**Reviews for “A Reactogenic “Placebo” and the Ethics of Informed Consent in Gardasil HPV Vaccine Clinical Trials: A Case Study from Denmark”**

**Authors:** Lucija Tomljenovic and Leemon B. McHenry

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**Original Submission**

**Reviewer #1**

**Reviewer Recommendation Term:** Accepted pending minor revisions

Are you willing to review the revision of this manuscript? Yes

Originality, novelty and significance of results: Good

Technical Quality of Work: Excellent

Comprehensibility and Presentation of Paper: Good

What is the overall impression: Good

Is the article significant to the field? [1-5] 5

Is the article appropriate for the journal? [1-5] 5

Is the work an original contribution? [1-5] 4

Are the conclusions adequately supported by the data? [1-5] 4

Is the research interesting and important? [1-5] 4

Is the level of English adequate? [1-5] 4

**Narrative (as sent to corresponding author):**

1. Is the paper logical with a concise ordering of ideas? [Yes]

2. Does the paper describe sound research methods, analysis & interpretation? [Yes] Are limitations to the study included and discussed? [No]

3. In case the authors used established methodology, are the results of all previous studies been searched for and presented in a concise form? Has the current work had impact on the local practice and policies? [Not applicable: this is a review article]

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin. [Many references are quite old: I could find one reference nearly a century old, from 1926]

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit? [Partially; focusses more on the risk rather than the benefit]

6. What is the quality of the readability of the paper in English? Is the presentation/layout clear? Have the author guidelines been followed? [Readability is good, though it can be made a bit more concise]

7. Are the ideas in the paper original and the significance of the research described? Are the results of likely interest to an international audience? [Yes]

8. Is the content timely? [Yes]

9. Does the paper build on and advance the knowledge of papers published in JRS and other international journals? If the paper describes methodology and results of original / experimental clinical (health) research, does it build on the existing knowledge, coming from systematic reviews? Have the searches for the rationale been rigorously done? [Appears so]

This represents my first review of the manuscript titled "A Reactogenic "Placebo" and the Ethics of Informed Consent in the Gardasil Vaccine Clinical Trials: A Case Study from Denmark" submitted to the IJRSM.

The authors have undertaken in-depth research of the ethics surrounding the use of reactogenic placebo in vaccine trials, and appears timely. The conflicts of interest section suggests that the authors do have a stake in Gardasil trials; however, it is worth publication in the journal, with a specific invite for a rebuttal from Merck.

In the introduction, the authors have made a comment on the sample size of the V501-018 trial, which I found to be unwarranted in the present paper because it deviates from the main issue, and suggests that there is some conflict of interest against Merck's products rather than against the reactogenic placebo in Gardasil vaccine alone.

Some of the references are really old: one is from 1926 which is nearly a century old. The authors should consider using newer and updated references.

The authors should also present the other side of the coin, if at all briefly, so that a balanced viewpoint is established. There must be some reason why the research containing reactogenic placebos got approval from different ethics committees and journals which published this research.

Finally, the authors should try to make the content a bit concise and more engaging.

All in all, it is a good effort on the part of the authors; we would like to know the viewpoint of Merck on this as well.

**Reviewer #2**

**Reviewer Recommendation Term**: Accept as is

Are you willing to review the revision of this manuscript? Yes

Originality, novelty and significance of results: Excellent

Technical Quality of Work: Excellent

Comprehensibility and Presentation of Paper: Excellent

What is the overall impression: Excellent

Is the article significant to the field? [1-5] 5

Is the article appropriate for the journal? [1-5] 5

Is the work an original contribution? [1-5] 5

Are the conclusions adequately supported by the data? [1-5] 5

Is the research interesting and important? [1-5] 5

Is the level of English adequate? [1-5] 5

**Narrative (as sent to corresponding author):**

1. Is the paper logical with a concise ordering of ideas?- YES

2. Does the paper describe sound research methods, analysis & interpretation? Are limitations to the study included and discussed? - YES

3. In case the authors used established methodology, are the results of all previous studies been searched for and presented in a concise form? Has the current work had impact on the local practice and policies?- YES

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin. - YES

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit?- YES

6. What is the quality of the readability of the paper in English? Is the presentation/layout clear? Have the author guidelines been followed?- YES

7. Are the ideas in the paper original and the significance of the research described? Are the results of likely interest to an international audience?- YES

8. Is the content timely?- YES

9. Does the paper build on and advance the knowledge of papers published in JRS and other international journals? If the paper describes methodology and results of original / experimental clinical (health) research, does it build on the existing knowledge, coming from systematic reviews? Have the searches for the rationale been rigorously done?- YES

**Reviewer #3**

**Reviewer Recommendation Term**: Reject outright

Are you willing to review the revision of this manuscript? **No**: This manuscript will need considerable revision, and the evidence and arguments proposed made more succinctly to be suitable for publishing in this journal.

Originality, novelty and significance of results: Inadequate

Technical Quality of Work: Adequate

Comprehensibility and Presentation of Paper: Inadequate

What is the overall impression: Inadequate

Is the article significant to the field? [1-5] 3

Is the article appropriate for the journal? [1-5] 2

Is the work an original contribution? [1-5] 2

Are the conclusions adequately supported by the data? [1-5] 2

Is the research interesting and important? [1-5] 3

Is the level of English adequate? [1-5] 5

**Narrative (as sent to corresponding author):**

1. Is the paper logical with a concise ordering of ideas?

This is an overly long manuscript. Many sections were in such detail that each could serve as individual manuscript topics. These sections were not always directly relevant to the ethical issue raised within the title.

2. Does the paper describe sound research methods, analysis & interpretation? Are limitations to the study included and discussed?

