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Original article

Coadministered pneumococcal conjugate vaccine decreases immune response to hepatitis A vaccine: a randomized controlled trial

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ABSTRACT

Objectives: We explored the influence of coadministration on safety and immunogenicity of the most common travellers' vaccine hepatitis A (HepA) and the pneumococcal conjugate vaccine (PCV) increasingly used both at home and before travel.
Methods: Volunteers aged ≥18 years (n = 305) were randomly assigned 1:1:1 into three groups receiving: 13-valent PCV (PCV13) + HepA, PCV13, or HepA. Anti-pneumococcal IgG concentrations, opsonophagocytic activity (OPA) titres, and total hepatitis A antibody (anti-HAV) concentrations were measured before and 28 ± 3 days after vaccination. Adverse events (AEs) were recorded over 4 weeks.
Results: After vaccination, the anti-HAV geometric mean concentration was significantly lower in the PCV13+HepA than the HepA group: 34.47 mIU/mL (95% CI: 26.42–44.97 mIU/mL) versus 72.94 mIU/mL (95% CI: 55.01–96.72 mIU/mL), p < 0.001. Anti-HAV ≥10 mIU/mL considered protective was reached by 71 of 85 (83.5%) in the PCV13+HepA group versus 76 of 79 (96.2%) in the HepA group, p 0.008. The increases in anti-pneumococcal IgG and OPA levels were comparable in the PCV13+HepA and PCV13 groups, apart from a bigger rise in the PCV13+HepA group for serotype 3 (one-way ANOVA: serotype 3 IgG p 0.010, OPA p 0.002). AEs proved more frequent among those receiving PCV13 than HepA, but simultaneous administration did not increase the rates: ≥one AE was reported by 45 of 56 (80.4%) PCV13, 43 of 54 (79.6%) PCV13+HepA, and 25 of 53 (47.2%) HepA recipients providing structured AE data.
Discussion: Coadministration of HepA and PCV13 did not cause safety concerns, nor did it impact the patients' response to PCV13, apart from serotype 3. However, coadministered PCV13 significantly impaired antibody responses to HepA. **Marianna Riekkinen, Clin Microbiol Infect 2023;29:1553**

Introduction

With international travel growing (in 2019, 685 million visitors to low-/middle-income countries [1]), pre-travel healthcare has become one of the few places where—apart from providing travel vaccines—basic immunization status is updated. Simultaneous administration of several vaccines is a well-established practice, yet

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data on the impacts of coadministration on immune responses remain limited.

We studied coadministration of the most commonly given travellers' vaccine HepA with PCV13 which most adults have not received [2]. Apart from providing protection against invasive pneumococcal disease, PCVs can to a growing extent be considered as travel vaccines [3,4]: (a) severe pneumococcal infections are preceded by colonization of upper respiratory tract; (b) resistant pneumococci are increasingly common in many countries rendering travellers at risk of colonization by resistant strains; (c) PCV vaccination can prevent pneumococcal colonization; (d) severe pneumococcal infection may have an abrupt onset; (e) many low-/middle-income countries cannot provide quickly accessible high-standard healthcare to handle severe, life-threatening pneumococcal infections. PCVs could be administered to immunocompetent adults as single dose [5] at pre-travel appointments. Of concern, however, is possible immune interference upon coadministration of glycoconjugated and other vaccines [3,6,7].

For long-lasting immunity, two inactivated hepatitis A vaccine doses administered at 0, 6–12 (18) months are required [8–11]. For travellers—who tend to visit clinics just shortly before departure—short-term protection afforded by the first HepA dose is considered sufficient [8,10].

Providing PCV13 together with HepA at pre-travel visits would be practical yet, up until this disclosure, data on coadministration among adults have been lacking.

Methods

Study design

This phase IV binational, open-label, randomized, parallel-group, two-centre study evaluated safety and immunogenicity of coadministered PCV13 and HepA. The research was conducted from 24 August 2013 to 28 October 2019 at the Travel Clinic of Aava Medical Centre, the Meilahti Vaccine Research Centre MeVac, Helsinki University Hospital, University of Helsinki, Finland, and the Department of Infectious Diseases, Mälar Hospital, Eskilstuna, Sweden.

The protocol was approved by regional ethics committees and Finnish and Swedish Medicines Agencies (EUDRA CT 2012-003484-22), and the study was recorded in the Clinical Trials Register (clinicaltrials.gov NCT01926860). All participants provided written informed consent.

Primary and secondary objectives/endpoints

Primary outcome/endpoint: demonstrating the impact of coadministration on immune response to PCV13 measured as levels of serotype-specific anti-pneumococcal serum antibodies and their opsonophagocytic activity (OPA) (PCV13 versus PCV13+HepA group) and interpreted as rates of seroprotection.

Secondary outcome/endpoint: demonstrating the impact of coadministration on immune response to HepA measured as levels of total hepatitis A serum antibodies (HepA versus PCV13+HepA group) and interpreted as rates of seroprotection.

Study population, randomization, and blood sampling

Adults aged ≥18 years with general good health, no immunosuppression, and no previous pneumococcal or hepatitis A vaccinations were randomly assigned 1:1:1 to receive either PCV13 coadministered with HepA (PCV13+HepA group), PCV13 alone (PCV13 group) or HepA alone (HepA group). Two different HepAs were used according to local practices: Havrix® in Finland (F-HepA and F-PCV13+HepA) and Epaxal® in Sweden (S-HepA and S-PCV13+HepA) (Fig. 1 and Table 1).

