Antibiotic Awareness Week 2012
Public Health Agency of Canada, November 16, 2012

Stacie Ross - My name is Stacie Ross and I am with NCCID, a partner in AntibioticAwareness.ca. Thank you for joining us and welcome to this webinar, which is presented as a part of Antibiotic Awareness Week. During this session we will hear from Canadian experts in the field of antimicrobial resistance. We will be recording the webinars and will provide the transcripts in French and English on the Antibioticawareness.ca site. We suggest that you listen to the presentations on your computer speakers, however if you need to, please feel free to listen by telephone using the toll free number and code listed on the right hand side of the screen. The upcoming presentations will be followed by a Q&A.

I would now like to introduce Marc-André Gaudreau. He is currently the manager of Strategic Issues, Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada. He will provide an overview of the agency's role with respect to antimicrobial resistance. Welcome Marc-André, please begin.

Marc-André Gaudreau - Thank you Stacy and good morning everyone. On behalf of my colleagues here at the Public Health Agency of Canada, I would like to thank you for taking the time to join us today for this webinar. I would like to present really briefly an overview of the Agency in terms of the national role that we play and also share with you some of the key activities we undertake to address antimicrobial resistance.

If you turn on slide 2, you'll find a mission and a vision for the agency. Our mission is to promote and protect the health of Canadians through leadership, partnership, innovation and action in public health and our vision: Healthy Canadians and communities in a healthier world.

If you turn to slide 3, you'll find listed the various roles the agency is responsible for undertaking. The agency is lead by the Chief Public Health Officer, Dr. David Butler-Jones, who reports to and advises the minister of health on public health matters. PHAC, or the Public Health Agency of Canada, works with health professionals, provincial and territorial governments as well as professional and voluntary organizations to affect real change where it matters most. By building these strong relationships at all levels, we are able to integrate and implement effective public health responses. We work to prevent and reduce the spread of infection, for instance. PHAC networks and surveillance systems help to ensure Canada's health professionals have reliable access to current information about chronic and infectious diseases, trends and treatments, and physical and mental health and wealth. We also help Canadians identify and overcome the factors leading to obesity, poor mental health and chronic diseases, which is cancer, heart disease, diabetes and respiratory

diseases, which are some of the common preventable and costly health problems facing Canadians as well as addressing infectious diseases.

If you turn to slide 4, that slide illustrates the organizational structure for the entire agency. If you look at the lower left-hand corner, you will see the Infectious Disease Prevention Control Branch, led by Dr. Rainer Engelhardt, our Assistant Deputy Minister. This is a branch where all the presenters today come from. You will be hearing later on from Irene Martin from the National Microbiology Lab in Winnipeg, which is led by Dr. Frank Plumber. You will also be hearing from Rita Finley from the Centre for Food-borne, Environmental and Zoonotic Infectious Diseases led by Dr. Mark Raizenne, and you will also be hearing from Dr. Tom Wong who works in the same centre that I am in, the Centre for Communicable Diseases and Infection Control under the direction of Dr. Howard Njoo.

If you turn to slide 5, you will get an overview of the Centre for Communicable Diseases and Infection Control, which is divided into four key areas: Surveillance and Epidemiology, Professional Guidelines & Public Health Practice, Programs & Partnerships as well as Strategic Issues & Integrated Management. In our centre, as is the case with many other centres within the agency, when we look at different issues such as antimicrobial use and resistance, we look at it from different perspectives and functions within each of the divisions. You can see how it can fit under different areas on the slide 5 provided here.

If we now turn to the next slide, you'll find a list of the AMR-related activities currently taking place within different jurisdictions at the federal, provincial/territorial levels as well as within non-government entities including industry, academia, professional associations, to name just a few. There are two federal programs which I would like to mention that particularly relate to antimicrobial resistance; the first one is the Canadian Nosocomical Infection Surveillance Program, or more commonly known as CNISP. This program was established in 1994 to program, track and rate in terms of how health care associated with infections at some Canadian health care facilities. The second program I would like to mention is CIPARS, the Canadian Integrated Program for Antimicrobial Resistance Surveillance. This is a nationally integrated antimicrobial resistance surveillance program developed by the agency in collaboration with federal and provincial partners. One of the key objectives of CIPARS is to monitor trends in development of antimicrobial resistance in the food chain. You'll be hearing a lot more about CIPARS from my colleague Rita Finley in a subsequent presentation. And I would also like to mention the provinces and territories as well as non-government players and coalitions also have a clear role in addressing AMR across Canada as is outlined on that particular slide. The webinar today is certainly an excellent opportunity and example of how we can all come together and gain greater knowledge and understanding of such an important issue and

obviously the need to address it from many different levels. Thank you very much.