This paper is primarily a descriptive and opinion-based review. There were sections within the paper that did not provide a wide or balanced presentation of the current research. No limitations of this manuscript were discussed by the authors.

3. In case the authors used established methodology, are the results of all previous studies been searched for and presented in a concise form? Has the current work had impact on the local practice and policies?

The information within this manuscript could be made more concisely.

The raised ethical issue is of significance to this field of research. This ethical issue and assertions of this manuscript, echo articles previously published by Petersen & Gluud (2021)1 as well as Doshi and colleagues (2019)2.

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin.

Many of the articles referenced predate the abovementioned 5-year period. There are instances when this manuscript references non-source publications. For example, section 3 ("Merck's rationale for using AAHS as a "placebo" in Gardasil clinical trial") references a table in the Doshi et al2 article, instead of the source documents.

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit?

This paper discusses risk but not benefit.

6. What is the quality of the readability of the paper in English? Is the presentation/layout clear? Have the author guidelines been followed?

This article is long but readable.

7. Are the ideas in the paper original and the significance of the research described? Are the results of likely interest to an international audience?

See answer to question 3.

8. Is the content timely?

See answer to question 3.

9. Does the paper build on and advance the knowledge of papers published in JRS and other international journals? If the paper describes methodology and results of original / experimental clinical (health) research, does it build on the existing knowledge, coming from systematic reviews? Have the searches for the rationale been rigorously done?

See answer to question 3.

References:

1. Petersen SB, Gluud C. Was amorphous aluminium hydroxyphosphate sulfate adequately evaluated before authorisation in Europe?. BMJ Evidence-Based Medicine 2021;26:285-289.

2. Doshi P, Bourgeois F, Hong K, et al. Adjuvant-containing control arms in pivotal quadrivalent human papillomavirus vaccine trials: restoration of previously unpublished methodology. BMJ Evidence-Based Medicine. 2020;25:213-219.

**Reviewer #4**

**Reviewer Recommendation Term**: Revise and resubmit pending major revisions

Are you willing to review the revision of this manuscript? Yes

Originality, novelty and significance of results: Good

Technical Quality of Work: Good

Comprehensibility and Presentation of Paper: Excellent

What is the overall impression: Good

Is the article significant to the field? [1-5] 4

Is the article appropriate for the journal? [1-5] 4

Is the work an original contribution? [1-5] 3

Are the conclusions adequately supported by the data? [1-5] 5

Is the research interesting and important? [1-5] 4

Is the level of English adequate? [1-5] 3

**Narrative (as sent to corresponding author):**

This paper makes the case that the consent form given to people participating in trials of Gardasil was unethical because it claimed that it was a placebo controlled trial whereas the aluminum adjuvant was not a placebo because it is highly immunogenic and may cause a host of adverse events.

This is a highly technical article and it is beyond my knowledge level to assess the validity of all of the arguments that it makes. However, having said that it appears to make a compelling case. I only have a few comments:

1. Presumably the clinical trial that the authors are referring to was subject to an ethics review. Were the authors able to get access to the report from the ethics review to see if any concerns were raised?

2. Page 4, first paragraph: The use of the word "obviously" could imply that the authors did sample size calculations based on the expected frequency of side effects? If they have done sample size calculations, then they should present the information.

3. Has AAHS been used in other vaccine trials and if so, is there evidence that it is associated with adverse effects?

4. In discussing global safety issues from HPV vaccines are the authors just referring to symptoms from the Merck vaccine or from vaccines made by other manufacturers? If the latter don't use the same aluminum adjuvant what would be causing the safety problems?

5. t appears that the term "Human Papillomavirus Vaccination Associated Neuroimmunopathic Syndrome" is a name proposed by a researcher rather than an "official" diagnosis.

6. Although the safety of the HPV vaccine has been contested, it has also not been deemed unsafe by independent drug bulletins, e.g., Prescrire International (Nov. 2019, pages 270-2).

**Author’s reply to the reviews:**

NOTE TO THE EDITOR

Dear Dr. Ziganshina

Herein we are submitting for your consideration the first revision of our article, "A Reactogenic 'Placebo' and the Ethics of Informed Consent in the Gardasil Vaccine Clinical Trials: A Case Study from Denmark." We hope we have satisfactorily addressed the reviewers comments and concerns.

We wish to note that such phrases as “in our opinion”, “in our view”, and “it appears that” are recommendations from legal for reducing libel risk (and in all of the previous articles published in IJRSM co-author Leemon McHenry adopted the same procedure). We sincerely apologize for the fact that our revision is one working day late than the deadline (15th September 2023).

Lucija Tomljenovic

&

Leemon McHenry

RESPONSE TO REVIEWERS

We would like to thank all the reviewers for their constructive criticism and the time invested in evaluating our manuscript.

RESPONSE TO Reviewer #1:

2. Does the paper describe sound research methods, analysis & interpretation? [Yes] Are limitations to the study included and discussed? [No]

Answer: We added a Limitation section to the manuscript:

8. Limitations

We did not include an overview of post-licensure safety studies of the Gardasil vaccine which are frequently cited as proof of its allegedly excellent safety [122-125], as this would have expanded the article beyond any reasonable length. Moreover, due to a Protective Order in the case, we are prevented from discussing the contents of documents produced by Merck, including the data from Merck’s clinical trials which are proprietary information.

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin. [Many references are quite old: I could find one reference nearly a century old, from 1926]

Answer: The 1926 reference is the work of Glenny et al. who were the first to describe the immunostimulatory effect of aluminum adjuvants. This discovery ushered the regular use of these adjuvants in veterinary and human vaccines. So it was the appropriate reference to cite when stating the start date of the use of alum adjuvants, and the fact that these compounds have indeed a very long history of use.