For inclusion and exclusion details, recruitment, and randomization, see Supplement 1.

Blood samples were drawn before vaccination (Day 0, Visit V1) and at 4 weeks (Day 28 ± 3, Visit V2).

Vaccines

Prevnar13® (Pfizer Inc., USA) contains polysaccharides of 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) conjugated to diphtheria toxoid (DT) variant CRM197, adjuvanted with aluminium phosphate.

Havrix® (GSK, Belgium) contains an inactivated HM175 hepatitis A virus (HAV) strain (1440 ELISA units/dose) adsorbed onto aluminium hydroxide. Epaxal® (Crucell/Janssen, the Netherlands) contains an inactivated RG-SB HAV strain (24 IU/dose) administered in an immunopotentiating reconstituted influenza virosome.

Prevnar13® (0.5 mL) and/or Havrix® (1.0 mL) or Epaxal® (0.5 mL) were administered intramuscularly in the deltoid region in both arms (PCV13+HepA group) or nondominant arm (PCV13 and HepA groups).

Immunological analyses

Quantitative test of HAV antibodies

The total (IgM + IgG) HAV antibody (anti-HAV) concentrations were assessed at the National Reference Centre of Hepatitis Viruses, Infectious Diseases in Humans, Sciensano Laboratory, Brussels, Belgium, using a standardized, quantitative, ELISA kit (ETI-AB-HAVK PLUS, DiaSorin Italy) [13] via an automated ELISA machine (ETI-Max 3000, DiaSorin Italy) following manufacturer's instructions. Concentrations <10 mIU/mL were set at 5 mIU/mL, lowest point on calibration curve.

Assays of serotype-specific pneumococcal antibodies

IgG antibodies specific to each PCV13 pneumococcal polysaccharide were measured using a validated Luminex-based multiplex direct immunoassay [14]. Values below serotype-specific lowest level of quantitation (LLOQ) were set to half of the LLOQ (Supplement 2).

Serotype-specific functional antibodies were assessed using a validated OPA as previously described [15,16]. Titres below LLOQ were set to half of LLOQ (Supplement 3).

All pneumococcal antibody analyses were undertaken with blinded samples at the Pfizer Pearl River Laboratory, USA.

Definition of seroprotection

Although WHO recommends 0.35 μg/mL as minimum protective concentration of anticapsular serotype-specific IgG antibodies [17], thresholds differ by serotype [3,18], and higher ones have been adopted for adults [19,20]. OPA antibody responses are generally accepted as a correlate of vaccine-induced protection [3,17], but no definite aggregate correlate of protection has been defined [3,18]. For the present study, pneumococcal IgG ≥1.0 μg/mL was defined as a surrogate of protection.

Serum anti-HAV levels between 10 and 33 mIU/mL have been used as correlates of protection [8–11,21]. For the present study, ≥10 mIU/mL was used [21]. To assess robustness of seroconversion, we recalculated the data by anti-HAV ≥20 and ≥ 50 mIU/mL.