Stacie Ross - If anyone has any questions at all for Marc-André, please feel free to type them into the box on the bottom right-hand of your screen and he can address those. That was an excellent introduction and the next presenter will be Rita Finley. Rita is a senior epidemiologist with the Surveillance Division of the Centre for Food-borne, Environmental and Zoonotic Infectious Diseases of the Public Health Agency of Canada and she will be presenting on “Monitoring AMR from Farm to Fork, Results from the Canadian Integrated Program for Antimicrobial Resistance Surveillance,” known as CIPARS. Welcome Rita.

Rita Finley - Thank you very much Stacie and thank you very much everyone. So today, as Stacie said, I will be talking about the Canadian Integrated Program for Antimicrobial Resistance Surveillance, which is a national program that looks at monitoring antimicrobial resistance and antimicrobial use in humans and animals. I’m just going to give a quick overview of what the objectives are of CIPARS and then an overview of CIPARS itself in terms of different components of the program and I will share with you some of the integrated results that we have with regards to Salmonella and some of the resistance patterns that we’re seeing, both on the human side and in the agri-food sector, and I will also briefly discuss some of the monitoring of antimicrobial use that we carry out on the human sector within CIPARS.

CIPARS is coordinated by the Public Health Agency of Canada by three different centres: the Laboratory for Foodborne Zoonoses, the National Microbiology Laboratory and my centre, CFEZID. The staff consists of various epidemiologists, microbiologists and biologists and we also have veterinarians that include specific species or commodity specialists. And our partners are several and include Health Canada, CFIA, Agriculture and Agri-Food Canada, the Provincial Agriculture and Public Health bodies, academia and the private industry.

So as I mentioned briefly, our objectives are to provide a unified approach to monitor trends in both antimicrobial resistance and antimicrobial use in humans and animals. Our aim is to disseminate results in a timely manner and with the objective of facilitating assessment of the public health impact of antimicrobials that are used both in humans and agriculture. We do have our methods set up so as to allow accurate comparisons with other countries that use similar surveillance systems, such as NARMS in the United States and DANMAP in Denmark.

So this is an overview of our CIPARS program. On the human side we have passive surveillance of Salmonella that goes from the provincial laboratory to the National Microbiology Laboratory. On the animal side we have different components; the first one obtains samples from sick

animals through diagnostics, samples that are submitted to laboratory for foodborne zoonosis. We have sentinel farm surveillance where we collect both antimicrobial resistance and antimicrobial use information. We collect samples at the abattoir level for beef, pork and chicken, and we also collect samples at the retail level which is the point closest to consumers so we're trying to ascertain the risk that is present in those products to Canadians. On the antimicrobial use side, we have collected information on the animal side through questionnaires that are implemented on the essential farm level and also from data that is provided by the Canadian Animal Health Institute, which consists of kilograms of antimicrobials distributed for use in animals. That information is not available at the commodity level, but it does provide some data to start calculating information for different commodities and to combine it with other resources. On the human side, and you'll hear a little bit more about this later in my presentation, we have three different sources of antimicrobial use information: the first one is physician diagnosis - the different diagnoses for which physicians are prescribing antimicrobials-, hospital purchases – so what hospitals are purchasing for use within the hospital and it already has exluded and returned, or drugs that haven't been used by those hospitals-, and then we also have information on what are the antimicrobials dispensed by pharmacies across the country. Moving on to integrated results that we have; Salmonella is the only pathogen for which we have data across all the different components within CIPARS. We can see that within the human information, the top three serovars are S. Enteriditis, S. Typhimurium and S. Heidelberg. Among the agri-foods samples that we collect, the top three serovars for Salmonella are S. Kentucky, S. Heidelberg and S. Enteritidis. So you can see there's a little bit of a difference, of variability in terms of what we're seeing on the human clinical cases and what we are isolating from agri-food sources. For Salmonella Enteritidis (SE), human incidence of the organism is high in all provinces and this is a #1 serotype coughing salmonellosis in Canada. The recovery of SE from retail chicken has been observed to be higher in the western provinces and we have observed decreasing trends in other regions across Canada. Resistance within SE that we have obtained both from the human and agri-food isolates. In the human isolates in 2011, 20% demonstrated resistance to more than one antimicrobial, the majority being resistant to nalidixic acid. Within the agri-food isolates we didn't observe any resistance to any of the antimicrobials tested, and we tested for a total of 15 antimicrobials, from any of the isolates obtained from retail or abattoir chicken samples. And as you can see in this graph, we have the incidence per 100,000 inhabitants in years, which is the light blue colour, and in darker blue we have the Salmonella recovery or the percent of samples positive for which SE was present. And you can see that across time, there has been an overall increase of SE incidence in Canada and also recovery from chicken, although as of 2009 we have seen a significant decrease in all provinces; with Quebec we didn't identify any SE in our retail products in 2011.

