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Raising the Floor and Lowering the Ceiling: What a Threshold Endpoint Cannot Show about CpG-Adjuvanted Hepatitis B Vaccination

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Abstract

Background: A hepatitis B vaccine adjuvanted with a Toll-like receptor 9 agonist achieves higher seroprotection rates than the conventional alum-adjuvanted vaccine in fewer doses, and is licensed on that basis. Seroprotection is defined as an anti-HBs concentration at or above 10 mIU/mL, a binary threshold. **Objectives:** To express the comparative benefit in absolute terms and by population; to identify where the reported comparisons are and are not like for like; and to examine what the reverse cumulative frequency data show about the distribution of antibody concentrations that a threshold endpoint cannot capture. **Methods:** Randomised comparisons of CpG-adjuvanted against alum-adjuvanted hepatitis B vaccine in adults reporting seroprotection rates were eligible. Absolute differences, confidence intervals and numbers needed to vaccinate were derived from reported proportions. Reported descriptions of the antibody concentration distribution were extracted and are presented schematically. Analyses were performed in Python 3. **Results:** Across four randomised trials comprising 7,056 recipients of the two-dose CpG-adjuvanted vaccine and 3,214 recipients of the three-dose alum-adjuvanted vaccine, seroprotection rates were 90.0% to 100.0% against 70.5% to 90.2%. In adults aged 18 to 55, the CpG vaccine reached 88.4% at week 8 against 26.7% for the comparator at the same visit—a contrast at which the comparator had received only two of three doses—and against its peak of 81.3% at week 28 the difference was 7.1% points (number needed to vaccinate 14.1). In adults aged 60 to 70 with type 2 diabetes the difference was 27.3% points (85.8% against 58.5%, 95% CI 18.0-36.8; number needed to vaccinate 3.7). Geometric mean concentration at week 8 was 83.1 against 6.5 mIU/mL and median time to seroprotection was five months earlier. Reverse cumulative frequency data show that more CpG recipients crossed the threshold and occupied the 10 to 1,000 mIU/mL band, while more alum recipients exceeded 1,000 mIU/mL and more failed to seroprotect at all. **Conclusions:** The CpG-adjuvanted vaccine confers a substantial and clinically meaningful advantage, largest in exactly the populations for whom conventional vaccination fails most often. The distributional data indicate that the adjuvant compresses the antibody response—raising the floor and lowering the ceiling—which a threshold endpoint cannot detect. Whether the smaller high-titre tail bears on duration of protection is a question the seroprotection endpoint is not constructed to answer, and it warrants long-term follow-up rather than inference.

Keywords: *Hepatitis B vaccine, CpG 1018, Toll-like receptor 9, Seroprotection, Adjuvant, Antibody distribution*

1. Introduction

Hepatitis B vaccination is among the most effective preventive interventions available, but the conventional

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three-dose alum-adjuvanted vaccine has two well-recognised weaknesses. It requires six months to complete, during which a substantial proportion of recipients are lost to follow-up, and it responds poorly in the groups at greatest need: older adults, people with diabetes, and those with chronic kidney disease (Expert Rev Vaccines, 2021; Janssen *et al.*, 2013).

Adding a Toll-like receptor 9 agonist to recombinant surface antigen addresses both (Krieg, 2006). The CpG-adjuvanted vaccine is given as two doses four weeks apart and produces higher seroprotection rates, and it was licensed on that basis after a programme of randomised comparisons.

The endpoint on which that programme rests is seroprotection: an anti-HBs concentration at or above 10 mIU/mL. It is a reasonable endpoint with a long history, and it is binary. A binary threshold records how many recipients cross a line and nothing about where above the line they land.

That distinction is usually immaterial. It becomes material here because the contributing trials reported reverse cumulative frequency distributions of antibody concentration, and those distributions show something the threshold does not: the two vaccines differ in the shape of the response as well as the proportion clearing the threshold.

This review therefore does three things. It expresses the comparative benefit in absolute terms and by population, since a relative claim of superiority conveys little about who gains. It identifies which reported comparisons are like for like and which are not, because the two schedules differ in dose number and timing. And it examines what the distributional data show.

