The National Minor Illness Centre

Meningitis B vaccination – the challenges
• The new Meningitis B (Men B) vaccination campaign, introduced in September 2015, has led to a change in the advice given to parents around the time of infant vaccination

• Previously, in line with advice from the Department of Health, nurses have advised parents not to administer prophylactic paracetamol at the time of vaccination because there was evidence that this was associated with a reduced response to the vaccine

• However the Men B campaign has specifically instructed parents to give paracetamol, and has even supplied branded sachets of Calpol for this purpose

• This is a particular problem because nurses have campaigned for many years to deter parents from requesting paracetamol on NHS prescription, and to convince them that generic paracetamol is equally effective as Calpol
Paracetamol and vaccine response

• There is understandable concern from Public Health England that fever is more likely with the addition of Men B, and if the first vaccinations make babies very unwell they may not be brought back for further vaccinations.

• However the Department of Health’s Green Book still states\(^1\):

  “It is not recommended that these drugs (antipyretics) are used routinely to prevent fever following vaccination, as there is some evidence that prophylactic administration of antipyretic drugs around the time of vaccination may lower antibody responses to some vaccines.”

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In 2009 a GSK sponsored trial on 459 babies\textsuperscript{2} showed a significant 35\% reduction in the immune response to several vaccines after giving paracetamol. This trial prompted the Green Book advice.

However a follow-up study of 220 of these children did not suggest a lasting effect\textsuperscript{3}.

The same lead author (Prymula) has recently published a further trial on 303 babies, sponsored by Novartis, which did not demonstrate a reduction in immune response after paracetamol\textsuperscript{4}.

But for hepatitis B vaccination in 2014, a GSK sponsored trial of 496 adults showed a significant 26\% drop in antibody response when paracetamol was given\textsuperscript{5}.

So overall the picture is still unclear.
A systematic review of the effect of prophylactic paracetamol on the antibody response to childhood vaccines was published in 2014. It included 13 RCTs and a total of 5077 children under 6. Prophylactic antipyretic administration significantly reduced the febrile reactions (≥38.0°C) after primary and booster vaccinations. Although there were statistically significant differences in the antibody responses between the two groups, the prophylactic paracetamol group still had protective levels of antibodies. This is reassuring.
Prophylactic Paracetamol Did Not Impact Immunogenicity of PCV7

*BEXSERO® given concomitantly with routine infant vaccines 2-3-4 month schedule

*N=135–140. Blood draw at 5 months. Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

How common is fever after Men B vaccine?

• “In clinical studies in infants vaccinated at 2, 4 and 6 months of age, fever (≥ 38°C) was reported by 69% to 79% of subjects when Bexsero® (Men B) was co-administered with routine vaccines (containing the following antigens: pneumococcal 7-valent conjugate, diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b), compared with 44% to 59% of subjects receiving the routine vaccines alone” (Bexsero® SPC)⁷

• However the following slide suggests an incidence of fever of around 50%, reduced to around 25% by paracetamol
Prophylactic Paracetamol at the Time of and Closely After Vaccination Reduced Fever When BEXSERO® is given concomitantly with routine infant vaccines

Post–dose 1
(of 2-3-4 month dosing schedule)

NPP: no prophylactic paracetamol (N=182); PP: with prophylactic paracetamol (N=178-179).
Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

What should be done if there is fever?

- By a conservative estimate, 25% of babies given Men B with the routine vaccines at eight weeks will develop a fever, even if prophylactic paracetamol is given.
- This fever usually resolves rapidly, certainly within 48hr of the vaccination.
- The Men B leaflet for parents recommends only seeking help if “you are concerned about your baby’s health at any time...(or) if your baby still has a fever more than 48 hours after vaccination”.
- But NICE guidance CG160 states that if a baby under three months has a fever of ≥38°C, they should be admitted to hospital for assessment under the “traffic lights” scheme.
- This NICE information has been promoted to parents, including (in Bedfordshire) an insert in the child’s Red Book.
In General, the Frequency of Medically Attended Fever Was Low

Percentage of Subjects With Medically Attended Fever
(Number of Subjects With Medically Attended Fever/Total Number of Subjects)

<table>
<thead>
<tr>
<th>Subset</th>
<th>BEXSERO® Vaccine + Routine Vaccines*</th>
<th>MenC+ Routine Vaccines*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer-Blind Subset</td>
<td>5.3% (26/493)</td>
<td>2.8% (13/470)</td>
</tr>
<tr>
<td>Open-Label Subset</td>
<td>1.4% (28/1966)</td>
<td>1.8% (12/659)</td>
</tr>
</tbody>
</table>

*Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.