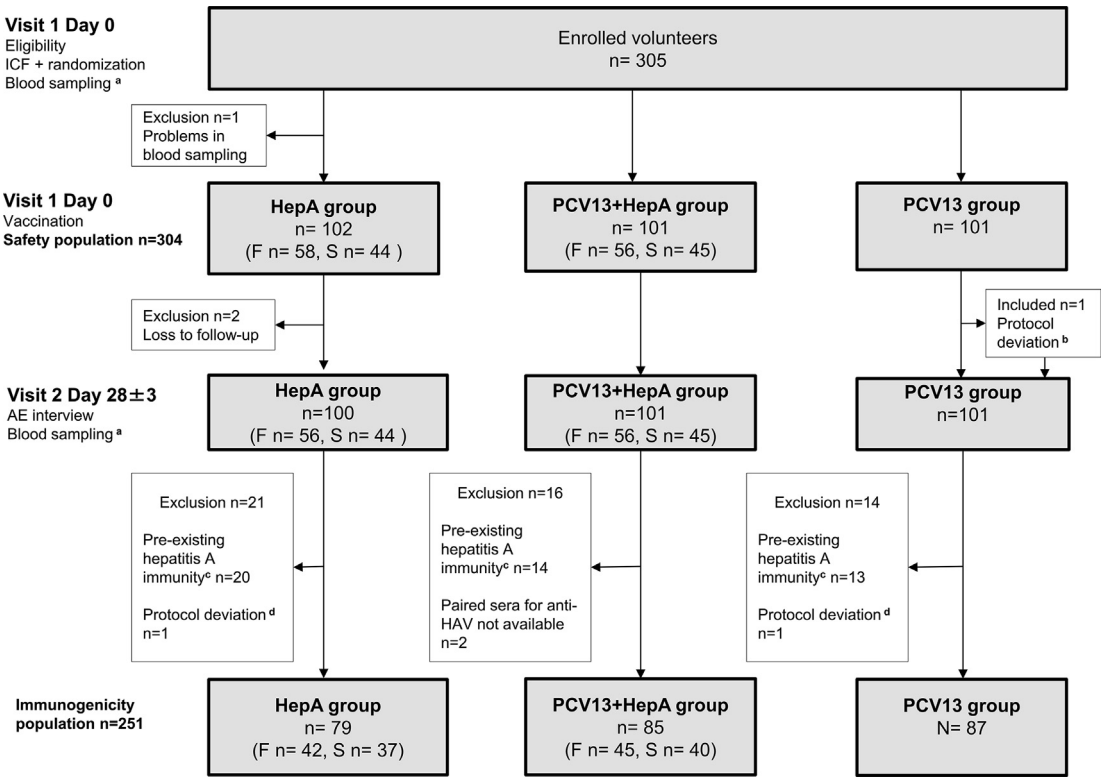

Fig. 1. Flowchart of conduct of open-label randomized parallel-group two-centre study looking at the safety and immunogenicity of coadministered 13-valent pneumococcal conjugate vaccine (PCV13) and hepatitis A vaccine (HepA). HepA: Havrix® in Finland (F), Epaxal® in Sweden (S); PCV13: Prevnar13® in Finland and in Sweden. AE, adverse event; ICF, informed consent form; *n*, number of participants. [a]Blood samples for analysis of anti-HAV and pneumococcal antibodies. [b]Visit 2 on day 28 + 5. [c]Previous hepatitis A vaccination/infection suggested by pre-vaccination anti-HAV antibodies ≥10 mIU/mL (39/47 participants) or their excessively robust rise from <10 mIU/mL to >1000 mIU/mL (8/47 participants) [10,12]. [d]Randomization error.

Safety

Adverse events (AEs) were monitored throughout the study. The participants were instructed to report all serious AEs up until 6 months after vaccination. In Finland, solicited and unsolicited AEs were noted during structured interviews at V2. In Sweden, participants were asked to freely describe unsolicited AEs at V2.

Statistical analysis

Sample size was determined by power calculation. The following variables were used: 5% as cut-off for statistical significance, 90% as power, and 95% protection among both PCV13 and PCV13+HepA recipients, yielding 82 participants/group to detect a 10% difference of mean OPA titres between the groups. Geometric means, corresponding 95% CIs, and reverse cumulative distribution curves (RCDCs) were calculated for anti-HAV concentrations, pneumococcal IgG concentrations, and OPA titres at both time points by vaccine group, and the 13 pneumococcal vaccine serotypes were analysed separately. Multivariable linear regression models on a natural logarithmic scale were adjusted by age, sex, and type of hepatitis A vaccine. AEs are reported with descriptive statistics (incidence rates). The statistical methods applied are described in Supplement 4.

Results

Participants, baseline characteristics, exclusions, and sampling

Volunteers were randomly assigned into three groups: PCV13 + HepA ($N = 101$), PCV13 ($N = 101$), and HepA ($N = 103$). All 304 vaccinees comprised the safety population and, after exclusions, 251 of 304 were included in immunogenicity analyses (Fig. 1, Table 1, and Supplement 5).

For baseline demographics, see Table 1. The three groups were balanced with respect to age and HepA type. The PCV13 group had fewer males than the others. The Epaxal® recipients were older and included more men than those given Havrix®.

Immune response to PCV13

Pre-vaccination IgG geometric mean concentrations (GMCs) and OPA geometric mean titres (GMTs) of the 13 serotypes were similar between the PCV13+HepA and PCV13 groups, apart from marginally higher baseline values in the PCV13 group for serotype 1 IgG GMC (p 0.030) and serotype 3 OPA GMT (p 0.054) (Supplement 6).

Also, post-vaccination IgG and OPA levels were comparable between the two groups, except for higher serotype 3 IgG GMC (p 0.049) and serotype 4 OPA GMT (p 0.045) in the PCV13+HepA group (Fig. 2 and Supplement 6). However, in variance analysis (one-way ANOVA) comparing the vaccine-induced increases in IgG and OPA values, only for serotype 3 there was evidence for difference between the groups with a more robust rise in the PCV13+HepA group both in IgG (p 0.010) and OPA (p 0.002) (Supplement 7). This was also observed in the RCDCs (Supplement 8): across most concentration/titre ranges, both the IgG and OPA curves of serotype 3 were lower at baseline and higher at 1 month in the PCV13+Hep A than the PCV13 group. For serotype 6B OPA RCDC, a similar, yet not significant, pattern was found.

Table 1
Baseline characteristics of study population in immunogenicity analyses

	HepA $n = 79$		PCV13+HepA $n = 85$		PCV13 $n = 87$
Mean age, y (SD)	46.9 (18.4)		44.6 (18.5)		46.9 (18.4)
Male, *n* (%)	30 (38)		34 (40)		28 (32.2)
	F-HepA $n = 42/79$ (53.2%)	**S-HepA** $n = 37/79$ (46.8%)	**F-PCV13+HepA** $n = 45/85$ (52.9%)	**S-PCV13+HepA** $n = 40/85$ (47.1%)	
Hepatitis A vaccine	Havrix®	Epaxal®	Havrix®	Epaxal®	
Mean age, y (SD)	36.4 (15.1)	58.6 (14.2)	31.4 (12.5)	59.4 (11.7)	
Male, *n* (%)	12 (28.6)	18 (48.6)	17 (37.8)	17 (42.5)	

Volunteers were randomly assigned to receive either hepatitis A (HepA), hepatitis A and pneumococcal (PCV13+HepA), or pneumococcal (PCV13) vaccines. Also included are data on Finnish and Swedish subgroups (F and S, respectively) by type of hepatitis A vaccine.
n, number of participants; PCV13, 13-valent pneumococcal conjugate vaccine; SD, standard deviation; %, proportion of participants (*n*) in respective group or subgroup.

