**The yin and yang of fever after meningococcal B vaccination**

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Meningococcal disease remains a major global cause of meningitis and septicaemia. In Europe and other industrialised countries, serogroup B (MenB) is responsible for most cases of invasive meningococcal disease (IMD) in young children and adolescents. An effective vaccine against MenB has been challenging to develop because its polysaccharide capsule is similar to human foetal nerve cells and is, therefore, poorly immunogenic. 4CMenB (Bexsero®) is a novel, multi-component, recombinant protein-based vaccine that includes major antigens on the surface of most meningococci. 4CMenB also includes the outer membrane vesicle (OMV) of the New Zealand MenB outbreak strain, containing additional major and minor surface antigens. It is this OMV component that makes the vaccine reactogenic.1

Around 50-65% of infants will develop fever ≥38.5°C when 4CMenB is given with other routine immunisations.1 The fever usually peaks after 6 hours and subsides within 24-48 hours. Prophylactic paracetamol significantly decreases the rate of fever after vaccination, as well as other local and systemic reactions. However unlike some previous studies, prophylactic paracetamol does not reduce the immune response to 4CMenB or any of the other routine infant immunisations. Consequently, the UK has recommended three doses of paracetamol to be given to infants receiving 4CMenB with their routine vaccinations at 2 and 4 months of age. Pre- and post-licensure studies have reported that around 1-2% of parents will still remain sufficiently concerned to seek additional medical attention following 4CMenB vaccination. Cost effectiveness analysis in the UK included the costs of treating medically-attended adverse reactions.

In the UK, 4CMenB was introduced into the national infant immunisation programme in September 2015 and rapidly achieved high vaccine coverage in eligible infants. Within 10 months of the programme, the vaccine was estimated to be 94% effective against the 88% of MenB strains predicted to be covered by the vaccine; most importantly, cases of IMD in vaccine-eligible infants have nearly halved compared to pre-vaccine estimates.2

More than three million dose of 4CMenB have been given in the UK and, so far, there have been no major safety concerns, although post-implementation surveillance is still on-going. In this issue, three different studies have identified a small but significant increase in hospital attendance among infants during the first few days after receiving 4CMenB at 2 and 4 months of age.

The Scottish study estimated an additional 1,440 infant hospitalisations annually in the UK after 4CMenB vaccination. Extrapolating the data in the Oxford study also estimated around 2,600 Emergency Department (ED) attendances, 1,300 admissions to the paediatric ward and 1,000 to the short-stay observation unit following 4CMenB at 2 and 4 months of age. In both the Oxford and the Belfast studies, the additional ED attendance were responsible for only 2-3% of total ED attendances among 1-6 month-olds and, therefore, likely to account for only a very small proportion of ED attendances in any single emergency department.

An important question is how these infants should be managed when they present to the ED. The risk of invasive bacterial infection falls rapidly after the first month of life.3 At the same time, data from 4CMenB clinical trials show that infants not only develop fever after 4CMenB vaccination, but also other non-specific symptoms that may mimic a serious underlying infection, especially irritability (71% of infants) and reduced feeding (63%), but also vomiting (26%) and diarrhea (23%).

Currently, the NICE guidelines recommend that all infants younger than 3 months who present with fever (≥38oC) as well as unwell infants aged 3-6 months with fever have bloods taken for a full blood count, blood culture and C-reactive protein (<https://www.nice.org.uk/guidance/cg160/resources/fever-in-under-5s-assessment-and-initial-management-pdf-35109685049029>). The guidelines also recommend lumbar punctures and parenteral antibiotics for all infants aged <1 months, as well as infants aged 1-3 months who appear unwell or have a peripheral white cell count <5×109/l or >15×109/l. Urinary tract infections are a relatively common cause of fever and should be tested for in all infants.3

The main difficulty for frontline clinicians is differentiating between a vaccine reaction and the rare possibility of an underlying serious bacterial infection. In the Belfast study, 71% of infants presented with fever and irritability, and 73% of infants who had a blood test performed had leukocytosis (>15×109/l). Many infants will also have raised inflammatory markers after 4CMenB. The NICE guidelines also emphasise that neither the height of the fever nor the response to antipyretics is useful in distinguishing between serious and non-serious infection. Consequently, a significant proportion (51% in the Belfast study and 72% in the Oxford study) will be admitted to hospital, have invasive investigations and receive empiric parenteral antibiotics.

In a recent review of the NICE Fever guidelines, topic experts expressed concern that the current guidance will lead to unnecessary septic screens, hospitalisations and antibiotic use in young infants who develop fever after vaccination. The response was to add a footnote to highlight that “*some vaccinations have been found to induce fever in children younger than 3 months*” [https://www.nice.org.uk/guidance/cg160/resources/surveillance-report-2017-fever-in-under-5s-2013-nice-guideline-cg160-4429528384/chapter/Surveillance-decision?tab=evidence]. This clearly does not address the issue. One suggestion would be to restrict the high-risk age group for serious bacterial infection from <3 months of age to <4 weeks, which would align with the NICE recommendations for performing lumbar punctures and initiating empiric antibiotic therapy, or to <8 weeks, before infants are offered their first 4CMenB dose.

The three studies in this issue highlight a need for further studies on how best to manage such infants because, while the risk of an underlying serious bacterial infection during the first 24-48 hours after vaccination remains extremely low, it is not zero. Until further guidance becomes available, infants seeking medical attention after 4CMenB will require careful clinical assessment by an experienced clinician, most likely with a period of close observation; monitoring the course of fever and response to antipyretics is unlikely to be helpful, and neither are blood tests. Where there is uncertainty, clinicians will be required to initiate empiric antibiotics until a serious bacterial infection can be safely ruled out. Unfortunately, this may be the price to pay for a vaccine that prevents one of the most feared and deadliest infectious diseases.

**Reducing healthcare utilisation after 4CMenB vaccination**

Another important question is how to reduce primary and secondary care attendances for fever after 4CMenB vaccination. In one clinical trial, parents who were informed of the risk of fever after 4CMenB were significantly less likely to seek medical attention compared to those who were blinded to their infants’ immunisations.4 Public Health England and NHS England have invested a lot of resources to raise awareness of fever and its management after 4CMenB vaccination among parents and healthcare professionals (<https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/483408/9413-paracetamol-menB-2page-A4-08-web.pdf>).

In the Oxford and Belfast studies, most parents reported knowing about the recommendation to give paracetamol after 4CMenB vaccination; however, it is difficult to know whether these recommendations were followed. Further investment in raising awareness of the prevention and treatment of post-vaccination fever among new parents, immunisers, and clinicians working in primary and secondary care is likely to be important. As the 4CMenB programme matures and the vaccine becomes more acceptable with increasing evidence of effectiveness, impact and safety, more parents will become accustomed to the routine use of prophylactic paracetamol for their infants. These should help reduce medical attendance rates over time. In the meantime, it is important that paediatricians play their part in reassuring parents of infants presenting to hospital with fever, encourage them to complete the recommended immunisation schedule in a timely manner and highlight the importance of prophylactic paracetamol when their infants receive their primary immunisations with 4CMenB.

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**Declaration of Interest**

Andrew Riordan is a member of the Joint Committee of Vaccination and Immunisation and chaired the Meningococcal Sub-Committee. He was also a Topic Expert for Surveillance report 2016 – Fever in under 5s (2013) NICE guideline CG160. Shamez Ladhani is the clinical lead for the meningococcal immunisation programme at Public Health England.