Antibiotic Awareness Week 2012
Dr. Low (14nov12)

Stacie Ross Good morning and welcome Dr. Low. My name is Stacie Ross and I am with NCCID, a partner in antibioticawareness.ca and we thank you very much for joining us and welcome to the webinar. It's presented as part of Antibiotic Awareness Week. During the session, you will hear from Canadian experts in the field of antimicrobial resistance. We will be recording the webinars and will be providing transcripts in French on the antibioticawareness.ca site. We suggest that you listen to the session on your computer speaker. However if you need to, please feel free to listen by telephone using the toll-free number and code listed on the right side of the screen. If you are not a presenter, put your phone on mute so that other participants don't hear you. The upcoming presentations will be followed by a Q&A. During the presentation we invite you to post questions by typing them into the box on the bottom right of your screen. - I would now like to introduce Dr. Donald Low, Chief of the Department of Microbiology at the University Health Network and Mt. Sinai Hospital. He is a professor at the University of Toronto in the Department of Laboratory Medicine and Pathobiology and the Department of Medicine. He is going to be presenting on "The Menace of Antimicrobial Resistance."

Welcome Dr. Low, are you still with us?
Dr. Donald Low - Still here!
Stacie Ross - Okay you may begin your presentation.
Dr. Donald Low - Thank you very much and welcome everybody. It really is a great opportunity to talk to colleagues and friends across Canada about an incredibly important topic, and one that is growing in importance. I remember getting interested in this in the 1980s and early 1990s when pneumococcal resistance started to appear and it looked like we were in a bit of a waxing and waning but boy! during the last 10 years we've really seen some important problems emerging and a real crisis, not only in bacteria which I'm going to speak to directly today, but also viruses, fungi, parasites, artisamen resistance in malaria being reported from Myanmar. Dylan Pillai had reported as well about a patient coming back to Canada. So it's everywhere.

So let's get started. We made some incredible achievements in public health over the last hundred years and those have been based primarily on sanitation and hygiene. Vaccination has had a very important impact as we all know, and of course antibiotics; really the antibiotics era being introduced towards the end of WWII when penicillin was available to treat wound infection in soldiers. It has a rich history. And if you look back 100+ years ago now, you can see that the 3 commonest causes of mortality worldwide were pneumonia including influenza, tuberculosis, diarrhea and enteritis. So we've come a long away in reducing mortality related to those diseases, but still if you look today at the leading infectious causes of death worldwide, you can see there's an acute

respiratory infections –still number 1-, diarrhoeal diseases, TB, malaria, measles, they're still up there. So when we look at especially acute respiratory infections, this is an area where there's need for cheap and effective antibiotics.

So let's talk about antibiotics resistance. This is a nice commentary that Bryan Spratt made in *Science* back in 2011 in response to a paper looking at the Strep. pneumo genome from a number of isolates from around the world and how bacteria have such unusual and variable sex lives from near celibacy to promiscuity, and it is so true in so many important bacteria. The ability not only to have quick mutations which can result in a reduced susceptibility to antibiotics, but literally taking in packets of DNA from other bacteria from the environment and incorporating them into their chromosome in order to encode for resistance; it really is quite amazing.
As I mentioned, things started to heat up again in about 2000 as shown on this slide when the WHO declared this antibacterial resistance as a global threat and in fact even last year dedicating World Health Day to antibacterial resistance. And the bottom line being any antibacterial resistance. No action today, no cure tomorrow; and that is just so true as we have opportunities out there to do something, we have to make sure we take advantage of those opportunities.

So what happened? Why did we end up in this predicament when you think that we really only started the antibiotic era in the late 1940s? And we're talking now of the potential for post-antibiotic era at least in some important bacteria. And Pogo is dwelling on this question and asking "Have we met the enemy?" One of the early problems that arose was the attitude. There really was this attitude with the introduction of antibiotics and vaccines and hygiene that we had really conquered the public health problem, and that especially with antibiotics, virtual elimination of infectious diseases as a significant factor in social health. Actually, a colleague I remember in the 1980s recommending to a resident that infectious diseases was not the place to go for a career because there was not much of a future because of the accomplishments that we had made to date. We now know that that was clearly wrong.