2. Methods

2.1. Design and reporting

This is a structured synthesis of randomised immunogenicity comparisons. No pooling of seroprotection rates was performed: the trials differ in population and the reported ranges are more informative than a weighted average would be. Reporting follows the PRISMA 2020 statement (Page *et al.*, 2021). The analysis was not prospectively registered; this is stated as a limitation.

2.2. Review question (PICO)

Population: Adults aged 18 years and above, including subgroups with type 2 diabetes and chronic kidney disease.

Intervention: Two-dose recombinant hepatitis B surface antigen with CpG 1018 adjuvant.

Comparator: Three-dose recombinant surface antigen with aluminium adjuvant.

Outcomes: Seroprotection rate at or above 10 mIU/mL, geometric mean antibody concentration, time to seroprotection and the distribution of antibody concentrations.

Unit of analysis: The randomised trial.

2.3. Eligibility criteria

Inclusion criteria:

- Randomised comparison of CpG-adjuvanted with alum-adjuvanted hepatitis B vaccine.
- Adult population.
- Reporting of seroprotection rate with a defined assessment timepoint.
- Full peer-reviewed publication or regulatory assessment document.

Exclusion criteria:

- Single-arm immunogenicity studies without an alum-adjuvanted comparator.
- Paediatric populations, in whom the schedule and response differ.
- Studies reporting only safety outcomes.

- Conference abstracts without extractable proportions.
- Duplicate reports of the same trial, except where a subgroup analysis added data.

2.4. Handling the schedule asymmetry

The two vaccines are given on different schedules: two doses at days 1 and 29 against three doses at days 1, 29 and 183. Any comparison before week 24 therefore contrasts a completed course with an incomplete one. We identify each reported comparison as like for like or not, and treat the contrast between the CpG vaccine at its assessment point and the alum vaccine at its own peak as the clinically meaningful one. This is the conservative choice and it reduces the apparent advantage substantially.

2.5. Statistical analysis

Absolute differences in seroprotection were computed from reported proportions with standard errors from the binomial approximation (Clopper and Pearson, 1934), and numbers needed to vaccinate as the reciprocal of the absolute difference. Where a source reported a difference and confidence interval directly, our recomputation is presented alongside as a check. Distributional findings were extracted as described in the source text; no data were digitised from published figures, and the corresponding figure in this review is a schematic reconstruction of the described pattern rather than a reproduction. Analyses were performed in Python 3 using NumPy and SciPy.

3. Results

3.1. Included sources

Six sources met the inclusion criteria and five contributed immunogenicity data: a review of four randomised trials comprising 10,270 randomised adults; a regulatory evidence assessment reporting the same seroprotection ranges (Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices); a pooled analysis of three pivotal trials reporting reverse cumulative frequency distributions (Hyer and Janssen, 2018); a post hoc analysis in adults with type 2 diabetes (Two-dose HBsAg/CpG 1018 in adults aged 60-70 years with type 2 diabetes mellitus: post hoc analysis of a phase 3 trial); and a trial in adults with chronic kidney disease. Characteristics are in Table 1.

Table 1: Characteristics of the contributing sources

Source	Population	Randomised	Seroprotection reported
Programme review	Adults 18–70	7,056 CpG/3,214 alum	90.0–100.0% vs 70.5–90.2%
Regulatory assessment	Adults	Same programme	90.0–100.0% vs 70.5–90.2%
Pooled pivotal trial analysis	Adults 18–70	Three trials	>90% vs 80–90%; distributions reported
Trial HBV-10	Adults 18–55	Not stated	88.4% wk 8 vs 26.7% wk 8; 81.3% wk 28
Diabetes post hoc analysis	Ages 60–70, type 2 diabetes	327 CpG allocated	85.8% vs 58.5% at week 28
Chronic kidney disease trial	Adults with CKD	Not stated	Long-term immunogenicity

Note: CpG, CpG 1018-adjuvanted vaccine; alum, aluminium-adjuvanted comparator; CKD, chronic kidney disease. Trials overlap between the programme review, the regulatory assessment and the pooled analysis, so the totals are not additive.