Salmonella Heidelberg (SH) is also one of the top three causes of salmonellosis in Canada and has been #3 for the last four or five years. We have observed significant increases in resistance to three Category-1 antimicrobials, which are those considered to be of very high importance in human medicine, such that they are very limited to almost no other antimicrobials that can be used in case of treatment failure when taking these antimicrobials. So 19% of the isolates received in 2010 were resistant to these three antimicrobials, which consist of Amoxicillin-clavulanic acid, Ceftiofur and Ciprofloxacin, and 33% were observed in 2011. The trend observed was on an increasing level for all the different provinces except British Columbia, and that was mainly because of face-type differences that we were serving in the other nine provinces compared to BC. The prominent face-type in 2011 in BC was face-type-19, which tends to be more susceptible when compared to some of the other face-types that tend to be more resistant to these three AM. At the retail level, we also observed similar increased resistance to these three same AM and smaller numbers were recovered from those in British Columbia.

So why are we concerned about this resistance to Category-1 antimicrobials, in particular Ceftiofur? Ceftiofur is a product that can be used in many animal species but has not been labelled for use in chicken in Canada. It is used as an extra-label to control E. coli omphalitis in broilers. They are injected into the egg the day before the egg hatches. And as I have mentioned, Salmonella Heidelberg is a frequent top 3 serovar in humans in Canada and it causes diarrhea, vomiting, fever, malaise and can be invasive, causing septicaemia, extra-intestinal infections and death. The treatment of concern is the fact is that if we observe resistance for Ceftiofur, we are very likely to see resistance to Ceftriaxone, which is one of the main drugs of choice for treating salmonellosis in pregnant women and children.

So as you can see in this graph, in orange we have the Salmonella Heidelberg prevalence of Ceftiofur resistance from chickens that were obtained at retail level, and in the blue line we have those Salmonella Heidelberg that were resistant to Ceftiofur from human isolates. You can see there's been, in some provinces, a similar trend in increasing resistance to Ceftiofur both in retail and on the human side.

Moving on to the next slide which shows the picture a little bit clearer, in 2003 and 2004 - and some of you might be familiar with this story - we observed high levels of Ceftiofur resistance in E. coli and Heidelberg from retail chickens which are the red and orange, and also in the human Heidelberg infections. In discussions with the ministers in Quebec and veterinarians and industry, in 2005 they implemented a voluntary withdrawal of Ceftiofur use *in ovo* in Quebec and we therefore saw a decrease in the levels of resistance of Ceftiofur in E. coli Heidelberg in

retail chicken and human Heidelberg infections. As of 2007, we know there's been a reinstitution of Ceftiofur use and we are continuing to track the increase in Ceftiofur resistance across these sectors as a result of the return to that use. Another serovar that we follow is S. Kentucky, and one of the reasons why I have included it here is although on the human sector it doesn't cause a lot of disease, in 2011 we observed a total of 18 cases, it is interesting to see that some of the resistance observed in the agricultural sector, we are actually seeing it also in the very limited number of human cases that we have. So on the left-hand side we have isolates that were recovered from the abattoir component, in the middle you have the retail meat component and on the right-hand side is the human component, and as you can see there's similar resistance trends to streptomycin tetracycline in the darker blue, as there are on the human side, but the main difference between the human clinical isolates and the agri-food animal isolates is the resistance to Ciprofloxacin, which is very prominent on the human isolates but is not present in the agricultural or agri-food isolates that we're receiving.

And lastly, moving on to some information on our antimicrobial use monitoring that we have within CIPARS. I'm just going to briefly touch on the human antimicrobial use side, because the people who are responsible for the veterinary side were unfortunately not available to be here, so if there are any questions for them I can definitely direct you to the right roots that look after the animal side. But on the human side, as I said, we collect and receive information from three different sources: what is being dispensed by pharmacies, what are hospitals purchasing for use in their organizations, and what are the diagnosis and prescriptions being provided by physicians across the country. The data is provided to us by IMS Health and they do the data collection and aggregation and all the data is then extrapolated using geographical interpolation methods to give us a sample data to "universe". And then once it arrives in the agency, we classify the data using the World Health Organization APC classification, we create, assign and define dosages for population basis and we also do interpretation, which we include in our annual reports. What we have observed in terms of trends across the different years since we started our surveillance program, is that there has been a decrease in the number of prescriptions that have been dispensed by pharmacies between 2007 and 2010 with a slight increase in 2011. However we need to make sure that we look at this trend also at the specific antimicrobial level, because although the number of prescriptions have been decreasing, these are mainly driven by decreases in tetracyclines, sulphonamide-trimethoprim combinations, there's an increasing trend being observed among the macrolides and fluoroquinolones. The total cost of antimicrobials dispensed through pharmacies has been adjusted to account for inflation and we have also observed a decreased trend in that. The overall inflation-adjusted dollars spent per 1,000 inhabitants has displayed a thin decline from year to year with an overall reduction of $12 per 1,000 individual days between 2000 and 2011, which translates to $13 million