Antibiotic reuse and misuse. In the early days when we had these great, safe antibiotics, we didn't really know how they worked. We didn't really know how resistance developed. We really didn't understand the area of pharmacokinetics and pharmacodynamics which really only came into existence in the 1990s which helps us understand when we use an antibiotic, how to use it best. So there was an awful lot of misuse and there continues to be an awful lot of overuse and misuse and it's not just in humans; we know that in the agricultural field there is a lot of antibiotic use. I think we do a much better job in Canada compared to some of our other friends and countries in South-East Asia where there is very little limitations on how antibiotics are used as a growth promoter and a

disease preventer and treater. Sometimes you get a bit frustrated thinking what can we do at home if we continue to have this threat from abroad and we have this global community coming together so quickly as I'll point out in a few slides later. But also in the family, we are using antibiotics. So I think that as we learn about microbiomes, and this evidence is starting to be teased out, is that antibiotics given are clearly important when indicated but when not indicated can upset the microbiome and may have long-term consequences and so there may be evidence that will grow to suggest that we have to be not only careful about how we use antibiotics because of the fear of resistance but also the impact on the patient that we're giving these drugs to. So that's a very exciting field which is evolving quite rapidly now that we have the technology and the software to manage the massive amounts of data that are generated from whole genome sequencing and looking at microbiomes.

And this slide is from the Food and Drug Administration but it shows you where... Here's the commonest prescriptions written for antibiotics. In the green is where antibiotics are said to be unnecessary, and that in itself has quite an impact when you look at the common cold: 18 million prescriptions, no indication for them. Bronchitis, 80% no indication. Sore throats, sinusitis. I'll tell you the data that has emerged over the last several years with clinical studies as many of those green lines extend much much farther to the right. And then I would argue in sinusitis, there has been a couple of studies now, one was actually a randomized controlled trial looking at moxyfloxacin versus placebo for the treatment of bacterial documented sinusitis and no difference in outcome and other studies have found similar. So that sinusitis inappropriate thing should probably move a lot farther to the right. Sore throats; I mean in this era when we don't see rheumatic fever in North America, do we really need to be treating sore throats even if they are group A strep? Because antibiotics will only reduce the symptoms by one day and the practice of using antibiotics in somebody who has a pharyngitis is in order to prevent rheumatic fever. That is the goal, that's the only bug we're looking for and maybe we should re-evaluate the use of antibiotics on sore throats. Ear infections; we know can often, especially in the age of two, can be managed conservatively – wait to see whether or not antibiotics are needed after an extras 72 hours of observation. So we have tremendous opportunities to improve the use of antibiotics and the consequences of using them.

So when do we use antibiotics? This is some data published in Emerging Infectious Disease from 20 European countries - compared antibiotic use with resistance trends in two of the major pathogens, pneumococcin and E. coli and you can see in countries where there is excessive use of antibiotics over the comparative countries, resistance rates are higher. It makes sense but this is just some data that supports that belief that we've always had. This it to show that it's not only humans where these resistant organisms are hanging out. This was a study published in *Clin*

Microbiol and Infection 2011 looked at Dutch patients, retail chicken, meat, poultry, and looking for one of our newer threats, the ESBL, the extended spectrum betalactamase genes, plasmas and strains, and what they found is different important (on the left-hand side here) ESBL genes that were found in poultry samples, poultry meat and humans. So there is a connection between animals and resistance and resistance in humans and it's a continuum and one moves from one to the other and can move in the other direction as well.

Travel... has really changed... I think that we've really seen this... and I am going to point this out with NDM1...the New Delhi betalactamase. Travel has really changed how quickly we can see a microbial pathogen traverse the world and really the only limiting factor is its fitness. We've got a great example here showing you how back in 1850 in the blue line you know how many days it took to traverse the world and you can see by 1975, by 2000, you can do that in a matter of hours. I can leave, and I did a few weeks ago, I left Beijing in the morning and was home in Toronto for dinner. A relatively short flight of about 14 hours and coming with me, as it has been demonstrated in some studies, sometimes the flora of some of these countries.