3.2. The comparison that is like for like, and the one that is not

In adults aged 18 to 55, the CpG-adjuvanted vaccine achieved seroprotection in 88.4% at week 8 (Halperin *et al.*, 2012), four weeks after its second and final dose. The alum-adjuvanted comparator achieved 26.7% at the same visit. That contrast is arithmetically correct and clinically misleading, because at week 8 the comparator has received two of its three doses and its third is not due until day 183.

Table 2: Reported and derived comparisons

Comparison	CpG-adjuvanted	Alum-adjuvanted	Difference	NNV
Programme range, seroprotection	90.0–100.0%	70.5–90.2%	—	—
Adults 18–55, week 8 both arms	88.4%	26.7%	+61.7 pp	Not like for like
Adults 18–55, CpG wk 8 vs alum peak wk 28	88.4%	81.3%	+7.1 pp	14.1
Type 2 diabetes, ages 60–70, week 28	85.8%	58.5%	+27.3 pp (18.0–36.8)	3.7
Geometric mean concentration, week 8	83.1 mIU/mL	6.5 mIU/mL	12.8-fold	—
Median time to seroprotection	—	—	5 months earlier	—
Proportion above 1,000 mIU/mL	Lower	Higher	Favours alum	—
Proportion failing to seroprotect	Lower	Higher	Favours CpG	—

Note: NNV, number needed to vaccinate for one additional seroprotected person. The week-8 both-arms row is reported for completeness and is not a like-for-like comparison, as the comparator had received two of three doses at that visit.

The informative comparison is against the comparator at its own peak. At week 28 the alum-adjuvanted vaccine reached 81.3% (Jackson *et al.*, 2018), and the CpG vaccine's week-8 figure of 88.4% remained significantly higher ($p < 0.001$). The difference on that basis is 7.1% points, corresponding to a number needed to vaccinate of 14.1. Both comparisons are shown in Figure 2.

Stating this does not diminish the result. Achieving a higher seroprotection rate five months earlier with one fewer dose is a substantial advantage, and completion rates for a two-dose schedule are better than for a six-month three-dose schedule in practice. The point is that the advantage is 7% points on the endpoint, not 62, and reporting the week-8 contrast without the schedule context invites the larger reading.

3.3. Where the advantage is largest

The programme's clearest justification lies in populations that respond poorly to conventional vaccination (Sablan *et al.*, 2012). Among adults aged 60 to 70 with type 2 diabetes, seroprotection at week 28 was 85.8% (235 of 274) with the CpG vaccine against 58.5% (76 of 130) with the comparator. Our recomputation gives a difference of 27.3% points (95% CI 17.9 to 36.7), matching the reported 27.3% (18.0 to 36.8).

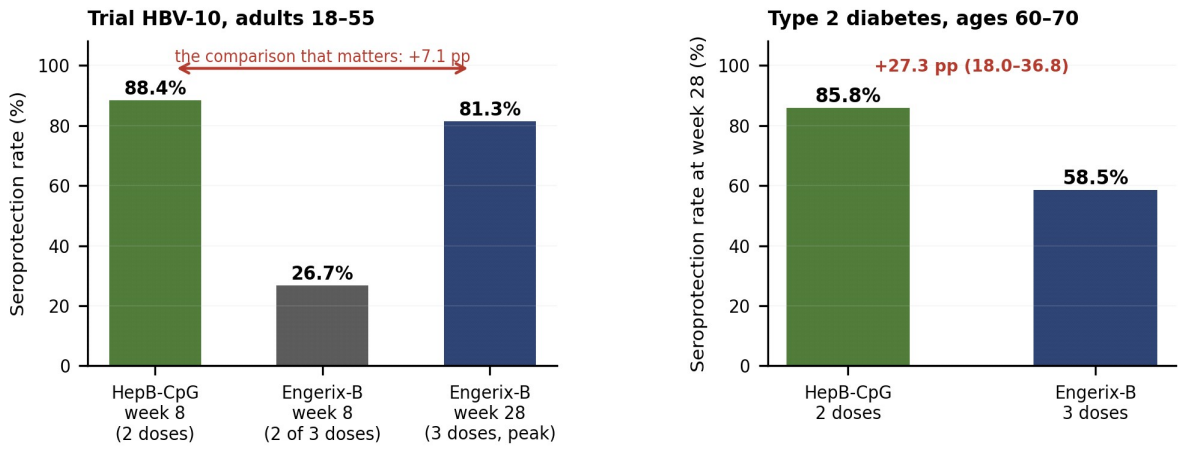

Figure 1: Left: seroprotection in adults aged 18 to 55. The week-8 contrast between arms is not like for like, since the alum-adjuvanted comparator has received two of three doses; against its own peak the difference is 7.1% points. Right: the same comparison in adults aged 60 to 70 with type 2 diabetes, where the difference is 27.3 points

