"Return of the Syphilis: New Tests, Pregnancy and Congenital Syphilis"
Symposium

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Speakers Present: Dr. Tom Wong
Dr. Barbara Romanowski
Dr. Ameeta Singh
Dr. Bernard Gonik
Dr. Joan Robinson

Segment 1 - 0:00:00 to 0:02:46

[…]

Introduction:

Dr. Tom Wong: It's being held here in Canada. I'll give perhaps a little bit of Canadian context. Way back in 1996, we have established the Canadian goals for STI prevention together with all of our partners, including our goals for infectious syphilis of under 0.5 per 100,000. Of course around that time, we already reached that goal. However, things did not turn out as well as we had hoped. Since that time there has been a skyrocketing of infectious syphilis rates; almost 10-fold in Canada as you can see in the next slide. You can see that the top line (blue) is males and the bottom line is females and yellow line in between is the overall rate. This is the reported rate of infectious syphilis in Canada by sex between 1993 and 2008. And as you can see there are major increases in particular in males and also in females. The female's increase in reported infectious syphilis rate seems to be plateauing; not so sure about males yet. There may be as I am turning around the corner but time will tell.

Now, where were they occurring over the past decade? Over the past decade, there has been a number of different places across Canada and some still with ongoing outbreaks. It's just not happening in one particular city or one particular jurisdiction. As you can see, whether it's Halifax, Montreal, or Ottawa, etc, they were happening in different parts of the country, including up

north as well and most recently in the Northwest Territories. Now some of the drivers in the different jurisdictions were different. Some were driven primarily by the MSM outbreak, whereas others heterosexuals, yet others both MSM and heterosexuals. The question for some is what about congenital syphilis? Indeed, we have seen resurgence of congenital syphilis. Before 2005 we used to have anywhere between zero and two cases a year reported in Canada, but ever since that time we had been seeing seven to eight cases reported a year.

Segment 2 – 0:00:00 to 0:36:42

With that, I'm going to introduce our first speaker, Dr. Barbara Romanowski who's going to explore with us some of the challenges and opportunities associated with new diagnostic tests in syphilis. First of all, welcome Dr. Romanowski. Dr. Romanowski is a clinical professor in infectious diseases, medical micro and immunology at the University of Alberta, where she is trained in both internal medicine and infectious diseases. She also had a cross-appointment at the University of Calgary. She used to hold the post of Director of the STD program for the province of Alberta from 1979 to 1998 and essentially built up that particular program. And of course, for those of who you know Dr. Romanowski, she needs no introduction. She has published extensively on STDs and sat on many editorial boards as well as funding agencies, grant review bodies. Without further ado, Dr. Romanowski.

First Speaker,
Dr. Romanowski: Thank you, Tom. Thank you to those of you who are still here for the end of the meeting, for what is going to be an interesting

symposium. If one is an infectious disease physician, probably sexually transmitted diseases are a good sub-specialty because I don't think it matters how good we are in public health or in epidemiology, human behaviour always prevails and even if you have good programs, someone is going to engage in very unsafe sexual behaviour and we will continue sadly from time to time to see outbreaks.

So my tasks over the next half hour is to review the diagnosis of syphilis. What I'm not going to talk about is the diagnosis of congenital syphilis. I will leave that to Dr. Gonik, Dr. Ameeta Singh, and Dr. Robinson to talk about later on. What I will review is currently available diagnostic tests for syphilis, tests that are new on the market and tests that are still in development. And I'm trying to be the comedian by entitling my talk "Diagnosis of Syphilis: The Bare Essentials". The objectives of the talk are to review the laboratory diagnosis of syphilis, to review new diagnostic tests, the appropriate tests to order by stage of syphilis, to very briefly review syphilis serology and HIV infected individuals because you could in fact do a separate talk on that talk topic alone, and then to review the interpretation of pre- and post-treatment serology. What I missed on the first slide is that I do not have any conflict of interest for this lecture.

Syphilis serology goes back to 1906. This is the title page from the original article by Wasserman whose name we all recognize in the area of syphilis serology. In 1901 the first compliment fixation test for syphilis was reported and it was improved upon in 1906 by Wasserman and his colleagues. Six years later there was a further advance in the introduction to Nichols stain and then it took another 10 years for the flocculation test to be introduced.

There was then a very long hiatus and the antibody test did not become available until 1949. It was another 10 years before we saw the fluorescent treponemal antibody test (FTA) be introduced and then in 1965, the hemagglutination tests were introduced. And really not much has happened since 1965 in terms of availability of new tests until the last five or six years when we are seeing rapid tests introduced and utilizing new laboratory technology to diagnose this disease.

So I'm going to divide this presentation into the three groups of tests that we have available: the direct detection of *Treponema pallidum* or the microscopic examination, the non-treponemal serology which generally we utilize for screening and to assess treatment response, and treponemal serology.

In terms of direct detection of *Treponema pallidum*, this test is sensitive and specific, but it is limited in its use to the availability of lesions. So, one needs to obtain specimens, most commonly in primary and secondary syphilis and sadly recently in North America from newborns with congenital disease. You need a moist lesion obviously to get a positive direct detection, one needs to also obtain a good specimen. The big advantage of the direct detection is that it permits an immediate diagnosis. We know that serology is useful but it can take days or weeks for it to become positive. So if one sees the organism you have the diagnosis. However, a negative dark-field examination does not necessarily exclude the diagnosis of syphilis. One, there could be sampling error. Two, if the individual put antibiotic ointment on, or the best story I've heard is cigarette ash, which he claimed healed the lesion. That certainly can interfere with getting a good sample and with seeing the organism.

The direct detection is divided into dark-field microscopy, which is very sensitive but is really a dying art. It requires very skilled personnel and a dark-field microscope, and dark-field microscopes are difficult to acquire. I don't know, by a show of hands, who has access to a dark-field microscope? [Show of hands presented]. So three or four individuals. And in Edmonton where we used to have a dark-field microscope at the STD clinic, we no longer do have. So I think those of us who have experience in dark-field microscopy need to keep our skills up to date. Dark-field microscopy at the bedside is largely being replaced by the DFA, direct fluorescent antibody tests, which detects and differentiates pathogenic from non-pathogenic treponemes. So, one of the limitations of dark-field microscopy is of course we make the diagnosis by the characteristic mobility and motility of *Treponema*, but we cannot differentiate under a conventional dark-field microscope pathogenic from non-pathogenic treponemes, but with the DFA you can do that. The test is based on an antigen antibody reaction, and can be used at extra-genital sites, so you can use it for oral lesions and you can use it for rectal lesions. **[Please note: In the latest version (January 2010) of the *Canadian Guidelines on Sexually Transmitted Infections* Syphilis chapter, fluorescent antibody testing and dark-filled microscopy are not recommended for oral or rectal lesions and in these cases, dependant on availability, NAAT may be an option]** The sensitivity is reported to be 100% if the specimens are fresh. The other advantage of the DFA is that samples can now travel. Patients with syphilis do not only live in urban areas close to reference laboratories. With a DFA you can collect a sample in northern Ontario or in the Northwest Territories, or in the far north of the Yukon, transport it to the laboratory and the

laboratory can stain it and give you an answer. There has also more recently become available molecular tests for *Treponema pallidum* like the PCR [polymerase chain reaction], but these tests are only available in large centres and I'm not going to spend anymore time talking about them.

So the characteristic, perhaps now old fashion dark-field microscopy with the characteristic corkscrew shaped organisms that one likes to see undulating across the microscope field and the perhaps more easy to differentiate with fluorescent treponemal antibody tests where these organisms really are very very easy to pick out.

Now the rest of my talk is going to deal with serology. I think the first point that is important to make is that serology differs by stage of disease because it takes time for IgG and IgM to develop. This table was taken from Larsen's publication in 1995 but really the data hasn't really changed. Looking at the conventional syphilis serology tests that are available, the bold yellow line, ¾ of the way down, separates the tests from non-treponemal and treponemal. So you can see for primary syphilis, I am going to point on the screen to the left here, for primary syphilis the non-treponemal tests all have sensitivities that are below 90% because most of those tests will measure IgG. By the time you get to secondary syphilis it doesn't matter which non-treponemal test you use, you can't expect that test to be positive. But as the patient develops latent syphilis, whether it is early or late disease, even without treatment, the non-treponemal tests will spontaneously serorevert. In late latent disease, you have a 25 to 30% chance of having a non-reactive non-treponemal test. And therein lays the huge problem of screening with currently utilized

non-treponemal tests only, because you run the risk of missing a significant number of cases of primary syphilis and late disease. The specificity of non-treponemal tests are very good. The two treponemal tests, the fluorescent treponemal antibody absorption test [FTA-ABS] and the micro hemagglutination for *Treponema pallidum* for primary syphilis are somewhat better at picking up infections. They are excellent as the non-treponemal tests are in secondary disease and they are much better in detecting cases of early, latent, and late latent disease, but as this table shows, they are far from being perfect in helping us confirm the diagnosis.

So the traditional non-treponemal tests that are available, VDRL [Venereal Disease Research Laboratory] was the first one that came to market followed by the rapid plasma reagin [RPR] test and then the unheated serum reagin [USR] test and the toluidine red unheated serum test [TRUST]. All of these measure reagin which is an anti-lipidoidal antibody that is directed against specific antigens of the treponemes. It takes one to four weeks for these tests to become positive and that's why they do not perform very well in primary syphilis. However, the advantage is that they are rapid, they are very easy for the labs to perform, and they are relatively inexpensive.

The non-treponemal tests are still the only tests that are quantifiable. So these are the tests that we rely on to help us stage an individual. So, if you have a dilution of 1:128, it is highly unlikely to be a case of latent syphilis. The non-treponemal tests are the only test available also that allow us to judge adequacy of treatment, so as you know we follow decreasing dilutions post therapy. They also are the only available tests that allow us to detect reinfection again by virtue of the quantitative nature of the

serology. Problems, reduced sensitivity in very early and very latent disease and most commonly in secondary syphilis, this pro-zone reaction, which is this overwhelming presence of antibodies which will react with the antigens giving you a false negative unless you ask the laboratory to dilute the specimen prior to doing the test.

Before I talk about treponemal tests, I had a corridor conversation with Rosanna Peeling this morning who informs me that WHO [World Health Organization] is in fact undertaking some field tests of new rapid non-treponemal tests. Apparently the results of those field trials should be available in the next month. That's the only information I have, but Rosanna is in the room so if anyone in the room has questions, perhaps she can answer them later on.

