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Primer on the Prevention of Invasive Meningococcal Disease: Perspectives from Pediatric Practices

Toronto - Invasive meningococcal disease (IMD) is a rare but catastrophic disease associated with high morbidity and mortality rates. Today by far and away the greatest proportion of IMD in Canada is caused by *Neisseria meningitidis* serogroup B and it disproportionately affects infants under 12 months of age and teens and young adults between the ages of 15 and 24. The novel 4-component vaccine, the 4CMenB vaccine, has been shown to be effective in infants and children as well as in adolescents in large-scale clinical trials and can safely be given concurrently with other routine infant vaccines. Given parental concerns about protecting their children in general, healthcare providers are in a good position to counsel parents about the opportunity to prevent an otherwise devastating illness especially in the most vulnerable.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

Now that there is a vaccine against meningococcal serogroup B disease, primary care providers are likely asking themselves: Are there good reasons why I should be recommending this vaccine for infants and teens in particular and perhaps for all young children in between?

Two of the country's leading pediatricians provided them with a lot of good answers during a pre-conference symposium held before the launch of "pri-med", formerly known as Primary Care Today. The first can simply be thought of as insurance. Current recommendations from the National Advisory Committee on Immunization (NACI) indicate that the new 4CMenB vaccine (Bexsero®) should be considered for use in certain high-risk patients but that there isn't enough evidence to recommend its use in routine mass immunization public health programs.

"But what we see in our emergency rooms and in our ICUs are healthy kids," Dr. John Yaremko, Assistant Professor of Pediatrics, McGill University, Montreal, said in an interview. "We see it in the teenage hockey player who goes from being healthy to being in the ICU or dying in 12 to 24 hours and the same for healthy infants who end up being very damaged neurologically because of this illness. To me, prevention is really the way to go."

Moreover, chances that infants and toddlers, especially infants under the age of 12 months along with teens between 14 to 20 years of age, will develop IMD because of serogroup B infection are overwhelming. In Canada today, serogroup B is the most common serogroup causing IMD in all age groups, noted Dr. Saul Greenberg, Associate Professor of Pediatrics, University of Toronto in the same interview.

"In young infants, serogroup B causes 80% plus of IMD," he added, "and in 1- to 4-year-olds", it's about 66% and almost the same percentage in 15- to 24-years-olds. So serogroup B infection causes more IMD than all of the other serogroups combined," Dr. Greenberg said. Depending on the province, the meningococcal B vaccine can be expected to conservatively cover about two-thirds of circulating meningococcal B strains in the community. (In Quebec, the 4CMenB vaccine offers almost 100% protection because the prevalence of serogroup B in the province is extremely high. The prevalence of serogroup B is also very high in Manitoba.)

Vaccine Safe and Effective

The vaccine has been shown to be safe and effective in large-scale clinical trials in infants, toddlers and teens. (The 4CMenB vaccine has also been shown to be effective in adults but it is not approved for use in adults in Canada.) Infants given the primary series at 2, 4 and 6 months as well as on alternative schedules develop high antibody responses to the 4 antigens contained in the vaccine and with a booster dose given between 12 and 23 months, are able to regain protective antibody responses if immunity against vaccine antigens has waned over time.

Similarly, toddlers between 1 and 4 years of age who received the 4CMenB vaccine in clinical trials developed 95 to 100% antibody responses after the primary series. Teens developed high antibody levels that approached 100% against the 4 vaccine antigens as well and they only required 2 doses of the vaccine, given about 1 month apart, to maintain high levels of protection for at least 18 months following the second dose. The need for a booster dose for children between 12 and

23 months of age, between 2 and 10 years of age and adolescents from 11 to 17 years of age has not been established.

The 4CMenB can also be given along with other routine infant vaccinations and there is no evidence to suggest that concomitant injections with multiple vaccines adversely affect the immunogenicity of any of the vaccines. "Fever is a common side effect with the 4CMenB vaccine in infants and there is more fever when the 4CMenB vaccine is given together with routine infant vaccines," Dr. Yaremko said.

On the other hand, the risk of fever can be significantly attenuated if the child is given prophylactic acetaminophen at the time of administration and for 24 hours thereafter, he added. Fever is less of a concern when the vaccine is given to teens, Dr. Greenberg observed. In clinical trials of adolescents being given the vaccine, local side effects including tenderness and swelling, were fairly commonly reported, he added.

But as two busy pediatricians, neither Dr. Yaremko nor Dr. Greenberg has yet to see a spike in phone calls or visits from concerned parents after their infant has been vaccinated. "If you prepare the family and tell them that there will be fever, that fever in itself is not dangerous, parents are more tolerant of any fever that might develop and they won't seek medical attention because they've been told about it," Dr. Yaremko emphasized.

Real Evidence of Protection

Unlike other far more common vaccine preventable illnesses, IMD caused by any serogroup is a rare disease. This means that investigators have not been able to definitely declare that the vaccine will protect against clinical infection, as only antibody correlates of protection had been available until recently.

However, concrete evidence from both Quebec and several sites in the US has shown that the 4CMenB vaccine does protect individuals against serogroup B disease in high-risk situations. Until the vaccine was available, Saguenay-Lac-Saint-Jean, an area in Quebec, had 10 times the incidence of meningococcal B disease than any other area in the province. After the Quebec government paid for the 4CMenB vaccine to be given to everyone between the ages of 2 months and 20 years in the region, "there hasn't been a single case of IMD in this area since," Dr. Yaremko said.

Furthermore, out of over 45,000 vaccine recipients in Saguenay-Lac-Saint-Jean – many thousands of them infants – no serious adverse effects were observed and this from what is the greatest number of recipients to have ever received the 4CMenB vaccine, he added. The same protective effect from 4CMenB vaccination was also seen among Princeton University students where after a series of IMD cases caused by serogroup B were reported in 2013 and 2014, no further cases have been reported in Princeton University students once those at risk had received the two-dose series recommended for teens.

Finally, there is the issue of parental acceptance of any new vaccine and its cost. None of the provinces currently fund the 4CMenB vaccine for healthy individuals (only high risk), so parents will have to decide if the insurance they want to take out on their child to protect them against a rare disease is worth it. "I think we have to be very proactive in terms of offering vaccines to our patients and letting the parents decide what they want in terms of protection and what they can afford," Dr. Yaremko said.

"If you look at other things we do to protect our children – helmets and car seats and everything else – there is a cost but you are trying to protect your child and it's the same thing with meningococcal B.

"The disease is not common and hopefully you'll never have had this infection but if you are unlucky enough to get it and you've been vaccinated, that will decrease your risk of developing disease." Dr. Greenberg seconded being pro-active:

"Mortality from the disease can be anywhere from 5 to 15% and the sequellae are so significant they can just be horrendous. So if you can save one child, it doesn't matter what the cost-effectiveness of the vaccine is, if you can save one child, why not give the vaccine?"

Compellingly, the United Kingdom has announced that they are going to use the 4CMenB vaccine in their routine infant vaccination series as the sole vaccine against IMD. □

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