That corresponds to a number needed to vaccinate of 3.7, against 14.1 in the general adult comparison—nearly a fourfold difference, shown in Figure 3. The advantage was reported as consistent regardless of sex, body mass index and smoking status, and the pattern extends to older adults and to chronic kidney disease.

This is the right shape for an improved vaccine. The benefit is concentrated where the existing product fails, rather than distributed evenly across a population most of whom would have been protected anyway.

3.4. Antibody concentration and speed

Geometric mean anti-HBs concentration at week 8 was 83.1 mIU/mL with the CpG vaccine against 6.5 mIU/mL with the comparator, a 12.8-fold difference—though again at a timepoint favourable to the two-dose schedule. Median time to seroprotection was five months earlier.

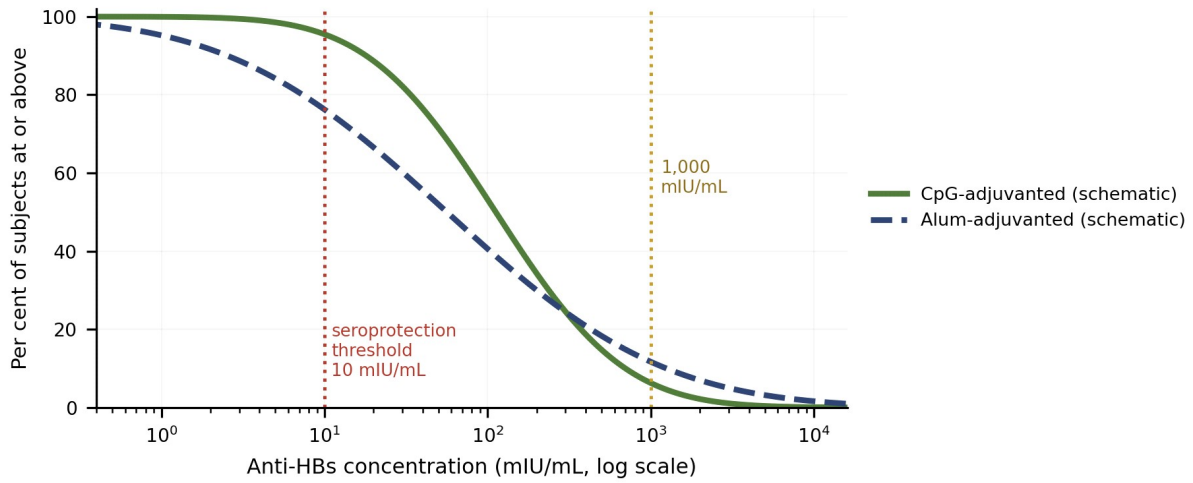

Figure 2: Schematic reconstruction of the reverse cumulative frequency pattern described in the pooled pivotal trial analysis. More CpG recipients clear the 10 mIU/mL threshold and occupy the band below 1,000 mIU/mL; more alum recipients exceed 1,000 mIU/mL and more fail to seroprotect. Curves illustrate the described shape and are not digitised data