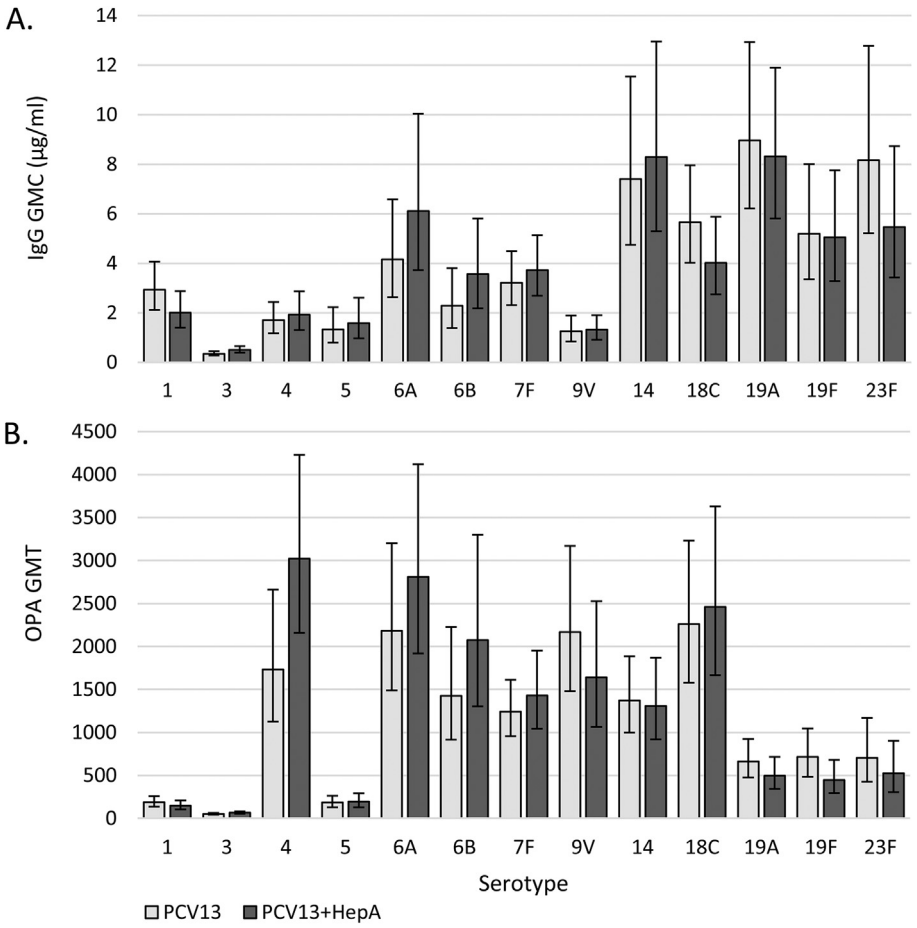

Fig. 2. Response to PCV13. Geometric mean concentrations of serum serotype-specific anti-pneumococcal IgG (IgG GMC) and geometric mean titres of opsonophagocytic activity (OPA GMT) 1 mo after vaccination for participants administered PCV13 singly or simultaneously with HepA (PCV13+HepA). HepA, hepatitis A vaccine; PCV13, 13-valent pneumococcal conjugate vaccine. Error bars indicate 95% CIs. Geometric means were calculated for all participants in the immunogenicity population with IgG or OPA results available to a given serotype 1 mo after vaccination (PCV13 IgG $n = 85$, OPA $n = 81–87$, and PCV13+HepA IgG $n = 85$, OPA $n = 75–85$).

After vaccination, the proportions of participants attaining serotype-specific IgG $\geq$1 µg/mL did not significantly differ between the PCV13+HepA and PCV13 groups. The greatest difference in seroconversion was observed for serotype 3 at 28.2% and 17.2%, respectively, (p 0.085) (Supplement 9).

In both groups, the lowest responses in OPA were seen to serotypes 1, 3, and 5, and in IgG to serotypes 3, 5, and 9V (Fig. 2).

For older participants, linear regression analysis estimates showed lower responses in OPA for 12 of 13 and in IgG levels for 6 of 13 serotypes. Sex and HepA type did not influence OPA or IgG responses (Supplement 10).

The HepA group exhibited similar pre- and post-vaccination serotype-specific IgG and OPA levels (data not shown).

Immune response to HepA

As only hepatitis A naive participants were included in immunogenicity analyses, all three groups had a baseline anti-HAV antibody GMC of 5 mIU/mL (half of LLOQ).

After vaccination, the anti-HAV antibody GMC was significantly lower in the PVC13+HepA than the HepA group: 34.47 mIU/mL (95% CI 26.42–44.97 mIU/mL) versus 72.94 mIU/mL (95% CI 55.01–96.72 mIU/mL), respectively ($p < 0.001$). Weaker anti-HAV response was observed in coadministration for both Havrix® and Epaxal®: F-PCV13+HepA (41.16 mIU/mL, 95% CI 28.39–59.66 mIU/mL) and S-PCV13+HepA (28.24 mIU/mL, 95% CI 19.4–41.11 mIU/mL) attained significantly lower post-vaccination anti-HAV GMCs

than F-HepA (94.25 mIU/mL, 95% CI 63.32–140.29 mIU/mL) and S-HepA (54.53 mIU/mL, 95% CI 37.17–79.98 mIU/mL), respectively. This showed in the RCDCs as lower anti-HAV levels for the coadministration groups than the respective HepA groups across the full range of antibody concentrations (Fig. 3). In the PCV13 group, the anti-HAV antibody GMC remained below LLOQ (data not shown).

