Overview of Syphilis Diagnostics: Background and History
Notes:

Welcome to the Association of Public Health Laboratory's overview of syphilis diagnostics. This presentation is the background and history of syphilis and will provide a brief overview of the basic history and epidemiology of syphilis and some of the challenges with syphilis diagnostics.
1.2 Treponema pallidum

Notes:

Syphilis is caused by the bacteria *treponema pallidum* which is a corkscrew or spiral bacterium and is a sexually transmitted disease transmitted by direct contact with ulcerative lesions. The ulcer, or chancre appears during the primary stage of syphilis and is teeming with the bacteria *treponema pallidum* and this makes this stage most infectious. Because open lesions can serve as a portal of entry for other bacteria and viruses primary syphilis has been linked to HIV infection and other STDs. Syphilis during pregnancy may result in serious complications such as spontaneous abortions, still birth and perinatal deaths. In congenital syphilis the infant is infected by the mother and is born with syphilis. If the infant survives a wide range of conditions including jaundice, anemia, deafness, nasal deformities and neuro-syphilis can occur.
1.3 History of Syphilis

Syphilis is an ancient disease. The first recorded epidemic was in the 1500’s when syphilis swept through Europe. The causative organism, *treponema pallidum* was first identified in 1905. Landsteiner introduced the dark field method for detecting *treponema pallidum* in 1906. In 1910 the German bacteriologist, August Wasserman developed the very first serology test, and Paul Erlich identified the first effective treatment. He called it a magic bullet which was an arsenic compound in 1910 but no effective cure existed until the 1940’s when penicillin was discovered.
1.4 Role of the Public Health Laboratory

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Public health and public health laboratory definitely have a role in syphilis diagnostics and reporting. Syphilis reporting is mandated by all state laws and information from syphilis cases is reported to CDC from all states and territories. Syphilis surveillance programs provide data for planning, implementation and evaluation for public health programs and interventions. Understanding the prevalence of syphilis and the proportion of persons in a population allows health officials to design and target interventions and allocate public health resources to the highest risk groups.
1.5 Syphilis Rates-Still Not Gone

This next slide shows syphilis rates over the past 50 years or more. In 1941 was when syphilis reporting was first mandated and you can see that that is probably the peak in cases per thousands on this slide. If we look and just look at total syphilis cases you can see that we had a nice drop down in the 1940's when we, remember, first had penicillin started being used to treat syphilis and we made huge inroads in cutting down the rate of syphilis.

Rates continued to decline all the way into like the 1980's and then there is a little blip again in about 1980 to 1990 which very well could have some relationship to the beginning of the HIV epidemic. Then we also came down again and in 2000 the syphilis rate was the lowest since reporting began in 1941.

The rate of primary and secondary syphilis in the United States declined almost 90 percent during 1990 to 2000. However, in 2001 it reemerged as a public health threat with case rates steadily increasing from 2001 to 2009 before decreasing again in 2010. The 2011 rate remained unchanged. However the rate again increased in 2012 and 2013 and 2013 has the highest case count and rate since 1995.
1.6 Highest Syphilis Rates Amongst Young Men

Notes:

The highest syphilis rates are among young men. In 2013 the rate of primary and secondary syphilis was highest among persons aged 20 to 24 and 25 to 29 years. This marks the sixth consecutive year that rates of primary and secondary syphilis among men have been highest among men aged 20 to 29 years. This data indicates a shift since 2006 when the highest rates were in men age 35 to 39 years.

The population group within that that is the largest contributing factor is increasing incidents and rate in MSM, men who have sex with men. The increase of cases in this population is most concerning since MSM are also significantly affected by HIV and syphilis infection can facilitate HIV transmission.

