Medical News & Perspectives

New Hope for a Gonorrhea Vaccine

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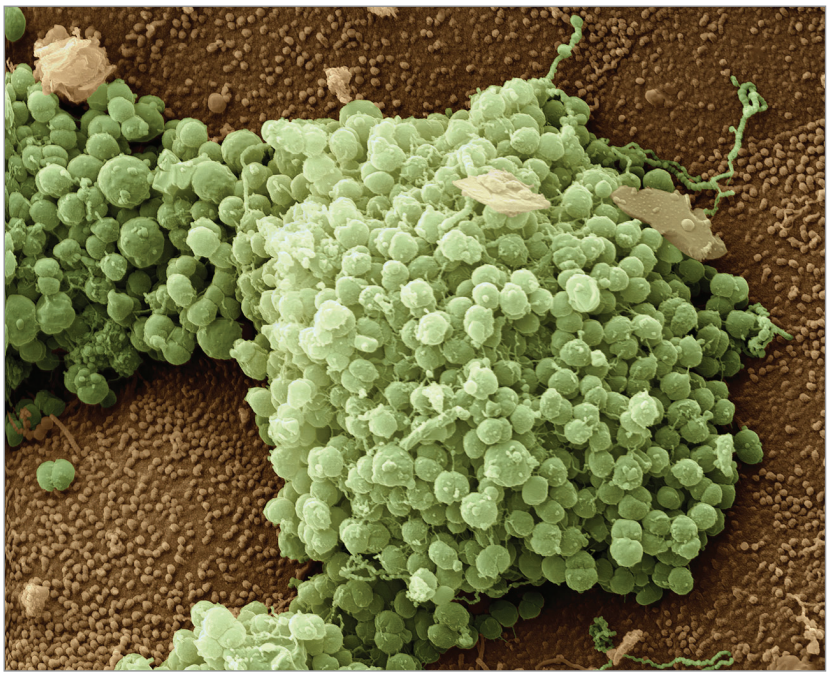
The fruitless search for a gonorrhea vaccine dates back more than a century. All 4 candidates that made it to clinical trials failed to provide any protection against the sexually transmitted infection (STI), which can cause pelvic inflammatory disease leading to ectopic pregnancy, infertility, and chronic pain in women, as well as increased HIV acquisition and transmission.

But now—as the growing worldwide threat of multidrug-resistant gonorrhea looms—hope has come in a surprising form: a meningococcal vaccine. Researchers recently reported that a group B meningococcal vaccine custom-made for an epidemic of that disease in New Zealand may also prevent gonorrhea infection in a third of vaccinated individuals.

The retrospective case-control study, published in *The Lancet* in July, examined records from almost 15 000 young adult patients at 11 sexual health clinics in New Zealand who were eligible to receive the outer membrane vesicle meningococcal B vaccine (MeNZB) between 2004 and 2008 and were diagnosed with either gonorrhea or chlamydia, or both. Patients who received MeNZB were substantially less likely to have been diagnosed with gonorrhea than chlamydia, and the researchers estimated the vaccine was 31% effective against the former.

Earlier this year, the same team also presented results from a cohort study of more than 600 000 individuals in New Zealand at a conference in Cuba. Those who were vaccinated with MeNZB were less likely to be hospitalized for gonorrhea than those who did not receive the vaccine, which appeared to be 45% effective against the STI in this group.

Discussing the study in *The Lancet*, Mark J. Mulligan, MD, a professor of medicine in the division of infectious diseases at Emory University who was not involved with the work, said, "It can't prove causation, because it's not designed to show that, but it does provide very interesting preliminary information that this could be the case."



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Correlation or Causation?

A lightbulb moment led to the discovery. In 2011, Steven Black, MD, a professor of pediatrics in the division of infectious diseases at Cincinnati Children's Hospital, noticed a striking correlation between meningococcal vaccination and reduced incidence of gonorrhea in public health data from New Zealand. He spotted the same trend later in data from Cuba.

New Zealand's National Immunisation Register records each vaccine dose administered in the country. This allowed a multidisciplinary team of researchers assembled by Helen Petousis-Harris, PhD, a senior lecturer in vaccinology at the University of Auckland, to track the MeNZB vaccine's possible effect on gonorrhea diagnoses at sexual health clinics. (The researchers were not able to conduct a similar study with Cuban data because information on vaccination status was not available on an individual level.)