This is another great example of how global travel has affected the distribution of microbes and it was the H1N1 outbreak back in 2009. This is from Khan and Arino here from St. Mikes Hospital in Toronto that tracked the spread of H1N1 and relating it, you can see that having started down in Mexico... it first appeared... and by the time we had our first recognition, that it was actually out there, we already had cases in Canada, cases described in Halifax in that boy's home. These people had got on a plane and returned home from March break not only within North America but also in Europe and of course from there, spreading around the globe in very short order.

This is just a brand new pathogen which was identified a few years back carbapenamase-producing Enterobacteriaceae. In France they started to recognize this first in 2004 but you can see how it has increased in frequency and that is related to travel as related to in some parts transmission and outbreaks but more related to travel, people returning with this strain as it became more prevalent in the countries they are coming back from.

What happened here? Well, bacteria learned how to become adaptable. Bacteria multiply, mutate and acquire resistant mechanisms; they're very adaptable and probably the earliest example that we always quote is the spread of the 23F serotype of pneumococcus called Spain 23F and showing how it originated back in the 1970s in Spain and was able to traverse the globe proving the relatedness by MLST typing mostly by Brian Spratt showing how this very fit strain of pneumococcus being able to travel to several different countries and becoming endemic in those

countries. By the late 1990s, 40% of penicillin-resistant pneumococcii in the USA was this phenotype. This is just showing the ancestral relatedness of one of our original clones, multiply antibiotic-resistant clones of pneumococcii and spreading to different countries and adapting to those countries and changing and becoming the predominant serotype in those countries causing disease.

So what is the impact of resistance? We see resistance and we actually get a lot of pushback from individuals, clinicians saying “Well you talk about resistance but I really don’t see the evidence of it in my practice.” But you know, there are good evidence in the literature, maybe not great but pretty good that attributable mortality and morbidity is associated with infection due to resistant bugs and when patients get discordant therapy, that is they get an antibiotic but the organism is resistant to the antibiotic prescribed. It results in prolonged lengths of hospital stay which are a cost to the healthcare system and other excess attributable costs. So there is a consequence to this resistance both in patient care and costs to the health care system.

In fact, the Infectious Disease Society of America has recognized that resistance is important and also that we don’t have a lot of alternatives out there. The antibiotic taskforce of the IDSA has identified four groups of problematic pathogens where we need to have new antibiotics: A. baumannii and P. aeruginosa, ESBL-producing Enterobacteriaceae, MRSA and vancomycin-resistant enterococcus. We need more antibiotic development. To show this more graphically, in the blue bars here, this was new antimicrobial agents approved by the USFDA and you can see that over the last ten years there has been a significant reduction. We’ve sort of grabbed the low-hanging fruit here and we’re now really scrambling to find new agents that are safe and effective, and this in the face of the red line of increasing antimicrobial resistance.

This attitude – and it’s an important attitude because where we see a lot of the drivers to this resistance is out in the community where most of the antibiotics are being used and it’s our responsibility to teach clinicians and healthcare providers that resistance is important because there’s this resistance paradox out there which has been referred to as the Polly Anna phenomenon where if you have a hundred patients at the office that all have a middle ear infection and you treat them with your favourite antibiotic the likelihood that you’re going to see recognized clinical failure is very low and the reason is that, partly as I have mentioned, many of these illnesses are self-limited so even if there is a resistant organism it’s going to get better. We don’t know what the organism is that is causing this infection because we don’t have testing available at the bedside to do that. And probably most importantly is the majority of these infections where we don’t know what the pathogen is will be viral or will be due to other bacteria that cause less serious disease. If we look at pneumococcus, streptococcus pneumonia, if you don’t treat it

appropriately you're going to see clinical failure. But that only makes 10 to 15% of otitis media and out of that 10 to 15% only about 30% will have susceptibility to the antibiotic that you're prescribing. So you get into this Polly Anna phenomena because you don't recognize the resistance when it does occur and it has consequences to it.

Let's take you through a couple of examples of really important problems that we're facing right now. One that I think we have not paid enough attention to is Neisseria gonorrhea. This is from about three weeks ago in *The New Yorker* called "Sex and the Super Bug" and describing the rise of drug-resistant gonococci, quite a good article that I would recommend reading. This threat of multidrug resistant gonorrhea has not had enough attention paid to it. "'We're sitting on the edge of a worldwide crisis,' says Manjula Lusti-Narasimhan, of WHO's Department of Reproductive Health and Research. 'There's this complacency around sexually transmitted infections because we've been so readily able to cure these infections in the past but that is changing rapidly. This is not just with gonorrhea, this is a problem that we're seeing with other bacteria.