Similarly, we cited many references describing adverse neurolological effects in various animal models that follow aluminum adjuvant injections. Most of these original research publications are older than 3-5 years, but they are crucial to our manuscript, and the point that aluminum adjuvants should not be used as placebos in vaccine clinical trials. We consider it poor practice to only cite a review that summarizes all these studies, as it may give the false impression that we did not actually read the original references.

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit? [Partially; focusses more on the risk rather than the benefit]

Answer: We added a Risk vs benefit section to the manuscript:

7. HPV vaccines’ risks versus benefits

In a 2020 systematic review with meta-analyses of clinical trial data from CSRs of Merck’s Gardasil and GSK’s Cervarix HPV vaccines, Jørgensen et al. [117] found that at 4 years follow-up the HPV vaccines reduced HPV-related carcinoma in situ, external genital lesions, and HPV-related treatment procedures. However, the HPV vaccines increased serious nervous system disorders and general harms. Jørgensen et al. [117] judged all 24 out of 50 eligible clinical study reports to be at high risk of bias for the following reasons:

1) 99% of study participants received an active comparator that included the adjuvant component of the trial vaccines;

2) Despite the fact that the vaccine manufacturers consider the aluminum containing comparators to be safe, 52% of the participants were only included in the trials if they had never received the study adjuvants before;

3) Two thirds of the participants were only included in the trials if they had no history of immunological or nervous system disorders, however, such conditions are not listed as warnings or contraindications in the package inserts of the approved HPV vaccines;

4) Serious AEs were incompletely reported for as many as 72% of study participants (all 24 clinical study reports contained redactions—especially of harms—and lacked significant parts such as serious harm narratives and case report forms);

5) Serious AEs in Merck’s clinical trials for Gardasil were only collected up to 14 days following each Gardasil injection (i.e., as apparently in the Vaqta Monroe Study trial which also used AAHS as a placebo [113]); beyond that period serious AEs were only collected if they were judged by the study investigators to be related to the injection;

6) Extended follow-up was not possible for 75% of the comparator participants, as they were offered HPV vaccination at trial completion.

The authors concluded that as the reviewed trials were primarily designed to assess benefits and were not adequately designed to assess harms, the extent to which the HPV vaccines’ benefits outweigh their harms is unclear [117].

To date, the most cited study allegedly demonstrating significant “real world” reduction of invasive cervical cancer in Gardasil recipients included 528,347 unvaccinated and 518,319 vaccinated Swedish girls and young women between 10 and 30 years of age [118]. During the study period, 538 women who had not received the Gardasil vaccine were subsequently diagnosed with cervical cancer compared to only 19 who had been vaccinated (adjusted incidence rate ratio (IRR) 0.37, 95% CI 0.21–0.57). The fully adjusted IRR for cervical cancer among women who were vaccinated before 17 years of age was 0.12 (95% CI 0.00-0.34). These results were hailed in the press as showing nearly 90% reduction in invasive cervical cancer incidence in girls who were vaccinated before 17 years of age [119]. It is noteworthy, however, that when the trumped reduction of the relative risk of invasive cervical cancer (96.4% for the total study population, Table 2) is translated to a reduction of absolute risk (0.098%, Table 2), the benefit of HPV vaccination becomes practically negligible in terms of public health impact. The absolute risk reduction figures stratified per birth cohorts are even less impressive, ranging from negative 0.008% for the older 1980-1984 cohort, and 0.027% for the younger 1990-1994 birth cohort (Table 2). Of note, the rate of serious AEs in the largest pre-licensure clinical trial of Gardasil—the FUTURE II trial—was 0.7%, of which less than 0.1% were judged by the Merck’s sponsored study investigators to be vaccine related [9]. Bearing in mind that the rate of serious AEs will be much higher in the real world setting due to vaccination of subjects with pre-existing medical conditions that were routinely excluded from Gardasil clinical trials, it appears that the benefit to risk ratio of Gardasil vaccination is not as overwhelmingly in favor of vaccination in developed countries as so often proclaimed by the health authorities [120]. This is because in the developed world, where cervical screening practices are well established, the incidence of cervical cancer is extremely low (4.9-6.9/100,000 [121]). Moreover, regular cervical screening must be maintained given that the currently licensed HPV vaccines do not cover all oncogenic HPV strains.

This section also includes Table 2.

6. What is the quality of the readability of the paper in English? Is the presentation/layout clear? Have the author guidelines been followed? [Readability is good, though it can be made a bit more concise]

Answer: The paper is long but not indigestible. In the revised manuscript we much shortened sections 1-4, and removed a part of section 6. HPV vaccine syndrome–a global safety signal, which dealt with the EMA assessment of Gardasil safety. We agree that this section deviates from the main topic, which are the scientific and ethical breaches involved in using a reactogenic adjuvant placebo in vaccine clinical trials. A small part of section 6 that lists the kind of disabling conditions reported by the FUTURE II trial participants was moved to section 5.

However, in order to address several other important comments by the reviewers, we had to add other sections to the manuscript, such as HPV vaccines’ risks versus benefits and Limitations (sections 7 & 8). We also added a discussion on other Merck’s AAHS vaccines that predated Gardasil, in order to show that AAHS safety has not been as solidly established as claimed by Merck and the regulatory agencies. In fact, the documentary evidence we provided shows that Merck was not transparent about the identity of AAHS as the adjuvant they used in several vaccines that predated Gardasil, but rather, Merck consistently and incorrectly stated to the U.S. and the European regulatory agencies that the adjuvant in these vaccines was aluminum hydroxide and not AAHS. In light of this fact, any claim made by Merck and the regulators that the safety of AAHS is “well characterised” lacks support.

The result of all these additions is that the revised manuscript is ~400 words hundred words longer than the original submission (~7500 words total count excluding, Title page, Abstract, Abbreviations, Declarations, Tables, Figures and References).

