Literature Review

National STD Curriculum Podcast

A Vaccine for Gonorrhea

February 25, 2022

Season 2, Episode 5

Development of an effective vaccine against Neisseria gonorrhoeae has been difficult, but there has been recent progress in the field. This episode will cover some updates published in the literature on this topic.

Topics:

- Gonorrhea
- Neisseria gonorrhea
- vaccination

Meena S. Ramchandani, MD, MPH
Associate Editor
Associate Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington

Disclosures

Disclosures for Meena S. Ramchandani, MD, MPH
Consulting Fee: Innoviva Specialty Therapeutics

References

Background Paper #1 Paper #2 Paper #3 Summary

Transcript

Read along with the audio or jump to a particular chapter.

In this episode:

[00.00] Introduction
Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

[00.19] Background

Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle

meningococcal vaccine against gonorrhoea in New Zealand: A retrospective case-control study. Lancet. 2017 Sep 30;390(10102):1603-1610. **[PubMed Abstract]**

We're going to focus this episode describing some recent published literature on a potential future vaccine for gonorrhea. With the possible threat of untreatable gonorrhea due to extensive antibiotic resistance, a vaccine to prevent this infection would be great. Now historically, vaccine development for this organism has been a huge challenge. Until very recently, there was a lack of an animal model to mimic natural disease. Now, thankfully, there's a female mouse model of gonococcal genital tract infection and actually a human model that is worth mentioning, so that's been helpful. With *Neisseria gonorrhoeae* infection, weak immunity develops, and there's evidence that the protective immune responses to *Neisseria gonorrhoeae* do not develop with natural infection. For example, people can get recurrent gonococcal infection, even with a similar strain. So previous infection does not seem to prevent new infection.

Now, there's 80-90% genetic homology in the sequences between *Neisseria gonorrhoeae* and *Neisseria meningitides.* Despite this genetic homology between these two organisms, there has been little evidence that widely used vaccines against *Neisseria meningitides* serogroups A, C, W, and Y protect against gonococcal disease. The vaccine against the group B strain of *Neisseria meningitides* is developed a little bit differently: it's based on the outer membrane vesicle, which is a complex membrane structure naturally released from the outer membrane of gram-negative bacteria. So, there was an exciting study that was published in 2017 from New Zealand, which found an older meningococcal group B vaccine, which is also called MeNZB, provided 31% protection against gonorrhea in those who were vaccinated. And similar findings were shown by epidemiological studies after the use of group B meningococcal outer membrane vesicle vaccines in both Cuba and Norway. So, this identified a possible breakthrough in gonococcal vaccine development. The original vaccine MeNZB, which was developed to control a meningococcal epidemic in New Zealand, is no longer available, but another recombinant meningococcal group B vaccine 4CMenB, also known as *Bexsero*, is used around the world. For some background, *Bexsero* contains the MeNZB outer membrane vesicle component, as well as additional recombinant antigens. Some of these articles we're going to go through in this episode are more lab-based, but I'll do my best to summarize them.

[02.49] Paper #1

Semchenko EA, Tan A, Borrow R, Seib KL. The serogroup B meningococcal vaccine *Bexsero* elicits antibodies to *Neisseria gonorrhoeae*. Clin Infect Dis. 2019 Sep 13;69(7):1101-1111. **[PubMed Abstract]**

The first article to discuss was published in *Clinical Infectious Diseases* September 2019 by Dr. Semchenko and colleagues. It is titled "The serogroup B meningococcal vaccine *Bexsero* elicits antibodies to *Neisseria gonorrhoeae.*" This study provides some data on the potential of meningococcal vaccine antigens to generate an immune response that recognizes gonococcal proteins, possibly through cross-reactive antibodies.

1. So first, the authors did a bioinformatics analysis to evaluate the similarity of major outer membrane vesicle in the MeNZB vaccine and the *Bexsero* vaccine and compared them to gonococcal proteins from available *Neisseria gonorrhoeae* genomes.
2. They found a high level of amino acid identity between most of the major outer membrane vesicle proteins found in MeNZB and *Bexsero*, as well as a *Neisseria gonorrhoeae* homologue. This suggests that the potential for the *Bexsero* vaccine, which is currently being used in outbreak situations, to also generate an immune response that recognizes gonococcal proteins, similar to what MeNZB vaccine did in New Zealand.
3. Of the recombinant antigens found in the *Bexsero* vaccine, they focused on the neisserial heparin-binding antigen as this is believed to be a surface-exposed protein, therefore accessible to vaccine-induced antibodies, and a nice target for the immune system.
4. They identified a high level of homology and cross-reactivity between the meningococcal and gonococcal neisserial heparin-binding antigens. This suggests that the *Bexsero* vaccine may result in

additional cross-protection against gonorrhea than what was seen with the MeNZB vaccine.
5. Serum from rabbits immunized with the antigens present in the *Bexsero* vaccine, such as the outer membrane vesicle component or the three recombinant antigens, was able to recognize gonococcal proteins, including the neisserial heparin-binding antigen. This suggests the capacity of *Bexsero* vaccine to induce anti-gonococcal antibodies.
6. In humans vaccinated with *Bexsero*, antibody titers were significantly increased from pre- to post-vaccination against whole-cell *Neisseria gonorrhoeae* as well as the gonococcal neisserial heparin-binding antigen.