With post-vaccination anti-HAV antibody cut-off at ≥10 mIU/mL, the seroprotection rate was lower in the PCV13+HepA than the HepA group at 83.5% (71/85) versus 96.2% (76/79), p 0.008, respectively (Table 2).

Multivariable linear regression analysis estimates revealed lower post-vaccination anti-HAV concentrations for old than young and male than female participants. Type of HepA did not influence anti-HAV responses (Supplement 11).

Safety

Among the 304 vaccinees, no immediate AEs were detected at V1, and no serious AEs reported. Because of differing AE collection approaches, the two countries' data are presented separately.

In Finland with structured AE collection at V2, 113 of 163 reported at least one AE: 25 of 53 (47.2%) in the F-HepA, 43 of 54 (79.6%) in the F-PCV13+HepA, and 45 of 56 (80.4%) in the F-PCV13 group. Compared with those only given HepA (Havrix®), the recipients of PCV13 (F-PCV13+HepA or F-PCV13) more often reported pain and swelling at injection site or temperature >37.5°C. However, there was no evidence of differences in AEs between the F-PCV13+HepA and F-PCV13 groups (Supplement 12).

In Sweden where unsolicited AEs were collected from 133 participants, three in the S-PCV13 group reported symptoms: pain $n = 2$, swelling at injection site $n = 1$, and a temperature >37.5°C $n = 2$.

Discussion

Our major finding was that although responses to most of the pneumococcal serotypes remained intact, coadministration impaired those to HepA.

Simultaneously given HepA: no major impact on PCV13 responses

Although the IgG and OPA responses in the PCV13+HepA and PCV13 groups were comparable with all the other PCV13 serotypes, coadministration elevated the levels to serotype 3. This increase should not greatly affect protection, for the absolute responses remained low in both groups. Previous studies report similar weak vaccine responses to serotype 3 [22], possibly accounting for it remaining a major cause of invasive pneumococcal disease despite PCV13 implementation [18,22,23]. Responses to pneumococcal serotypes declined with age, consistent with earlier reports [19,20,24].

Coadministration with PCV decreases response to HepA

Coadministration with PCV13 impaired antibody responses to HepA: a significant decrease was found both in anti-HAV GMCs and proportion of vaccinees with anti-HAV above the limit of protection (≥10 mIU/mL). Consistent with our linear regression analyses, some studies report responses to HepA lower for men than women [9–12,24–26] and for the elderly than the younger [8–12,24–26].

Our findings accord with previous investigations describing immune interference for glycoprotein vaccines upon coadministration. Conjugate vaccines with DT-variant CRM197, DT, or tetanus toxoid as carrier protein have been shown to induce immune interactions when coadministered with other vaccines; PCV7 when given concomitantly with *Haemophilus influenzae* type b and

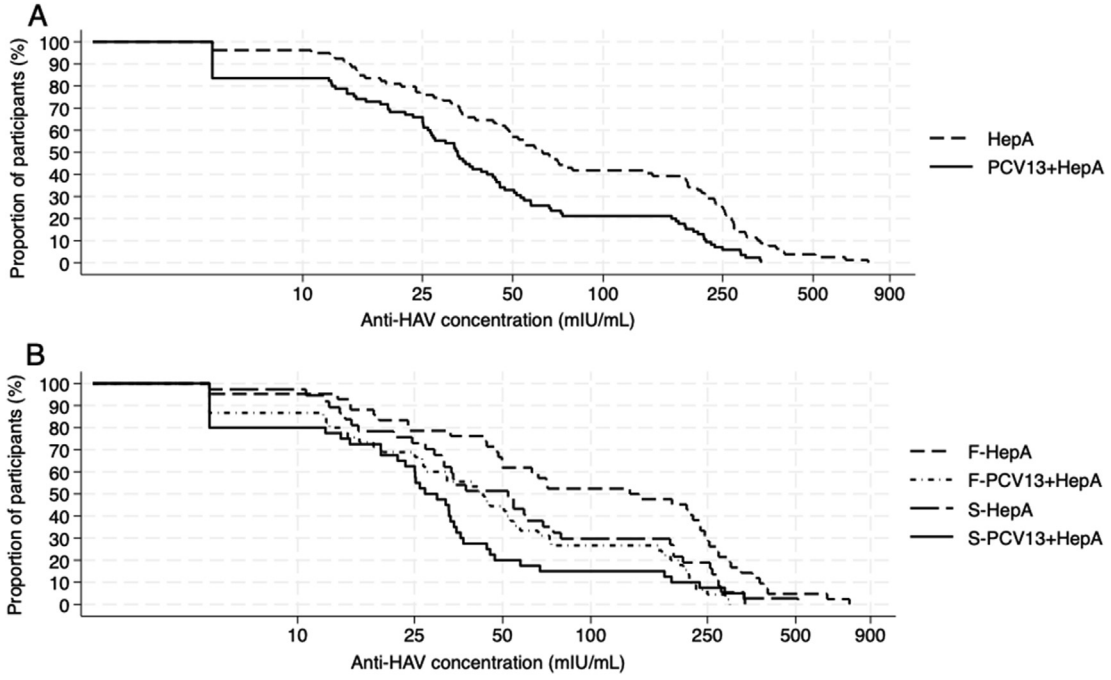

Fig. 3. Response to hepatitis A vaccine. Reverse cumulative distribution curves for serum anti-HAV concentrations 1 mo after vaccination. Panel A presents all participants given hepatitis A vaccine singly (HepA, $n = 79$) or simultaneously with 13-valent pneumococcal conjugate vaccine (PCV13+HepA, $n = 85$). Panel B shows subgroup analyses by type of hepatitis A vaccination: Havrix® was used in Finland (F-HepA, $n = 42$ and F-PCV13+HepA, $n = 45$) and Epaxal® in Sweden (S-HepA, $n = 37$ and S-PCV13+HepA, $n = 40$).