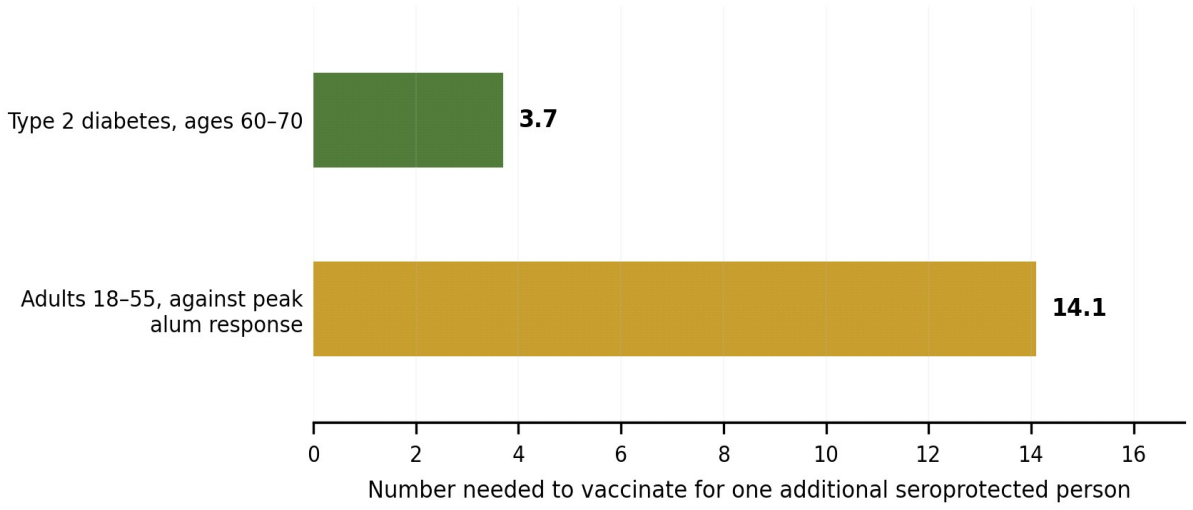

Figure 3: Number needed to vaccinate for one additional seroprotected person, derived from the reported seroprotection differences. The benefit is nearly four times greater in the population with poor baseline response than in general adults compared against the alum peak

The speed finding deserves separate weight from the rate finding. In populations where loss to follow-up between doses is substantial, a schedule that confers protection at week 8 rather than week 28 protects people who would otherwise have been unprotected during the interval, and protects some who would never have returned for a third dose. That benefit is real and is not captured by comparing completed courses.

3.5. What the threshold endpoint cannot show

The pooled analysis of three pivotal trials reported reverse cumulative frequency distributions of antibody concentration, and these show a pattern that the seroprotection endpoint conceals. A higher proportion of CpG recipients reached the 10 mIU/mL threshold, as expected. A higher proportion of CpG recipients also fell in the band between 10 and 1,000 mIU/mL. But a higher proportion of alum recipients exceeded 1,000 mIU/mL, while a significantly higher proportion of alum recipients failed to seroprotect at all.

The adjuvant is therefore compressing the response distribution rather than simply shifting it. It raises the floor, which is the licensed claim and a real benefit, and it lowers the ceiling. The source describes this as a more consistent immune response with less variability, which is accurate and is a fair way to put it. The schematic in Figure 3 shows the pattern.

Whether the smaller high-titre tail matters is not answerable from these data. Anti-HBs concentrations decline over years, and if duration of protection depends on peak titre then a population with fewer very high responders might show earlier waning even while more of it is protected initially. That is a hypothesis, not a finding, and the contrary argument is equally available: immune memory rather than circulating antibody may govern long-term protection, in which case peak titre matters little.

The point we would press is narrower and methodological. A binary threshold endpoint is by construction incapable of detecting a change in the shape of the distribution above the threshold, and here the distribution demonstrably changed. Long-term follow-up rather than inference is what settles it, and such follow-up has been initiated in the chronic kidney disease population (Girndt *et al.*, 2022; Vaccine, 2023).

5. Discussion

The CpG-adjuvanted hepatitis B vaccine achieves seroprotection in 90% to 100% of adults against 70.5% to 90.2% for the alum-adjuvanted comparator, with two doses over one month rather than three over six. In adults aged 60 to 70 with type 2 diabetes the difference is 27.3% points and the number needed to vaccinate is 3.7. These are strong results and the licensing decision they supported is well founded.

Two observations qualify how the evidence should be read, neither of which undermines the conclusion.

The first concerns presentation. A week-8 comparison between a completed two-dose course and an incomplete three-dose course returns a difference of 61.7% points, and that figure appears in the literature without the schedule context that makes it uninterpretable as a measure of vaccine efficacy. Against the comparator at its own peak the difference is 7.1 points. Both numbers describe something real—the first describes the value of speed, the second the value of the adjuvant at completion—and conflating them overstates the latter.

