

Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials



Roman Prymula, Claire-Anne Siegrist, Roman Chlibek, Helena Zemlickova, Marie Vackova, Jan Smetana, Patricia Lommel, Eva Kaliskova, Dorota Borys, Lode Schuerman

Summary

Background Although fever is part of the normal inflammatory process after immunisation, prophylactic antipyretic drugs are sometimes recommended to allay concerns of high fever and febrile convulsion. We assessed the effect of prophylactic administration of paracetamol at vaccination on infant febrile reaction rates and vaccine responses.

Methods In two consecutive (primary and booster) randomised, controlled, open-label vaccination studies, 459 healthy infants were enrolled from ten centres in the Czech Republic. Infants were randomly assigned with a computer-generated randomisation list to receive three prophylactic paracetamol doses every 6–8 h in the first 24 h (n=226) or no prophylactic paracetamol (n=233) after each vaccination with a ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) co-administered with the hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H *influenzae* type b (DTPa-HBV-IPV/Hib) and oral human rotavirus vaccines. The primary objective in both studies was the reduction in febrile reactions of 38·0°C or greater in the total vaccinated cohort. The second objective was assessment of immunogenicity in the according-to-protocol cohort. These studies are registered with ClinicalTrials.gov, numbers NCT00370318 and NCT00496015.

Findings Fever greater than 39·5°C was uncommon in both groups (after primary: one of 226 participants [$<1\%$] in prophylactic paracetamol group vs three of 233 [1%] in no prophylactic paracetamol group; after booster: three of 178 [2%] vs two of 172 [1%]). The percentage of children with temperature of 38°C or greater after at least one dose was significantly lower in the prophylactic paracetamol group (94/226 [42%] after primary vaccination and 64/178 [36%] after booster vaccination) than in the no prophylactic paracetamol group (154/233 [66%] after primary vaccination and 100/172 [58%] after booster vaccination). Antibody geometric mean concentrations (GMCs) were significantly lower in the prophylactic paracetamol group than in the no prophylactic paracetamol group after primary vaccination for all ten pneumococcal vaccine serotypes, protein D, antipolyribosyl-ribitol phosphate, antidipteria, antitetanus, and antipertactin. After boosting, lower antibody GMCs persisted in the prophylactic paracetamol group for antitetanus, protein D, and all pneumococcal serotypes apart from 19F.

Interpretation Although febrile reactions significantly decreased, prophylactic administration of antipyretic drugs at the time of vaccination should not be routinely recommended since antibody responses to several vaccine antigens were reduced.

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Introduction

Fever is part of the normal inflammatory response and frequently occurs in response to infection. This host-defence mechanism has a beneficial effect on many infections and can enhance survival. Fever is also a well described event after vaccination.^{1–4} It is produced by endogenous pyrogens, mainly interleukin 1 and tumour necrosis factor α , and is associated with heightened T-cell activity, enhanced antigen recognition, and immune responses.⁵ Although generally benign and self-limiting,⁶ fever after vaccination is frequently a concern for parents and health-care professionals, driven by fears of febrile convulsion and by beliefs that it represents a serious pathological change.^{7,8} These notions can result in medical visits, unnecessary

laboratory investigations, and avoidance or deferral of subsequent vaccinations.

The prophylactic administration of antipyretic drugs has thus become routine practice and is even recommended in some countries for vaccination against diphtheria, tetanus, and whole-cell pertussis (DTPw), combination vaccinations,^{9,10} or for children with a history of febrile convulsion.¹¹ Evidence lending support to this approach is scarce; the level of fever is unrelated to the onset of convulsion,^{12,13} and antipyretic drugs are ineffective in prevention of benign febrile convulsion in children who are at risk.¹⁴

We assessed the effect of the prophylactic administration of paracetamol at the time of vaccination and within the next 24 h on the rate of febrile reactions

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Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic (Prof R Prymula MD, R Chlibek MD, M Vackova MD, J Smetana MD); Center for Vaccinology and Neonatal Immunology, University of Geneva, Geneva, Switzerland (Prof C-A Siegrist MD); Centre of Epidemiology and Microbiology, National Institute of Public Health, Prague, Czech Republic (H Zemlickova MD); Global Clinical Development Center, GlaxoSmithKline Biologicals, Rixensart, Belgium (P Lommel BScB, D Borys MD, L Schuerman MD); and GlaxoSmithKline, Prague, Czech Republic (E Kaliskova MD)

Correspondence to: Prof Roman Prymula, University of Defence, Department of Epidemiology, Faculty of Military Health Science, Trebesska 1575, 50012, Hradec Kralove, Czech Republic
prymula@pmfhk.cz

and vaccine responses in infants after primary vaccination with a ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine (PHiD-CV) co-administered with the hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-*H influenzae* type b vaccine (DTPa-HBV-IPV/Hib) and oral human rotavirus vaccine (HRV), followed by a booster dose of PHiD-CV plus DTPa-HBV-IPV/Hib.

Methods

Study design and participants

Two consecutive (primary and booster vaccination) phase 3, randomised, controlled, open-label studies were undertaken in ten centres in the Czech Republic from Sept 18, 2006, to April 10, 2007 (primary vaccination study), and from July 2, 2007, to April 1, 2008 (data lockpoint for reported analysis, while the study continued for nasopharyngeal carriage endpoints, booster vaccination study).

Study participants were healthy infants aged 9–16 weeks at time of enrolment and 12–15 months at time of boosting. Participation in the study was offered by paediatricians in health centres. Infants were excluded from participation if prophylactic antipyretic therapy was required for reasons unrelated to the study or if they had a contraindication to paracetamol treatment. Other exclusion criteria were previous vaccination against pathogens targeted by PHiD-CV, DTPa-HBV-IPV/Hib, and HRV, or previously described exclusion criteria.¹⁵

Both studies were undertaken according to Good Clinical Practice and the Declaration of Helsinki (Somerset West, 1996 version). Protocols were approved by ethics review committees of participating centres. Before enrolment in each study, written informed consent was obtained from the parents or guardian of every participant.

Randomisation and masking

Primary vaccine doses of PHiD-CV and DTPa-HBV-IPV/Hib were administered to all participants at 3, 4, and 5 months of age. HRV was administered at 3 and 4 months of age. Children were enrolled and randomly assigned (1:1 ratio) into two groups: one group received three doses of paracetamol preventively administered every 6–8 h within the first 24 h after each vaccine dose and the other received no paracetamol prophylaxis. The control group did not receive a placebo drug. The paracetamol treatment was therefore not blinded and the parents were aware of the prophylactic antipyretic treatment assignment. At the time of participant enrolment, the investigator obtained the group allocation via an internet-based randomisation procedure. The randomisation list was generated with a standard SAS program (version 8.2 for primary vaccination study; version 9.1 for booster study) with a blocking scheme to ensure that the balance between the

treatment groups was maintained. The investigator was not aware of the randomisation block size to avoid the possibility that the next treatment sequence could be derived from the previous treatment allocations.

Booster doses of PHiD-CV and DTPa-HBV-IPV/Hib, with or without prophylactic paracetamol, were administered between 12 and 15 months of age. Children retained their original treatment group assignment (with or without prophylactic paracetamol). When the primary vaccination immunogenicity results became available, the administration of prophylactic paracetamol at the time of booster vaccination was discontinued via a protocol amendment. As a consequence, results of the booster study are presented for three study groups (figure 1): the group in which children received primary and booster vaccination with prophylactic paracetamol (children boosted before amendment); the group who received prophylactic paracetamol only during primary vaccination (boosted after protocol amendment); and the group who received no prophylactic paracetamol during either primary or booster immunisation and who were boosted before the amendment. To avoid bias, participants from the group receiving no prophylactic paracetamol who were boosted after implementation of the amendment were not considered for group comparisons.