So in terms of treponemal tests, the old tried and true are the FTA-ABS, the *Treponema pallidum* passive agglutination [TP-PA] and the micro-hemagglutination test. These are tests that measure anti-treponemal antibody against *T. pallidum*. It measures both IgG and IgM and the [IgM] appears about two weeks after infection and the IgG about four weeks after infection. This is post-infection, not post-symptom which can be very different. So if someone was exposed two weeks ago, their serology may be positive but they may not develop their primary lesion for another few days. Generally speaking, these tests are the first test to become positive in early syphilis. The treponemal tests are used to confirm a diagnosis of syphilis if you use non-treponemal tests as screening and if you find they are reactive. The treponemal serology however, unless you treat someone very early in their disease, these tests will remain positive for life. So a positive treponemal serology does not absolutely confirm the

presence of new infection. The lab interpretation is subjective, especially for the FTA absorption. It is in the eye of the laboratory technologist who is undertaking the test. And these tests do not differentiate venereal from non-venereal disease. So if you are utilizing these tests in areas of the world where there is a lot of non-venereal syphilis, you will see a lot of false positives.

And we see false positive reactions with almost every lab test available. For the non-treponemal serologic test I've spoken about, viral infections, pregnancy, malaria, leprosy, being elderly, injection drug use, active IDUs can certainly have false positive serology, and individuals with auto-immune disease. For the treponemal infections, auto-immune disease, genital herpes; probably 8% of individuals with genital herpes have false positive treponemal serology from time to time, which can be a huge problem if you don't recognize that they have genital herpes and are trying to diagnose their genital ulcers. Of course the non-venereal treponemal infections, yaws and pinta, and conditions like cirrhosis.

There are a number of new and very exciting treponemal tests that are currently available or still in development and ones I'm going to cover are the enzyme immunoassay [EIA] treponemal tests, the line immunoassay [LIA], the rapid point of care tests and the chemiluminescent assay [CLIA].

So first of all, the syphilis enzyme immunoassay, I'm not going to talk about specific manufacturers, but rather give you an overview of these tests. So all of the manufacturers of the EIA kits say that they measure IgG and IgM. But if you are thinking of switching to EIA, I would caution you to carefully look at the material and

make sure that the test does measure both IgG and IgM because although some of the manufacturers claim that they do, in fact, they do not. The best study I have read looked at ten different EIA kits and they compared the performance of those kits against 114 archived samples from patients who had confirmed syphilis. The sensitivity was very wide, anywhere from 94% up to 99%, but the specificity was 100%. It performed well at all stages of infection, but again false positives were seen most commonly in primary syphilis and most commonly in the kits that were not so good at picking up IgM. The advantages of the EIA is that it is easy to perform. The laboratory has the ability to automate the EIA tests and generate objective results if they utilize plate readers. The disadvantages are the false negatives. Again one cannot differentiate venereal from non-venereal treponematosis. As I said all kits claimed that they measured IgG and IgM, but in fact they didn't. Again, this is a treponemal test so it will remain positive for life, but there is more and more interest in some jurisdictions including our own that switched the screening algorithm away from the traditional non-treponemal tests to the treponemal tests utilizing the EIA.

The line immunoassays [LIA] for *T. pallidum* utilize recombinant and synthetic polypeptide antigens. In the review that I cited on this slide, they compared the LIA to 531, again archived, what they called reactive samples, and their definition of reactive was somewhat not standard. So they defined a positive serology as positive by VDRL and/or TPHA plus a reactive FTA-ABS and/or a positive Western blot and/or a positive enzyme immunoassay (EIA). The sensitivity of the LIA was fabulous at 100% with a specificity of 99.3, so this certainly, looks like an excellent treponemal test that perhaps one might use for confirmation.

There are also rapid point-of-care treponemal tests that have come to the forefront. Again, these utilize recombinant treponemal antibodies. Evaluations have been carried out by the WHO, have been tested in eight laboratories in Africa, Asia, and Eastern Europe, and the Americas, Central America and the U.S. Each lab was provided with 100 archived samples that were previously tested with the RPR, the TPHA, and the TP-PA, and asked to evaluate the kits. Sensitivity was pretty good, 84.5 to 97.7, with specificity of 93 to 98%. These tests are very inexpensive. They are extremely simple for individuals who do not have access to laboratory equipment and who do not have a centrifuge. You can use whole blood, serum, or you can utilize plasma with rapid results available in less than 30 minutes. No refrigeration. All you need is blood and the kit. These rapid point-of-care tests also have the advantage of not being prone to the prozone reaction, so regardless of how much antibody there is in the sample, you'll get a positive result. However, again they cannot differentiate past from present infection, and they are not quantifiable, so one cannot utilize these tests to monitor therapeutic response.

The chemiluminescent test [CLIA] utilizes micro particles against three recombinant antigens from *T. pallidum*. In this study, they looked at 129 sera from untreated cases and they compared it with the EIA, the TP-PA and the VDRL. It performed very well, 97.5% in primary syphilis, so again it's not picking up as much as we would like it to, but 100% for all other stages, secondary, early latent, and late latent with a superb specificity if 99.1%. The test is automated and rapid, but I don't know if it's inexpensive or expensive because it is generally not yet available.

In summary for the serologic tests for syphilis, in the past most laboratories and programs have tended to do is to use a two-step algorithm, first screening with the non-treponemal test like the RPR and following that with a specific treponemal confirmatory test. Many centres are now utilizing the new technology and switching to an algorithm using a rapid screening treponemal test like the enzyme immunoassay (EIA), following this with an acceptable confirmatory test, which would also be a treponemal test and then adding the RPR, which gives you your only quantifiable result to help stage disease and monitor therapy.

I just want to spend a few minutes talking about syphilis serology and HIV infection. There has been and continues to be lots of discussion on how useful syphilis serology is in individuals who are HIV positive and do we need to investigate those individuals differently. This is an article that was published two years ago that looks at an HIV positive group and an HIV negative group and compares reactivity of syphilis serology. So among the HIV positive individuals, 28% had early syphilis, which they defined as primary or secondary. The HIV negative group had much more early disease and therefore the HIV positive group had more latent disease. In terms of reactivity of the RPR, there were more low-reactive RPRs, but that could well be explained by the fact that the majority of the HIV positive individuals had late latent disease. There was no significant difference in the titration at 1:16 to 1:64. And the greater than 64, as expected one would see, because of the stage of presentation, there were less in the HIV positive. So, this study and many others that have been published suggest that syphilis serology is very useful in the HIV positive individual. That group may have more aggressive disease, but

there is no reason to suggest that one needs to utilize different syphilis serologic tests in that population.

I would also like to say a few words on “cerebral syphilis” as it was called in 1923. Basically, the diagnosis of neurosyphilis is one you have to have reactive serology in the serum, whatever your algorithm is. It has to involve a treponemal test and hopefully a non-treponemal test as well, and then interpretation of the cerebral spinal fluid [CSF]. There probably should be two abnormalities, although some of the articles in the literature define neurosyphilis on one abnormality alone, but what one is looking for is pleocytosis, elevated protein, and reactive VDRL. The article that I’m going to cite is Marra’s article from 2004 in JID [*Journal of Infectious Diseases*], where they looked at HIV infected and non-infected individuals and a number of factors to look at the probability that someone with syphilis may also have neurosyphilis.

So first of all, if you look at the HIV uninfected subjects that were reviewed in this study, in the adjusted ORs, the only test that was significant was the titre of the RPR. So if the titre was 1:32 or higher, the chance of the individual having neurosyphilis was significantly higher. This conversation happens everyday at the STD clinic. You have someone who’s RPR is 16 and they don’t have any neurological symptoms. Should they be investigated for neurosyphilis or not, versus someone who has a RPR of 128, but who probably presents with a chancre. You treat the chancre, the serology falls, I don’t think this discussion comes into play, but if the serology remains above 1:32 then the question of neurosyphilis and the need for a LP [lumbar puncture] does need to be reviewed. And if you look at the larger sample in this study

of HIV positive individuals, they had 233 individuals, again the only significance was the serum RPR; same level as the non-HIV infected population, and the other significance was that the CD4 count was less than 350, which was highly significant. So the data suggests that the investigation of HIV and non-HIV positive individuals at least at the time of their initial presentation is probably not much different.

After treatment, the only way we can define adequate response is by tube dilutions. And according to the guidelines, if you're treating someone for primary syphilis, is that at 6 months there should be a two-tube dilution, and at 12 and 24 months a three and four-tube dilution. Secondary syphilis, you're going to start with much higher titres and they are going to fall much faster as we're looking for three and four-tube dilutions at 6 and 12 months. Early latent syphilis, you're lucky if you see a two-tube drop at 12 months.

Now it is possible for patients to serorevert, or for their RPR to be non-reactive after treatment, but the chance of that happening depends on how early we treat the patients. So if you look at the red line, these are patients that had their first episode of primary syphilis. One would think that once you've had this, you wouldn't do it again, but these are results from a huge outbreak we had in Alberta in the mid-80s. There were a large number of individuals who did not learn the first time and were cured of their primary syphilis and months later reappeared with another chancre. So if they were treated early the first time they had primary syphilis at 36 months, 80% of those individuals had a negative RPR, but the later they were treated, the less likely their RPR was to

seroconvert. So really what we are looking for is a decrease in quantitation, not necessarily a non-reactive RPR.

So, if we know syphilis in all its manifestations and relations and all other things clinical will be added onto you. It really is true for this disease that I think many individuals thought belonged in a realm of the ancient venereologists and no one paid much interest to it. But sadly now that we are seeing more and more cases of congenital disease, more people are jumping on the bandwagon. Thank you for your attention.

Segment 3 – 0:00:00 to 0:23:18

Introduction of 2nd Speaker.

Dr. Ameeta Singh: Thank you very much Barb for an excellent overview of testing in syphilis and I think in the interest of time, we will move onto the next talk. I am very pleased to present Dr. Bernard Gonik who is a graduate of the Michigan State University School of Medicine and is currently professor and chair of Perinatal Medicine in the department of Obstetrics and Gynaecology at Wayne State University in Detroit, Michigan. So, Dr. Gonik has published extensively in the field of infectious diseases and obstetrics, and I should also mention that he did tell me that he is in part Canadian because he has a place on Lake Huron and he visits here regularly. So without further ado, Dr. Gonik will present a little bit about the epidemiology of syphilis primarily related to pregnancy and congenital syphilis and also data mostly from the United States.