Black, who coauthored the study, said the findings are proof of concept: "This is the first time it's been shown that you could have a vaccine that would protect against gonorrhea. And if these results are confirmed in

another setting, that would mean that it would be very reasonable … to go forward with developing perhaps a more targeted vaccine." Pending evidence of a causal effect, a new vaccine against gonorrhea could still be at least a decade off, Black said.

Exactly how a vaccine against *Neisseria meningitidis* may protect against *Neisseria gonorrhoeae* isn't yet known, but the bugs' names likely provide a big hint. The bacteria are closely related, sharing somewhere between 80% and 90% of their primary genetic sequences, Petousis-Harris said.

MeNZB, which is no longer available, was composed of purified protein components from buds on the cell surface of a strain of meningococcal B.

"An outer membrane vesicle has a mind-blowing number of antigens that are possibly presented to the immune system," Petousis-Harris said. Which of those meningococcal antigens, if any, also prime the immune system against gonorrhea? "That's the billion dollar question," she said.

Such cross-reactive protection has been seen before, Mulligan pointed out: "The greatest success in vaccinology, the eradication of smallpox from the human population, resulted from using a cousin, the cowpox *Vaccinia virus*, as a vaccine."

Reducing the Pressure

MeNZB's more broadly protective successor, 4CMenB (marketed as Bexsero by GSK Vaccines, which funded the new study) contains it, along with 3 genetically engineered meningococcal proteins. Two of these proteins are shared with gonorrhea and could enhance the vaccine's effectiveness against it.

If 4CMenB proves to be as effective against gonorrhea in randomized, double-blind, placebo-controlled trials as the New Zealand vaccine appears to be, Mulligan believes it would lead to additional efforts to improve the protection.

Even without a boost in efficacy, the vaccine could substantially reduce gonorrhea cases. Although 31% protection is modest—and lower than most approved vaccines—modeling published in 2015 suggests a vaccine against gonorrhea with such efficacy could decrease prevalence of the STI by more than 30% within 15 years.

According to Mulligan, "31% [protection] … could have a big impact on a disease that is estimated to cause nearly 80 million infections a year."

A GSK spokesperson told *JAMA* the company plans to explore 4CMenB's potential to help protect against gonorrhea. The Cuban meningoccal BC vaccine should also be studied further, Petousis-Harris said.

If randomized clinical trials are favorable, the vaccines' indications could be broadened to include gonorrhea. 4CMenB is already is part of the infant vaccination schedule in the United Kingdom, and it's possible that the recommendation could be expanded there to include a booster shot in adolescence to protect against gonorrhea. Two-for-one protection might also justify adding the vaccine to schedules in other parts of the world, according to Black.

The vaccine news comes as health agencies sound the alarm on the emergence of gonorrhea strains resistant to the current last-resort treatment, extended-spectrum cephalosporins (ESCs). Fifty-one of 77 countries that provided gonorrhea surveillance data to the World Health Organization (WHO) between 2009 and 2014 had ESC-resistant strains, according to a new report. The Centers for Disease Control and Prevention now categorizes *N gonorrhoeae* as 1 of the top 3 antibiotic-resistant threats in the United States, alongside *Clostridium difficile* and carbapenem-resistant Enterobacteriaceae.

The WHO began recommending dual antimicrobial therapy for gonorrhea last year. But dual therapies may prove to be inconvenient and impractical, especially in low-resource settings—and the first treatment failures with the 2-drug approach have already been reported. Yet only 3 new antimicrobials against the bug are in clinical development today.

Meanwhile, gonorrhea is on the rise. In the United States, the incidence increased 23% between 2011 and 2015, from 321 849 to 395 216 cases. The WHO has set a goal of reducing annual gonorrhea infections by 90% by 2030.

"If you can reduce the number of cases and reduce the amount of antibiotic use through vaccines, then you're reducing the pressure for new resistant strains, and that will allow, potentially, current antibiotics to be used longer," Black said. "It buys a little bit of breathing room, if you will, for development of new antibiotics."

Ultimately, a preventive vaccine could be the only sustainable solution to a nimble bug that has proven adept at developing resistance. "We can't assume that we can easily treat this disease anymore," Petousis-Harris said. ■

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