So, this study provides some exciting data to help support gonorrhea vaccine development. They identified several proteins present in the *Bexsero* vaccine that are also present in *Neisseria gonorrhoeae* with a high level of sequence identity and were also able to show that the vaccine can induce antibodies that recognize gonococcal proteins, including identifying potential vaccine targets.

[05.29] Paper #2

Leduc I, Connolly KL, Begum A, et al. The serogroup B meningococcal outer membrane vesicle-based vaccine 4CMenB induces cross-species protection against *Neisseria gonorrhoeae*. PLoS Pathog. 2020 Dec 8;16(12):e1008602. **[PubMed Abstract]**

The next article I'd like to discuss was published in *PloS Pathogens* in December 2020. This manuscript is titled "The serogroup B meningococcal outer membrane vesicle-based vaccine 4CMenB induces cross-species protection against *Neisseria gonorrhoeae,*" and this was published by Dr. Leduc and colleagues.

1. The authors evaluated the in vivo efficacy of the licensed *Bexsero* vaccine in a female mouse model of *Neisseria gonorrhoeae* lower genital tract infection.
2. Mice were vaccinated with the *Bexsero* vaccine by either the subcutaneous or intraperitoneal routes and then inoculated with *Neisseria gonorrhoeae*. They also had a control population.
3. The authors found that the *Bexsero* vaccination induced antibodies, more specifically, serum IgG as well as vaginal IgA and IGG, that cross-reacted with *Neisseria gonorrhoeae.*
4. They also found that the immunization with the vaccine accelerated clearance and reduced gonorrhea bacterial burden compared to controls. So, for example, 70 to 88% of mice given *Bexsero* vaccine by the subcutaneous and intraperitoneal routes cleared gonorrhea by day 7 compared to only 25 to 30% of mice in control groups.
5. Now, to examine the cross-reactivity of the *Bexsero*-induced antibodies against *Neisseria gonorrhoeae* surface proteins, the authors evaluated pooled antisera from immunized mice, and they found they recognized four prominent bands (or different proteins) in the fractionated outer membrane vesicle preparations of six different strains of gonorrhea. And antibodies from vaccinated mice recognized at least five *Neisseria gonorrhoeae* surface proteins, including the neisserial heparin-binding antigen that was mentioned earlier.
6. They compared the reactivity of serum from the *Bexsero*-immunized mice with that of immunized humans and identified additional *Neisseria gonorrhoeae* proteins that appeared to be recognized by both mice and humans. For example, they found cross-reactive antibodies against *Neisseria gonorrhoeae* antigens: such as an antigen called the outer membrane exigent antigen called PilQ, as well as the neisserial heparin-binding antigen, and possibly several unidentified proteins based on similarities in apparent molecular weight in both humans and mice.

So, authors found in the study is that in immunized mice, *Bexsero* reduces *Neisseria gonorrhoeae* bioburden, accelerates clearance of infection, and induces antibodies that recognize *Neisseria gonorrhoeae* outer membrane proteins or surface antigens, several of which are promising vaccine targets. This study also validates the female mouse model as a possible system for studying vaccine-induced protection against gonococcal disease.

[08.10] Paper #3

Norris Turner A, Carter A, Tzeng YL, et al. Infection with the US *Neisseria meningitidis* urethritis clade does not lower future risk of urethral gonorrhea. Clin Infect Dis. 2021 Sep 20:ciab824. **[PubMed Abstract]**

Bazan JA, Turner AN, Kirkcaldy RD, et al. Large cluster of *Neisseria meningitidis* urethritis in Columbus, Ohio, 2015. Clin Infect Dis. 2017 Jul 1;65(1):92-99. **[PubMed Abstract]**

The third article to discuss is more clinical. This is a manuscript published in *Clinical Infectious Diseases* September 2021 by Dr. Turner and colleagues. It is titled "Infection with US *Neisseria meningitidis* urethritis clade does not lower future risk of urethral gonorrhea."