We nonetheless believe that all the remaining sections are necessary and relevant to the ethical issue of informed consent, mainly, the scientific and regulatory matters pertaining to the use of aluminum adjuvants in vaccines. The reason for this is that our article deals with a very controversial and contested topic. Because of this we found it rather impossible to do both: 1) make a manuscript more concise, and 2) fulfill the journal’s limit on the number of allowed references (80). Neither of these two requirements would have been an issue, were we not challenging decades of entrenched dogma, and were we discussing issues that were, at least to some notable extent, agreed upon. We found it for example essentially impossible to limit ourselves to a few most influential articles in making the point that there is a large body of experimental research refuting the entrenched notion that aluminum adjuvants are safe and only associated with local adverse reactions. That would amount to making a false claim. The onus is on us–the authors–to prove our case since we are challenging the widely established consensus. If we were to make the current revision shorter and remove many references from it, this would in our opinion compromise the evidence-based character of the manuscript (which was our target), and would make it appear as no more valid than an unsubstantiated opinion piece.

9. The authors have undertaken in-depth research of the ethics surrounding the use of reactogenic placebo in vaccine trials, and appears timely. The conflicts of interest section suggests that the authors do have a stake in Gardasil trials; however, it is worth publication in the journal, with a specific invite for a rebuttal from Merck.

In the introduction, the authors have made a comment on the sample size of the V501-018 trial, which I found to be unwarranted in the present paper because it deviates from the main issue, and suggests that there is some conflict of interest against Merck's products rather than against the reactogenic placebo in Gardasil vaccine alone.

Answer: We are not opposed to a response from Merck, and we actually expect it.

Regarding V501-018, we respectfully disagree that a comment on the sample size of the V501-018 trial deviates from the main issue. The main issue is whether or not the AAHS adjuvant is an appropriate placebo, which Merck and the regulators affirm, but we contest. The U.S. FDA specifically requested of Merck to conduct a Gardasil trial without the aluminum in the placebo arm, and in response Merck had to conduct such a trial (see Doshi et al. BMJ Evid Based Med. 2020; 25(6):213-219). That was the V501-018 trial, and it was supposed to demonstrate the safety of the AAHS-formulated HPV vaccine, which obviously none of the other trials could do since they used AAHS as a placebo. Nonetheless, we have both shortened and revised that section, and removed from it a statement that implies certainty, and replaced it with a statement that expresses the authors’ doubt in the notion that the results of the V501-018 trial provide support for the safety of an AAHS-containing vaccine.

Submitted manuscript:

Moreover, the V501-018 trial was grossly underpowered as it recruited only 1,781 children—both male and female (9-15 years of age), who were randomized in a 2:1 ratio to receive either Gardasil or the “placebo.” Only 597 children were injected with a “placebo” [8]. By contrast, the largest pre-licensure Gardasil trial V501-015 (the FUTURE II trial), recruited 12,167 women between 15 and 26 years of age, 6,087 of whom were randomized to the vaccine and 6,080 to the AAHS “placebo” group [9]. It is hard to understand why Merck recruited such a small number of subjects in the pivotal V501-018 trial, since, unlike other Gardasil trials, V501-018 aimed to evaluate safety and efficacy in largely sexually naive preadolescents and young adolescents, i.e., the primary target population for HPV vaccination. Obviously, the V501-018 trial population was far too small to provide a reliable measure of safety. This is especially true for conditions of greatest interest, e.g., autoimmune diseases, which are sometimes triggered by vaccinations [10-12], and for which the baseline prevalence in the general population is low [13, 14]. V501-018 study results [7, 8] therefore provide no assurance in the safety of the Gardasil vaccine.

Revised manuscript:

Notably, unlike other V501 trials, V501-018 evaluated Gardasil safety and efficacy in sexually naive preadolescent and adolescent girls which were the primary target population for HPV vaccination. Nonetheless, only 1,781 children between 9 and 15 years of age were included in this trial; both male and female who were randomized in a 2:1 ratio to receive either Gardasil or the “placebo.” The effect of this randomization was that only 617 girls received the Gardasil vaccine, and 322 received the “placebo” [8]. By contrast, the largest pre-licensure Gardasil trial V501-015 (the FUTURE II trial), recruited 12,167 subjects, all females between 15 and 26 years of age, who were randomized in a 1:1 ratio to receive either Gardasil or the AAHS injection [9]. It is thus highly questionable whether the V501-018 trial provided a reliable measure of safety for Gardasil given the small size of its study population.

[9. continued] The authors should also present the other side of the coin, if at all briefly, so that a balanced viewpoint is established. There must be some reason why the research containing reactogenic placebos got approval from different ethics committees and journals which published this research.

Answer: We did present the other side of the coin, namely, Merck’s view that the safety of AAHS is well established, and the endorsement of that view by the regulatory agencies such as the EMA, which claims that no additional research involving aluminum alone versus an inactive control is required, e.g.:

Of further relevance, in 2019 in response to a question about when and how the EMA assessed the safety of each of the aluminum-adjuvanted vaccines that it approved (including Gardasil), the Agency stated the following: “Data generated from clinical trials with aluminum containing vaccines worldwide and the safety data gathered from the use of aluminum containing vaccines over six decades have shown that their safety profile is acceptable, with only local reactions as possible side effect linked to aluminum, which normally resolve in a short timeframe … For marketing authorization purposes, no new clinical safety studies are needed comparing aluminum alone versus inactive control” [53] [emphasis added]. Accordingly, in 2016 the EMA’s Deputy Executive Director Noel Wathion stated that, “The safety of aluminum adjuvant is considered well characterised … In addition non-clinical studies for HPV vaccines, such as conventional studies of safety pharmacology, acute and repeated dose toxicity … revealed no potential risk for humans” [95] [emphasis added].