per year. And on this page is just a summary of the different recent requisitions which is classified using the ICD-9 code, the total diagnostic visits that physicians observed during this time period, the number of prescriptions that were provided and the number of those prescriptions that were for antimicrobials. So between 2007 and 2011, there were a total of 1.5 billion patient visits to physicians. The majority of the visits were due to diseases of the respiratory system, circulatory system and musculoskeletal diseases. 58% of all visits resulted with some type of treatment being prescribed or recommended and of these 14% were with oral antimicrobials. However of all the antimicrobials prescribed, 48% were given to patients with diseases of the respiratory system followed by 15% with UTIs and 13% with skin/tissue disorders. Within the specific disorders, we identified 75% of patients that visited a physician for a urinary tract infection and were provided a treatment were given a prescription for AM. Similarly, for disorders of the ear, 61% of those receiving treatment were provided prescriptions for AM and 46% for respiratory system disorders.
And lastly, in terms of trends on what antimicrobials are being purchased by hospitals for use and cost, we have observed an increase in total active kilograms of antimicrobials being purchased by hospitals between 2001 and 2011. It is not a huge increase but there is a bit of an increase that has been observed. The cost associated to whether injectable or oral antimicrobial has been adjusted for inflation as well, and we can see that after 2007 there has been a decrease in the cost associated with purchasing injectable AM whereas the cost of oral has remained relatively stable.

So some of the take-home messages from today's presentation are that there is evidence of resistance to medically important antimicrobial resistance among bacteria of food animal origin. In terms of resistance to Category-1 antimicrobials, in particular Ceftiofur, among Heidelberg isolates, we see a similar resistance in human clinical isolates and also in the pseudo-animal origin isolates. We observed multiclass resistance S. Kentucky human clinical cases but there is different resistance patterns observed among the average crude isolates. With regards to antimicrobial use information, the use of having multiple measures allows for a more complete picture of prescribing use and associated costs than using only one source at a time. It provides us opportunities to identify areas that could require further education and stewardship programs and identify impact of formulary or prescription changes over time and how these are also implemented or absorbed by physicians in terms of looking at the prescription pattern. And this information also allows us to enhance the current knowledge of uses of AM by integrating it with animal use information through CIPARS. And as you can see there is a numerous amount of people that are involved in this program, both internally within the agency and also externally at the government level, industry and agri-food levels and ministry. Back to you, Stacy.

Stacie Ross - Thank you, Rita. This is incredible data and gives us a lot to think about, and I do see a question posed. I am not sure if you can see it, Rita, so I'll just say it; "What does the average consumer of meat products have to be concerned about?" That's the first part, and the second part is "How can they protect themselves? Is buying organic meat the answer?"

Rita Finley - I think that as long as the meat products are cooked properly, there shouldn't be any concerns regarding meat products. We know that bacteria can be eliminated by heat treatment and also by following proper hygiene procedures in the kitchen that reduces any risk at all present to the consumer. In terms of whether there's an advantageor not in terms of purchasing or eating organic, antibiotic-free products compared to the regular products, I know there are some studies on the go right now looking at those differences, but I'm not privy to the results being observed in that so I imagine that in the next year or so you'll probably be seeing that information being shared through scientific publications. And perhaps it is something we can bring back to this group at the Antibiotic Awareness Week next year.

Stacie Ross - Okay, that's great. Thank you for that answer, Rita, and I have another one posted: "At the primary care level, should there be more surveillance of antimicrobial use?"

Rita Finley - I'm not sure there could be more surveillance as we are trying to capture some of that information. I think that there probably is a need to have more local-level information in terms of what is being used at the primary care level. I think that Do Bugs Need Drugs is doing an excellent job in doing that out in BC. They present some of that information that is being sent back to the primary care level physicians and then trying to have some impact on that. So I believe that we're on a good road right now, in terms of starting at the national level and seeing what are the areas we are seeing potentially need more surveillance. I know that at the local level as well there is a lot of interest in developing antimicrobial stewardship practices and in trying to better understand what are the uses and correlations with resistance that we're seeing in some of the organisms.