2nd Speaker,

Dr. Bernard Gonik: Good Morning.

[….]

I am an obstetrician and gynaecologist and from the United States. I'm going to very loosely represent both the obstetrician gynaecologist perspective and some of the data from the United States in general related to syphilis. I have no disclaimers or conflicts.

So briefly if we look back on the reporting of syphilis in the United States, and the epidemiology of syphilis, we first started reporting the United States in 1941. From that time, soon after 1947, the peak rates that have ever been reported in the United States were 66.4 per 100,000 population. With the advent and introduction of penicillin in the general population, there was a rapid decline in the cases of syphilis reported to the CDC [Centers for Disease Control], such that by 1956 the reported rate was 3.6 per 100,000. Since that time, there have been some peaks and troughs reported in terms of syphilis cases, with an overall trend downward, such that in 2000, the reported cases of syphilis in the United States was 2.1 per 100,000 population. That being the case, the CDC thought this was a perfect opportunity to introduce a national plan to eliminate syphilis from the United States. In fact, the plan was developed and instituted in 1999, just prior to the lowest levels ever reported, as I mentioned, in 2000.

The main impetus for introducing such a plan was that we thought we had the disease on the run, and as the disease was in the decline, there was a good opportunity to, in essence, try to eliminate the disease. The strategy that was used relied on the public health service and the initiatives within the public health

service to enhance surveillance, to get the community involved and to attack or deal with rapid outbreak responses to expand clinical and laboratory services and to enhance health promotion. Those efforts were hopefully going to achieve the goal of reducing the cases of primary and secondary syphilis to less than 1000 cases per year. That would translate into a rate of 0.4 cases per 100,000 population.

Now, why was this thought to be important? I think the answer is pretty straight forward, and I've listed some of the reasons on the slide here. It's important because it's an important disease and in reducing the disease, of course reduces the health burden within that population. In addition to that, the persistence of the disease is a good surrogate marker for a public health effort that has in essence failed. So that's an important gauge by which these efforts that I outlined in the previous slide could be judged in terms of their success or failure. The other key issue is that syphilis is really a sentinel event that is associated with a number of other health-related issues, including a condition such as HIV that was briefly discussed in the previous talk. It also relates to risky sexual behaviour in a number of ethnic and racial boundaries issues that we deal with on a regular basis.

So that's a great plan. It seemed like we were headed in the right direction and then as you can see from this slide, in 2006, the CDC reframed that plan. The reason that it required reframing was because instead of the disease remaining on the decline, in fact syphilis has continued to increase within the United States. There were gains that were achieved based on the initial efforts and those were highlighted in the report that was revised by the CDC in 2000 and those gains included a reduction in rates among

Blacks, among women, a reduction in congenital syphilis, and a reduction in the black/white disparity. However, the new challenges from the data that were generated were pretty clear. For example, we were seeing syphilis emerge in specific and special populations, including men having sex with men (MSM). That population has and continues to be a significant concern as it relates to syphilis. Also, one of the major changes that we saw occurring within the United States was a shift from the STD or public health service identification of the disease more into the private sector. To highlight the observation of concerns related to men having sex with men and the rates of syphilis, the estimated proportion of primary and secondary syphilis cases, attributable to men having sex with men (MSM), increased from about 4% in the year 2000 to 62% in 2004. That really highlights that specific population.

In terms of new goals that were established in 2006 that are applicable today. They are to reduce the overall incidence of syphilis to a more modest less than 2.2 cases per 100,000 population. At the same time to continue to attempt to reduce the rate of congenital syphilis, here the goal being of less than 3.9 per 100,000 live births. And then to continue with a reduction in the black/white disparity, such that we can achieve a less than 3:1 difference in terms of those two populations. Again, this new strategy focused on public health related efforts; these focused on now specific populations and applied culturally competent interventions. As an aside, and sort of a selfish aside for someone like myself, an obstetrician gynaecologist, when the public health efforts are focused on those populations we sometimes will lose in terms of the continuing efforts related to congenital syphilis and syphilis within women. So it’s always something we have to be

vigilant about in terms of watching what happens with those populations as well.

Now in terms of some of the data, to highlight some of the things I have just presented to you, this is data from the CDC. As you can see on the X-axis we are looking at years 1941 through to 2007 actually recorded on this slide, and this is broken up into primary and secondary syphilis, latent syphilis and total cases of syphilis. As I mentioned before, […] again, when cases were first reported, these were the overall peak cases reported in 1946 and 1947; the highest cases with a reduction, subsequently there was a subsequent peak here in the early 90s, but overall a reduction in cases of syphilis, again with an introduction of penicillin around this point in time.

This slide looks at primary and secondary syphilis and it breaks it down by regions within the United States; the Midwest, northeast, southwest, and then the target goal for 2010, shown on the bottom portion of the slide. You can see all the numbers are above that target goal for 2010. But I think it's important to recognize that within the United States, there are significant regional differences. This continues to be the case where the south portions of the United States have the highest rates and continuing to increase those rates even as we speak today. There's a relatively flat curve in the Midwest regions and some differences increasing in the west as well, which is something that needs rather careful surveillance.

These are data that are based on looking at primary and secondary syphilis, and now it's looking at the reporting source and the sex within the population. Again, it's broken down into the non-STD

clinic male population, the non-STD clinic female population, STD male clinic population, and the STD female clinic population. Again, as I mentioned on the previous slide, what's dramatic is this non-STD male clinic population that is sort of surging upwardly on the graph that's divergent from the rest of the population. Here is where we are seeing a significant concern, because that's now where a lot of the public health efforts have previously been applied.

This is also represented here in this bar graph looking at heterosexual men and women and men having sex with men [MSM]. This is actually the bar that demonstrates the non-STD clinic. The private physician HMO [Health Maintenance Organization] population is represented in this bar. This is disproportionate in contrary to the two populations where the numbers are still below those of STD clinics where most of the syphilis surveillance and interventions are being handled.

Looking now at a breakout of the data from the United States on male versus female, again not unexpected that the male cases are significantly higher than the female cases. This is the total cases of primary and secondary syphilis, with males being represented here on the rise and females being represented here. Although it looks flat, these numbers continue to rise and females, also along with males, continue to show an increase in cases of syphilis within the United States.

I'm going to focus a little bit more on women and congenital syphilis for the remainder of my presentation on the data here. This is now again CDC data looking at primary and secondary syphilis in the United States for women and this is broken up

based on racial differences, the lowest numbers are of the Asian-Pacific and white population, followed by the Hispanic population, the Indian-Alaskan population and the highest rates are identified within the black female population within the United States. Again, relatively flat numbers down here with a divergent and rising incidence of syphilis within this specific section of the female population.

This is broken down again into region and the data is consistent for women within region as well. The highest numbers and the rising numbers again within the south of the United States, again relatively flat for the Midwest, and for the northeast as well, represented here. In terms of age of the female population where primary and secondary syphilis had been identified, it's not surprising these data remain relatively consistent over these periods of time, the age range as well, within the reproductive years and therefore we have the significant concern for congenital syphilis. There is this secondary peak within the female population somewhere in the early 40's and early 50's.

Now, here is a bar graph looking at congenital syphilis within the United States reported as a rate per 100,000 live births, and as you can see, the numbers from 2003 through to 2007 were on the decline. The lowest numbers for this short period of time was in 2005 and now we are seeing a march forward where the numbers have significantly increased in the year 2007. That rate, in case you cannot read it, is somewhere a little over 10 per 100,000.

To break it down in terms of congenital syphilis, the data remain consistent related to ethnic variations. Here, the black population in terms of syphilis compared to a white or Hispanic population of

syphilis. Again, significant differences between those different racial and ethnic populations.

For the last portion of my presentation, I'd like to focus a little bit on congenital syphilis and actually deal with some of the difficulties in establishing the diagnosis and how those diagnoses are recorded, and I think this is actually an eye-opener for individuals who don't sort of peel the onion to get down to some of the actual reporting requirements for syphilis. This stems from a report within the United States, related to Detroit, which I will present to you in just a moment. For some background information, if we talk about congenital syphilis, it is important to recognize that the risk of fetal infection is related to the stage of maternal infection; that being more common if the mother has primary or secondary syphilis, and a lower risk of congenital infection as the disease goes on in terms of time in the mom. Primary and secondary syphilis, if it remains untreated the general rules are that about 40% of those individuals who are pregnant will have spontaneous abortions or stillbirths or perinatal deaths. Another 40% of those individuals who have primary or secondary syphilis that remains untreated will have congenital infection or congenital lesions. So, a significant proportion. Maybe the overwhelming majority of those moms who are pregnant will have adverse events related to their fetus or infants pertaining to syphilis. Now importantly, those individuals who get appropriately treated, there is about a 98% prevention of congenital infection estimated for this patient population. Thus, the elimination of congenital syphilis requires prenatal screening and prompt treatment, and this is sort of the "call to arms" for all of us who deal in any obstetric patient population, because we have such a dramatic effect of syphilis on the incubating fetus,

and because intervention/treatment has such a dramatic effect on improving that adverse outcome, this is obviously where we have to spend a lot of our effort and time.

So, this is the data that I was telling you about. We published a paper in the *Infectious Diseases of Obstetrics and Gynaecology* in 2006 and we had a title for the paper, "*Is congenital syphilis really congenital syphilis?*" It was intended to be provocative in terms of a title and it really stems from a 2003 report coming from out of the city of Detroit, where the congenital syphilis rate was reported at 250 cases per 100,000. That was for 2003; the highest within the United States. Now, as a backdrop again to look at how important or high that number is, in the rest of the United States in 2003, it was a 10.3 per 100,000 live birth numbers. So, rather it was a dramatic difference. We thought and investigated this as being a possible anomaly based on the health department use of CDC evaluation reporting processes. In order to understand that, let me briefly define that for you right now.

