully that would be great. So thank you very much.

Matthew Moore: Thanks. What state are you from?

Question cont'd: West Virginia.

Matthew Moore: Okay. Thanks.

Coordinator: All right our next question comes from...Ma'am, you have an open line. All right I guess our next question, sir you now have an open line.

Question: Can you hear me?

Matthew Moore: Yes we can, go ahead.

Question cont'd: Okay. In listening to your presentation I get the sense of - about the sort of advocating or maybe that's a little too strong but the idea of possibly using antivirals along with empiric antibacterials and you talked about the fact that you only tested for a limited number of bacteria.

So what I'm wondering is in terms of the antibacterial coverage how broad, you know, how broad would you kind of think about using antibacterial coverage? I mean, for example would you think about covering for something like pseudomonas? Would you think about covering for, you know, MRSA?

So, you know, with these patients that, you know, H1N1 patients who are fairly sick and hospitalized.

Matthew Moore: Yes, that's a great. Thanks for bringing that up. I think that for adults the answer is pretty straightforward because we have excellent guidelines from the IDSA and the American Thoracic Society that kind of help us through those sorts of issues.

And at this point from what we've observed and described to you we're not really seeing pathogens that are, you know, terribly unusual; they're among the most common causes of bacterial community acquired pneumonia and therefore for adults the IDSA/ATS guidelines would do a nice job of covering that.

And those guidelines do specifically address when you should think about covering for MRSA and when perhaps you don't need to as well as for other things like pseudomonas and legionnaires disease and so on.

For children it's a little bit more difficult because we don't have kind of a single guidelines to point to. However I guess I would just say that my understanding of routine clinical practice for treatment of children with pneumonia is that the pathogens that we've described here would be covered under what is sort of the current standard of care even though we don't have a guidelines upon which to base that.

Question cont'd: Okay thank you.

Matthew Moore: Sure.

Coordinator: We have a question. Sir, you have an open line.

Question: Yes, a question on the Group A strep is do you have the age range for those patients?

Dianna Blau: Yes, the age range was 9 up to 56 years old.

Question cont'd: Nine to...

Matthew Moore: Nine years.

Dianna Blau: Nine years old to 56.

Question cont'd: Okay thank you.

Coordinator: And we have a question. Ma'am, you have an open line.

Question: Yes, good morning. Thank you. I'm curious have you compared your data to that of other nations? And if so any differences?

Matthew Moore: Yes, we're not aware of anyone who...

Question cont'd: Okay.

Matthew Moore: ...who has these kinds of data from submitted autopsy specimens in other countries.

Question cont'd: Okay thank you.

Coordinator: Okay and as a reminder I will need your name recorded for you to ask a question so that I may announce you. And you may press star 1 on your phone

and record your name if you have a question. And we are showing no further questions at this time.

Alycia Downs: I would like to thank our presenters for providing our listeners with this very timely information. I'd also like to thank our participants for joining us today. If you have any additional questions or comments please send an email to coca@cdc.gov - C-O-C-A @cdc.gov.

The recording of this call and the transcript will be posted to the COCA Website, emergency.cdc.gov/coca - again that is emergency.cdc.gov/coca as soon as we get them.

We are having a COCA conference call tomorrow entitled National Obstetrics Grand Rounds: Pandemic H1N1 2009 Influenza and Pregnancy. This call will have two sessions, one starting at 8:00 Eastern and one starting at 11:00 am Eastern.

For more information please visit emergency.cdc.gov/coca/callinfo. We will be having another COCA call on Wednesday on H1N1 vaccine safety at 2:00 pm. We'll be sending out a notice through COCA so if you're not already signed up to receive updates please send an email to coca@cdc.gov again that email address is coca@cdc.gov and we'll put you on our distribution list.

I want to thank everyone again for participating and have a wonderful day.

Coordinator: Thank you and that concludes today's conference. Thank you for participating you may disconnect at this time.

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