The yin and yang of paracetamol and paediatric immunisations

Although highly effective, whole-cell pertussis vaccines are associated with high rates of injection-site reactions, fever, and less commonly febrile seizures. Two trials in the 1980s showed that rates of postimmunisation fever could be reduced through the prophylactic administration of paracetamol (acetaminophen),12 which led the US Advisory Committee on Immunization Practice to recommend “it is reasonable to consider administering antipyretics (such as acetaminophen) at age-appropriate doses at the time of vaccination and every 4–6 h for 48–72 h to children at higher risk for seizures than the general population”.3 In practice, the administration of paracetamol to all children receiving whole-cell pertussis vaccine became widespread. In Canada, the National Advisory Committee on Immunization advised “because of the lower incidence of fever associated with [acellular pertussis] vaccines, there may be less justification for routine use of prophylactic acetaminophen, as had been recommended with the whole-cell pertussis vaccines”.4 Lewis and colleagues1 had cautioned about the possible effects of anti-inflammatory agents on a diminished immune response. But, because no effect on immunogenicity was noted with paracetamol and whole-cell pertussis vaccine,3,4 the extensive prelicensure trials with acellular pertussis studied the effect of paracetamol on reactogenicity, not immunogenicity.7,8

In The Lancet today, Roman Prymula and colleagues are the first to examine this issue carefully with a current paediatric vaccine regimen.5 Unexpectedly, they found reduced immunogenicity of common paediatric vaccines with use of paracetamol in open-label randomised trials for both primary and booster doses. The investigators discuss several potential mechanisms for the observed effect on the antibody response. Prevention of inflammation and fever is unlikely because the immune responses (and the effect of paracetamol) in children with and without fever were similar. The authors propose that the most attractive mechanism is interference with the early interactions of dendritic cells, T cells, and B cells of the primary immune response through a reduction of inflammatory signals at the injection site, which would also explain the decreased effect of paracetamol on immunogenicity of the booster dose. However, despite being an inhibitor of cyclo-oxygenase 2 (COX-2), paracetamol’s anti-inflammatory activity is contested, perhaps related to inhibition of activity in high-peroxide environments that are common at sites of inflammation.10 Paracetamol’s COX-2 inhibiting activity might be restricted to the CNS, where oxidative stresses are more tightly controlled. An anti-inflammatory mechanism would be of particular concern with ibuprofen for the prevention and treatment of adverse events after immunisation. Ibuprofen is a more potent COX-2 inhibitor with greater anti-inflammatory activity than paracetamol, particularly at peripheral sites of tissue inflammation. The effect of ibuprofen on the antibody response postimmunisation (and postinfection) is not known.
Regardless of biological plausibility and the proposed mechanism of action, are the results of today’s study true or the result of bias or unmeasured confounding? Several findings support the integrity of the randomisation scheme. Systematic bias is unlikely to have resulted consistently across ten sites. Although no comparison was presented of baseline characteristics by prophylaxis group, seroprotection/seropositivity rates were similar in the groups. Further, adverse events not likely to be affected by use of paracetamol, including diarrhoea, vomiting, and upper respiratory illness, occurred with similar frequency in both groups. Although the use of paracetamol was not masked, diaries were kept of administration of both paracetamol and therapeutic antipyretic doses, which allowed the investigators to conclude that adherence to treatment was high, while use of therapeutic antipyretics was low. The conclusion of an effect of paracetamol on immunogenicity was further supported by post-hoc analyses from ten previous trials, suggesting the greatest effect in the 24 h after immunisation. The finding that antibody concentrations were reduced was consistent across almost all the antigens studied.

The more important question is the clinical and public health implications of reduced antibody concentrations with use of paracetamol. In today’s study, the high proportion of vaccine recipients reaching seroprotective antibody levels suggests that the effect of paracetamol for any given individual might be small; further assessment at the individual level, such as whether or not paracetamol increases the proportion of vaccine non-responders, is warranted. However, a larger question is the extent to which paracetamol might reduce population protection. This point has implications, especially for Haemophilus influenzae and pneumococcus, for which higher and sustained antibody concentrations are needed to interrupt the carrier state and reduce transmission within the population, and for pertussis, the bacterial vaccine-preventable disease that is the least well controlled. Active immunisations protect by mimicking the adaptive immune response to wild infections. The art of vaccine development balances the attenuation of reactogenicity without over-sacrificing immunogenicity. Prymula and colleagues are correct to conclude that the risks associated with paracetamol might have changed.

Vaccine policy makers must now assess the implications for vaccination programmes. Prymula and colleagues present a compelling case against routine use of paracetamol during paediatric immunisations. Whether this rule applies to all antipyretics, all age groups, whole-cell pertussis vaccines that continue to be received by about 70% of the global birth cohort (Gacic-Dobo M, WHO/FCH/IVB/EPI+, Geneva, Switzerland; personal communication), and subgroups with different risk–benefit considerations (eg, those at risk for febrile seizures), requires further study. Going forward, when an intervention against reactogenicity is planned in vaccine trials, investigators must be mindful of the effect on immunogenicity (and vice versa) as they are likely to be intertwined natural and complementary dualities (yin and yang in Chinese).