Stacie Ross - Okay. Thank you and there's another follow-up question to the first: "I was referring to the risks of becoming resistant to antibiotics, by eating meat that has been injected with antibiotics."

Rita Finley - Animals that are injected with antimicrobials, there are in the system maximum residue levels that should be present if at all in meat products, so I don't think that there's any risks in meat with regards to there being residues present. That's something that is highly regulated across the different commodities in Canada. A person itself cannot become resistant to an antibiotic; it's only the bacteria or the organisms that are

resistant to them. So it all comes down to whether or not there's bacteria present in the food and that's why my comment about if you actually make sure to cook the food properly, and that you follow good hygienic procedures in the kitchen and home environment then the risk will be reduced. So again, I think there are stringent regulations in place to make sure that there are no residues present in meat so that prevents or reduces it even more for any potential for developing resistance among the different bacteria, and secondly, humans do not become resistant to antimicrobials, it's the organisms that cause the infections that are resistant to the AM themselves.

Stacie Ross - Okay, thank you, Rita. Very interesting. Excellent program. Thank you so much and wonderful presentation.
Next to speak is Irene Martin. Irene heads up the Streptococcus and SDI unit of the National Microbiology Laboratory, Public Health Agency of Canada. Today Irene will speak on antimicrobial resistant N. gonorrhoea in Canada and give a national perspective.

Irene Martin - Great. Thank you very much, Stacie. Here at the National Microbiology Lab (NML), we have been conducting antimicrobial susceptibilities of Neisseria gonorrhoeae isolates as part of a national surveillance program since the mid 80s. This is a passive surveillance system, and we get isolates submitted to us voluntarily from all provinces. Isolates are submitted to us if they are resistant to at least one antibiotic tested by the submitting lab, and the labs that don't do any susceptibility testing will send us all of their isolates, including susceptible ones. One of the biggest challenges we are currently facing is that fewer cultures are available for testing. This is due to an increase in Nucleic Acid Amplification Testing (NAAT) for diagnosis. There are many benefits to using NAAT including the increased sensitivity and a non-invasive specimen; however we still need cultures to determine susceptibilities. In addition to the challenge of fewer cultures to work with we are also experiencing increasing antimicrobial resistances in gonorrhoeae, and this threatens to compromise effective treatment and disease control efforts. On the next slide, this increase in antimicrobial resistance seen in Canada is also being identified around the world, specifically becoming less susceptible to Ceftriaxone and Cefixime which are the current recommended treatment options, and global treatment failures to Cefixime and Ceftriaxone have been reported. Since the MICs for Cephalosporins and even Azithromycin continue to increase, the WHO has identified the antimicrobial resistance in gonorrhoeae a global public health issue. Earlier this year, the WHO released a document called the "Global action plan to control the spread and impact of antimicrobial resistance in Neisseria gonorrhoeae" to address these concerns. Here at the NML we determine the MICs, which is the minimum concentration of antibiotic required to inhibit growth using a CLSI-approved agar dilution method. We test eight antibiotics, including Penicillin, Tetracycline, Erythromycin, Spectinomycin, Cyprofloxacin, Ceftriaxone, Cefixime and

Azythromycin. Once we have the MIC, we classify the strains into different characterizations, including CMRNG, which are Chromosomal Mediated Resistant Neisseria gonorrhoeae, and these display resistance to Penicillin, Tetracylcine and Arythromycin. Other strains can be identified as having plasma-mediated resistance, which would include PPNGs, which are Penicillinase Producing Neisseria gonorrhoeae, or even TRNG, which are Tetracycline Resistant Neisseria gonorrhoeae. Over the last ten years or so, we have been experiencing a steady increase in the number of reported cases of gonorrhoeae from a low of about 6,000 cases in 1997, to over 11,000 cases in 2010. During the same period, fewer cultures were available for testing and resistance levels continued to rise. One thing I'd like to mention here is that to determine a percent resistance we pull each of our submitting provinces for the number of isolates they have tested and that becomes our denominator in our percent resistance calculations. Over the last ten years we've seen a steady increase in resistance to Penicillin, Tetracycline, Erythromycin and Cyprofloxacin. Historically, gonorrhoeae has developed a resistance to antibiotics used for treatment. In the 1970s, we saw an emergence to the resistance of Penicillin, in the 80s, to Spectinomycin, in the 90s, to Ciprofloxacin. If we use these examples as predictors, then the Cephalosporins are next at risk.