Table 2
Proportions of participants (%) with anti-HAV ≥10, ≥20, and ≥50 mIU/mL 1 mo after vaccination

Post-vaccination anti-HAV	% (95% CI)	% (95% CI)	p
	HepA ($n = 79$)	**PCV13+HepA** ($n = 85$)	
≥10 mIU/mL	96.2% (92.0–100)	83.5% (75.6–91.4)	0.008
≥20 mIU/mL	81% (72.4–89.7)	68.2% (58.3–78.1)	0.061
≥50 mIU/mL	57% (46.0–67.9)	32.9% (22.9–42.9)	0.002
	F-HepA ($n = 42$)	**F-PCV13+HepA** ($n = 45$)	
≥10 mIU/mL	95.2% (88.8–100)	86.7% (76.7–96.6)	0.167
≥20 mIU/mL	83.3% (72.1–94.6)	68.9% (55.4–82.4)	0.116
≥50 mIU/mL	61.9% (47.2–76.6)	44.4% (29.9–59)	0.103
	S-HepA ($n = 37$)	**S-PCV13+HepA** ($n = 40$)	
≥10 mIU/mL	97.3% (92.1–100)	80% (67.6–92.4)	0.018
≥20 mIU/mL	78.4% (65.1–91.6)	67.5% (53–82)	0.284
≥50 mIU/mL	51.4% (35.2–67.5)	20% (7.6–32.4)	0.004

HepA group ($n = 79$) received hepatitis A vaccine singly; 42/79 Havrix® (F-HepA) and 37/79 Epaxal® (S-HepA). PCV13+HepA group ($n = 85$) received PCV13 simultaneously with hepatitis A vaccine; 45/85 with Havrix® (F-PCV13+HepA), and 40/85 with Epaxal® (S-PCV13+HepA).
Anti-HAV, total hepatitis A antibodies; HepA, hepatitis A vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

hepatitis B vaccines, for example [3,6,7]. Bystander interference, carrier-induced epitopic suppression, and carrier-specific T-cell helper interactions have been suggested as underlying mechanisms [3,6]. The latter two, carrier-induced epitopic suppression or carrier-specific T-cell helper interactions (carrier-hapten interactions or pre-existing carrier-specific immunity), appear not to explain our observation of decreased anti-HAV responses when PCV13 is coadministered with either Havrix® or Epaxal®: the two hepatitis A vaccines are differently adjuvanted, neither of them is conjugated, nor do they have common antigens with PCV13. Administration site-dependent interactions seem unlikely, as the two vaccines were given in different arms.

Two previous paediatric studies exploring coadministration of PCVs and HepA found no immune interference [27,28]. They cannot be compared with ours, however. First, the immune systems of under 2-year olds and adults are not similar. Second, the children were not naive but had been primed with three PCV doses; only one of the two studies reports hepatitis A antibodies after the first HepA dose [27,28].

Correlate of protection against hepatitis A

The use of anti-HAV antibodies as correlates of protection may need to be discussed. The first estimates were derived from concentrations of gamma globulin employed to protect travellers against hepatitis A: maintaining concentrations of ~10 mIU/mL was considered sufficient protection against the disease [21]. In accord with this, later hepatitis A vaccine studies have used 10–33 mIU/mL of anti-HAV antibodies as correlate of protection [8–11]. Analysis of our data with respect to various concentrations (10, 20, and 50 mIU/mL, see Table 2) showed the response to be significantly lower in the coadministration group even with the concentration of 10 mIU/mL. We applied reverse cumulative distribution curves (Fig. 3) to demonstrate that the difference persists across the full anti-HAV concentration range. Indeed, in clinical practice, the concentration of 10 mIU/mL is sometimes selected as a cut-off when assessing whether a booster dose should be administered.

Impact of HepA regimen

Previous research reports significantly lower anti-HAV levels for Epaxal® than Havrix® 1 month after the first [25,29] and second doses [25]. A Korean study exploring immune responses 11 months after a single HepA dose shows lower seroconversion rates with Epaxal® than Havrix® for men, but not women [30]. In our data, anti-HAV concentrations proved lower in Sweden than Finland. Rather than HepA type per se, sex and age-adjusted analyses ascribed this to older age and/or male predominance of the Swedish participants given Epaxal®. Most importantly, as shown by RCDCs and linear regression analyses, the weaker response to HepA seen in the PCV13+HepA group could not be ascribed to age or sex imbalance between the subgroups receiving Epaxal® and Havrix®.

Safety

All three licensed study vaccines have been proven safe and well-tolerated [3,8–10,22,25,26,29]. Although safety was not our primary focus, coadministration as such entailed no safety issues. The difference in numbers of reported AEs between structured collection method (AEs $n = 181$) and unstructured interviews (AEs $n = 5$) demonstrates the weakness of a non-structured approach to safety data collection.

Limitations

Further research is needed to explore whether the difference in post-vaccination anti-HAV levels between PCV13+HepA and HepA groups persists in longer follow-up, and whether the second HepA dose given without PCV13 could compensate for the lower anti-HAV levels in the PCV13+HepA group, as reported for those with no measurable anti-HAV responses left a few years after immunization [12]. Likewise, the post-second dose waning of hepatitis A antibodies should be monitored, because lower initial concentrations may signify a response with shorter persistence, i.e. life-long protection may not be secured. The mechanisms of immune interference also warrant further research.