The Centers for Disease Control has a number of different ways to define congenital syphilis. For example, if an infant or stillborn is born with classic features in an infected mother, the baby obviously has congenital syphilis and would be classified as such. In addition, you can have what's called confirmed cases and that would be where there is laboratory evidence of the organism in a neonate or in a placenta. What I thought I saw in Dr. Romanowski's slide, this is the basis by which congenital syphilis is established within Canada and that's something I need to know more about and it might lead to an interesting discussion after we finish with our formal presentations. Now, there is also a probable category and that again is listed as congenital syphilis and

“probable” in this case means either inadequate, no, or unknown maternal treatment for syphilis regardless of the infant status. So, if the mother has inadequate or no treatment or unknown treatment, again that infant, regardless if he is infected or not, however it looks, is classified as congenital syphilis. In addition, if they did receive an appropriate therapy for syphilis, but they have an inappropriate, no, or unknown maternal serologic response to syphilis, that defined by the CDC is a four-fold or more decrease in the RPR or VDRL over a period of three months. And remember, most of the time we talk about six months outside of this pregnancy related event in terms of looking at this four-fold or more decrease. In those circumstances, with appropriate treatment, but in unknown, inappropriate or no serologic response and in these infants, if they are examined and have evidence of an abnormal CSF, or abnormal bone X-rays, or (this is a key issue) they are not evaluated, those would be categorized within the probable category, and therefore would be a case definition of congenital syphilis by the CDC. And we are going to focus on this probably category because that is where most of the reported disease turns out to be present.

Here are data from the Detroit area from 2002 to 2004. These are the total number cases of congenital syphilis that were reported. And as you can see there are no confirmed cases; there were a couple stillbirths in this period of time. One infant was born in 2004 with classic signs of syphilis, but the overwhelming majority of cases in each of these years were probable cases. That is, congenital syphilis cases that were reported to the CDC from the health department were 94%, 97%, and 100% in 2002 all probable cases, such that when you look at the total over that period of time about 97% of those cases, which were congenital syphilis cases,

were defined as probable. So, if we break down that probable category for those same years, we can appreciate that about half of them fell into the no, unknown, or inadequate treatment group and the other half (45% or so) fell into the no, unknown or inadequate serologic response to adequate treatment group. Again, these are the different number of cases over the different number of years. If you take just this group (38 cases that had adequate treatment but no, unknown or inadequate serologic response) you can see that the overwhelmingly majority, 35 of those 38 had no study of the CSF or X-ray of long bones and therefore were not adequately evaluated. Therefore, they had to fall into the congenital syphilis cases, regardless if they had congenital syphilis or not. Only three cases were evaluated in terms of their CSF and were found to be abnormal for the total group of 38, and none had x-ray abnormalities of long bones.

If you summarize quickly this data, you can see that within the probable cases, about two-thirds of the cases where there was question about the treatment itself, about two-thirds of those cases had no prenatal care. Interestingly, of those cases about one-third of them had an RPR that was either 1:1 or 1:2 and because we had inadequate treatment documentation, these could not be designated as serofast but most likely represented a serofast group. For the no, unknown, or inadequate serologic cases, about two-thirds of them had prenatal care, likely had RPR and VDRL drawn as part of their prenatal care, and likely had appropriate therapy for their incubating syphilis. The summary of the data in what I think hopefully will generate a discussion really relates to the reporting mechanisms and what that really means in terms of true congenital syphilis cases. Our data first is not intended to be critical, of the public health system or the Center for Disease

Control in their effort to define the problem. Clearly it's a difficult task and it's quite difficult when you have a number of different communities that you are dealing with in terms of surveillance population. Given the heterogeneity of the individual health department resources however, their follow-up protocols and so on, these data highlight that it's likely an overestimate of the true incidences of congenital syphilis in some populations. That is really a function of the ability to follow-up with those neonates after they were born. I think the results do emphasize the importance of neonatal assessment in this process and if resources needed to be applied, we really need to identify and chase down those neonates that were born of mothers who have had syphilis identified in their pregnancy and have those neonates more thoroughly evaluated. It is also important to recognize these limitations in CDC-based congenital syphilis reporting where we need to allocate future resources related to the public health system. With that, I think I'll stop. And I'll answer questions and participate in the panel discussion after this.

Segment 4 – 0: 00:00 to 0:27:26

Introduction of 3rd Speaker. Dr. Wong: This is a perfect introduction to the very exciting case discussions. There are a number of cases going to be discussed and each of them would no doubt draw out very interesting aspects of syphilis, and maternal and congenital syphilis. With this, we are going to have Dr. Ameeta Singh and Dr. Joan Robinson leading us through these cases. First of all, I'm going to introduce Dr. Singh. She was trained in infectious diseases including internal medicine at the University of Alberta and subsequent to that she received graduate training in epidemiology at Harvard. For the past ten years, until very recently, she was the provincial consultant for sexually

transmitted blood-borne infection in Alberta and has been and still is the medical director at the Edmonton STD clinic. She currently holds an academic appointment as a clinical professor at the University of Alberta in the division of infectious diseases. As well, she is a Senior Medical Consultant at Public Health Agency of Canada. With that, Ameeta.

3rd Speaker:
Dr. Ameeta Singh: Thank you Tom. I'd like to introduce my co-presenter, Dr. Joan Robinson, who grew up in rural Alberta and I know there may be a few non-Canadians in the room, so I'll just mention that Alberta is one of western Canadian provinces; one province in from British Columbia, which is on the far west coast. So that just sets the setting for you I guess, because we seem to have a predominance of Alberta speakers here today. Anyways, Dr. Robinson graduated from Medical School at the University of Alberta in 1983 and completed her paediatrics at the University of British Columbia. She then returned to Alberta in 1989 to complete a fellowship in paediatric infectious diseases and has been on staff there at the Scholar Children's Hospital since 1991. She is presently professor in the division of paediatric infectious diseases at the University of Alberta and continues to do clinical work as well as extensive research in a number of areas in infectious diseases. So, in addition to that, I've had the pleasure of not only training with Joan, but now working with her. Just by way of background, Alberta is experiencing a very significant outbreak, resurgence in infectious syphilis since 2005 and concurrent with that we've seen a number of cases of syphilis in pregnancy and also an alarming number of cases of congenital syphilis. This is in a province that has been experiencing a pretty significant economic boom and almost certainly the outbreak has been related to that. So, what we are going to try to do here is go

through some cases that we've actually seen and to ask for input from our distinguished panel members as we go along. So I'll start right now with the objectives.

Using illustrative cases, this presentation will provide an overview of the management and follow-up of pregnant women with reactive syphilis serology, and an overview of the assessment, treatment, and follow-up of infants born to mothers with reactive syphilis serology. I want to just quickly recap syphilis testing in both Canada and I think in many parts of the world as well as the United States. We do have two screening options available in Canada and this varies quite significantly by province and territory. Some provinces and territories continue to screen with a non-treponemal test, which is predominantly the RPR. This is followed by one or more treponemal tests, typically the TP-PA and/or FTA-ABS, while in other provinces and territories, the initial screen is with a treponemal test, such as the enzyme immunoassay [EIA]. Here in the province of Ontario with the CMIA, which is then followed by an RPR plus or minus another confirmatory treponemal test, which can be the TP-PA or as we heard, the syphilis INNO-LIA™.

Case #1

Our first case is a 25 year old woman who presents at routine prenatal screening at 10 weeks of gestation with a syphilis enzyme immunoassay which is positive, RPR non reactive and a syphilis INNO-LIA™ positive and that is equivalent to our RPR which is non-reactive, TP-PA reactive, and FTA-ABS reactive. Just to put this question to the panel, what other questions would be important to this point?

Dr. Romanowski: The important questions would be history and physical examination. I think the obvious differential diagnosis is does this woman have early syphilis where the RPR is not yet reactive? Is it old disease that was treated five years previously or ten years previously, or is it unrecognized old disease? So I would start with the tried and true history and physical.

Dr. Gonik: Also, as you had mentioned in your talk, if that patient came from a region where there were other non-venereal syphilis. That's the example where you can have a positive treponemal test but not have venereal syphilis. It's interesting because this is a great case to look at our screening process. If you come from an area where you only screen with the non-treponemal tests, the VDRL, or the RPR, this patient would have never gone onto the next level of testing and would never have had a specific test as was done here. Thus, it would have made it a lot easier for the panel because we wouldn't have had this question, because everyone would say, "well why would you screen her if her RPR was negative?" But it does present an interesting example of those differences in screening methodologies, leads to these different sorts of issues.

Dr. Singh: Those are all excellent points and it is interesting to mention that, because in Alberta we switched from the RPR as the primary screen to a syphilis enzyme immunoassay [EIA] in September of 2007 and we had a lot of these new cases suddenly presenting, and saying "well, wait a minute, when I was in my last pregnancy, I screened negative and now I am testing positive and how could that be?" So it is a very important point and we anticipated with the switch to the EIA that we would pick up approximately 40% more late stage cases and also perhaps some early infections as well. Although as Dr. Romanowski pointed out, some of the data

suggests that the EIA might in fact miss early primary infections. You are absolutely right, and we will go back to our case.

Ethnicity; she is a black woman and her immigration history reports being a refugee from Sudan to Canada in 2005 and immigration medical examination at the time of immigration was negative, so in fact the screen as we note was a non-reactive VDRL or the non-treponemal test done in Nairobi. So, that wouldn't be surprising here. Now, we've certainly seen a number of cases present in exactly this fashion. In reviewing her sexual history as well, she reports a single lifetime partner, husband since the age of 19, and he tested negative in fact on a syphilis EIA, and he has no current signs or symptoms of infectious syphilis. So what's her diagnosis and stage of infection now? And what should our management be?

Dr. Romanowski: Because of her history of birth, I think the next critical test is to obtain HIV serology on her, because that will change all subsequent management. If she is HIV negative, if her husband is HIV negative, so one is not concerned about seroconversion, assuming that the physical was otherwise healthy, I would stage her as having latent syphilis, probably late latent syphilis and I would treat her with 7.2 million units of benzathine. I would not consider undertaking a lumbar puncture in this woman because she's asymptomatic, physical examination is unremarkable, and RPR is non-reactive.

Dr. Gonik: I guess it still doesn't answer, I don't know endemically where other non-venereal syphilis cases come from but it still doesn't answer endemically whether she is an individual who has been previously infected with a non [...]**.** So that to me is a significant

question still that needs to be answered. In our population again, this patient would have never presented for this question of whether she would have never been treated; the likelihood if she does have late latent syphilis is fortunately reduced in terms of transmitting that infection to the neonate. So, in the real world she would have not been treated. If the presumption is that she had late latent syphilis, then of course she would get three injections of 2.4 million units of benzathine penicillin.