As for the reason why “the research containing reactogenic placebos got approval from different ethics committees and journals which published this research”; the answer is because of the prevailing dogma that aluminum adjuvants in general have a long-established excellent safety record. We have attempted to provide evidence that this is not the case in section 4 of our manuscript: Aluminum adjuvant safety: What are the facts?

Moreover, the reason why the use of reactogenic adjuvant placebos is approved by the regulators has been discussed in detail in the last part of revised section 6, which now has an additional sentence (re ACIP meeting October 24-25. 2007):

Another glaring inconsistency is that even though vaccine adjuvants are recognized and regarded as active components of a vaccine formulation from an immunological standpoint, for all regulatory intents and purposes they are regarded as inactive ingredients or excipients by both the U.S. FDA and the EMA [67]. Since such an inherently illogical position cannot be evidence-based, the reason for it has to be sought elsewhere. Admittedly, according to a 2013 report of a workshop on adjuvanted vaccines which gathered scientists from academia, regulatory agencies and the vaccine manufacturer industry, “if adjuvants were to be considered active ingredients from a regulatory perspective, clinical trials demonstrating that each active ingredient in the vaccine formulation contributes to the claimed effect would be required. Thus, this may significantly increase the size and cost of clinical trials. If considered excipients, such clinical studies would not need to be required” [67].

Therefore, the reason why the regulators falsely regard adjuvants as inactive ingredients is to spare the vaccine manufacturers the inconvenience of conducting larger and costlier clinical studies. What makes this situation even more bizarre is the fact that the WHO acknowledges that, “since adjuvants have their own pharmacological properties, which might affect both the immunogenicity and the safety of vaccines, safety assessment is essential” [64]; and further, that, “short-term and long-term safety evaluation and prediction are important, as is the evaluation of the pharmacokinetics of the adjuvant alone” [64] [emphasis added]. The EMA agreed with this in their 2004 guidelines on adjuvants in vaccines for human use where the Agency affirmed that, “the adjuvant should be tested alone” [71] [emphasis added]. Finally, during the discussion on HPV vaccines at the U.S. CDC ACIP meeting in October 24-25, 2007, ACIP member Franklyn Judson commented that, “experience over the years with hepatitis B and other protein-alum combinations indicates that the reactogenic part is predominantly the alum and that studies that use alum minus the active protein are not really placebos in terms of reactogenicity” [116]. Given these statements, it is difficult to understand why vaccine manufacturers are still permitted to use aluminum adjuvants as “placebos” in vaccine clinical trials.

In addition, to more specifically answer the question why, “the research containing reactogenic placebos got approval from different ethics committees”, note that according to Petersen and Gluud (2020) the Danish Medicines Agency and the Danish National Committee on Health Research Ethics were presented with contradictory information about the “placebo” in the Future II. To document this fact we added the following to section 5. of our manuscript (Informed consent in Merck’s FUTURE II trial of Gardasil in Demark):

It is also important to note that the Danish Medicines Agency and the Danish National Committee on Health Research Ethics, were presented with contradictory information about the “placebo” in the Future II trial, since they were given the study protocol which stated that the “placebo” contained the aluminum adjuvant, whereas the recruitment brochure and the informed consent form stated that the “placebo” contained saline [74].

Finally, in the grand scheme of things, we could not really present a balanced view since we contend that Merck has misled the clinical trial participants and made it impossible to evaluate the true harms of their proprietary aluminum adjuvant. This appears all the more to be the case given the fact that the first vaccines in which AAHS was used as an adjuvant were apparently incorrectly described to both the U.S. and the European regulators as containing “aluminum hydroxide”, rather than AAHS. This means that the regulators were under a mistaken impression that the adjuvant used in several Merck’s vaccines that were licensed prior to Gardasil was not a novel and proprietary aluminum compound, but rather, one of the conventional aluminum adjuvants that has been in use in human vaccines for many decades (see section 6).

[9. continued] Finally, the authors should try to make the content a bit concise and more engaging.

Answer: As already explained, we agree that the content of our manuscript could be made more concise, which is why we significantly shortened sections 1-4, and deleted the discussion on the EMA’s assessment of Gardasil safety. However, we needed to add other sections in order to address other comments by the reviewers. We nonetheless believe that the added content (especially the revised section Inconsistent claims by the regulatory agencies and Merck on the identity and safety of AAHS, which is now section #6), does indeed make the manuscript far more engaging, as it presents critical to our topic information that, to the best of our knowledge, has not been presented before in the peer-reviewed and other literature.

RESPONSE TO Reviewer #2:

No comments to address.

RESPONSE TO Reviewer #3:

1. Is the paper logical with a concise ordering of ideas?

This is an overly long manuscript. Many sections were in such detail that each could serve as individual manuscript topics. These sections were not always directly relevant to the ethical issue raised within the title.

Answer: As per our answer to the first reviewer:

The paper is long but not indigestible. In the revised manuscript we much shortened sections 1-4, and removed a part of section 6. HPV vaccine syndrome–a global safety signal, which dealt with the EMA assessment of Gardasil safety. We agree that this section deviates from the main topic, which are the scientific and ethical breaches involved in using a reactogenic adjuvant placebo in vaccine clinical trials. A small part of section 6 that describes the kind of disabling conditions reported by the FUTURE II trial participants was moved to section 5.

However, in order to address several other important comments raised by the reviewers, we had to add other sections to the manuscript, including section #7 HPV vaccines’ risks versus benefits and #8 Limitations sections. We also added a discussion on other Merck’s AAHS vaccines that predated Gardasil, in order to show that AAHS safety has not been as well established as claimed by Merck and the regulatory agencies. In fact, the documentary evidence we provided shows that Merck was not transparent about the identity of AAHS as the adjuvant they used in several vaccines that predated Gardasil, but rather, Merck consistently stated to the U.S. and the European regulatory agencies that the adjuvant in these vaccines was aluminum hydroxide and not AAHS. In light of this fact, any claim made by Merck and the regulators that the safety of AAHS is “well characterised” lacks support.