Our study did not cover obesity and smoking, two factors reported to impair immune response to HepA [8,9,11,24].

Considerations for clinical practice

According to recommendations, travellers planning a short trip can rely on immunity elicited by a single HepA dose [8,10]. Our data suggest, however, that coadministration of the first HepA dose and PCV13 may not provide sufficient protection against hepatitis A. Particular caution is needed when simultaneously giving the two vaccines to elderly men only taking one HepA dose before travel. Ensuring early single-dose protection against hepatitis A may require that travellers opting for both HepA and PCV immunization will not be given the vaccines together.

Author contributions

LR and AK conceptualized and supervised the study and provided resources. AK provided funding and performed validation. SHP, LR, and AK designed the methodology. MR, SHP, LR, and AK were responsible for the administration and acquired the data. VH and IR conducted the anti-HAV laboratory analyses. MR curated the data. JO conducted the statistical analyses. MR, SHP, JO, HK, CH, LR, and AK interpreted the data. MR and JO visualized the data. MR and AK wrote original draft of the manuscript. SHP, VH, IR, JO, HK, CH, and LR revised and edited the manuscript. All authors approved the final version of the manuscript.

Transparency declaration

AK reports a research grant from Valneva, unrelated to this manuscript. MR reports honoraria for lectures from GSK and Pfizer, and support for attending a conference from MSD, unrelated to this manuscript. LR reports honoraria for lectures from GSK, Pfizer, and Valneva, unrelated to this article. All other authors report no conflicts of interest. This work was supported by an investigator-initiated grant from Pfizer Oy, Finland (ID 53234819 to AK); the Finnish Governmental Subsidy for Health Science Research, Finland (to AK); and the Doctoral School in Health Sciences, University of Helsinki, Finland (to MR).

Data availability

AK and MR have full access to all data, and other authors to pseudonymized data. AK is the guarantor for the data.

Part of the data was presented in an ePoster at the 18th Congress of the International Society of Travel Medicine (CISTM18) in Basel, Switzerland, 21–25 May 2023.

ClinicalTrials.gov identification NCT01926860.

Trial registration EudraCT Registration No: 2012-003484-22.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.08.006.

References

[1] UNWTO. World tourism barometer January 2020 EXCERPT, Volume 18, Issue 1. https://webunwto.s3.eu-west-1.amazonaws.com/s3fs-public/2020-01/UNWTO_Barom20_01_January_excerpt.pdf. [Accessed 13 July 2023].

[2] CDC Centers for Disease Control and Prevention. Vaccination coverage among adults in the United States, national health interview survey, 2019–2020. https://www.cdc.gov/vaccines/imz-managers/coverage/adultvaxview/pubs-resources/vaccination-coverage-adults-2019-2020.html. [Accessed 13 July 2023].

[3] Klugman KP, Malley R, Whitney CG. Pneumococcal conjugate vaccine and pneumococcal common protein vaccines. In: Orenstein WA, Offit PA, Edwards KM, Plotkin SA, editors. Chapter 47, vaccines. 8th ed. Philadelphia, PA, USA: Elsevier; 2022. p. 826–68.

[4] Andrejko K, Ratnasiri B, Hausdorff WP, Laxminarayan R, Lewnard JA. Antimicrobial resistance in paediatric *Streptococcus pneumoniae* isolates amid global implementation of pneumococcal conjugate vaccines: a systematic review and meta-regression analysis. Lancet Microbe 2021;2. https://doi.org/10.1016/S2666-5247(21)00064-1. e450–60.

[5] CDC Centers for Disease Control and Prevention. Advisory committee on immunization practices ACIP pneumococcal vaccine recommendations. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/pneumo.html. [Accessed 13 July 2023].

[6] Dagan R, Poolman J, Siegrist CA. Glycoconjugate vaccines and immune interference: a review. Vaccine 2010;28:5513–23. https://doi.org/10.1016/j.vaccine.2010.06.026.

[7] Scheifele DW, Halperin SA, Smith B, Ochnio J, Meloff K, Duarte-Monteiro D. Assessment of the compatibility of co-administered 7-valent pneumococcal conjugate, DTaP.IPV/PRP-T Hib and hepatitis B vaccines in infants 2–7 months of age. Vaccine 2006;24:2057–64. https://doi.org/10.1016/j.vaccine.2005.11.021.

[8] Nelson NP, Weng MK, Hofmeister MG, Moore KL, Doshani M, Kamili S, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the advisory committee on immunization practices. MMWR Recomm Rep 2020;69:1–38. https://doi.org/10.15585/mmwr.rr6905a1.

[9] World Health Organization. WHO immunological basis for immunization series: module 18: hepatitis A, update. 2019. https://apps.who.int/iris/handle/10665/326501. [Accessed 13 July 2023].

[10] André F, Van Damme P, Safary A, Banatvala J. Inactivated hepatitis A vaccine: immunogenicity, efficacy, safety and review of official recommendations for use. Expert Rev Vaccines 2002;1:9–23. https://doi.org/10.1586/14760584.1.1.9.

[11] Herzog C, Van Herck K, Van Damme P. Hepatitis A vaccination and its immunological and epidemiological long-term effects – a review of the evidence. Hum Vaccin Immunother 2021;17:1496–519. https://doi.org/10.1080/21645515.2020.1819742.