We're seeing the antibiotic resistance, that's clear but we're also seeing a change in testing, we're seeing a shift in molecular testing and we especially see that with chlamydia and gonorrhea and we're doing it as well as a rapid test for throat cultures. When you're doing a nucleic acid amplification test, which in the US accounts for 90% of testing if not more, what it is, is that you don't have the organism; all you have is the yes or no, whether the bug is there or isn't there, go ahead and treat it or not. It doesn't tell you whether or not it's susceptible and that's happening also with TB. We also have the increasing asymptomatic reservoirs of gonorrhea, pharyngeal infections where it's a perfect environment for the exchange of genes from other closely related strains of organisms.

So, antibiotic resistant gonorrhea. There is this story, it's quite dramatic. Look back, here in the 1930s: the first antibiotic, and as we move from left to right, new antibiotics introduced resistance to them emerging. In 2001, we saw the first treatment failures with cefixime which had become the drug of the day for the treatment of gonorrhea. Cefixime is incredibly valuable; one dose, you can observe the dosage, give it to the patient, you can also give a prescription to be given to the patient to take home to their partner because they're going to have gonorrhea and they're not coming to the clinic with them. It's safe and effective. But unfortunately, ciprofloxacin is not a great drug; it does not have a great affinity to the penicillin-binding proteins in Neisseria gonorrhea and what we've seen is the step-wise emergence of the alteration of the penicillin-binding protein and decreasing MICs. We've also seen this with ceftriaxon and that's really the last drug we have. So after cefixime is gone, and cefixime is no longer recommended by the CDC as of six weeks ago because of its poor activity. Once it's gone we're going to have to rely on ceftriaxon, that means in the doctor's office we're going to have to give injections. What about the

partner at home? How are they going to get treated? It raises a whole bunch of problems and it also raises problems that we eventually have to face. We must think about different processes here. We've got to think about (test of cure?)***, we've got to think about combination antibiotics, we've got to change the whole paradigm of how we deal with gonorrhea.

So lots of mechanisms by how Neisseria gonorrhea can alter that penicillin-binding protein so that cefixime no longer binds so well and ceftriaxon also has decreased binding affinity. This is going to be a real challenge for us. This shows you that this is happening in real-time in Ontario: in the blue are the MICs to cefixime at 2005 and here they are in 2010 you can see quite a shift to the right. You can see the same with ceftriaxone MICs with a shift to the right. So, we are losing this drug, in fact we have a paper that has been submitted documenting nine clinical failures of cefixime therapy of Neisseria gonorrhea that we hope will be published soon.

Let's look at the clones. As I mentioned adaptability results in a very fit clone that is able to transmit effectively from person to person from one geographical area to another. Two examples I would like to use that are very important is MRSA and the enterobacteriaceae. We know Staph aureus is an important pathogen; it's an important cause of infections both in the out-patient setting as well as the in-patient setting but with the introduction of MRSA, our first cases back to the late 60s and 70s this was heralded as a new era for Staph aureus. Here I was a resident in Toronto, and this was my first publication that described an outbreak of MRSA that occurred at the Toronto General Hospital back then. Since then this has grown in magnitude with increasing hospitalization associated with MRSA and with the spread of MRSA worldwide, a very effective, very adaptable, very fit organism which has done very well and this is the data in Canada up to 2009 from Andy Simor's Canadian Nosocomical Infection Surveillance Program you can see that infections related to MRSA increasing over the years especially in the western parts of Canada.