Procedures

All vaccines were manufactured by GlaxoSmithKline Biologicals (GSK), Rixensart, Belgium. PHiD-CV contained 1 µg of each capsular polysaccharide of serotypes 1, 5, 6B, 7F, 9V, 14, and 23F, and 3 µg of serotype 4, conjugated individually to protein D; 3 µg of capsular polysaccharide of serotype 18C conjugated to tetanus toxoid; and 3 µg of capsular polysaccharide of serotype 19F conjugated to diphtheria toxoid. Each dose of DTPa-HBV-IPV/Hib vaccine (Infanrix hexa) contained 30 IU or more diphtheria toxoid; 40 IU or more tetanus toxoid; 25 µg pertussis toxin; 25 µg filamentous haemagglutinin; 8 µg pertactin; 10 µg recombinant hepatitis B surface antigen (HBsAg); 40D, 8D, and 32D antigen units of poliovirus types 1, 2, and 3, respectively; and 10 µg *H influenzae* type b polyribosyl-ribitol-phosphate conjugated to tetanus toxoid. Each dose of HRV (Rotarix) contained $1 \times 10^6.5$ median cell-culture infective doses of the RIX4414 vaccine strain. PHiD-CV and DTPa-HBV-IPV/Hib vaccines were administered intramuscularly into the right and left thigh or deltoid (booster dose), respectively. HRV was administered orally.

The prophylactic antipyretic treatment consisted of three doses of paracetamol given via suppositories within the first 24 h after each vaccine dose. The first administration of paracetamol (Calpol, GSK) was given by study staff immediately after vaccination. The second and third administrations were done at home every 6–8 h. The dose of paracetamol was based on bodyweight: 80 mg

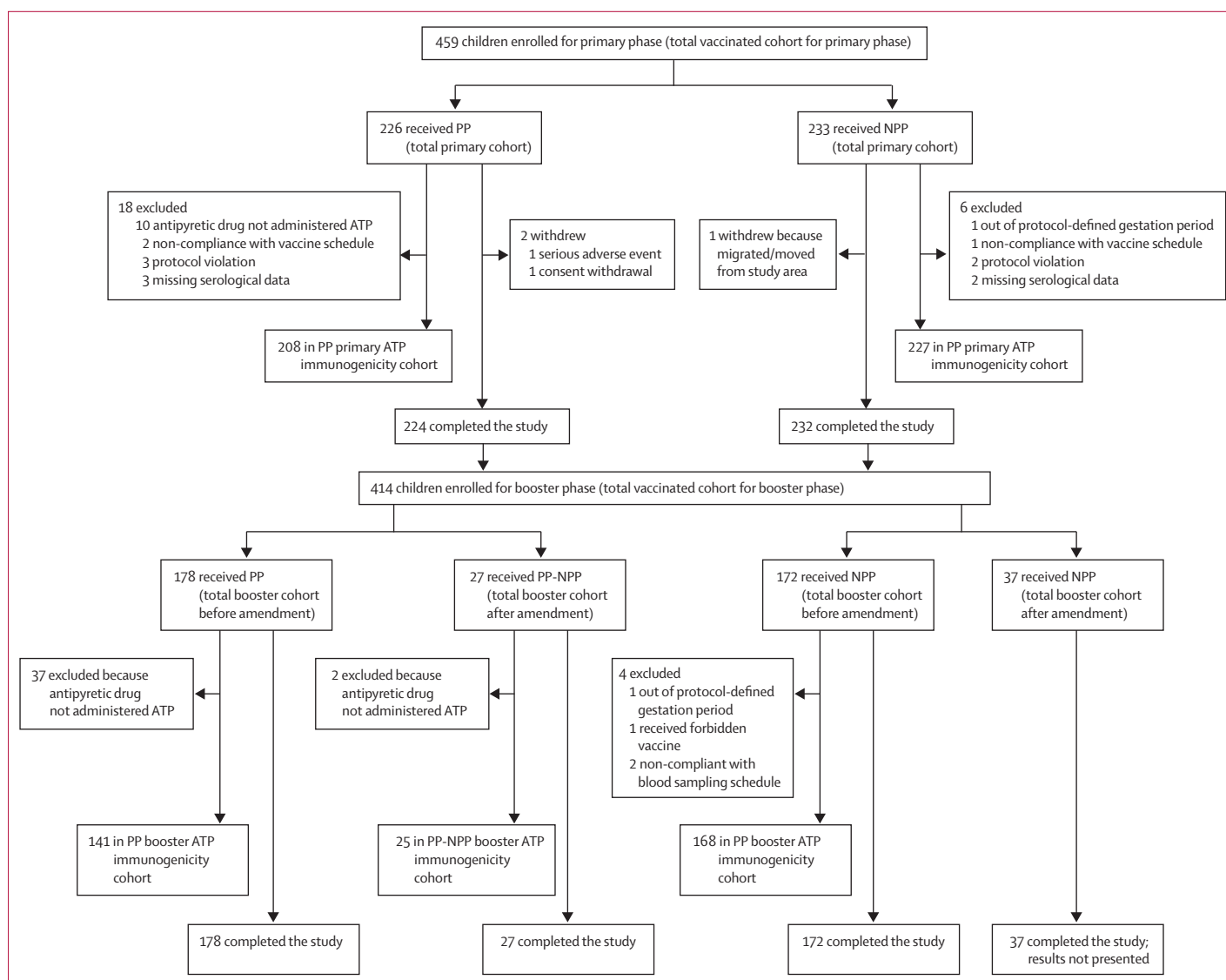


Figure 1: Study profile

PP=prophylactic paracetamol. NPP=no prophylactic paracetamol. PP-NPP=primed with prophylactic paracetamol and boosted without prophylactic paracetamol. ATP=according to protocol.

per administration ($53.3\text{--}34.3\text{ mg/kg/24 h}$) for infants weighing between 4.5 kg and less than 7 kg , and 125 mg per administration ($\leq 53.6\text{ mg/kg/24 h}$) for infants weighing 7 kg or more. At booster vaccination, the same dose was given to infants weighing between 7 kg and less than 9 kg , and those with bodyweight of 9 kg or greater received four administrations of 125 mg paracetamol each within 24 h ($\leq 55.6\text{ mg/kg/24 h}$). Antipyretic drugs for therapeutic use were allowed at the discretion of the child's parents or study physician in both groups, but paracetamol was allowed no earlier than 6 h after the last protocol prescribed prophylactic dose in the group receiving prophylactic paracetamol.

Reactogenicity and safety data were collected on diary cards completed by parents or guardians on the day of

vaccination and for 3 subsequent days after each vaccine dose. Local symptoms (pain, redness, and swelling at the injection site) and general symptoms (temperature, irritability/fussiness, drowsiness, and loss of appetite) were actively solicited, and episodes of vomiting and diarrhoea were recorded after administration of HRV. Unsolicited adverse events were recorded for 31 days after each dose, and serious adverse events from the first primary vaccine dose up to the end of the 6-month post-primary safety follow-up and from booster vaccination up to 1 month after the booster dose.

The intensity of adverse events was graded on a scale from 0 (absent) to 3. The study physician assessed the relation to vaccination of each solicited general symptom and all unsolicited symptoms.