Dr. Romanowski: I think the very important point that you [Dr. Gonik] raised a few minutes ago is that we need to re-look at how we screen individuals. That if one has a national program for screening with non-treponemal tests only, if that's the stand, then the downside is that it may be cheap and it may be simple, but you are going to miss a large number of cases. And certainly the answer of whether this woman has venereal or non-venereal treponematosis with the current availability of testing will never be answered. I say to the patient, if I'm faced with this individual, I'm going to assume that you have venereal syphilis, because I can't answer the question.

Dr. Gonik: With the availability of PCR, does that help? So would PCR in this specific case give you that differential that would make the difference between treatment and non-treatment?

Dr. Romanowski: No

Dr. Robinson: Can I ask Barbara, if she has latent disease and she's not treated, what do you think the chances of her having long-term sequelae?

Dr. Romanowski: If she has late latent disease and isn't treated, I'm not an obstetrician or paediatrician, but I wouldn't be especially

concerned about the child, but she's a young woman and I would be concerned about her health 20-30 years in the future and the possibility of developing grumbling CNS disease. I think the risk of that, if you look at natural history, is low, but the treatment is so simple and so effective and so safe; I would prefer to see her treated.

Dr. Gonik: There is no such thing as a free lunch. How many people out here think she has syphilis? And how many do not? [….]

Dr. Singh It's about 50/50 here. Half thinks it's syphilis and half thinks it's non-venereal treponematosis.

Dr. Gonik: We love audience participation.

1st Audience Member: I am [*inaudible*] and I work at SickKids in this city. So, Ontario switched not so long ago to this, and the most common thing I see now in my congenital infection clinic is women who are EIA positive, TP-PA positive, RPR negative; their babies never have congenital syphilis. I don't think they do either. They are almost always immigrants, with a few exceptions. They are either from the Caribbean, Africa or Southeast Asia. None of them have a history of any symptoms and I wonder because there are some downsides to this because public health gets involved and they go through contact tracing and this can have implications for those women that are sometimes not good. I'm not sure I am that confident with these tests in terms of specificity.

Dr. Romanowski: If I can make a comment. I don't think we really know the answer, but I would caution you against assuming or concluding

that the majority of women have non-venereal infection because I don't think non-venereal treponematosis is that common. I think we frequently blame it, but I don't think it is a disease of epidemic proportions in the country where these women come from.

2nd Audience Member: I have a question in regards to screening because this has come up about three times now; do you screen with a non-specific test or do you screen with a treponemal test? I think that currently standing, the contribution that Wasserman made, he did not get it right. I think he was extremely lucky, and as we say in the literature, he made a fortuitous discovery and fortunately that's all there was at the time and there became a paradigm. I think the time has come to look at the screen test and what it is supposed to do. If we compare syphilis with HIV screening we see huge differences. First of all, cost does not seem to come into the picture, but secondly with HIV we seem to increase the sensitivity and then rule out, with syphilis we seem to rule out and see what happens. I think it is wrong to assume that the RPR is adequate. If you apply the standard algorithm, you could show that the efficacy is only 60% for primary cases, which means 40% can go on infecting others. I think the time has come to use the most sensitive and affordable test, which is the treponemal test based on recombinants**,** because even the TP-PA, FTA-ABS, and all the other standard syphilis tests can show to be false positives and false negatives at times.

Dr. Singh: Thank you. I think it's also important to mention in fact the WHO guidelines that have been in place since 1985 recommending the incorporation of treponemal tests for the screening of syphilis. So, this whole area is evolving and interestingly in Canada, many

provinces and territories have switched to using treponemal tests for screening, while in the United States, there is much opposition to this switch. Primarily, because I think we really don't understand what the long-term implications are of untreated late stage syphilis in the antibiotic era. Much of the information we have is from the pre-antibiotic era and we certainly know from Alberta data though that there is this low background incidence of tertiary syphilis. We have no way currently to predict who will progress and who will not so our approach has been to treat individuals with late stage syphilis, with the idea being to prevent those long-term complications. A couple of quick comments.

2nd Audience Member: We have done quite a few different studies regarding both treponemal and non-treponemal and definitely that case that you presented, which is a very interesting case and that gentleman had mentioned that they have seen such cases in Toronto as well. I think that syphilis as you all know is a not easy thing to diagnosis, but in most of the cases it is, but the problem lays in one or two or three. In those cases, in my experience, multiple testing is needed, so we might have to do more than one, but this particular individual has been tested EIA negative and [*inaudible*] is positive and the other [*inaudible*] is positive and healthy. Treating is easy; you can treat anybody you want. People are treating for Lyme disease now with antibiotics. So, how will you envision the whole management issue? Either [*inaudible*] based medicine or empirical medicine, this is up to the physician. I think that the syphilis diagnosis, treponemal, is a great test and a huge advantage. Similarly, RPR is also a great test and a huge advantage, so I think that we will have to see in a rational fashion how will we deal with this particular issue.

3rd Audience Member: I just want to reinforce what Dr. Romanowski said about the difficulty of sorting out venereal and non-venereal treponemal infections. In the part of South Sudan, where I think this lady actually came from, they recently started providing prenatal care which had never been available before, which just reflects how there is so little healthcare of any kind available. They found astronomically high rates of positive treponemal specific serology, which is the test that they were using. In fact, they are not seeing large numbers of kids with lesions of yaws, that historically you are supposed to see, but neither are they seeing men or women presenting with typical lesions of syphilis. So, it's a huge problem where this woman came from, but it's not clear how much is venereal and how much is not. And in South Sudan, they are assuming that these women have syphilis in treating them and I guess that's what we have to do too.

Dr. Gonik: If you follow the discussion that went on for the last couple of minutes, I think people are throwing their hands up saying, "I don't know if she has syphilis or not". That's a fair statement and I think given the fact that the intervention is relatively benign and certainly inexpensive, many people would say lets just treat her. Personally I don't have a problem with that. I think be cautious in terms of a significant serious disease, again the risks to the fetus are relatively small, but her long-term risks may be up there. But if there is one caveat that I ask people to walk away with is the importance of how careful you have to counsel this woman, and perhaps this couple, because in our institutions unfortunately we think you have syphilis, you're going to get three injections a week apart, you need to go home and talk to your husband. That can lead to tremendous strife and so, all of the academic

discussion that just took place, all the unsure questions of whether we should treat her or not, but in the discussion with her, it has to all come out as well. She's getting an intervention for perhaps not having the disease, but since we don't have a better scientific approach to it, that's why we are treating her; not because we just tell her she has syphilis. That would be a huge error.

Dr. Singh: Thank you. Those were all very excellent comments, and if you don't mind, I will try to move on with this particular case.

4th Audience Member: There's more contribution because the field is still moving; it's not stagnant and I think that it is important to recognize that we are not looking at one antibody; we are looking at antibodies through multiple determinants. If one analyzes the response to treatment through these individual determinants, yes you can use treponemal tests to establish efficacy of treatment.

Dr. Singh: Thank you. I think what all of this excellent discussion basically summarizes is that unfortunately we have no way, either clinically or serologically or based on any other laboratory test, to distinguish between non-venereal treponematosis and late stage syphilis. I wanted to just comment further on PCR. Unfortunately, the yield on PCR in late stage syphilis is extremely low and it's not unfortunately a useful test in this setting. So, today we have no way to distinguish between these two diagnoses and despite the extremely low risk of transmission here to the infant in this type of setting, our practice has been to recommend treatment for syphilis with all the caveats that had been discussed; counselling, within the partnership, additional follow-up of other children if that is thought to be necessary. Our standard treatment in both Canada and the United States will be with benzathine penicillin

G-long acting, and the preparation that is most widely available is Bicillin L-A ®, given 2.4 million units weekly intramuscular by intramuscular injection for three doses and as Dr. Romanowski had mentioned, assuming that there are no neurologic signs or symptoms. In terms of the follow-up with the mother, no serologic follow-up would be required because remember the RPR is the test that we use to look at the response to treatment, but since her baseline RPR is already non-reactive, there is no need for a follow-up in this setting, unless she is potentially re-exposed to syphilis in the future. But in this scenario it seems unlikely. What about the follow-up with the infant? I'll have Joan comment.

Dr. Robinson: I think any woman who has reactive serology for syphilis, the infant does deserve follow-up just to ensure that those passive antibodies disappear. We do not know how long it takes for treponemal antibodies transferred across from the placenta to disappear, but based on what we know about HIV and Hepatitis C, they are probably gone by 18 months of age. So I think it's useful to do serology at roughly six months when many of them will be seronegative. If they are not by then, do them one more time at 18 months. This would be my approach, not based on any real good data.

Dr. Romanowski: Joan, would you recommend neonatal serology at birth?

Dr. Robinson: I think only if you think there is some chance that the mother actually could have got reinfected. And you think there's a chance that the baby could have a reactive RPR, because basically that's all you are looking for.

Dr. Romanowski: If serology is done at birth, it must not be done on cord blood.

Dr. Robinson: Absolutely. That is no longer, because cord blood mixes maternal blood and fetal blood, so it is not really useful.

Dr. Gonik: In what case, what serology would be done?

Dr. Robinson: I think that six months I would do a treponemal test and a RPR.

Dr. Singh: Yes, and I have to say that in this type of situation if there is concern, then we recommend that a baseline test be done at birth simply to provide the baseline if follow-up is going to be done. But I have to say that I don't insist that all of these babies get follow-up testing if there is concern on wanting to watch for clearance of passively transferred maternal antibodies. Just to follow up on how long it takes for the antibodies to serorevert, there is some data for the standard treponemal test such as TP-PA and FTA-ABS, but we really don't know for the syphilis enzyme immunoassay or other EIA tests, and we do have the opportunity to look at some of our data in the province in Alberta. So, we hope to do so soon. It does look, though, like some babies will be taking longer to serorevert than we saw with other tests.

I just want to make a note about treatment. As I mentioned, this product Bicillin L-A® is the one that is most widely available in Canada and the United States. It was off the Canadian market for several years and is now available as of June of last year again. I wanted to mention that this is a special long acting preparation of benzathine penicillin-G. Two injections need to be given. So one vial is 1.2 million units, so an injection into each buttock and this long acting preparation provides therapeutic levels of penicillin

for 10 to 14 days. It's important to recognize this because there is another Bicillin® product, Bicillin C-R® which is controlled release and not adequate for the treatment of syphilis. We've also seen a number of patients treated with short acting penicillin in our hospitals and we've had to go back and say, "Well, we know you didn't use this product because it's stored and available only through certain pharmacies in our province."