If we look at what happened with Cyprofloxacin as a recent example of how quickly the resistance emerges; the resistance to Cyprofloxacin was first reported in Asia and spread internationally from there. Looking specifically at how it developed in Canada, we see that in early 2000, resistance levels hovered around 2%, but by 2004 resistance had jumped to 5.5%. This exceeds the 3 to 5% threshold which is the acceptable level of resistance for a recommended treatment option. We have been documenting an MIC "creep" for Cefixime and Ceftriaxone over the last few years. CLSI does not have a recommended resistance cut-off point for the cephalosporins but they do specify a non-susceptibility cut-off of greater than or equal to 0.5mg/L. However, since the last WHO document that I just described came out, they have now have a recommended decrease of susceptibility cut-off for Cefixime of greater than or equal to 0.25mg/L and for Ceftriaxone at 0.125mg/L. By using this criterion, we can see that since 2007, the steady increase of number of isolates with those MICs. Looking specifically at Cefixime, we see a steady increase of isolates with MIC=0.25mg/L from about 0.2% in 2007 to 11% in 2011. On the next slide, we look at Ceftriaxone, where we see a steady increase of isolates with MIC=0.125mg/L from 1.19% in 2007 to 17% in 2011. Isolates with MICs=0.25mg/L have also increased from 0.7% in 2007 to 1.1% in 2011. Azithromycin is also something we should be aware of. It doesn't have a recommended CLSI cut-off point for resistance, but we use the CDC recommended resistance at 2.0mg/L. We have seen a steady increase of isolates with MIC=1.0mg/L, which is just one dilution lower than the resistance cut-off, and we've seen an increase of 0.72% of all isolates tested in 2007 to 5.3% in 2011. Between 2006 and 2011, isolates

at the resistance cut-off of 2.0 fluctuated from 0.5% in 2006 to a high of 3.0% in 2010.

In addition to testing antimicrobial susceptibilities, in 2010 we started a sequence-typing based analysis on all our strains. This method analyzes two genes: the porin gene which encodes the goncoccal outer-membrane porin, and TPP gene which encodes a transfer in binding protein. This is an internationally used method called NG-MAST Neisseria gonorrhoeae multi-antigen-based sequence-typing. The NG-MAST sequence type of ST-1407 is the most prevalent circulating type in 2010, and 13.3% of all our isolates in 2010 were 1407. When we arrange all the ST types that we have identified in a phylogenetic cluster diagram, we can see that 1407 falls within cluster A. Although the isolates in cluster A only differ by one to four base-pairs, so they're highly related, and when you take that into account that means that 44% of all isolates tested are related to 1407, or are 1407.

I'm drawing attention to 1407, because it is an international identified clone, it was first described in Scotland in 2007. It was recently linked to Ceftriaxone and Cefixime treatment failures in Europe. The ST1407s identified in Canada also have the highest MICs to the cephalosporins. That is basically a summary of what we've been doing here. We are trying to make improvements to the current passive surveillance system with a new proposal. This is a sentinel site surveillance program where we would integrate our laboratory and epidemiological data and standardize the sampling framework. This gives us an opportunity to monitor and report treatment failures at a national level. The surveillance is important to rapidly identify changes in antimicrobial susceptibilities and assess risk factors associated with the development of resistance. This will also hopefully prevent the spread of drug-resistant gonorrhoea and assure appropriate treatment. To make this proposal work, we have set up a web-based data sharing platform that's accessible to all involved parties; that includes the submitting provincial laboratories, the provincial and federal epidemiology departments, and ourselves, the federal lab. This platform is available on CNPHI, which stands for the Canadian Network for Public Health Intelligence. The databases on CNPHI are secure and access is jurisdictionally controlled. Currently, our GC database is housed on CNPHI, our provincial lab partners can log on and find sample testing status, use an online cluster analyzer and view our annual reports, and this is the database that has been set up with the proposed central site program in mind. So in conclusion, I would like to say we need to continue culturing Neisseria gonorrhoea, and it's absolutely necessary to continue to monitor susceptibilities of gonorrhoea, to identify emerging resistance patterns, to monitor the spread of resistant gonorrhoea and to ensure that appropriate treatments are being used. I would like to thank our provincial lab partners for sending in isolates and the group here at NML that does all the testing.

Stacie Ross - Thank you very much, Irene. That was an excellent presentation. We will give a moment to see if any questions pop up. If there are any questions that come up, we can address them at the end with Irene. We'll move on to our next presenter. We will now be hearing from Dr. Tom Wong, the Director of Professional Guidelines and Public Health Practice Division, Centre for Communicable Diseases and Infection Control at the Public Health Agency of Canada. Dr. Wong will be speaking on "Public Health Updates on the Management of Multi-Drug Resistant Gonorrhea." Welcome Dr. Wong.