1. This is a fascinating study, and there is a bit of a backstory. In 2015, there were clusters of phylogenetically linked cases of urethritis that were reported in the U.S., and the cause was a novel *Neisseria meningitidis* clade.
2. In the present article, the authors did a retrospective cohort study from 2015-2018 in Columbus, Ohio, to examine the risk of *Neisseria gonorrhoeae* among men who previously had the U.S. *Neisseria meningitidis* urethritis clade infection, So I'm just going to say *Neisseria meningitidis* urethritis for short, but just remember it was a specific clade that was found in the U.S. The goal was to find out whether *Neisseria meningitidis* urethritis infection confers protection against subsequent gonorrhea.
3. The study population included 887 participants; 65% were Black, 82% were heterosexual, and the median age was 28 years. During the follow-up period, 43% of men returned to the STI [sexually transmitted infection] clinic. Seventy-three men (or 57% of those that followed up) had baseline urethral *Neisseria meningitidis* infection.
4. Now, what they found is that men with a baseline urethral *Neisseria meningitidis* infection had a similar urethral *Neisseria gonorrhoeae* risk during follow-up as men with baseline urethral *Neisseria gonorrhoeae* infection—and this was an adjusted hazard ratio of 1.27. They had a slightly increased urethral *Neisseria gonorrhoeae* risk compared to those with a baseline urethral *Chlamydia trachomatis* infection, but this was not significant. That adjusted hazards ratio was 1.51.
5. Men with a baseline urethral *Neisseria meningitidis* infection had increased urethral *Neisseria gonorrhoeae* risk compared to men with *no* baseline urethral gonorrhea or chlamydia infection, and this was significant. This had an adjusted hazard ratio of 3.55.
6. The authors also evaluated sequences in the U.S. *Neisseria meningitidis* urethritis strain, and two *Neisseria gonorrhoeae* strains for the core outer membrane vesicle-derived and recombinant protein antigens that are found in the *Bexsero* vaccine. We just discussed these antigens in the previous articles, which are thought to elicit cross-protective antibodies.
7. They found the median sequence similarities for the shared outer membrane vesicle-derived proteins were greater than 97%. The recombinant protein antigen—neisserial heparin-binding antigen, which we had mentioned earlier—had greater than 78% sequence similarity.

So, in summary, urethral *Neisseria meningitidis* infection did not protect against future *Neisseria gonorrhoeae* infection, despite the high sequence similarities in shared protein antigens. Compared with men with a history of urethral *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, men with a history of urethral *Neisseria meningitidis* infection had a similar risk of gonococcal disease. It is interesting that men with a prior urethral *Neisseria meningitidis* urethritis had a higher risk of acquiring urethral *Neisseria gonorrhoeae* than men who were baseline negative for urethral gonorrhea or chlamydia infection. What this study shows is that if urethral *Neisseria meningitidis* urethritis infection elicited a cross-reactive immune response in the mucosal surface, it was just not potent, durable, or specific enough to protect against *Neisseria gonorrhoeae* acquisition. It will be interesting to see further research into how shared gonococcal and meningococcal antigens contribute to cross-protective immunity.

[12.08] Summary

Safety and efficacy study of meningococcal group B vaccine rMenB+OMV NZ (*Bexsero*) to prevent gonococcal infection. ClinicalTrials.gov identifier: NCT04350138. Updated February 11, 2022. **[NCT]**

To conclude, I'd like to summarize some key points from this session:

1. There's a pressing need for a gonorrhea vaccine due to the high disease burden associated with gonococcal infections globally as well as a rapid evolution of antibiotic resistance in *Neisseria gonorrhoeae*.
2. There are several proteins present in the meningococcal group B vaccine that are also present in *Neisseria gonorrhoeae,* and they have a high level of sequence identity. And the vaccine can also induce antibodies that recognize gonococcal proteins.
3. The *Bexsero* vaccine reduces *Neisseria gonorrhoeae* bioburden and accelerates clearance of infection in the female mouse model, and the female mouse model may be a good system for studying vaccine-induced protection
4. In patients, urethral *Neisseria meningitidis* infection has not been shown to protect against future *Neisseria gonorrhoeae*.
5. There is now an ongoing clinical trial in the U.S.A. and Thailand that is evaluating the *Bexsero* as a vaccine to prevent gonococcal infection. I look forward to seeing results from this trial.

[13.07] Credits

This podcast is brought to you by the National STD Curriculum, the University of Washington STD Prevention Training Center, and is funded by the Centers for Disease Control and Prevention.

Transcripts and references for this podcast series can be found on our website, the National STD Curriculum, at www.std.uw.edu. Thank you for listening and have a wonderful day.