The result of all these additions is that the revised manuscript is ~400 words hundred words longer than the original submission (~7500 words total count excluding, Title page, Abstract, Abbreviations, Declarations, Tables, Figures and References).

We nonetheless believe that all the remaining sections are necessary and relevant to the ethical issue of informed consent, mainly, the scientific and regulatory matters pertaining to the use of aluminum adjuvants in vaccines. The reason for this is that our article deals with a very controversial and contested topic. Because of this we found it rather impossible to do both: 1) make a manuscript more concise, and 2) fulfill the journal’s limit on the number of allowed references (80). Neither of these two requirements would have been an issue, were we not challenging decades of entrenched dogma, and were we discussing issues that were, at least to some notable extent, agreed upon. We found it for example essentially impossible to limit ourselves to a few most influential articles in making the point that there is a large body of experimental research refuting the entrenched notion that aluminum adjuvants are safe and only associated with local adverse reactions. That would amount to making a false claim. The onus is on us–the authors–to prove our case since we are challenging the widely established consensus. If we were to make the current revision shorter and remove many references from it, this would in our opinion compromise the evidence-based character of the manuscript (which was our target), and would make it appear as no more valid than an unsubstantiated opinion piece.

2. Does the paper describe sound research methods, analysis & interpretation? Are limitations to the study included and discussed?

This paper is primarily a descriptive and opinion-based review. There were sections within the paper that did not provide a wide or balanced presentation of the current research. No limitations of this manuscript were discussed by the authors.

Answer: The revised manuscript includes now section 8 on limitations. As per our response to the first reviewer, we did provide contrary opinion to our main contention that aluminum adjuvants have a questionable safety record, and should therefore not be used as placebos in vaccine clinical trials. We did so by presenting Merck’s view that the safety of AAHS has been well established, and the endorsement of that view by the regulatory agencies such as the EMA, which claims that no additional research involving aluminum alone versus an inactive control is required. The contrary view that aluminum adjuvants have an excellent and established safety record is moreover so wide-spread, well-known and well-represented in the peer-reviewed literature that it was hardly worth repeating. Doing so would have added more unoriginal content and made the manuscript even lengthier than it is.

Moreover, as per our response to the first reviewer, in the grand scheme of things, we could not really present a balanced view since we contend that Merck has misled the clinical trial participants and made it impossible to evaluate the true harms of their proprietary aluminum adjuvant. This appears all the more to be the case given the fact that the first vaccines in which AAHS was used as an adjuvant were apparently incorrectly described to both the U.S. and the European regulators as containing “aluminum hydroxide”, rather than AAHS. This means that the regulators were under a mistaken impression that the adjuvant used in several Merck’s vaccines that were licensed prior to Gardasil was not a novel and proprietary aluminum compound, but rather, one of the conventional aluminum adjuvants that has been in use in human vaccines for many decades (see section 6).

3. In case the authors used established methodology, are the results of all previous studies been searched for and presented in a concise form? Has the current work had impact on the local practice and policies?

The information within this manuscript could be made more concisely.

The raised ethical issue is of significance to this field of research. This ethical issue and assertions of this manuscript, echo articles previously published by Petersen & Gluud (2021)1 as well as Doshi and colleagues (2019)2.

Answer: Regarding conciseness: we already addressed that in our response to the first question. As for the parts that were added to the revised manuscript to address the reviewers’ comments, and which inevitably made the manuscript somewhat longer than the original submission: we believe that the added content (especially the revised section Inconsistent claims by the regulatory agencies and Merck on the identity and safety of AAHS, which is now section #6), makes the manuscript more engaging, and moreover, adds original content, as it presents critical to our topic information that, to the best of our knowledge, has not been presented before in the peer-reviewed literature. For this reason our paper goes well beyond the previously published papers by Doshi et al. (2019) and Petersen and Gluud (2021). Neither of these two papers presented a comprehensive overview of research studies dealing with neurotoxicology and biodistribution of injected aluminum adjuvants in animal models. Additionally, although Petersen and Gluud show that in 2004, during the marketing renewal of Procomvax, Merck proposed to the EMA “to update the excipient name of aluminium hydroxide to amorphous aluminium hydroxyphosphate sulphate”, they do not trace how far back and for how many AAHS-adjuvanted vaccines did Merck originally incorrectly state to the regulators that the adjuvant component was aluminum hydroxide. Petersen and Gluud’s paper likewise did not include the fact that Merck used AAHS as a placebo in their hepatitis A vaccine Vaqta that was licensed long before Gardasil.

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin.

Many of the articles referenced predate the abovementioned 5-year period. There are instances when this manuscript references non-source publications. For example, section 3 ("Merck's rationale for using AAHS as a "placebo" in Gardasil clinical trial") references a table in the Doshi et al2 article, instead of the source documents.

Answer: As per our response to the first reviewer, our oldest reference is the 1926 reference by Glenny et al. who were the first to describe the immunostimulatory effect of aluminum adjuvants. That discovery ushered the regular use of aluminum adjuvants in veterinary and human vaccines. So it was the appropriate reference to cite (since the journal does require source publications) when stating the start date of the use of alum adjuvants, and the fact that these compounds have indeed a very long history of use.

Similarly, we cited many references describing adverse neurolological effects in various animal models that follow aluminum adjuvant injections. Most of these original research publications are older than 3-5 years, but they are crucial to our manuscript, and the point that aluminum adjuvants should not be used as placebos in vaccine clinical trials. We consider it poor practice to only cite a review that summarizes all these studies, as it may give the false impression that we did not actually read the original references.