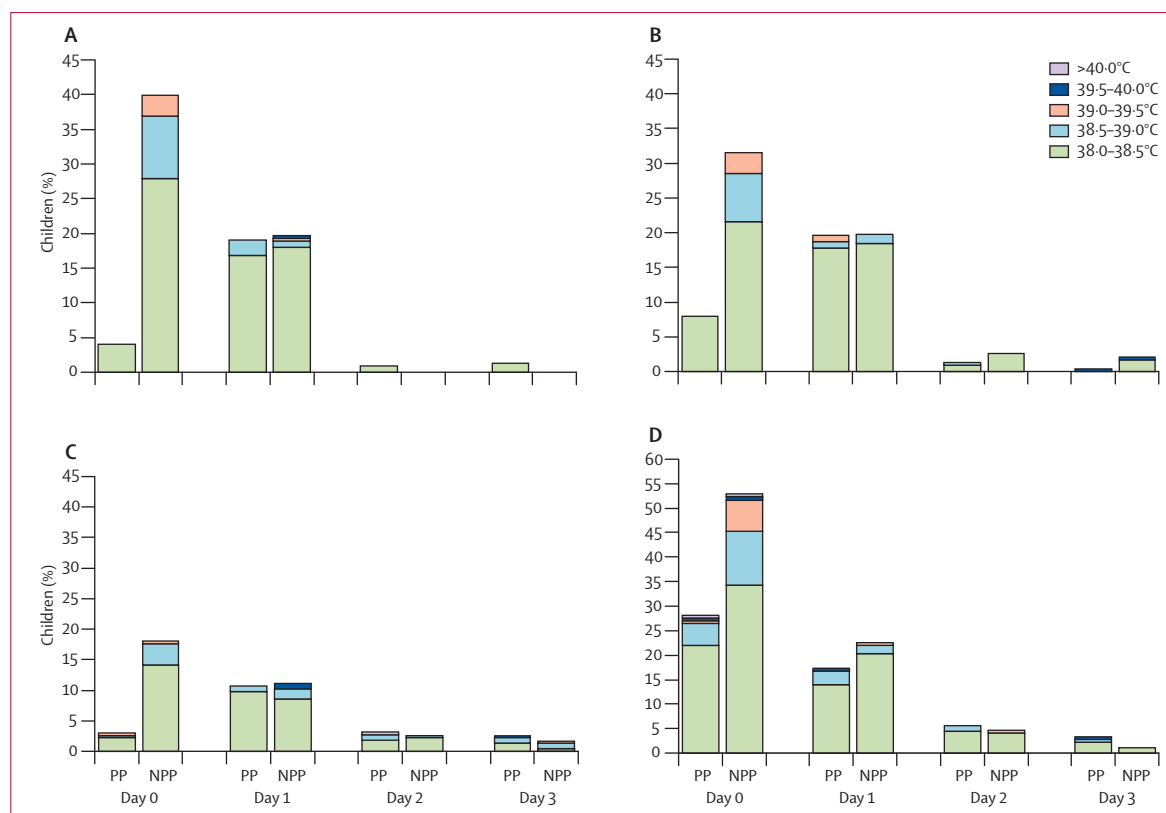


Figure 2: Daily prevalence of fever during the 4-day (days 0–3) period after each vaccination (total vaccinated cohort)
 (A) Dose 1. (B) Dose 2. (C) Dose 3. (D) Booster dose. PP=prophylactic paracetamol. NPP=no prophylactic paracetamol.

Temperature was measured rectally on the evening of the day of vaccination, the morning and the evening of the first day after vaccination, and in the evening of the second and third days after vaccination, with thermometers supplied to the parents. In case of multiple or additional temperature measurements, the highest temperature was recorded for each day of collection.

Blood samples were collected before the first dose and 1 month after primary vaccination, and before and 1 month after the booster dose. Sera were analysed with validated methods at GSK's laboratory in Belgium or a designated laboratory. All laboratory personnel were masked to the group assignment of the analysed sera.

Serum antipneumococcal IgG concentrations were measured by GSK's 22F-inhibition ELISA,^{16,17} with standard reference serum 89-SF.¹⁸ The assay cut-off was set at 0.05 µg/mL. An antibody threshold value of 0.2 µg/mL with this 22F-inhibition ELISA was shown to be equivalent to the WHO recommended reference value of 0.35 µg/mL with the non-22F ELISA at the WHO reference laboratory in London, UK.^{17,19} Opsonophagocytic activity was measured by a killing assay with a HL60 cell line.²⁰ The results were presented as the dilution of serum (opsonic titre) able to sustain 50% killing of live pneumococci under the assay conditions. The cut-off of the assay was set at an opsonic titre of 8 (reciprocal of dilution 1:8).

IgG antibodies to non-typeable *H influenzae* protein D were measured by a classic ELISA with the non-lipidated protein D as coating material and expressed in ELISA units per mL. The assay cut-off was 100 ELISA units per mL. Antipolio antibodies were assessed with a microneutralisation test with an assay cut-off of 1:8 dilution.²¹ Serum antirotavirus IgA antibodies were measured with an ELISA developed by Ward and colleagues.²² All other antibodies were assessed with standard ELISA methods. Seroprotection was defined as an antibody concentration at or above 0.1 IU/mL for diphtheria and tetanus, 0.15 µg/mL for *H influenzae* type b, 10 mIU/mL for hepatitis B, and 1:8 dilution for poliovirus types 1, 2, and 3. Seropositivity was defined as 5 ELISA units per mL for antibodies to each of the acellular pertussis antigens, and 20 U/mL for rotavirus IgA antibodies.

Statistical analysis

The analysis of the safety and reactogenicity was done on the total vaccinated cohort. The primary objective of the primary and the booster vaccination studies was to measure the reduction in febrile reactions at 38.0°C (100.4°F) or greater on day 0–3 when prophylactic paracetamol was administered compared with the non-use of prophylactic antipyretic drugs. The primary

	Prophylactic paracetamol			No prophylactic paracetamol		
	N	Children with concentration ≥ 0.2 $\mu\text{g/mL}$ (n [%; 95% CI])	GMC ($\mu\text{g/mL}$; 95% CI)	N	Children with concentration ≥ 0.2 $\mu\text{g/mL}$ (n [%; 95% CI])	GMC ($\mu\text{g/mL}$; 95% CI)
Serotype 1	207	202 (97.6%; 94.5–99.2)	0.92 (0.83–1.03)	226	224 (99.1%; 96.8–99.9)	1.45 (1.31–1.61)*
Serotype 4	206	205 (99.5%; 97.3–100)	1.33 (1.18–1.50)	226	225 (99.6%; 97.6–100)	2.13 (1.91–2.37)*
Serotype 5	207	206 (99.5%; 97.3–100)	1.42 (1.28–1.58)	227	226 (99.6%; 97.6–100)	2.04 (1.85–2.25)*
Serotype 6B	206	128 (62.1%; 55.1–68.8)	0.26 (0.22–0.31)	225	170 (75.6%; 69.4–81.0)*	0.46 (0.38–0.54)*
Serotype 7F	208	206 (99.0%; 96.6–99.9)	1.57 (1.43–1.72)	227	226 (99.6%; 97.6–100)	2.16 (1.96–2.37)*
Serotype 9V	204	200 (98.0%; 95.1–99.5)	1.03 (0.92–1.15)	225	222 (98.7%; 96.2–99.7)	1.48 (1.34–1.64)*
Serotype 14	207	206 (99.5%; 97.3–100)	2.30 (2.05–2.58)	225	224 (99.6%; 97.5–100)	3.57 (3.16–4.03)*
Serotype 18C	208	199 (95.7%; 91.9–98.0)	1.19 (1.03–1.38)	227	226 (99.6%; 97.6–100)	2.65 (2.37–2.98)*
Serotype 19F	208	203 (97.6%; 94.5–99.2)	3.46 (3.01–3.98)	227	227 (100%; 98.4–100)	5.59 (4.99–6.26)*
Serotype 23F	204	164 (80.4%; 74.3–85.6)	0.49 (0.42–0.59)	225	196 (87.1%; 82.0–91.2)	0.76 (0.64–0.90)*

N=number of children with available results. GMC=geometric mean antibody concentration. PHiD-CV=ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine. DTPa-HBV-IPV/Hib=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H *influenzae* type b vaccine. ATP=according to protocol. *Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 1: Antipneumococcal IgG antibody responses 1 month after primary vaccination with PHiD-CV, DTPa-HBV-IPV/Hib, and human rotavirus vaccine with or without prophylactic administration of paracetamol (ATP immunogenicity cohort)