Dr. Gonik: The short acting penicillin is unfortunately benzylpenicillin, which sounds a lot like benzathine penicillin, and that's why the error occurs. It happens either from the ordering or the pharmacy, so it's important to recognize that their fairly significant distinction.

Segment 5 – 0: 00:00 to 0:07:32

Case #2

Dr. Singh: So here's another typical case again for our province. 29 year old Aboriginal woman; routine prenatal screen at 15 weeks gestation showing a positive syphilis EIA, RPR reactive at two dilutions, with a syphilis INNO-LIA™ positive. She's street-involved, actively using crack cocaine, is possibly a sex trade worker, and living in the city of Edmonton, which I had mentioned, is experiencing a resurgence and currently an outbreak of predominantly heterosexually acquired infectious syphilis. So, back to our panel again. What would the additional questions be here, and thoughts about the maternal stage of syphilis?

Dr. Gonik: So, obviously other STD screening would be critically important in this individual, including HIV screening, and Hepatitis screening as well. Does anyone think she doesn't have syphilis?

No. To me, it seems relatively straightforward in terms of a diagnosis and if on physical exam, a chancre was identified, and then she would have primary syphilis. If not and she had other lesions, she would have secondary syphilis or even early latent syphilis perhaps. In the United States, we are fortunate enough to track many of these individuals for previous RPRs sometimes just related to previous pregnancies and that will help us time the event to decide in terms of early or late disease, and therefore, whether we get a single injection of benzathine penicillin or three injections a week apart.

Dr. Romanowski: I was going to ask the same question. She's 29 years old. I'm going to make an awful assumption; this is probably not her first pregnancy, so assuming that she accessed prenatal care with her other pregnancies, what were the results of the serology and HIV would be extremely important.

Dr. Singh: In terms of past history of syphilis, she indicated that she was treated for syphilis in Edmonton "a long time ago", but has no current signs or symptoms of syphilis. And on further interviewing, does currently work sex trade, and uses condoms for vaginal sex but not for oral sex. She has no oral lesions as well. We do have a provincial syphilis registry in the province of Alberta; we checked that registry. In fact she was treated for primary syphilis in 1985 with benzathine penicillin-G 2.4 million units by IM injection. Her pre-treatment RPR was reactive at 64 dilutions. The last RPR we have on file was from August 1999 and that was reactive at one dilution. So what's the patient's syphilis status at the moment and what are the recommendations for further management?

Dr. Romanowski: I would classify her as adequately treated primary syphilis. The difference between an RPR dilution of 1:1 and 1:2 is in the eye of the beholder; it's exactly the same. Her serology has not changed and there is documentation of receipt of benzathine penicillin. I would do nothing with her, but because she is pregnant I would do serology at each trimester; she's clearly at a very, very high risk of reinfection. I would do nothing more than that.

Dr. Gonik: Her initial dilution was what again?

Dr. Singh: It was two dilutions. This pregnancy she's reactive at two dilutions and the last one on file from August 1999, it was reactive at one dilution.

Dr. Gonik: So, that single difference probably isn't enough to re-establish a diagnosis of reinfection, so I think that would be an adequate approach.

Dr. Singh: That's exactly the conclusion here, because there has only been a one-tube change in her RPR and no clinical evidence of reinfection. We would conclude at this point that there is no serologic or clinical evidence of reinfection or treatment failure from her previous episode of primary syphilis. However, we know that she continues to be at high risk, so although we are not recommending any treatment at the moment, given her high risk behaviours, sex trade and unprotected oral sex, in a city that we know is experiencing a resurgence of infectious syphilis, we would attempt to provide some advice regarding as to how syphilis is passed on, including that it can be passed on with oral sex, and discussing ways to reduce transmission through oral sex including the use of condoms for oral sex. You'd also consider in

this case repeating her RPR monthly until, and at the time of delivery, again looking for two-tube or four-fold rise in RPR and/or any symptoms of infectious syphilis. So any additional comments about that from our panel or from the audience?

Dr. Robinson: In this situation, I don't think we require any investigation because she's previously treated. I'd certainly want to see an RPR at the time of delivery in this situation.

Dr. Gonik: I don't know if it's true for you as it is for us, but in our general obstetric community, generalists who are really in the trenches seeing these patients, these patients get commonly treated and over-treated regularly. They'll get anything that comes up positive with the knee-jerk response "what's the harm, let's go ahead and treat them." You'll see that these individuals will get multiple doses of treatment unnecessarily because they haven't been followed through the process. It is unfortunate because the health department, at least in Detroit and its surrounding community, is really accessible and so its not difficult to get someone with expertise on the phone to follow through that sort of logic, look through some of our old data, and based on that, make an informed decision. We find these patients get treated multiple times, and sometimes naively if they re-do the treponemal test and it's still positive, which it likely will be, they will treat them again, even during the same pregnancy. So it's an unfortunate overuse of resources in that case.

Dr. Singh: That is really an excellent point and sort of highlights the need for maintaining a centralized registry particularly for syphilis because having old treatment information is incredibly important and

informing, whether retreatment should occur or not. So I will move on now to our 3rd case. […]

Segment 6 – 0: 00:00 to 0:20:28

3rd Case:

[…]

Dr. Singh: 23 year old woman who was referred at 26 weeks gestation, so she didn't have an earlier screen in this particular pregnancy. After she was found to have an RPR reactive at 256 dilutions, I am showing you this serology cause this is actually her results prior to the switch to the EIA seen in September 2007, so RPR reactive at 256 dilutions, TP-PA and FTA were both reactive. We know that her RPR was non-reactive in December of 2006 during another pregnancy. She reported to have no signs or symptoms of syphilis at the time that the serologic test came up.

So while interviewing this lady, she reports she has a partner now of approximately 10 months who told her the previous night that he had sex with a woman in Fort McMurray, which is a northern town in Alberta which is the centre of our oil industry, so we have an influx of a large number of unattached single males into that city and resurgence as well of syphilis in that area. He indicates to his partner that he had sex with a woman up there a few months ago, and she also has a child who is now eight months old and tells me that the child was admitted to our Children's Hospital at three months of age for work up of rash, hepatosplenomegaly and anaemia, and the child was diagnosed as having possible juvenile myelomonocytic leukemia [JMML].

So when I examined her, she has these lesions here, so I'm wondering if either of our panel members want to comment on those lesions.

Dr. Romanowski: It's a typical case of condyloma lata. A lot of the mucous membrane lesions of secondary syphilis that can be easily confused with condyloma cuminata or venereal warts. The big difference is that these lesions are soft, patients often don't complain of anything and sadly the patients don't even know they are there on many occasions, and it would fit with her serology.

Dr. Singh: And those as you say are classic lesions of condyloma lata, in fact the first time I saw a patient with condyloma lata. I wanted to put this case in to highlight the importance of detailed physical examination when attempting to accurately stage syphilis. Because, when she was referred to me, I was told she had no signs or symptoms of syphilis and that occurs commonly and then when you go and actually do a detailed physical exam, of course that includes a detailed genital examination, lesions may be present. So, what is her maternal stage of syphilis? I think Barbara already indicated that, but I think we would try to focus on how the pregnant woman should be managed and then we'll talk about the infant. In terms of the patient herself, how should she be managed at this point?

Dr. Gonik: It's important, without identifying the lesion, although historically you may think this is early latent syphilis based on the one year or less contact with the other individual. In fact, I think that historically it's a little difficult to accept. So if you go back on her RPR data, the only information you have is three years ago she was RPR negative. So, I think many people without carefully

assessing her would have classified her as late latent and then she would have been treated with three injections of benzathine penicillin.

Dr. Singh: Sorry, just to clarify. In December of 2006, her RPR was non-reactive and then in April of 2007, it was reactive at 256 dilutions.

Dr. Gonik: Sorry, I was thinking to date. So it would be a difference between early latent syphilis and secondary syphilis. The treatment would be the same in that they would receive 2.4 million units at one time of benzathine penicillin. I guess one of the issues that would come up of course in a young lady who is 26 weeks gestation, there is at least some identified risk of a JH [Jarisch-Herxheimer] reaction, which would at least lead to some additional counselling on the patient but not necessarily require her to be hospitalized for her therapy. There's a lot of controversy of how to approach these patients because they are at slightly higher risk of fever, chills, rigors, uterine contractions, fetal heart rate decelerations, but I think this patient could be treated on an ambulatory basis with careful instruction. Some people differentiate between 20 weeks gestation, before 20 weeks gestation and after 20 weeks gestation and again its controversial whether they need or don't need in-house therapy. You would've made it that much complicated if you told me she was penicillin allergic because, we see this all the time; so many of our patients quote penicillin allergies when in fact they don't have penicillin allergies. Just a careful history is sometimes all you need. For example, so many of our patients' say that they are penicillin allergic but can take amoxicillin just fine. So, obviously they are not penicillin allergic. In those individuals, without sensitivity testing or without desensitization,

we just go ahead and give them penicillin. If there's any question at all, we will bring them into the hospital at least for observation.

Dr. Romanowski: The only additional comment I would make is that I'm concerned about the first child. She has an 8 month old that's in hospital with symptoms that are compatible with congenital syphilis with symptoms that raise the possibility of HIV infection as well in my mind. One, I would suggest she would have HIV serology, her husband as well and two, I would like to talk to the individual caring or investigating child number one.

Dr. Singh: In terms of the mother's maternal stage of syphilis as we discussed, her serology was non-reactive in December of 2006 and it's now reactive at 256 dilutions, four months later with a presence of condyloma lata. So, we would now stage her as secondary syphilis although she would have been classified as early latent syphilis if a physical examination had not been done. Dr. Gonik had alluded to some of the recommendations around management of pregnant women using the gestational age. It does look like women over 20 weeks gestation are at higher risk, not only for intrauterine transmission of syphilis, but also if they have fetal abnormalities, at increased risk of going into premature labour as a result of the Jarisch-Herxheimer reaction which is an immunologic phenomenon that occurs with the treatment itself. So, our recommendation is that this woman at this point would have a detailed perinatal ultrasound done, and since we actually had one woman go into labour the day of treatment, we're trying to get as many woman as possible over 20 weeks gestation admitted for observation for about 24 hours after the first treatment dose. As it has been recommended repeatedly, an HIV test is absolutely critical in all of these cases, and in fact I now say

to our clinic staff that if you have a diagnosis of syphilis, HIV test is not really an optional test at that point. It does need to be done as it will impact treatment and the follow-up, and it has been pointed out as well, testing for other sexually transmitted infections including Chlamydia and gonorrhea.