Tom Wong - Thank you very much. The Canadian STI guidelines is a resource from the Public Health Agency of Canada for clinical and public health professionals. An expert working group helps us to update evidence based recommendations in an evergreen fashion with the latest updated chapters available electronically. The focus of today's update is on gonorrhea. Gonorrhea is the second most reported bacterial STI in Canada, with over 11,000 cases reported a year, in recent years, and young Canadians continue to be the most affected. Gonorrhea can lead to pelvic inflammatory diseases and infertility. As well as increasing the risk of HIV transmission and acquisition. The reported rate of Gonorrhea in Canada has been rising in the past decade. Over the years, gonorrhea has developed resistance to many classes of antibiotics, beginning with sulphonomides in the 40's, Penicillin in the 70's, Tetracyclines in the 80's, and Quinolones in the past decade.

There are signs that gonorrhea is becoming a superbug, resistant to all effective antibiotics in the near future. In response, updated treatment recommendations for gonorrhea have been developed. I would like to highlight some of the key changes in the past year, in our recommendations in gonorrhea management, including the changes in the treatment of choice, Cephalosporin dosing, combination gonorrhea treatment, culture, and test of cure. Further changes anticipated as the evidence evolves. By adopting these recommendations, we can all play in important part in slowing down the spread of multidrug resistant gonorrhea or MDR GC. The minimum concentrations of cephalosporins needed to inhibit the growth of gonorrhea is steadily rising, suggesting the waning effectiveness of cephalosporings, with oral cefixime waning more than injectible Ceftriaxone. A similar phenomenon but to a lesser degree is happening with Azithromycin. There is increasing evidence that rising Cefixime MIC's and treatment failures are more noticeable among men having sex with men, or MSM, similar to the emergence of quinolone resistance initially among MSM, before spreading to other populations a decade ago. Cefixime PO at 400mg doesn't give us drug levels as high, nor as sustained as Ceftriaxone 250mg IM. Cefixime is also less efficacious for pharyngeal gonorrhea, as such, it is important to use IM Ceftriaxone 250mg especially in MSM, and pharyngeal infections. If not possible, Cefixime PO 800 mg can be considered in circumstances where treatment the failure of oral Cephalosporins is not expected.

Over the years, gonorrhea has developed resistance to almost every antibiotic used for the treatment, leaving us with a public health threat of untreatable MDR-GC. With this latest development, it is a matter of time before we will be losing Cephalosporins altogether for the treatment of gonorrhea. The more we use oral Cefixime, the more gonorrhea may develop resistance to all Cephalosporins. Shifting the use of PO Cefixime to IM Ceftriaxone and doubling the dose for now, may help buy us some time, to keep these third generation Cephalosporins as viable treatment a little longer. Combination therapy using a third generation cephalosporin, and another antibiotic with activity against gonorrhea at a different molecular target, and activity against chlamydia co-infection is recommended. The use of Azithromycin rather than Doxycycline as a second antibiotic used in combination is advantageous for the following reasons: First Azithromycin is taken as a single dose addresses adherence challenge to a seven day does of Doxycycline for patients, and secondly, there is a much higher risk of gonorrhea resistance to Doxycycline than to Azithromycin, especially with some strains with susceptibility to Cefixime. Note that Doxycycline is contraindicated for children under 9 and pregnant women.

In situations when higher tissue penetration is necessary to achieve cure, such as pharyngeal infection and complicated cases, such as PID and epididimitis, Ceftriaxome 250mg IM is recommended. Gonorrhea cultures should be done when possible to allow for antimicrobial sensitivity testing under certain circumstances, such as sexual abuse of children, sexual assault, treatment failure, evaluation of PID as appropriate, in MSM as a test of cure. Now NAAT nucleic acid amplification tests has the advantage when transport and storage conditions adversely affect the viability of gonorrhea needed for culturing, and when non-invasive screening, asymptomatic individuals is offered. Follow-up test of cure by culture at least four days after the completion of therapy is essential in any of the following situations: All pharyngeal infections, persistent symptoms or signs post treatment such as developed treatment failure, cases treated under a regimen other than the preferred regimen, cases linked to a drug resistant or treatment failure case. Repeat gonorrhea testing is recommended 6 months after completion of treatment to detect possible re-infection.

Now in summary Ceftriaxone 250mg IM is the first line choice for pharyngeal infections and MSM. Ceftriaxone 250mg IM for uncomplicated cases is the ideal treatment. However if it is not possible, Cefixime 800mg PO single dose can be considered in circumstances where treatment failure with oral Cephalosporin is not expected. Compared to previous recommendations, there recommendations for treating gonorrhea has been doubled to 800mg PO for Cefixime, and 250mg IM for Ceftriaxone to minimize the risks of treatment failures, It is recommended to treat gonorrhea with combination therapy with Ceftriaxone IM plus Azithromycin PO single dose or Doxycycline 7 day course as an alternate.