And then to top it all off what do we end up with? We find a new strain of MRSA, a community-associated strain of MRSA which created a whole bunch of new problems because this was predominantly out in the community and it has really grown quite rapidly. These are reports of community-associated MRSA in a number of different parts of the world in and around the same time, providing new challenges, not only in the sense that it was a virulent organism but that it had toxin genes which appeared to cause more severe skin and soft-tissue and pneumonia. So this is something that we really have had to struggle with. This is the classic paper that was in the *New England Journal of Medicine* in 2006. This is by Moran and colleagues that looked at 11 hospital affiliated emergency departments in August of 2004 and they looked at all Staph aureus isolated from the patients that came into the emergency department. Staph aureus was frequent, it was quite frequently MRSA but

what was more surprising is that it was the MRSA USA300 strain, which was a community-associated strain. So this strain was now out in the community and remember this was just done in 2004, this was out in the community and it had literally spread over the country and was responsible for the large number of patients coming into the emergency rooms with skin and soft-tissue infection having this USA300 strain that had this PVL toxin gene associated with it. And this is just a diagram of the prevalence of MRSA in the different emergency rooms that participated in that country. Again, in Canada we've been fortunate it has been mostly on the West coast, we're starting to see increasing frequency in the East coast but not as much as has been seen in British Columbia and Alberta.

A paper in JAMA 2007 showing the impact, how important MRSA is in the hospital setting: 32 per 100,000 greater than the combined rates in 2005 of pneumococcal disease, group A strep disease, meningococcal disease and H. influenzae, a really important player. And I will make a note: I think this really woke people up. It really changed, in fact, the veterans program in the US adopted screening of MRSA in all of their patients using molecular techniques and there has been a reduction of MRSA in the hospital setting as it continues to increase in the community setting – a little bit of evidence that we might be able to do something about this. And this just showing that different strains have become endemic within different parts of the world. This is showing a slide from Chip Chambers in San Francisco looking at the different types of MRSA in his hospital and look at 2004; USA300 that has come from the community and has become the dominant isolate in the hospital setting. So it's not happy, it's not satisfied with causing disease in the community but actually coming into the hospital setting and establish itself as an important cause of hospital acquired infections.
And it's not just in humans, it's in animals. This is the MRSA sequence type 398 which has been found in horses, cattle, dogs and swine, and has been transmitted to farmers, to people, causing disease reports in the Netherlands, reports in Canada, Scott Weese reporting this out of Guelph, in the US and in Europe. In the Netherlands it is responsible for more than 20% of all MRSA infections. So we are in close contact, sharing bacteria with our agriculture colleagues and friends.

So I'm going to end up with enterobacteriaceae quickly, this is such an important topic. I really don't know how eventually we're going to solve it but we know a host of different ways in which gram negatives can become resistant to bacteria, whether it's not letting them in, whether it's pumping them out, whether it's breaking them down with enzymes, or whether it's modifying their targets so the antibiotic doesn't bind. It's really quite amazing. But if we focus on the enzymes that these gram negative produce to break down the penicillins and the carbapenamases and the cephalosporinases. ESBL has become a real player, a real problem which has emerged over the last 10-15 years and has been so effective in

spreading. This is just data in the Ron Jones' SENTRY program looking at different countries in Europe showing the increase in prevalence of Klebsiella and E. coli that contain extended spectrum beta-lactamases. But what changed? And this is unusual; you would think okay.. the ESBLs essentially they were derived from TEM and SHV beta-lactamases and there were literally hundreds of them. But now what we're seeing is a strain of ESBLs, a strain called CTX-M and it is not derived from the TEMs and SHVs that are normally found in gram negative bacteria, but rather it escaped from Kluyvera and into other enterobacteriaceae that causes disease in humans and that accounts for the CTX-M type ESBLs and look how successful these are. They have traversed the globe and if you look especially at this CTX-M 15, it is everywhere. It is the predominant one in Canada, and in the US; been very fit, very effective in transmission almost like H1N1.

And then of course finally the carbapenamases. This is a disaster. These are enzymes which are breaking down our last major group of antibiotics. There's the serine-beta-lactamases, best represented by KPC. You've all heard of KPC which was first recognized in 2001. This is a paper by Fred Tenover describing KPC-1 in Northern Virginia, and look what's happened here in the US. Here's the first recognition of KPCs down here, these are serine-beta-lactamases; just look how quickly these things have emerged across the United States and many of them ST 258 being the most common of the ones identified... being the most fit. And this is just worldwide distribution; it's everywhere.