Regarding citing non-source publication in the section Merck's rationale for using AAHS as a "placebo" in Gardasil clinical trials, we are not entirely certain which exact reference the reviewer is referring to. In the revised manuscript this section has been greatly shortened, and Doshi et al. article is cited whenever we refer to the statements made in Merck’s CSR-related documents and informed consent forms which were obtained by Doshi et al. Although we have access to these documents as well (since they were released to us by Merck in the course of the litigation), they are under a Protective Order, so we can only publicly cite Doshi et al. as the source reference for this information.

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit?

This paper discusses risk but not benefit.

Answer: We added section #7 in the revised manuscript that discusses risk vs benefit, since other reviewers also noted that it was lacking.

RESPONSE TO Reviewer #4:

1. Presumably the clinical trial that the authors are referring to was subject to an ethics review. Were the authors able to get access to the report from the ethics review to see if any concerns were raised?

Answer: Note that this is the same question raised by Reviewer 1. It appears that the Danish National Committee on Health Research Ethics overlooked the problem. We added the following to section 5. of our manuscript to address this comment:

It is also important to note that the Danish Medicines Agency and the Danish National Committee on Health Research Ethics, were presented with contradictory information about the “placebo” in the Future II trial, since they were given the study protocol which stated that the “placebo” contained the aluminum adjuvant, whereas the recruitment brochure and the informed consent form stated that the “placebo” contained saline [74].

2. Page 4, first paragraph: The use of the word "obviously" could imply that the authors did sample size calculations based on the expected frequency of side effects? If they have done sample size calculations, then they should present the information.

Answer: We asked a pharmacovigilance expert to do the power analysis but decided not to include it, as it would add unnecessary length to the manuscript. Plus, it is an issue that we plan to address in greater detail in another manuscript. However, we both shortened and revised that section, and removed from it a statement that implies certainty, and replaced it with a statement that expresses the authors’ doubt in the notion that the results of the V501-018 trial provide support for the safety of an AAHS-containing vaccine.

Submitted manuscript:

Moreover, the V501-018 trial was grossly underpowered as it recruited only 1,781 children—both male and female (9-15 years of age), who were randomized in a 2:1 ratio to receive either Gardasil or the “placebo.” Only 597 children were injected with a “placebo” [8]. By contrast, the largest pre-licensure Gardasil trial V501-015 (the FUTURE II trial), recruited 12,167 women between 15 and 26 years of age, 6,087 of whom were randomized to the vaccine and 6,080 to the AAHS “placebo” group [9]. It is hard to understand why Merck recruited such a small number of subjects in the pivotal V501-018 trial, since, unlike other Gardasil trials, V501-018 aimed to evaluate safety and efficacy in largely sexually naive preadolescents and young adolescents, i.e., the primary target population for HPV vaccination. Obviously, the V501-018 trial population was far too small to provide a reliable measure of safety. This is especially true for conditions of greatest interest, e.g., autoimmune diseases, which are sometimes triggered by vaccinations [10-12], and for which the baseline prevalence in the general population is low [13, 14]. V501-018 study results [7, 8] therefore provide no assurance in the safety of the Gardasil vaccine.

Revised manuscript:

Notably, unlike other V501 trials, V501-018 evaluated Gardasil safety and efficacy in sexually naive preadolescent and adolescent girls which were the primary target population for HPV vaccination. Nonetheless, only 1,781 children between 9 and 15 years of age were included in this trial; both male and female who were randomized in a 2:1 ratio to receive either Gardasil or the “placebo.” The effect of this randomization was that only 617 girls received the Gardasil vaccine, and 322 received the “placebo” [8]. By contrast, the largest pre-licensure Gardasil trial V501-015 (the FUTURE II trial), recruited 12,167 subjects, all females between 15 and 26 years of age, who were randomized in a 1:1 ratio to receive either Gardasil or the AAHS injection [9]. It is thus highly questionable whether the V501-018 trial provided a reliable measure of safety for Gardasil given the small size of its study population.

3. Has AAHS been used in other vaccine trials and if so, is there evidence that it is associated with adverse effects?

Answer: Revised section #6 addresses that very question. In particular, the documentary evidence we provided shows that Merck was not transparent about the identity of AAHS as the adjuvant they used in several vaccines that predated Gardasil, but rather, Merck consistently and incorrectly stated to the U.S. and the European regulatory agencies that the adjuvant in these vaccines was aluminum hydroxide and not AAHS. In light of this fact, any claim made by Merck and the regulators that the safety of AAHS is “well characterised” lacks support.

4. In discussing global safety issues from HPV vaccines are the authors just referring to symptoms from the Merck vaccine or from vaccines made by other manufacturers? If the latter don't use the same aluminum adjuvant what would be causing the safety problems?

Answer: Even though our analysis focused only on Merck’s two HPV vaccines, there is evidence that the GSK’s bivalent HPV vaccine Cervarix is associated with a similar profile of adverse reactions. The reason for this is that both Merck’s and GSK’s HPV vaccines contain a unique combination of potent aluminum adjuvant formulations, and highly immunogenic VLPs with many peptide sequences similar to those found in human antigens. Therefore, it seems plausible that due to this shared molecular mimicry, both Gardasil and Cervarix are able to trigger a similar profile of harms in susceptible individuals.

Cervarix moreover seems to be even more reactogenic than Gardasil. We believe the reason for this is that Cervarix contains an even more potent adjuvant than AAHS, namely – a combination of aluminum oxyhydroxide and the toll-like receptor 4 agonist monophosphoryl lipid A (MPL). In head-2-head studies comparing Gardasil and Cervarix, the latter has consistently induced higher levels of anti-HPV antibodies, and showed somewhat higher reactogenicty.