Medical intervention less likely with knowledge of vaccine received
Should we refer a feverish baby after imms?

- It seems from the previous slide that, if parents are told to expect a fever after immunisation, they are unlikely to seek help from a health professional.
- But if they do, the health professional is obliged to admit the baby according to NICE guidance because of the small possibility that the fever is not caused by the vaccine but by a serious illness.
- This advice has been confirmed by Professor Monica Lakhanpaul, Programme Director, Children, Young People and Maternal Health (UCL Partners).
- Such advice will inevitably increase hospital attendances at PAU (at a cost of £235 in Luton) or A&E.

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If you are concerned about your baby's health at any time, then trust your instincts and speak to your GP or call NHS 111 in England and 0845 46 47 in Wales for advice.

If your baby still has a fever more than 48 hours after vaccination you should speak to your GP or call NHS 111 in England and 0845 46 47 in Wales for advice.

Is it OK for small babies to have paracetamol?
Paracetamol is approved for managing fever in children from the age of two months. The patient information leaflet that comes with the pack may say that children aged two to three months should only be given two doses before talking to a doctor or pharmacist.

Although paracetamol is safe in very young children, the advice on the packaging is there to avoid parents giving paracetamol to a child with an unexplained fever. Such a fever could be a sign of a serious infection and treating this for too long may delay a parent seeking medical help.

As fever after vaccination is common, however, experts have advised that it is OK to give paracetamol for up to 48 hours after the MenB vaccine without seeking medical advice. Fever in this time period is much more likely to be caused by the vaccine than by an infection. The paracetamol will also make your child feel better, and there is no risk of an over dose.

Why does the manufacturer's patient information leaflet (PIL) contain different information?
You will find a patient information leaflet (PIL) in the supply of paracetamol you purchase. The PIL with the infant paracetamol suspension 120mg/5ml may provide different dosing instructions from the experts' recommendations for use following MenB vaccination. Here, in this leaflet, we give the details of the specific recommendations for the use of paracetamol following a MenB vaccination. For full information about the paracetamol product, please see the manufacturers PIL.

Does my baby need paracetamol with the booster vaccinations at 12 months?
By the age of 12 months your baby's risk of fever after MenB vaccine is the same as with the other vaccines. So, your baby does not need to take three doses of paracetamol with their routine 12 month vaccinations. However, if your baby does get fever at home or appears to be in discomfort, you can give your baby infant paracetamol using the...
• Fever phobia is a driver for many paediatric attendances at A&E
• NICE CG160 was very clear that fever benefits the immune response, that routine lowering of fever is unnecessary, and that giving antipyretics may delay the recovery from infections
• It has been an uphill struggle to get this message across
• The new Men B information leaflets for parents needs careful explanation, otherwise it may give them the impression that when their child has a fever for any reason, they should always dose the child with paracetamol
Men B vaccine – the challenges

• To promote a clear message to parents about the significance and treatment of fever:
  – Post-vaccination
  – In babies under six months, in other circumstances
  – In older children

• Currently there is conflict between NICE guidance CG160 and the Men B information leaflet

• What is an appropriate response when a baby is brought to a health professional with a fever of ≥38°C after their first Men B vaccination?

• A small working group has been set up to review this problem and consider a new NICE guidance supplement or a DoH directive

• For the moment, all such babies should be referred to hospital

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   http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0106629
6. Das (2014):
   http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0106629

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Slides 6, 8 and 10 were taken from the “Training the Trainer slideset” provided by Public Health England
Slide 12 is from the Public Health England leaflet for parents “Using paracetamol to prevent and treat fever after Men B vaccination”:

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