	Prophylactic paracetamol			No prophylactic paracetamol		
	N	Children with OPA titre ≥ 8 (n [%; 95% CI])	GMT (95% CI)	N	Children with OPA titre ≥ 8 (n [%; 95% CI])	GMT (95% CI)
Serotype 1	164	57 (34.8%; 27.5–42.6)	10.3 (8.3–12.8)	176	97 (55.1%; 47.4–62.6)*	23.7 (18.2–31.0)*
Serotype 4	163	163 (100%; 97.8–100)	788.3 (691.8–898.4)	175	175 (100%; 97.9–100)	744.6 (649.2–854.2)
Serotype 5	159	127 (79.9%; 72.8–85.8)	32.2 (25.9–40.0)	171	159 (93.0%; 88.1–96.3)*	72.5 (59.9–87.7)*
Serotype 6B	157	129 (82.2%; 75.3–87.8)	386.7 (270.0–554.0)	162	151 (93.2%; 88.2–96.6)*	684.8 (523.9–895.3)
Serotype 7F	158	158 (100%; 97.7–100)	2458.2 (2096.0–2883.0)	170	169 (99.4%; 96.8–100)	2345.3 (1970.7–2791.2)
Serotype 9V	154	154 (100%; 97.6–100)	1658.1 (1438.3–1911.4)	169	168 (99.4%; 96.7–100)	1230.3 (1026.8–1474.0)
Serotype 14	160	158 (98.8%; 95.6–99.8)	897.6 (753.2–1069.6)	175	174 (99.4%; 96.9–100)	1161.6 (985.0–1369.8)
Serotype 18C	157	144 (91.7%; 86.3–95.5)	135.0 (106.6–171.0)	170	167 (98.2%; 94.9–99.6)	202.2 (170.4–240.0)
Serotype 19F	155	142 (91.6%; 86.1–95.5)	244.6 (187.4–319.4)	165	156 (94.5%; 89.9–97.5)	369.5 (295.6–461.9)
Serotype 23F	160	150 (93.8%; 88.8–97.0)	1163.6 (885.4–1529.2)	170	166 (97.6%; 94.1–99.4)	1497.2 (1215.0–1845.1)

N=number of children with available results. OPA=opsonophagocytic activity. GMT=geometric mean antibody titre. PHiD-CV=ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine. DTPa-HBV-IPV/Hib=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H *influenzae* type b vaccine. ATP=according to protocol. *Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 2: OPA responses 1 month after primary vaccination with PHiD-CV, DTPa-HBV-IPV/Hib, and human rotavirus vaccine with or without prophylactic administration of paracetamol (ATP immunogenicity cohort)

objectives were reached if the lower limit of the standardised asymptotic 95% CI for the difference between groups in terms of percentage of participants with rectal temperature 38.0°C or greater after at least one vaccine dose was above 0%. The percentage of doses followed by each solicited and unsolicited symptom was calculated with 95% CIs.

The secondary immunogenicity analysis was done in the per-protocol cohort, comprising all participants with assay results available and who had complied with the vaccination and antipyretic schedules as defined in the protocol.

Seropositivity and seroprotection rates were calculated for all antigens with exact 95% CIs, as well as the

seroconversion rates to HRV (defined as the appearance of antirotavirus IgA antibodies ≥ 20 U/mL in children who were initially seronegative). ELISA geometric mean antibody concentrations (GMCs) or opsonophagocytic activity titres (geometric mean titres [GMT]) were calculated with 95% CIs by taking the antilog of the mean of the log concentration or titre transformations. Antibody concentrations and titres below the assay cut-off were given an arbitrary value of half the cut-off for the purpose of GMC and GMT calculation. For exploratory immunogenicity comparisons, statistical significance was based on the non-overlap of the 95% CIs.

These studies are registered with ClinicalTrials.gov, numbers NCT00370318 and NCT00496015.

	SP cut-off	Prophylactic paracetamol			No prophylactic paracetamol		
		N	SP/SC (n [%; 95% CI])	GMC/T (95% CI)	N	SP/SC (n [%; 95% CI])	GMC/T (95% CI)
Anti-PRP	≥0.15 µg/mL	207	199 (96.1%; 92.5–98.3)	2.278 (1.883–2.755)	224	224 (100%; 98.4–100)*	4.264 (3.673–4.951)*
Anti-PRP	≥1.0 µg/mL	207	153 (73.9%; 67.4–79.8)	..	224	205 (91.5%; 87.1–94.8)*	..
Antidiphtheria	≥0.1 IU/mL	206	206 (100%; 98.2–100)	2.670 (2.417–2.950)	225	225 (100%; 98.4–100)	3.561 (3.294–3.849)*
Antitetanus	≥0.1 IU/mL	206	206 (100%; 98.2–100)	1.639 (1.474–1.822)	225	225 (100%; 98.4–100)	2.669 (2.434–2.927)*
Anti-PT	≥5 ELU/mL	205	205 (100%; 98.2–100)	39.3 (36.5–42.3)	224	224 (100%; 98.4–100)	42.3 (39.2–45.7)
Anti-FHA	≥5 ELU/mL	204	204 (100%; 98.2–100)	148.0 (134.5–162.8)	224	224 (100%; 98.4–100)	166.2 (151.9–181.8)
Antipertactin	≥5 ELU/mL	206	205 (99.5%; 97.3–100)	59.0 (52.1–66.8)	225	224 (99.6%; 97.5–100)	78.0 (70.5–86.2)*
Anti-HBs	≥10 mIU/mL	50	48 (96.0%; 86.3–99.5)	254.2 (171.6–376.6)	66	64 (97.0%; 89.5–99.6)	306.6 (218.6–430.1)
Antipolio 1	≥1:8	20	20 (100%; 83.2–100)	215.3 (135.4–342.1)	25	25 (100%; 86.3–100)	142.7 (78.7–258.8)
Antipolio 2	≥1:8	19	19 (100%; 82.4–100)	171.7 (91.1–323.7)	23	23 (100%; 85.2–100)	108.6 (59.8–197.3)
Antipolio 3	≥1:8	17	17 (100%; 80.5–100)	409.1 (222.2–753.4)	23	23 (100%; 85.2–100)	284.3 (165.9–487.1)
Antirovirus IgA	≥20 U/mL	176	142 (80.7%; 74.1–86.2)	156.3 (120.1–203.4)	193	163 (84.5%; 78.6–89.3)	184.1 (144.3–234.8)

N=number of children with results available. GMC/T=geometric mean concentration/titre. SP/SC=children with seroprotective/seropositive antibody concentrations, or seroconversion for rotavirus IgA antibodies (initially seronegative children who became seropositive ≥20 U/mL after vaccination). PRP=polyribosyl ribitol phosphate. PT=pertussis toxin. FHA=filamentous haemagglutinin. HBs=hepatitis B surface antigens. ELU/mL=ELISA units per mL. PHiD-CV=ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine. DTPa-HBV-IPV/Hib=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H influenzae type b vaccine. ATP=according to protocol. *Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 3: Antibody responses after primary vaccination with PHiD-CV, DTPa-HBV-IPV/Hib, and human rotavirus vaccine with or without prophylactic administration of paracetamol (ATP immunogenicity cohort)

Role of the funding source

The sponsor of the study was involved in all stages of the study conduct and analysis, and in the development of the report and its approval for submission. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Results

459 participants were enrolled and vaccinated in the primary vaccination study and 414 in the booster study (figure 1). Results from 37 participants from the group not receiving prophylactic paracetamol and who were boosted after the protocol amendment were not included in the reported analyses. One child (no prophylactic paracetamol group) withdrew due to a serious adverse event, encephalitis 27 days after the second vaccine dose, which was not considered by the investigator to be causally related to vaccination.

The mean age of the vaccinated cohort at the time of the first dose was 12.3 weeks (SD 2.13) and the mean weight was 5.9 kg (0.80). 223/459 (49%) were girls; 458 were white and one in the prophylactic paracetamol group was of mixed African-white descent. The mean age at the time of boosting was 12.7 months (SD 0.82) and the mean weight was 10.0 kg (1.23). The total daily dose of prophylactic paracetamol administered was between 40 mg/kg and 50 mg/kg after each vaccine dose.