Additionally there are increasing race disparities within the syphilis rate among blacks, having eight times higher rates than whites in 2008, and the rate of reported syphilis cases among Hispanics was double that of whites. Certainly there is concern about the increasing disparities in certain populations.
1.7 Which demographic group had the highest rate of primary and secondary syphilis in 2013?
1.8 Syphilis Challenges

There are definitely challenges in syphilis diagnostics because you can tell that our efforts to eliminate syphilis are falling short. We have known that penicillin works since the 1940’s and so it is very easy to treat yet we are still not eradicating syphilis. And why has that been the case? Is it the lack of knowledge? Has syphilis really been eliminated? There are certainly some states in the United States that have very low rates of syphilis and have difficulty trying to decide if the lesion that they see is a herpes lesion or a syphilis lesion. So we end up depending on serologic tests to actually detect syphilis because many times the primary lesion which is the first sign of syphilis is missed. So when we have to depend on serology then what we’re looking at is indirect evidence for an infection. We’re not looking like we can for Chlamydia and GC and find that we can look for the actual organism. We have to look for the serologic response and that requires a normal immune response which we know does not always happen, especially in somebody who might be infected with HIV and we know that there will be non-specific false positives and false negative reactions as well.
1.9 Diagnosis of Syphilis is Challenging

So the diagnosis of syphilis is challenging. Syphilis is the great imitator and certainly when I mentioned that we don’t know if a lesion is herpes or syphilis or some other ulcerative lesion, it can be difficult to diagnose. People can present without symptoms or signs and that primary chancre, that primary painless lesion, can sometimes be a non-visible site locations and resolve without treatment, and people don’t really recognize that they had a chancre. There are also latent infections that occur and it is very difficult to use serology to identify that as well. Culture is not a diagnostic option as the bacterium does not grow well in a clinical laboratory setting. And there are no FDA approved direct detection tests available for doing early infection diagnosis.
1.10 Syphilis Infection

Notes:
This slide shows a progression of syphilis infection with overlapping stages of varying durations lasting weeks, months and years. Primary, secondary and early latent comprise early syphilis and are the infectious stages. Late syphilis is generally considered non-infectious. Primary syphilis occurs after about three to 90 day incubation from time of exposure to the primary chancre which is that painless ulcerative lesion which spontaneously resolves within about three to six weeks without treatment. If the treatment does not occur then syphilis will progress to the secondary stage and this is a macular papular rash and skin lesions which are not itchy, and they appear on the palms and soles of the feet and it is quite descriptive if you’re thinking syphilis this secondary rash is quite diagnostic.

Other non-descript signs include fevers, swollen lymph glands, sore throat, headaches. We did talk about it being the great imitator and these are many of the same kind of things that you get with an infectious syndrome. So the latent stage then, you have apparently no signs of disease and it is only diagnosed by having a reactive treponemal test. Early latent period, the clinical relapse can occur and the patient can become infectious again. And then we finally have tertiary syphilis. The tertiary stage, without treatment, about 15 percent of infected individuals progress to the latent stage, anywhere from 5 to 30 years after initial infection. This of course, is the most severe disease and can lead to neurosyphilis, some cardiovascular problems, even death. Neurosyphilis can cause slurring of speech, dementia, mimic other CNS diseases, so it’s very difficult to diagnose tertiary syphilis.
1.11 Common Patterns of Serologic Reactivity

The common patterns of serology reactivity are shown on this slide. The direct detection of *Treponema pallidum* would provide laboratory test results of the time of infection, however, as we mentioned, there is no FDA approved test for the direct detection and so we’re left to looking at serological detection. We can see that IgM peaks normally, just like it does for many infectious diseases and IgG stays up.