The second concerns what the endpoint measures. Seroprotection is a threshold, and the reverse cumulative frequency data show that the two vaccines differ in distribution shape and not merely in the proportion crossing that threshold. The CpG vaccine produces fewer non-responders and fewer very high responders; the alum vaccine produces more of both. A threshold endpoint records the first difference and is blind to the second.

We want to be careful about what follows. It does not follow that the compression is harmful. A more consistent response is arguably preferable to a variable one, and the population-level benefit of converting non-responders into responders is concrete and immediate whereas any consequence of a smaller high-titre tail is speculative and distant. Nor does it follow that peak titre determines durability, since immune memory may govern long-term protection with circulating antibody a poor proxy for it.

What does follow is that the question exists and the licensing endpoint cannot address it. Anti-HBs concentrations decline over years and the two vaccines start their decline from differently shaped distributions.

Whether they converge, diverge or track each other is an empirical matter that requires long-term serological follow-up, which has been initiated in at least one population. Reporting that follow-up by distribution rather than by threshold would be the informative form.

For practice the recommendation is straightforward and favourable. Where conventional vaccination responds poorly — older adults, diabetes, chronic kidney disease — the adjuvanted vaccine offers a large and well-evidenced advantage, and the two-dose schedule addresses a real completion problem. The distributional question is a research priority rather than a reason for hesitation.

6. Limitations

- Seroprotection rates were extracted as reported and not pooled, since the contributing trials differ in population and assessment timing. The reported ranges therefore reflect population heterogeneity as well as vaccine effect.
- The two schedules differ in dose number and timing, so no comparison at a single timepoint is entirely clean. We have identified which contrasts are like for like, but the underlying asymmetry cannot be removed.
- The diabetes finding derives from a post hoc analysis of a phase 3 trial rather than a prespecified comparison, and post hoc subgroup estimates are subject to selection.
- Distributional findings were extracted from narrative descriptions of reverse cumulative frequency plots. No data were digitised, and Figure 3 is a schematic reconstruction of the described pattern rather than a representation of the underlying data.
- The hypothesis that a smaller high-titre tail could affect durability is generated by this review and is not supported by outcome data in either direction.
- Seroprotection at 10 mIU/mL is a correlate of protection rather than protection itself (Jack *et al.*, 1999), and no contributing trial reported hepatitis B infection as an outcome, which would require far larger and longer studies.
- Long-term follow-up data were available for the chronic kidney disease population but were not analysed here in sufficient depth to address the durability question.
- Safety was reported as comparable between vaccines across 9,871 subjects but was not the subject of this review, and rare adverse events would not be detected at that scale.
- Populations studied were adults aged 18 to 70; findings do not extend to children, pregnancy or immunosuppression.
- Several contributing analyses include authors affiliated with the manufacturer, as disclosed in the source publications.
- No pooling was performed and no publication bias assessment is reported.
- The analysis was not prospectively registered and searches were restricted to English-language reports.

7. Conclusion

A CpG-adjuvanted hepatitis B vaccine given as two doses over one month achieves seroprotection in 90% to 100% of adults against 70.5% to 90.2% for the three-dose alum-adjuvanted comparator, reaching seroprotection a median of five months earlier. Against the comparator at its own peak the difference in general adults is 7.1% points; among adults aged 60 to 70 with type 2 diabetes it is 27.3 points, a number needed to vaccinate of 3.7. The benefit is concentrated where conventional vaccination fails, which is the right shape for an improved product.

The reverse cumulative frequency data show that the adjuvant compresses the antibody distribution, producing fewer non-responders and fewer very high responders than the comparator. A threshold endpoint records the first and cannot record the second. Whether the smaller high-titre tail bears on duration of protection is unresolved and not resolvable from seroprotection rates; it requires long-term serological follow-up reported by distribution rather than by threshold.

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Public health note

Both vaccines discussed are licensed and effective against hepatitis B. Nothing in this review argues against hepatitis B vaccination with either product, and the distributional question raised is a research priority rather than a reason to defer immunisation.

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