Prophylactic antipyretic administration was done according to the protocol (prophylactic paracetamol was administered after a single vaccine dose to one child in the no prophylactic paracetamol group). Therapeutic antipyretic drugs were administered after only nine primary doses (1.3%) in the prophylactic paracetamol

group, compared with 64 primary doses (9.2%) in the no prophylactic paracetamol group. After the booster, therapeutic antipyretic drugs were administered to three children (1.7%) receiving prophylactic paracetamol at primary and booster vaccinations, compared with five (18.5%) in the group receiving prophylactic paracetamol only during primary vaccination and 22 (12.8%) in the no prophylactic paracetamol group.

Fever greater than 39.5°C was uncommon in both groups (after primary: one of 226 participants [$<1\%$] in prophylactic paracetamol group vs three of 233 [1%] in no prophylactic paracetamol group; after booster: three of 178 [2%] vs two of 172 [1%]). The percentage of children with temperature of 38°C or greater after at least one dose was significantly lower in the prophylactic paracetamol group (94/226 [42%] after primary vaccination and 64/178 [36%] after booster vaccination) than in the no prophylactic paracetamol group (154/233 [66%] after primary vaccination and 100/172 [58%] after booster vaccination). The primary objectives of both studies were met, since the lower limit of the 95% CI around the group difference was greater than 0 (primary vaccination group difference 24.50% [95% CI 15.49–33.11], booster vaccination group difference 22.18% [11.78–32.11]).

For each vaccine dose, the percentage of participants with temperature of 38°C or higher was 40–50% less in the prophylactic paracetamol versus the no prophylactic paracetamol group (figure 2). The effect of prophylactic paracetamol was greatest after the first dose: 50 of 226 (22%) participants in the prophylactic paracetamol group had temperature 38°C or higher versus 117 of 223 (50%) in the no prophylactic paracetamol group (group difference 28.09% [95% CI 19.52–36.27]). For

	Primed and boosted with prophylactic paracetamol			Primed with prophylactic paracetamol and boosted without prophylactic paracetamol			Primed and boosted without prophylactic paracetamol		
	N	Children with concentration ≥ 0.2 $\mu\text{g/mL}$ (n [%; 95% CI])	GMC ($\mu\text{g/mL}$; 95% CI)	N	Children with concentration ≥ 0.2 $\mu\text{g/mL}$ (n [%; 95% CI])	GMC ($\mu\text{g/mL}$; 95% CI)	N	Children with concentration ≥ 0.2 $\mu\text{g/mL}$ (n [%; 95% CI])	GMC ($\mu\text{g/mL}$; 95% CI)
Serotype 1	140	140 (100%; 97.4–100)	1.67 (1.47–1.90)	24	24 (100%; 85.8–100)	1.64 (1.08–2.47)	167	167 (100%; 97.8–100)	2.62 (2.30–2.99)*
Serotype 4	141	141 (100%; 97.4–100)	3.01 (2.69–3.36)	24	24 (100%; 85.8–100)	2.84 (1.98–4.08)	167	167 (100%; 97.8–100)	4.21 (3.72–4.76)*
Serotype 5	140	140 (100%; 97.4–100)	2.30 (2.04–2.60)	24	23 (95.8%; 78.9–99.9)	2.00 (1.31–3.06)	167	167 (100%; 97.8–100)	3.68 (3.26–4.15)*
Serotype 6B	140	134 (95.7%; 90.9–98.4)	1.35 (1.12–1.61)	24	21 (87.5%; 67.6–97.3)	0.89 (0.46–1.72)	167	166 (99.4%; 96.7–100)	2.45 (2.17–2.77)*
Serotype 7F	140	140 (100%; 97.4–100)	2.90 (2.59–3.25)	25	25 (100%; 86.3–100)	2.37 (1.86–3.03)	167	167 (100%; 97.8–100)	4.13 (3.69–4.63)*
Serotype 9V	141	141 (100%; 97.4–100)	2.86 (2.52–3.23)	25	24 (96.0%; 79.6–99.9)	2.57 (1.73–3.81)	167	167 (100%; 97.8–100)	4.39 (3.91–4.94)*
Serotype 14	140	140 (100%; 97.4–100)	4.58 (4.05–5.18)	24	24 (100%; 85.8–100)	4.37 (3.01–6.33)	167	166 (99.4%; 96.7–100)	5.95 (5.28–6.71)*
Serotype 18C	141	141 (100%; 97.4–100)	4.96 (4.40–5.60)	25	25 (100%; 86.3–100)	3.46 (2.35–5.09)	167	167 (100%; 97.8–100)	7.00 (6.28–7.79)*
Serotype 19F	141	138 (97.9%; 93.9–99.6)	6.00 (5.08–7.08)	25	25 (100%; 86.3–100)	4.84 (3.47–6.77)	167	165 (98.8%; 95.7–99.9)	7.55 (6.48–8.79)
Serotype 23F	140	135 (96.4%; 91.9–98.8)	1.99 (1.67–2.38)	24	21 (87.5%; 67.6–97.3)	1.33 (0.64–2.78)	167	163 (97.6%; 94.0–99.3)	2.92 (2.50–3.40)*

N=number of children with available results. GMC=geometric mean antibody concentration. PHiD-CV=ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine. DTPa-HBV-IPV/Hib=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H *influenzae* type b vaccine. ATP=according to protocol. *Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 4: Antipneumococcal IgG antibody responses 1 month after booster vaccination with PHiD-CV and DTPa-HBV-IPV/Hib with or without prophylactic administration of paracetamol (ATP immunogenicity cohort)

	Primed and boosted with prophylactic paracetamol			Primed with prophylactic paracetamol and boosted without prophylactic paracetamol			Primed and boosted without prophylactic paracetamol		
	N	Children with OPA titre ≥ 8 (n [%; 95% CI])	GMT (95% CI)	N	Children with OPA titre ≥ 8 (n [%; 95% CI])	GMT (95% CI)	N	Children with OPA titre ≥ 8 (n [%; 95% CI])	GMT (95% CI)
Serotype 1	130	118 (90.8%; 84.4–95.1)	144.6 (109.6–190.6)	23	21 (91.3%; 72.0–98.9)	193.4 (95.8–390.8)	156	153 (98.1%; 94.5–99.6)	417.0 (330.6–526.2)*
Serotype 4	130	130 (100%; 97.2–100)	1547.9 (1357.9–1764.4)	22	22 (100%; 84.6–100)	971.6 (615.8–1532.7)	158	158 (100%; 97.7–100)	2297.0 (2005.8–2630.4)*
Serotype 5	130	127 (97.7%; 93.4–99.5)	134.3 (109.8–164.2)	23	21 (91.3%; 72.0–98.9)	105.0 (55.9–196.9)	156	156 (100%; 97.7–100)	289.3 (243.5–343.7)*
Serotype 6B	130	117 (90.0%; 83.5–94.6)	496.7 (351.4–702.2)	22	16 (72.7%; 49.8–89.3)	148.3 (46.5–472.5)	157	155 (98.7%; 95.5–99.8)	985.7 (807.1–1203.9)*
Serotype 7F	130	130 (100%; 97.2–100)	4025.8 (3457.3–4687.9)	23	23 (100%; 85.2–100)	1749.0 (1144.2–2673.4)*	158	158 (100%; 97.7–100)	4674.7 (4102.2–5327.0)
Serotype 9V	129	129 (100%; 97.2–100)	2234.8 (1905.7–2620.7)	23	23 (100%; 85.2–100)	752.9 (476.9–1188.8)*	157	157 (100%; 97.7–100)	2403.7 (2092.3–2761.4)
Serotype 14	130	130 (100%; 97.2–100)	1581.7 (1381.1–1811.4)	22	22 (100%; 84.6–100)	1515.0 (911.2–2519.0)	154	154 (100%; 97.6–100)	1865.2 (1633.4–2129.9)*
Serotype 18C	128	128 (100%; 97.2–100)	652.9 (553.5–770.1)	22	20 (90.9%; 70.8–98.9)	269.7 (128.9–564.3)	154	154 (100%; 97.6–100)	737.8 (633.6–859.1)
Serotype 19F	130	125 (96.2%; 91.3–98.7)	629.4 (496.6–797.7)	23	22 (95.7%; 78.1–99.9)	372.9 (180.1–772.5)	156	154 (98.7%; 95.4–99.8)	1062.2 (871.8–1294.3)*
Serotype 23F	130	130 (100%; 97.2–100)	2335.7 (2016.2–2705.7)	23	23 (100%; 85.2–100)	1223.1 (910.6–1642.8)*	157	156 (99.4%; 96.5–100)	3154.0 (2658.0–3742.4)

N=number of children with available results. OPA=opsonophagocytic activity. GMT=geometric mean antibody titre. PHiD-CV=ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine. DTPa-HBV-IPV/Hib=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H *influenzae* type b vaccine. ATP=according to protocol.

*Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 5: OPA responses 1 month after booster vaccination with PHiD-CV and DTPa-HBV-IPV/Hib with or without prophylactic administration of paracetamol (ATP immunogenicity cohort)

all primary doses, a reduction in fever greater than 39.0°C was noted in the prophylactic paracetamol group. A similar finding was recorded after the booster dose. The prevalence of fever was mainly reduced during the first 24 h after each dose (figure 2). The percentage of children with fever greater than 39.5°C after primary or booster vaccination was within the same range in each group.

The percentage of doses after which medical advice was sought for fever was similar in groups receiving or not receiving prophylactic paracetamol after primary immunisation (0.4% [95% CI 0.1–1.3] vs 0.6% [0.2–1.5]) and after booster immunisation (0.6% [0.0–3.1] vs 0.0% [0.0–2.1]).

After primary vaccination, a lower frequency of each solicited symptom was recorded in the prophylactic paracetamol group than in the no prophylactic paracetamol group (webappendix p 1), apart from diarrhoea and vomiting (data not shown). After boosting, pain and irritability were reported less frequently in the prophylactic paracetamol group than in the no prophylactic paracetamol group (webappendix p 1).

Grade 3 solicited symptoms were uncommon. Swelling and redness greater than 30 mm were the most frequently reported grade 3 symptoms. A lower incidence of grade 3 symptoms was recorded in the prophylactic paracetamol group than in the no prophylactic paracetamol group for most solicited symptoms,

See Online for webappendix

although the difference between groups was not statistically significant (webappendix p 1). Vomiting and diarrhoea occurred after no more than 6.1% of HRV doses in both groups (data not shown), in line with previous reports.²³

Unsolicited adverse events were reported after 20.6% (95% CI 17.6–23.8) of primary doses in the prophylactic paracetamol group and after 22.8% (19.7–26.1) in the no prophylactic paracetamol group, and after 12.4% (7.9–18.1) and 13.4% (8.7–19.4) of booster doses, respectively. Pharyngitis, nasopharyngitis, and bronchitis were the most frequently reported unsolicited adverse events in all groups (data not shown). Adverse events that were considered by the investigators to be causally related to vaccination were reported after five primary doses (four in the no prophylactic paracetamol group: two cases each of flatulence and injection-site induration; and one in the prophylactic paracetamol group: upper respiratory tract infection), and after one booster dose (in the no prophylactic paracetamol group: vomiting). Grade 3 unsolicited adverse events were infrequent ($\leq 0.6\%$ of doses).

The percentage of doses after which medical advice was sought for any solicited or unsolicited symptom was within the same range in the prophylactic paracetamol group versus the no prophylactic paracetamol group after primary vaccination (17.6% [95% CI 14.8–20.7] vs 20.1% [17.2–23.3]) and after booster vaccination (10.7% [6.6–16.2] vs 9.9% [5.9–15.4]). Medical visits for fever were uncommon, occurring after three primary doses in the prophylactic paracetamol group, four primary doses in the no prophylactic paracetamol group, and once after the booster dose (in the prophylactic paracetamol group). 39 participants reported at least one serious adverse event (20 participants in the prophylactic paracetamol group and 17 in the no prophylactic paracetamol group during primary study; two participants in the prophylactic paracetamol group during booster phase) but none was considered to be causally related to vaccination. No cases of convulsions were reported during the entire follow-up period.

Before the first vaccine dose, seroprotection and seropositivity rates and antibody GMCs and GMTs were within the same range in groups receiving or not receiving prophylactic paracetamol (data not shown).

PHiD-CV was immunogenic for all pneumococcal vaccine serotypes (table 1). For each serotype apart from 6B and 23F, at least 95.7% of children reached antipneumococcal antibody concentrations of 0.20 µg/mL or greater after primary vaccination. The percentage of children with antibody concentrations of 0.20 µg/mL or greater against serotype 6B was significantly lower in the prophylactic paracetamol group than in the no prophylactic paracetamol group, as were antipneumococcal antibody GMCs against all ten vaccine serotypes (table 1). The percentage of children with opsonophagocytic activity titres of 8 or greater was significantly lower in the prophylactic paracetamol group than in the no prophylactic

paracetamol group for serotypes 1, 5, and 6B (table 2). For other serotypes at least 91.6% of participants had opsonophagocytic activity titres of 8 or greater in both groups (table 2). Lower opsonophagocytic activity titres (GMT) were recorded in the prophylactic paracetamol group for most serotypes, with significant differences for serotypes 1 and 5 (table 2).

All but two children in the prophylactic paracetamol group were seropositive for antiprotein D antibodies after primary vaccination. However, the antiprotein D antibody GMC was significantly lower in the prophylactic paracetamol group than in the no prophylactic paracetamol group (985.4 ELISA units per mL [95% CI 872.9–1112.4] vs 1599.1 ELISA units per mL [1434.6–1782.5]).

After primary vaccination, at least 96.0% of children had seroprotective antibody concentrations against *H influenzae* type b, diphtheria, tetanus, hepatitis B, and the three acellular pertussis antigens, and all children were seropositive for poliovirus types 1, 2, and 3 (table 3). However, lower seroprotection rates against *H influenzae* type b (at the 0.15 µg/mL and 1.0 µg/mL cut-offs) and lower GMCs for antibodies against *H influenzae* type b, diphtheria, tetanus, and pertactin were recorded in the prophylactic paracetamol than in the no prophylactic paracetamol group (table 3). The antirotavirus IgA seroconversion rates and antibody GMCs were within the same range in both groups (table 3).

A post-hoc analysis was done to assess whether the lower antibody responses observed in the prophylactic paracetamol group were a direct effect of paracetamol or an indirect effect due to the reduction of fever. In both groups, immunogenicity was assessed according to whether fever (temperature $\geq 38^{\circ}\text{C}$) occurred or not after at least one vaccine dose (webappendix p 2). Fever had little effect on vaccine responses within a given study group. By contrast, prophylactic paracetamol had similar effects for children with and without recorded fever (webappendix p 2).

Before the booster dose, lower antibody GMCs were detected for all vaccine serotypes in the prophylactic paracetamol group than in the no prophylactic paracetamol group, with fewer children with antibody concentrations of 0.20 µg/mL or greater for most vaccine serotypes (data not shown). Similarly, opsonophagocytic activity GMTs and seropositivity rates were lower in the prophylactic paracetamol group for most serotypes (apart from 9V), although for several serotypes these differences were not statistically significant (data not shown).