We have a little sliding here that shows that VDRL antibodies where they show if they are untreated or if they’re treated. But you can see that the serologic detection of treponemal antibodies would actually precede the detection of the non-treponemal antibodies, the cardiolipin that we’re looking for when we do VDRL’s and RPR’s. So treponemal antibodies could actually be detected sooner than the no-treponemal antibodies.
1.12 What laboratory assay is most widely used for diagnosing syphilis infection?
1.13 Direct Detection

Direct detection would be the ideal way to diagnose syphilis. However we do know that available tests right now are not FDA cleared. Dark field microscopy is very useful if you have a fresh lesion and the testing can be performed within minutes of the specimen being collected. However that is the limited availability. There is immunostaining. A DFA test but again, even getting the controls for that test is difficult. We do know that there are more Nucleic Acid Amplification tests (NAAT) that are being produced. Again, not FDA cleared. They would be laboratory developed tests. But we really don't know if it has any utility outside of the primary chancre because we just don't know if it is sensitive enough to identify *treponema pallidum* in blood serum spinal fluid. So there are definitely challenges in trying to do direct detection for syphilis. The limited availability and the lack of FDA cleared tests.

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Serologic Diagnosis of Syphilis

Always requires detection of two types of antibodies

- **Non-Treponemal antibodies**
  - Directed against lipoidal antigens
  - Most common tests: RPR and VDRL

- **Treponemal antibodies**
  - Directed against *T. pallidum*
  - Most common tests: FTA-ABS, TP-PA, EIA, CIA and MBIA

- **POC Testing**
  - FDA-cleared: Syphilis HealthCheck (Treponemal Ab only)
  - Non FDA-cleared: Chembio: Treponemal and Non-treponemal Ab

Notes:

Serologic disease of syphilis always requires the detection of two types of antibodies. This slide will just go into an overview and module two will delve into this a little bit more deeply. The non-treponemal antibodies are directed against lipoidal antigens like cardiolipin and are the most common tests. The RPR and the VDRL. The treponemal antibodies are directed specifically against the bacterial itself, *treponema pallidum*, and the most common test for that are the FTA-ABS, The *treponema pallidum* particle aglutination test, the EIA, CIA and microbead immunoassays. There is also point of care testing that can be performed. One is FDA cleared, the Syphilis HealthCheck. It is treponemal antibody only, and then there is another test in the pipeline which is not yet FDA cleared. Produced by Chembio which is the Treponemal and Non-treponemal Antibody test. It has both markers on that point of care test which would really help in the aid of diagnosis.
1.15 Syphilis diagnostic testing has evolved over the years so that it is easy to look at the test results and diagnose a case of syphilis.
1.16 Syphilis Diagnosis

No testing algorithm can take the place of clinical judgment

- Test results must be used in conjunction with the patient’s clinical symptoms, medical and sexual history, and other clinical and/or laboratory findings to produce an overall clinical diagnosis.

Notes:

As I hope that I have shown, syphilis diagnosis is not easy. There is no testing algorithm that can take the place of clinical judgment. Test results must be used in conjunction with the patient’s clinical symptoms, their medical and sexual history and other clinical and laboratory findings that produce an overall clinical diagnosis. There is certainly a controversy about which algorithm needs to be used. We will talk about that more in the next module.

There are problems with false positive results when doing serology. Non-treponemal tests are not specific enough. Sometimes other infections can cause a false positive result. And there can also be false negative results. People with latent syphilis can have negative results and certainly if we are performing the testing before even the production of a chancre we’re probably not going to be able to detect antibodies yet.

Certainly an HIV infection we’re concerned because high HIV titers along or in combination with signature antibodies can cause a false negative result as well. So there are many challenges with syphilis diagnosis.
1.17 Thank You for Participating!

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Overview of Syphilis Diagnostics: Background and History

Course complete

Notes:

This concludes the background and history presentation which is part of the series from the APHL overview of syphilis diagnostics. Please see the CDC and APHL websites for more information on these topics.
1.18 References

**References**


**Notes:**

The next few slides contain references and resources associated with this module and can be found on the APHL website.
1.19 Resources

Resources

Images

- http://phil.cdc.gov/phil/home.asp

General

- CDC Sexually Transmitted Disease Surveillance 2013
- STD Treatment Guidelines 2015
- Syphilis Fact Sheets
- Laboratory Diagnostic Testing for Treponema pallidum, Expert Consultation 2009
- CDC Division of STD Prevention (DSTDP)
- APHL STD Homepage