[12] Hatz C, van der Ploeg R, Beck BR, Frösner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis a vaccine delayed up to 11 years. Clin Vaccine Immunol 2011;18:885–7. https://doi.org/10.1128/CVI.00358-10.

[13] Anastassopoulou CG, Kafatos G, Nardone A, Andrews N, Pebody RG, Mossong J, et al. The European Sero-Epidemiology Network 2 (ESEN2): standardization of assay results for hepatitis A virus (HAV) to enable comparisons of seroprevalence data across 15 countries. Epidemiol Infect 2009;137:485–94. https://doi.org/10.1017/S0950268808001155.

[14] Tan CY, Immermann FW, Sebastian S, Pride MW, Pavliakova D, Belanger KA, et al. Evaluation of a validated Luminex-based multiplex immunoassay for measuring immunoglobulin G antibodies in serum to pneumococcal capsular polysaccharides. mSphere 2018;3:e00127-18. https://doi.org/10.1128/mSphere.00127-18.

[15] Rose CE, Romero-Steiner S, Burton RL, Carlone GM, Goldblatt D, Nahm MH, et al. Multilaboratory comparison of *Streptococcus pneumoniae* opsonophagocytic killing assays and their level of agreement for the determination of functional antibody activity in human reference sera. Clin Vaccine Immunol 2011;18:135–42. https://doi.org/10.1128/CVI.00370-10.

[16] Cooper D, Yu X, Sidhu M, Nahm MH, Fernsten P, Jansen KU. The 13-valent pneumococcal conjugate vaccine (PCV13) elicits cross-functional opsonophagocytic killing responses in humans to *Streptococcus pneumoniae* serotypes 6C and 7A. Vaccine 2011;29:7207–11. https://doi.org/10.1016/j.vaccine.2011.06.056.

[17] World Health Organization. Recommendations to assure the quality, safety and efficacy of pneumococcal conjugate vaccines, Annex 3, TRS No 977. https://www.who.int/publications/m/item/pneumococcal-conjugate-vaccines-annex3-trs-977. [Accessed 13 July 2023].

[18] Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect Dis 2014;14:839–46. https://doi.org/10.1016/S1473-3099(14)70822-9.

[19] Goldblatt D, Southern J, Andrews N, Ashton L, Burbidge P, Woodgate S, et al. The immunogenicity of 7-valent pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in adults aged 50–80 years. Clin Infect Dis 2009;49:1318–25. https://doi.org/10.1086/606046.

[20] van Deursen AMM, van Houten MA, Webber C, Patton M, Scott DA, Patterson S, et al. Immunogenicity of the 13-valent pneumococcal conjugate vaccine in older adults with and without comorbidities in the Community-Acquired Pneumonia immunization Trial in Adults (CAPiTA). Clin Infect Dis 2017;65:787–95. https://doi.org/10.1093/cid/cix419.

[21] Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol 2010;17:1055–65. https://doi.org/10.1128/CVI.00131-10.

[22] Stacey HL, Rosen J, Peterson JT, Williams-Diaz A, Gakhar V, Sterling TM, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults. Hum Vaccin Immunother 2019;15:530–9. https://doi.org/10.1080/21645515.2018.1532249.

[23] Ladhani SN, Collins S, Djennad A, Sheppard CL, Borrow R, Fry NK, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000-17: a prospective national observational cohort study. Lancet Infect Dis 2018;18:441–51. https://doi.org/10.1016/S1473-3099(18)30052-5.

[24] Zimmermann P, Curtis N. Factors that influence the immune response to vaccination. Clin Microbiol Rev 2019;32:e00084-18. https://doi.org/10.1128/CMR.00084-18.

[25] Holzer BR, Hatz C, Schmidt-Sissolak D, Glück R, Althaus B, Egger M. Immunogenicity and adverse effects of inactivated virosome versus alum-adsorbed hepatitis A vaccine: a randomized controlled trial. Vaccine 1996;14:982–6. https://doi.org/10.1016/0264-410X(96)00042-4.

[26] D'Acremont V, Herzog C, Genton B. Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal®) in the elderly. J Travel Med 2006;13:78–83. https://doi.org/10.1111/j.1708-8305.2006.00001.x.

[27] Trofa AF, Levin M, Marchant CD, Hedrick J, Blatter MM. Immunogenicity and safety of an inactivated hepatitis A vaccine administered concomitantly with a pneumococcal conjugate vaccine in healthy children 15 months of age. Pediatr Infect Dis J 2008;27:658–60. https://doi.org/10.1097/INF.0b013e31816907bd.

[28] Yetman RJ, Shepard JS, Duke A, Stek JE, Petrecz M, Klopfer SO, et al. Concomitant administration of hepatitis A vaccine with measles/mumps/rubella/varicella and pneumococcal vaccines in healthy 12- to 23-month-old children. Hum Vaccin Immunother 2013;9:1691–7. https://doi.org/10.4161/hv.24873.

[29] Bovier PA, Farinelli T, Loutan L. Interchangeability and tolerability of a virosomal and an aluminum-adsorbed hepatitis A vaccine. Vaccine 2005;23:2424–9. https://doi.org/10.1016/j.vaccine.2004.11.024.

[30] Lim J, Song YJ, Park WS, Sohn H, Lee MS, Shin DH, et al. The immunogenicity of a single dose of hepatitis A virus vaccines (Havrix® and Epaxal®) in Korean young adults. Yonsei Med J 2014;55:126–31. https://doi.org/10.3349/ymj.2014.55.1.126.