The effect of prophylactic paracetamol persisted after boosting, with no indication that not administering paracetamol at the time of booster vaccination improved antibody responses in children who had received prophylactic paracetamol during primary vaccination. For each vaccine serotype, at least 95.7% of children reached antipneumococcal antibody concentrations of 0.20 µg/mL or greater 1 month after the booster vaccination (table 4). Although antipneumococcal

	SP cut-off	Primed and boosted with prophylactic paracetamol			Primed with prophylactic paracetamol and boosted without prophylactic paracetamol			Primed and boosted without prophylactic paracetamol		
		N	SP/SC (n [%; 95% CI])	GMC/T (95% CI)	N	SP/SC (n [%; 95% CI])	GMC/T (95% CI)	N	SP/SC (n [%; 95% CI])	GMC/T (95% CI)
Anti-PRP	≥0.15 µg/mL	141	141 (100%; 97.4–100)	23.1 (18.8–28.3)	24	24 (100%; 85.8–100)	26.0 (15.6–43.5)	167	167 (100%; 97.8–100)	27.4 (22.9–32.7)
Anti-PRP	≥1.0 µg/mL	141	138 (97.9%; 93.9–99.6)	..	24	24 (100%; 85.8–100)	..	167	166 (99.4%; 96.7–100)	..
Antidiphtheria	≥0.1 IU/mL	140	140 (100%; 97.4–100)	10.1 (9.0–11.3)	24	24 (100%; 85.8–100)	9.8 (7.5–12.9)	166	166 (100%; 97.8–100)	12.3 (11.2–13.5)
Antitetanus	≥0.1 IU/mL	139	139 (100%; 97.4–100)	7.4 (6.6–8.2)	24	24 (100%; 85.8–100)	8.7 (6.4–11.8)	167	167 (100%; 97.8–100)	9.6 (8.9–10.3)*
Anti-PT	≥5 ELU/mL	138	138 (100%; 97.4–100)	83.3 (73.8–94.0)	24	24 (100%; 85.8–100)	81.6 (62.2–106.9)	166	165 (99.4%; 96.7–100)	82.0 (73.4–91.7)
Anti-FHA	≥5 ELU/mL	140	140 (100%; 97.4–100)	467.9 (422.4–518.3)	24	24 (100%; 85.8–100)	431.1 (318.8–582.9)	167	167 (100%; 97.8–100)	453.8 (412.6–499.1)
Antipertactin	≥5 ELU/mL	140	140 (100%; 97.4–100)	222.8 (193.9–256.0)	24	24 (100%; 85.8–100)	153.4 (97.5–241.2)	167	167 (100%; 97.8–100)	254.9 (225.8–287.8)
Anti-HBs	≥10 mIU/mL	105	101 (96.2%; 90.5–99.0)	1883.9 (1332.9–2662.7)	16	16 (100%; 79.4–100)	1460.6 (816.4–2613.2)	130	127 (97.7%; 93.4–99.5)	2133.0 (1615.0–2817.1)
Antipolio 1	≥1:8	93	93 (100%; 96.1–100)	1193.0 (993.8–1432.2)	12	12 (100%; 73.5–100)	1534.2 (952.0–2472.5)	114	113 (99.1%; 95.2–100)	1058.7 (870.2–1288.0)
Antipolio 2	≥1:8	93	93 (100%; 96.1–100)	1354.1 (1115.8–1643.3)	12	12 (100%; 73.5–100)	2047.9 (1246.0–3365.9)	113	113 (100%; 96.8–100)	1413.2 (1174.3–1700.7)
Antipolio 3	≥1:8	92	92 (100%; 96.1–100)	2354.2 (1946.1–2847.9)	12	12 (100%; 73.5–100)	2233.3 (1300.9–3834.0)	114	114 (100%; 96.8–100)	2647.5 (2221.5–3155.3)

N=number of children with results available. SP/SC=percentage of children with seroprotective (0.15 µg/mL for PRP, 0.1 IU/mL for diphtheria and tetanus, 10 mIU/mL for HBs, 8 for polio types) antibody concentrations, or who were seropositive for PT, FHA, and PRN (≥ 5 ELU/mL). GMC/T=geometric mean concentration/titre. PRP=polyribosyl ribitol phosphate. PT=pertussis toxin. FHA=filamentous haemagglutinin. HBs=hepatitis B surface antigens. ELU/mL=ELISA units per mL. PHiD-CV=ten-valent pneumococcal non-typeable *Haemophilus influenzae* protein D-conjugate vaccine. DTPa-HBV-IPV/Hib=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H *influenzae* type b vaccine. ATP=according to protocol. *Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 6: Antibody responses after booster vaccination with PHiD-CV and DTPa-HBV-IPV/Hib with or without prophylactic antipyretic administration (ATP immunogenicity cohort)

antibody GMCs after the booster remained significantly lower in the prophylactic paracetamol group than in the no prophylactic paracetamol group for all vaccine serotypes apart from serotype 19F (table 4), a similar booster response was observed in both groups (four-fold to 11-fold antibody GMC increase in the prophylactic paracetamol group and four-fold to nine-fold increase in the no prophylactic paracetamol group).

The percentage of children with OPA titre of 8 or greater 1 month after the booster dose was similar for most vaccine serotypes in both groups: at least 96.2% for each serotype apart from serotypes 1 and 6B in the prophylactic paracetamol group and at least 98.1% in the no prophylactic paracetamol group (table 5). Lower opsonophagocytic activity GMTs were recorded in the prophylactic paracetamol group than in the no prophylactic paracetamol group, reaching significance for serotypes 1, 4, 5, 6B, and 19F (table 5).

At least 95.8% of children in each group were seropositive for antiprotein D antibodies after the boosting (data not shown), although antibody GMC remained significantly lower in the prophylactic paracetamol group than in the no prophylactic paracetamol group (1654.0 ELISA units per mL [95% CI 1399.9–1954.4] vs 3134.2 ELISA units per mL [2765.4–3552.1]).

1 month after boosting, at least 96.2% of children in each group had seroprotective antibodies or were seropositive against the DTPa-HBV-IPV/Hib antigens (table 6). The magnitude of the booster response (increase in antibody concentrations from before to after booster) was not modified in the prophylactic paracetamol group (data not shown). 1 month after booster, antibody concentrations were similar for all antigens, apart from tetanus, in groups receiving or not receiving prophylactic paracetamol (table 6).

Discussion

This study shows how prophylactic paracetamol reduces febrile reactions after infant primary and booster vaccination. The percentage of children reporting fever of 38°C or greater after each vaccine dose was 40–50% lower when prophylactic paracetamol was administered at the time of vaccination and for the next 24 h. The effect ceased once paracetamol administration ended. However, febrile episodes greater than 39.5°C were uncommon even in the group without prophylactic paracetamol; medical attention for fever or any solicited or unsolicited symptom was rare and did not differ substantially between treatment groups. The tendency for parents to seek medical advice for fever could have been modified in this study, since parents were

	Children receiving 7vCRM and DTPa-HBV-IPV/Hib with paracetamol given at day 0 after each of the vaccine doses 1, 2, and 3			Children receiving 7vCRM and DTPa-HBV-IPV/Hib without any antipyretic use at days 0–3 after doses 1, 2, and 3		
	N	Children with concentration ≥ 0.2 $\mu\text{g/mL}$ (n [%; 95% CI])	GMC ($\mu\text{g/mL}$; 95% CI)	N	Children with concentration ≥ 0.2 $\mu\text{g/mL}$ n [%; 95% CI]	GMC ($\mu\text{g/mL}$; 95% CI)
Serotype 4	40	40 (100%; 91.2–100)	2.11 (1.68–2.65)*	216	216 (100%; 98.3–100)	2.97 (2.70–3.26)*
Serotype 6B	40	22 (55.0%; 38.5–70.7)*	0.31 (0.20–0.48)*	214	176 (82.2%; 76.5–87.1)*	0.63 (0.53–0.74)*
Serotype 9V	40	39 (97.5%; 86.8–99.9)	1.69 (1.32–2.16)*	216	215 (99.5%; 97.4–100)	2.88 (2.60–3.19)*
Serotype 14	40	40 (100%; 91.2–100)	3.28 (2.42–4.45)	216	216 (100%; 98.3–100)	4.72 (4.16–5.36)
Serotype 18C	40	39 (97.5%; 86.8–99.9)	1.67 (1.27–2.19)*	216	214 (99.1%; 96.7–99.9)	2.61 (2.32–2.93)*
Serotype 19F	40	39 (97.5%; 86.8–99.9)	2.58 (1.90–3.50)	217	215 (99.1%; 96.7–99.9)	3.67 (3.34–4.04)
Serotype 23F	40	37 (92.5%; 79.6–98.4)	1.01 (0.72–1.41)	216	211 (97.7%; 94.7–99.2)	1.58 (1.36–1.83)

Data are from a post-hoc analysis of a seven-valent pneumococcal conjugate vaccine (7vCRM) primary vaccination study.²⁸ N=number of children with results available. GMC=geometric mean antibody concentration. DTPa-HBV-IPV/Hib=hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-H influenzae type b vaccine. ATP=according to protocol. *Significant difference (no overlap of 95% CIs) between the prophylactic paracetamol group and the no prophylactic paracetamol group.