Now we get to the class B, the metallo-beta-lactamases and of course, the big player here is the NDM-1 Superbug which we all just became aware of in the media, in our laboratories in the last couple of years. This is the mother of all resistance complexes. It's a metallo-beta-lactamase which is able to break down carbapenamases, but get this; it can't do it on its own. What does it want? It's got NDM, what else could it want? and in fact it wants a lot more. It not only is on a transposon that has NDM-1 in it but it has a multitude of other genes that are resistant to antibiotics and they are very promiscuous. In the same patient you can see it in E. coli, in Klebsiella, in Morganella. It is one of the most promiscuous transposon. Look here; back in 2003, the first isolate that was identified in a UK laboratory, quickly increasing in frequency. The grey are the NDM-1s and the reds are other carbapenamases. Because of global travel, mostly originating from India where the strain got its name New Delhi beta-lactamases. This is one of the first we had here in the public health lab in Ontario; look at what it had: it had NDM-1, CTX-M-15, SHV-11, OXA-1, TEM-1. What else does it need? I mean how selfish can you possibly be? Taking all of those resistant mechanisms and then when you test them, you can see here, you don't have any drugs to treat. Even tigecycline and colistin which were thought to be saviours, something to treat these, we've actually found resistance to both of them in some of our isolates. We've also just published a paper showing an outbreak of carbapenamase

in a hospital in Ontario with no history of travel, which is quite bothersome.
What are we going to treat these patients with? Well, there's few or no options. In Greece they reported – not a great study – but attributed to mortality, if someone has a real infection of one of these things, 50%. So, yeah we have a problem here. We need new drugs.
And where is this thing coming from? It's not only coming from hospital settings in Pakistan and India but it's also in the drinking water, also in the seepage water. This study that was published in Lancet was able to identify it in both of those sources. So that if you go there visiting, there is a very good chance you might come back with it, or an ESBL or CTX-M, just by being exposed to the environment.

Finally I just have to mention class D. This is an OXA-48. They've seen a number of these cases in Ottawa and the problem is they're tough to diagnose in the lab. We don't have a natural inhibitor which might give us a clue that it's an OXA-48 and it often comes along with other ESBLs which makes it difficult to identify, so this is a real threat. It could become endemic within our hospitals before we even recognize that we have it. This is just a number of reports showing problems that it has caused in a number of different countries.

So I just want to end on one note here, medical tourism. This is a growing business where people go to other countries to get medical procedures that are cheaper there than here. Cheaper for insurance companies and also the technology and expertise is excellent, but the infection control is not so good. The control of antibiotic use is not so good, so often these patients will become colonized or infected with one of these strains, and when they come home for convalescence they bring it back with them. So medical tourism is a real problem that I am not sure how to address but is going to continue to raise its ugly head over the next few years.
What's the solution? We can't give up. Education; critical. Stewardship; important. Use of PK/PD principles to prevent; also critical. So, there's a long way to go, but for us in infectious disease and microbiology and infection control it's exciting times. I mean we've got challenges coming every which way and we've got it from the community, from sexually transmitted diseases, from hospitals, from return travelers; I mean it's a very interesting time and it just tells you and reinforces how important it is to have this week where we recognize the importance of antimicrobial resistance. And so, with that, I'll thank you for your attention and I'll be glad to take some questions.

Stacie Ross - I'll give everyone a little bit to think if they have anything to ask but I'd like to give a big thank you to Dr. Low for that really incredible presentation. It was excellent. We can always follow up later if any questions are asked and forward them on to Dr. Low. Another big thank you to all partner organizations, whose logos are featured on the last slide and they partner to put on Antibiotic Awareness Week each year. If you

note on the last slide, please click on the survey; it's about a 1 minute survey and your feedback will greatly enhance Antibiotic Awareness Week Activities in Canada for 2013. Dr. Low briefly discussed multidrug-resistant gonorrhea. Please join us on Friday at the same time for more information on this subject. Speakers from the Public Health Agency of Canada will be providing information on strain-typing of gonorrhea and new treatment guidelines - and it looks like that's it. I don't see any questions posed, so thank you so much Dr. Low.

Dr. Donald Low - Okay. Thank you!

Stacie Ross - Have a great day. Thank you everybody! Thanks to all of the participants as well.