We did a perinatal ultrasound in this woman and there were no fetal abnormalities. We elected to treat with benzathine penicillin-G long acting 2.4 million units in hospital with fetal monitoring for the first 24 hours and a second dose of Bicillin L-A® given one week later as an outpatient. I'm going to talk a little bit more about why we gave the second dose in a few minutes, but first I wanted to just hand over to Joan [Dr. Robinson] to talk briefly about the impact of congenital syphilis.

Dr. Robinson: Thank you Ameeta. As was mentioned earlier, the risk of transmission varies with the stage of maternal syphilis, and whether the mother is treated and when she actually is treated. Transmission has been described as early as nine weeks gestation, so certainly the risk is much higher after 20 weeks than earlier on. Certainly stillbirth is a fairly common outcome and we've had several cases in Alberta of stillbirth that had been proven due to untreated syphilis. Certainly, infants with congenital syphilis can be totally asymptomatic or can present with multi-organ involvement.

Dr. Singh: And so, our current recommendation about the management of pregnant woman, and I think this is consistent with the U.S. guidelines as well, are that in woman under 20 weeks of gestation, we treat with one to two doses. The *Canadian Guidelines* say one to two doses. **[Please note: Within the *Canadian Guidelines on***

Sexually Transmitted Infections **the recommended treatment for all pregnant women with primary, secondary or early latent infection, regardless of gestational age, is one to two doses of benzathine penicillin G].** Treatment should be offered as per syphilis stage at the time of diagnosis, and the recommendations to do the usual serologic follow-up in addition to serology at the time of delivery, and that's primarily looking at the RPR. In woman who are treated successfully and are not at high risk of reinfection, there's relatively lower risk of transmission to the infant in this setting, and at minimum, however, we would recommend a clinical assessment of the infant at the time of birth. Any additional comments about that?

Dr. Gonik: So, this issue with the ultrasound is a good point and it does help in terms of prognostically discussing with the patient her risk whether she already has evidence of transmission to the fetus or not, although a normal ultrasound scan does not eliminate that possibility. It doesn't change, at least in my understanding, our approaches to therapeutic intervention. This issue of one versus two doses is quite controversial. I think the current CDC guidelines, regardless of gestational age and regardless of ultra sound findings still say that a single dose of 2.4 million units of benzathine penicillin is the appropriate intervention with the caveat. I think there is an asterisk that says some experts recommend a second dose. […]. It's difficult because if you look at the actual data, there's not a lot and the data, at least at the present time, does not support adding that second dose in terms of improving efficacy for fetal outcome. That being said, there are good experts all over the world that feel strongly about that second dose.

Dr. Singh: Thank you. I am going to talk further about treatment in a few minutes, but the *Canadian Guidelines* are just being revised now to add more extensive recommendations about the management of pregnant women with syphilis. The recommendation will be that in women over 20 weeks of gestation, if it is possible to do so, then ideally a detailed perinatal ultra sound should be done. That is in contrast to a routine obstetric ultrasound, which is much more readily available of course. Just to give you an example, we did see a case just within the last few months where the routine obstetric ultrasound showed mild fetal hydrops and when a detailed perinatal ultrasound was done, it showed multiple fetal abnormalities, including cardiomegaly, ascites, doppler changes consistent with severe anemia, so it could potentially change the management in that situation. As we've already discussed, treatment can precipitate a Jarisch-Herxheimer reaction, and this is set to occur especially if fetal abnormalities are present. It may precipitate the onset of labour, and certainly in that type of situation, we would strongly consider hospitalization with fetal monitoring and treatment. Most recently, we elected to treat a case of a mother who's fetus had multiple fetal abnormalities with a course of intravenous penicillin on the basis that there are a few case reports in the literature, suggesting better outcome if that is done. So I have to tell you up front, there is no good data to support that and in fact, there is also one case in literature reporting similar resolution of all fetal abnormalities after single dose benzathine penicillin. Regardless, the newborn needs detailed assessment at birth in this type of situation, whether with or without treatment depending on the time of maternal treatment, and particularly if treatment has occurred in the last four weeks of pregnancy.

These are the current *Canadian Guideline* recommendations which are pretty similar to the U.S, recommending that for pregnant women with primary, secondary and early latent syphilis, so within the first year of infection, you'll see it says one to two doses with a C-III level of evidence for the two doses. And making the clear recommendation that there is no satisfactory alternative to the use of penicillin. And if we are concerned about serious allergy then we typically elect to desensitize then to treat with benzathine penicillin. So, why the recommendation for the two doses? As Dr. Gonik had mentioned, with a diagnosis of secondary syphilis in late pregnancy and despite the administration of the recommended penicillin regimen, as many as 14% will have fetal death or deliver infants with clinical evidence of congenital syphilis. Given the complexity of accurately staging early syphilis, some experts recommend that in primary, secondary and early latent cases in pregnancy be treated with two doses of benzathine penicillin-G 2.4 million units one week apart, but the efficacy of this regimen in preventing fetal syphilis is not known. So it is our practice in Alberta to do so, but there is an absence of any overwhelming evidence to support that. So, I'm going to ask Joan now to comment on what happened with this mother's neonate (26 week old).

Dr. Robinson: Here you can see the results of the investigations that were done on this neonate. This baby was actually only treated for four days and I must say that I would have given a full 10 days of penicillin, because the CSF is abnormal. So, even though we have no proof of congenital syphilis, I certainly would have went on the side of caution and treated.

Dr. Singh: So this neonate was clinically well with normal hemoglobin, but as you can see, has got three CSF abnormalities but interestingly when we reviewed the case file, in fact, treatment was stopped at four days and unfortunately this infant is now lost to follow-up. Would you agree as well, Dr. Romanowski and Gonik that this baby ideally should have been treated with 10 days?

Dr. Robinson: These are complicated decisions and the Canadian Paediatrics Society has recently come out with guidelines to try to deal with the different parts and scenarios and they're available on the Canadian Paediatric Society website.

Dr. Singh: I think we've agreed that this infant would've been treated with a full 10 day course of IV penicillin, and I won't spend any time on this in the interest of time, but simply wanted to reiterate what Dr. Gonik had said that currently in Canada, the surveillance criteria for confirmed cases of congenital syphilis includes that, in addition to some documented laboratory evidence of infection, the infant have clinical laboratory or radiographic evidence of clinical congenital syphilis. So that currently we do not count probable cases as part of our surveillance criteria. Joan, did you want to comment on what the clinical lab and radiographic findings you need to look for in the first few months of life.

Dr. Singh: This would be rash, anemia, and osteochondritis involving long bones. I'm just going to skip ahead here to the baby. I know everyone is interested in what happened with the baby here.

Dr. Robinson: I had seen this baby at three months of age with hepatosplenomegaly and the oncologist thought the child had JMML. That made perfect sense to me. Someone ordered syphilis

serology but the unit clerk ticked off the wrong box on the requisition so it never got done and never got followed-up which was my fault. Anyway, at eight months of age when this whole story unfolded, the child had done well since three months, but of course still had hepatosplenomegaly and had further tests done shown on the slide, and absolutely for certain had congenital syphilis. But fortunately had no evidence of CNS involvement so the baby got ten days of IV penicillin and as far as I know has done well.

Dr. Romanowski: If I could just go back to that case. So the eight month old child has congenital disease, so one would surmise that the mother had unrecognized primary syphilis in her previous pregnancy in her third trimester.

Dr. Singh: I think she acquired it near term. Her new partner was within two months of delivery. I didn't show you the information on the sexual partner, but we did review him and in fact his serology showed an RPR reactive at 8 dilutions with a TP-PA and FTA-ABS reactive and he was staged as an early latent syphilis because he did not have any signs or symptoms and was treated with benzathine penicillin and tested negative to HIV, gonorrhea and Chlamydia.

[…]

Segment 7 – 0: 00:00 to 0:19:10

Case #4:

Dr. Singh: So this is another lady that I saw. A 26-year-old Métis woman, who is also a sex trade worker, uses alcohol and crack cocaine. Another prenatal screen at about 10 weeks gestation has a positive syphilis EIA, RPR reactive at 32 dilutions and a positive syphilis INNO-LIA™. She has no previous history of syphilis but reports genital ulcers in April 2008. So this is a month previously she is reporting genital ulcers. This is an actual case by the way; that is why you are seeing so much detail here.

She then gets treated with two doses of Bicillin® May 20 and May 27, 2008 and in July her RPR is at 64 dilutions. Remember it was 32 in May and its now 64 dilutions in July. So she is pregnant obviously at this point and in August, it's still at 64 dilutions, so at this point she is staged as a reinfection and retreated with two further doses of Bicillin® on August 26 and September 2. I wanted to put this in because it really highlights the difficulty of trying to figure out what is going on when you don't have sufficient time to do follow-up. We would like to see the titre at least moving in the right direction i.e. downwards, so even though this is a one-tube change, it was going in the wrong direction and I concur in the decision to retreat at that point. So in December of 2008, she did deliver a stillborn infant at 39+ weeks and histology on the placenta showed mild chorionitis and unfortunately she declined autopsy so we don't know if that baby had congenital syphilis or not. Here we are now in March of 2009, her RPR is still 32 dilutions, so I'm wondering what you think is going on here and what should the next steps be?

Dr. Romanowski: I'm going to make the assumption you know she is HIV negative at this stage.

Dr. Singh: Yes she is HIV negative at this stage.

Dr. Romanowski: It's difficult. Part of her RPR reactivity may be related to her illicit drug use. She may have been a treatment failure from day one. I may have treated her in August with three doses of benzathine penicillin instead of two and at that stage one, probably had a discussion of whether a lumbar puncture would be indicated, but as we know, these individuals are sometimes very difficult to get them to agree to that procedure. At this stage, I would strongly recommend that she be lumbar punctured to see if there are any abnormalities, which would dictate any future microbial indications.