Table 7: Effect of antipyretic administration on antipneumococcal ELISA antibody responses in 376 children primed at 2, 3, and 4 months of age with 7vCRM and DTPa-HBV-IPV/Hib (ATP cohort for immunogenicity)

counselled about how to manage fever. However, counselling is part of routine infant immunisation, and febrile reactions triggered by DTPa-based combination vaccines are milder than are those elicited by DTPw.²⁴

Although prophylactic paracetamol was effective in reducing febrile reactions commonly encountered after vaccination, these mild-to-moderate reactions were of little concern. Parents were not questioned about their concerns related to febrile reactions, but in view of the low rate of visits for fever, this symptom might have been of relatively minor importance to parents. The sample size of our study did not allow assessment of whether febrile convulsions can be prevented by prophylactic paracetamol, and evidence for such prophylactic effect of antipyretic drugs on febrile seizures is not available at present.⁷

The primary objective of the study was to assess the effect of prophylactic paracetamol on fever, with assessment of immunogenicity being a secondary descriptive objective. An unexpected finding was a substantial reduction in the primary antibody responses to each of the ten pneumococcal conjugate vaccine serotypes and to Hib polysaccharide, diphtheria, tetanus, and pertactin antigens. To our knowledge, such an effect of prophylactic paracetamol on postimmunisation immune responses has not been documented before. Remarkably few published studies have assessed the effects of antipyretic drugs on child vaccine responses. Antibody responses were unaffected in children given DTPw followed by a single prophylactic dose of paracetamol 4 h after vaccination,²⁵ or in children who received therapeutically administered paracetamol within 48 h of DTPw vaccination.²⁶

The interference of paracetamol on antibody responses could result from the prevention of inflammation. Cell-mediated responses are highly dependent on temperature,^{5,27} and attenuation of the physiological febrile response after vaccination could reduce their efficacy. However, immune responses were similar in children with or without fever, whereas prophylactic paracetamol

similarly affected antibody responses in children with or without febrile reactions after immunisation. Therefore, an indirect mechanism through the reduction of postvaccination febrile reactions seems unlikely.

Paracetamol could exert a direct effect on cell-mediated responses. It acts as a selective inhibitor of cyclooxygenase 2, which is secreted by human B cells and is needed for maximum antibody production.²⁸ However, cell-mediated responses develop over days and weeks, whereas paracetamol was only administered over 24 h and has a half-life of roughly 1.7 h.²⁹

Not all vaccine responses were equally affected by prophylactic paracetamol, which essentially interfered with primary responses to conjugate and toxoid vaccines that need potent interactions between activated dendritic cells, T cells, and B cells. Our preferred hypothesis is therefore that prophylactic paracetamol interfered with the early interactions between dendritic, B, and T cells, possibly through a reduction of inflammatory signals at the site of injection. This hypothesis could be supported by the recorded reduction of pain at the injection site in the prophylactic paracetamol group, although a direct analgesic effect of paracetamol could also have contributed.

Prophylactic paracetamol had an effect on postbooster responses against some pneumococcal vaccine serotypes and tetanus. However, differences between the groups receiving or not receiving prophylactic paracetamol decreased after boosting, suggesting a higher effect of paracetamol on B-cell differentiation into plasma cells than into memory cells. Booster responses were similar in infants primed with prophylactic paracetamol and boosted with or without prophylactic paracetamol. This finding is in accordance with the fact that interactions between dendritic, B, and T cells have a lower importance for secondary than for primary responses. Thus, the effect of prophylactic paracetamol is best explained by interference on early innate and adaptive responses, and its consequences on Germinal Centre induced

plasma-cell or memory-cell differentiation. Should this hypothesis be correct, paracetamol should interfere with responses only if administered before the generation of local inflammatory signals, at the time of or early after immunisation.

To explore this hypothesis further, a post-hoc analysis was undertaken on children who received PHiD-CV or seven-valent pneumococcal conjugate vaccine (7vCRM) with DTPa-HBV-IPV/Hib at 2, 3, and 4 months of age, in a randomised controlled clinical trial.³⁰ Children were stratified according to paracetamol use on the day of each dose, no use of any antipyretic drugs between days 0 and 3 after each dose, and any other antipyretic use not included in the previous categories. Similar trends of reduced antibody GMCs associated with paracetamol use on the day of vaccine administration were calculated for most pneumococcal serotypes in both groups, with significant differences for several serotypes in the 7vCRM group (table 7).

Post-hoc analyses were extended to ten previous clinical trials^{2,23,31–40} including around 3700 participants who received primary vaccination with DTPa-HBV-IPV/Hib or DTPa-IPV/Hib and HBV, the licensed 7vCRM, *H influenzae* type b, or *H influenzae* type b-*Neisseria meningitidis* serogroups C and Y conjugate vaccines; and around 700 children who received a booster dose of DTPa-HBV-IPV/Hib, 7vCRM, DTPw-HBV/Hib, or DTPw-HBV plus *H influenzae* type b. Comparison of antibody GMCs was done with an ANOVA model on log-transformed antibody concentrations, with paracetamol exposure as a continuous effect and study as a fixed effect. A two-sided p value was computed to indicate a significant effect of paracetamol exposure on antibody concentrations after immunisation. A significant reduction in antibody GMCs associated with paracetamol use was detected for all 7vCRM pneumococcal serotypes, apart from serotype 14 (N=about 1000). The effects were most pronounced in participants who took paracetamol on the day of each primary vaccination. This finding lends supports to the hypothesis that paracetamol maximally interferes with vaccine responses if administered early, whereas if used therapeutically once fever and the corresponding inflammatory signals have been established, its effect (if any) can be expected to be smaller.

In summary, prophylactic paracetamol significantly reduced inflammatory febrile and local pain reactions, but had no effect on the occurrence of fever greater than 39.5°C or medical attention visits for fever, which were uncommon. Conversely, prophylactic paracetamol significantly reduced several vaccine antibody responses, independently from its effect on fever. Post-hoc analyses of previous studies suggested similar trends after primary vaccination with the pneumococcal 7vCRM vaccine. The clinical relevance of these immunological findings is unknown and needs further assessment. Prophylactic administration of antipyretic drugs at the time of

vaccination should nevertheless no longer be routinely recommended without careful weighing of the expected benefits and risks.

Contributors

All authors participated in the design, implementation, analysis, and interpretation of the study; the writing of the report; and the decision to submit for publication. RP was the coordinating investigator, LS led the clinical team, and DB managed the study at GlaxoSmithKline, Belgium. C-AS provided expert advice in interpreting the data. RC was an investigator. HZ, MV, and JS were responsible for laboratory processing and testing. PL was responsible for the statistical analyses. EK directed the clinical development team in Czech Republic.

Conflicts of interest

HZ, MV, and JS declare that they have no conflicts of interest. RP is a consultant to GSK and has received travel grants or honoraria within the past 3 years. C-AS has received honoraria for participation in scientific advisory boards and research grants from GSK, Wyeth, and SanofiPasteur within the past 3 years. RC has received honoraria and travel grants from GSK Biologicals in the past 3 years. PL, EK, DB, and LS are employees of GlaxoSmithKline Biologicals. DB, EK, and LS report ownership of equity or stock options.

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