Culture permits monitoring of AMR, whereas NAAT does not. Follow-up culture test at least 4 days after the completion of therapy, for certain circumstances recommended. By preventing gonorrhea and by following these treatment recommendations, we can slow down the spread of untreatable MDR-GC. Thank you.

Stacie Ross OK, Dr. Wong, I see we have one question up for you and one for Irene as well, if Irene is still on the line. We will start with the question for Dr. Wong, and it is: How fast is the antibiotic resistant gonorrhea evolving into an even more resistant strain?

Tom Wong – As you can see from global data as well as from Canadian data that Irene Martin has shown, we are very concerned. The speed at which what we call right-shifting of the MIC's, which is a reflection of the waning effectiveness of these antibiotics, Cephalosporins, as well as Azithromycin, we are worried that the future may be closer than we think, the future of untreatable multi-drug resistant gonorrhea. That's why both globally at the WHO, as well as here at the Public Health Agency, we are re-doubling our efforts in trying to slow down MDR GC. Obviously we can't do it without you, all over Canada.

Stacie Ross – Thank you very much, and I have another question for you. Are we seeing AMR among any other STI's?

Tom Wong – For other STI's, like Syphillis, there's been some other published report of resistance to a class of drug that's called Azithromycin, and those kinds of resistance have developed very quickly, and for those of you who are interested, there are a number of published articles in the literature regarding this. And the future regarding Azithromycin resistance for Syphillis, is a distinct possibility and therefore we have to be very vigilant to monitor for resistance to Azithromycin as far as Syphillis is concerned.

Stacie Ross – Have nucleic acid tests for antibiotic resistance in GC been attempted in Canada or elsewhere? Could they be included in routine testing?

Tom Wong – This is an excellent question. As a matter of fact, the Public Health Agency of Canada along with Provincial Territorial Partners, along with universities are looking at possible ways of using nucleic acid amplification test to predict drug resistance to Azithromycin as well as to Cephalosporins. A number of countries are also embarking to address this using a similar approach. With that I'm going to also turn over to Irene for further comment from NML.

Irene Martin – Good Tom, thanks. I agree with what you said. We've been looking at the possibility and looking at actually a whole genome sequencing, to identify genetic resistance markers. Currently it's more

complicated than it seems. It seems in theory that it should be simple enough to do PCR and identify mutations in the mechanisms or resistance, but it's a little more complicated than that. We have specimen types that are a little bit more difficult to work with, when you have urine, extracting the DNA from urine is a little more difficult than using a pure isolate. Those are some of the complications that we face, but it's definitely being worked on.

Stacie Ross – Okay, Irene, I have another question that's come in for you. Could you expand upon the use of NAATs as well as what is limited their use? You had addressed these points briefly in the first part of your presentation.

Irene Martin – There are pros and cons to diagnosing gonorrhea using NAATs and culture. I was just trying to get to the point that for us to maintain our antimicrobial susceptibility testing, we needed to have culture, so diagnosis by culture was required. With regards to nucleic acid testing, it's a preferential choice sometimes in the doctor's office because it's non-invasive verses obtaining a culture and it also provides increased sensitivity for diagnosis.

Stacie Ross – Are you recommending Ceftriaxone injections for all contacts or just those laboratory confirmed cases? Thank you Tom.

Tom Wong – Sure, as I mentioned earlier, we are recommending the shift from Cefixime to Ceftriaxone injections, so the preference is to use Ceftriaxone injectible for gonorrhea and in situations where it is not possible for logistic reasons and at the same time that it is not anticipated that Cephalosporin treatment failure or resistance will be the case, then one can very cautiously use PO Cefixime, but the preference is to switch to Ceftriaxone. As I said before it is just a matter of time before we will lose Cefixime and Cetriaxone altogether and we just want to buy us some time.

Stacie Ross – Okay, thank you Dr. Wong. I don't see any more questions coming in. That was very engaging, terrific questions and answers. Thank you very much, and so if that is all the questions for now, I would like to give a big thanks to the Public Health Agency of Canada and your four presenters. Really incredible presentations and thank you very much for the opportunity to listen and learn. Another big thank you to all the partner organizations, whose logos are featured on this last slide, and of course to all of you participants who took the time to log in, thank you. You can see on the last slide here, there is a survey link. Your one minute feedback would be really appreciated and greatly enhance Antibiotic Awareness Week activities in Canada for 2013 so please do that when you log out. That's it so please remember to use antibiotics wisely, when needed and as prescribed. Thank you.