Dr. Gonik: Other than it is a confusing case. The sense is that you have persistent disease. I think that this is the case where you would want to do more thorough work and that would include an LP.

Dr. Singh: I'm glad you agree because I have to tell you, when I heard about this, my heart sank because I was told by our clinic staff that there was no way we were going to find her to get her in for the LP, but we have an excellent outreach team in our city. So we booked her for an LP, she went in, had it done and I got paged to say that her CSF results were abnormal and her white count in CSF was elevated at 24 with 98% lymphocytes. And of course the VDRL certainly at our lab takes about 10 days, so based on the white count alone, even though the other parameters were normal, I did manage to get her admitted to hospital where amazingly she stayed for 10 days and received a course of intravenous penicillin.

As you'll see the VDRL was reactive at one dilution and that was certainly the situation here. I wanted to quickly review the criteria for doing a lumbar puncture with patients with syphilis; certainly the presence of neurologic or ophthalmic symptoms or signs, congenital syphilis, previously treated patients who fail to achieve an adequate serologic response to treatment, tertiary syphilis, and HIV positive patients with neurologic symptoms or signs, and depending on which recommendations or guidelines you read, those with late latent syphilis, RPR more than 32 dilutions, and a CD4 less than 350. Some experts say all HIV positive patients. And I must say, the longer I manage syphilis, the lower my threshold gets for doing LP's in HIV positive patients and if CSF is to be done, it should be sent for a cell count and differential, protein, glucose, VDRL, and the FTA-ABS. As Dr. Romanowski, I think indicated, the VDRL is very insensitive but if it is reactive, is indicative, of neurologic involvement with syphilis, the FTA however is frequently positive and it's only if it's negative that it helps to rule out the neurologic involvement with syphilis.

So, just back to this case, what's her syphilis stage and what should her follow up be at this point?

Dr. Romanowski: She has neurosyphilis and her follow up should be as if she has infectious syphilis in terms of serologic follow up. The question then arises, I believe she clearly has neurosyphilis; it would be very nice to repeat her lumbar puncture in six months time if she is agreeable.

Dr. Singh: In fact, she was staged as an asymptomatic neurosyphilis, asymptomatic obviously reflecting the fact that she has no signs or symptoms of syphilis, and the RPR follow up is as per the

guideline recommendation: one, three, six and twelve months. **[Please note: This patient is being followed up serologically as an infectious syphilis case (primary, secondary or early latent) and therefore the timing for follow-up varies from the follow-up recommendations for neurosyphilis contained in the *Canadian Guidelines on Sexually Transmitted Infections* which recommends follow-up serological testing at 6, 12 and 24 months]** I just wanted to just mention the one-month follow-up. That one I guess is a less standard recommendation and we have elected to routinely do a one month follow up in the context of the outbreak and we are really looking at the point for any further rises in the RPR, particularly in individuals who are at high risk of reinfection. Ideally, a follow up lumbar puncture at 6 month intervals to follow the CSF parameters and we are looking in this particular situation for that white count to normalize and for that VDRL to revert to non-reactive. And so, I'm going to stop there if there are any final questions. I would like to acknowledge the staff. We have outstanding provincial STD services and also the staff of our Edmonton STD clinic and our Provincial Public Health Lab. And I wanted to point out that I have not put up the U.S. guideline links but obviously they are readily available through CDC's website and the *Canadian Guidelines* are also available on the Public Health Agency of Canada's website as well as new recommendations for congenital syphilis on the Canadian Paediatric Society website.

So thank you very much to all of you for staying and we'd be happy to take any last questions if there are any.

5th Audience Member: In case number four, I think one opportunity was there to do PCR on the placenta from the mother to confirm the diagnosis because the RPR we didn't know that for what reason, that was done. […]

Dr. Singh: Unfortunately, by the time we found out about the intrauterine death it was too late, but yes you are absolutely right and in fact our lab is validating a PCR and had we known about this at the time of delivery, then we would have certainly done that. We have looked at the PCR in other similar situations of stillborn or intrauterine death and we've had a number of positives.

5th Audience Member: In B.C., we do have some experience in this kind situation at least in two occasions from the placenta, PCR actually helped a lot.

Dr. Singh: In fact, if we had known, we could have looked at PCR from a cord sample, but we didn't know about it at the time of delivery.

4th Audience Member: In your opinion of the panel, how reliable is RPR seroconversion for reinfection or vice versa? How many times is a superimposed infection missed looking at the RPR?

Dr. Singh: Do you mean, how often would we miss a case of reinfection, simply by looking at an RPR?

4th Audience Member: In the literature, there is very little information with this regard. It says you can measure this by RPR, but when you look for data there isn't much. In my opinion, you don't see it very often.

Dr. Singh: We've certainly seen RPR rises. I think probably part of the concern, however, is that it does take time for a serologic

response to develop and often in pregnant women, people are reluctant to wait for weeks to watch the serologic trend.

Dr. Romanowski: Certainly, there are cases where with reinfection you don't see changes in titre but that, in my experience, are unusual.

Dr. Singh: Often people are not willing to wait for the time that it would take for that to happen, so that's why we say if the person is at high risk for infection and have any lesions, suggestive again of reinfection, then that should prompt treatment at that point without waiting for the RPR to rise.

6th Audience Member: I had a comment about the claim on the risk of transmission with late latent syphilis was 10% with pregnancy. Here in Ontario we were using non-treponemal screening and then switched to a treponemal screening so it was a whole raft of people who did have latent syphilis and never got treated. So the recommendations are very cautious and are not compatible with what we were practicing before. I would think that retrospectively looking at people who were RPR negative and are now EIA positive, who we believe did not have endemic syphilis, that picture would give a more accurate estimate of the risks. So do you think the recommendations are a little too cautious?

Dr. Singh: That's an excellent point. The historical literature indicates that the risk of transmission of syphilis in women with late latent syphilis is about 10%, but I don't believe that in the current antibiotic era personally. We have a syphilis registry in Alberta that has been in place since the 1930's and to my knowledge, for the past 30 years, we have not yet seen a single case that was prior to this switch to the EIA. I know we are in a low prevalence

setting. The trouble is though, as we discussed, the historical literature, again, indicates that the risk of progression from late latent to tertiary syphilis is between 15% and 40%. But this again is in the pre-antibiotic era. I think its much less now, and there are no factors that we could use to help to predict who will go on to develop tertiary complications and who will not. I think as discussed earlier by Dr. Romanowski, the woman with presumed late latent syphilis, we were perhaps treating primarily in that situation to prevent her from going on to develop late latent syphilis and perhaps doing something to further reduce an extremely low risk of transmission to the infant to virtually nothing.

6th Audience Member: Do you think there is any provincial or national jurisdiction where this question could be better answered because we had a change in technology from a lab testing point of view, where one could look retrospectively at people who were negative via non-treponemal test and now positive and then see if their childrens' developmental records could be pulled? […]

Dr. Singh: We do have at this meeting one of our obstetric residents, who did review several years of our data, and there were no transmissions in those few years from women who had late latent syphilis. But, it's important to bear in mind though that if we make the diagnosis of late latent syphilis, we do always treat. We never leave them untreated. I think it would be problematic ethically to leave those women untreated at this point.

6th Audience Member: Just to get from a sociological perspective, with the patients it can be very challenging where nothing happens with the prior pregnancies and all of a sudden everyone is excited. That's the tough side of it.

7th Audience Member: In most areas, geriatricians tend to order VDRL or RPR testing on elderly patients, so they come up with cases of very late syphilis that were acquired decades ago. In patients who may have not been treated and some that were referred to me, patients were never treated for syphilis and we have no previous record of testing; it's too old. So, our bias is to treat those patients but their titres for RPR are very low. They are maybe 1:1 and 1:2, so what is your advice in treating a 75-year-old male or female person who has an incidental finding of syphilis?

Dr. Singh: Similar issues again. In the absence of any predictors for who will progress on to tertiary syphilis or not, it has been our practice in Alberta to routinely treat those individuals and if they have any neurological signs or symptoms, to do a lumbar puncture prior to treatment.

8th Audience Member: Just to follow up on what Dr. [*inaudible*] brought up on these latent cases in pregnancy. So, there hasn't been a lot of evidence in terms of transmission. What would you do in the case where you find a woman in pregnancy who has been staged as late latent, but is allergic to penicillin? Would you desensitize her or would you watch and wait?

Dr. Singh: To be honest, I probably would desensitize. We have desensitized a number of women now and treated successfully with penicillin without any problems. In fact, after you've done the first desensitization and administer the first dose, you don't need to desensitize again to administer the second and third doses. So, it's very safe, well tolerated, and in luckily our city, very easy to do.

Dr. Gonik: [***inaudible***]

Dr. Singh: We can't give pregnant women doxycycline, that's the trouble.

Dr. Gonik: I'm talking about desensitization.

Dr. Singh: It has been our policy to have them come into an outpatient IV clinic, simply based on the rational that if they do develop a serious reaction an in-hospital team is available to deal with it.

Dr. Gonik: Do you desensitize orally?

Dr. Singh: Yes, we use an oral desensitization protocol.

Dr. Gonik: First of all, most of those patients who are penicillin allergic are not penicillin allergic. Fortunately, the majority of those patients, when you tease out their history, you find out that they are not.

Dr. Singh: Sometimes I elect to just give it a try to be honest, if the history is very soft.

Dr. Gonik: Again, in those patients, I'm sure you do in-house or better supervision just in case.

Dr. Singh: Yes, they get to stay longer.

Dr. Gonik: It's a pretty easy process in terms of desensitization and so, to err on the side of giving therapy makes the most sense.

9th Audience Member: Do you ever observe any discordance between two different treponemal tests, for example one test would be positive and the

other test would be negative and how would you deal with such cases?

Dr. Singh: We have seen that on odd occasions. I wouldn't say it's a frequent event. For example, we have gone back and done retesting when the pattern of serologic testing isn't making sense on any given occasion or over a period of time. So, our lab has been great about repeating and re-pulling those specimens, all those sera are fortunately stored, to go back and do the retesting. So, if something isn't making sense we do go back and rerun the test and then take a look at the whole situation, review the scenario that way, but it can be really difficult.

I'm sure that everyone is ready to leave, and I'm not sure if there is a closing session. Thank you very much everyone and I guess we will be moving onto the closing session.