References:

[1] Leung TF, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and 4vHPV vaccine administered according to two- or three-dose schedules in girls aged 9-14 years: Results to month 36 from a randomized trial. Vaccine. 2018 Jan 2;36(1):98-106.

[2] Leung TF, et al. Comparative immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine administered according to 2- and 3-dose schedules in girls aged 9-14 years: Results to month 12 from a randomized trial. Human vaccines & immunotherapeutics. 2015;11(7):1689-702.

[3] Einstein MH, et al. Comparison of long-term immunogenicity and safety of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine and HPV-6/11/16/18 vaccine in healthy women aged 18-45 years: end-of-study analysis of a Phase III randomized trial. Human vaccines & immunotherapeutics. 2014;10(12):3435-45.

We further agree with the reasoning by Beppu et al (2017; reference #82 in our paper):

"The reason why HPV vaccines cause these characteristic adverse effects remains to be studied in the future, but one of the most plausible explanations is that these vaccines are designed to maintain an extremely high antibody titre over a long period of time. Since prolonged inflammatory reactions associated with infection are known to cause autoimmune diseases and worsening of autoimmune reactions (14), longtime antigen stimulation with HPV vaccines might also induce complex autoimmune reactions via a mechanism similar to that seen with prolonged infection."

Finally, in many countries Gardasil is the HPV vaccine that is exclusively used, given that it covers more HPV strains than the bivalent HPV vaccine Cervarix. As a result of this, 90% of all HPV vaccine-related AEs reported to U.S. VAERS to date relate to Merck’s quadrivalent and nine-valent HPV vaccines, which is why we focused our analysis on them.

5. It appears that the term "Human Papillomavirus Vaccination Associated Neuroimmunopathic Syndrome" is a name proposed by a researcher rather than an "official" diagnosis.

Answer: HANS is not an “official” diagnosis indeed, but a diagnostic term proposed by Japanese researchers. In order to make that point more explicit we rephrased the original statement as follows: In Japan, “Human Papillomavirus Vaccination Associated Neuroimmunopathic Syndrome” (HANS) has been suggested as a diagnostic term for the alleged HPV vaccine-induced syndrome [90].

6. Although the safety of the HPV vaccine has been contested, it has also not been deemed unsafe by independent drug bulletins, e.g., Prescrire International (Nov. 2019, pages 270-2).

Answer: We were not able to gain access to this Prescrire article so we cannot provide specific comments. However, it should be taken into consideration that research by the independent pharmacovigilance experts from the WHO-collaborating Uppsala Monitoring Centre (UMC) indicates that there is a safety signal related to HPV vaccines that is worthy of further investigation. See:

[1] Chandler RE, Juhlin K, Fransson J, Caster O, Edwards IR, Noren GN. Current Safety Concerns with Human Papillomavirus Vaccine: A Cluster Analysis of Reports in VigiBase((R)). Drug Saf. 2017; 40(1):81-90.

[2] Chandler RE. Safety Concerns with HPV Vaccines Continue to Linger: Are Current Vaccine Pharmacovigilance Practices Sufficient? Drug Saf. 2017; 40(12):1167-1170.

**Reviewers’ response to the revision 1:**

**Reviewer #1**

**Reviewer Recommendation Term:** Accepted pending minor revisions

Are you willing to review the revision of this manuscript? Yes

Originality, novelty and significance of results: Good

Technical Quality of Work: Excellent

Comprehensibility and Presentation of Paper: Adequate

What is the overall impression: Good

Is the article significant to the field? [1-5] 5

Is the article appropriate for the journal? [1-5] 5

Is the work an original contribution? [1-5] 4

Are the conclusions adequately supported by the data? [1-5] 4

Is the research interesting and important? [1-5] 4

Is the level of English adequate? [1-5] 4

**Narrative (as sent to corresponding author):**

1. Is the paper logical with a concise ordering of ideas? [Yes]

2. Does the paper describe sound research methods, analysis & interpretation? [yes] Are limitations to the study included and discussed? [Yes, but not discussed at length]

3. In case the authors used established methodology, are the results of all previous studies been searched for and presented in a concise form? Has the current work had impact on the local practice and policies? [Not applicable]

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin. [yes; authors provided rationale for including old references which appears valid]

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit? [Risks are highlighted, and benefits are mentioned briefly]

6. What is the quality of the readability of the paper in English? Is the presentation/layout clear? Have the author guidelines been followed? [Readability is good, but the length of the paper is even longer than the previous version, thereby making comprehension difficult]

7. Are the ideas in the paper original and the significance of the research described? Are the results of likely interest to an international audience? [Yes]

8. Is the content timely? [Yes]

9. Does the paper build on and advance the knowledge of papers published in JRS and other international journals? If the paper describes methodology and results of original / experimental clinical (health) research, does it build on the existing knowledge, coming from systematic reviews? Have the searches for the rationale been rigorously done? [Appears so]

This represents my second review of the manuscript titled "A Reactogenic "Placebo" and the Ethics of Informed Consent in the Gardasil Vaccine Clinical Trials: A Case Study from Denmark" submitted to the IJRSM. The authors have responded to my queries from the first review satisfactorily, except to the point that the manuscript is exceedingly long. In fact, after responding to reviewers comments, the manuscript has become even longer. I believe the authors should work on making the manuscript concise, focussing on the core aspect of safety of AAHS, and try to remove some points that do not directly contribute. Though the authors have included a section on 'benefits', they have in fact discussed further risks under this heading as well: as a result, I am not inclined to call this review as a 'balanced opinion'. This makes it even more important to specifically call for Merck for a rebuttal.

Backed by these points, I believe this is an interesting and timely article, but is very lengthy, and deserves a publication; it will be beneficial if the authors consider reducing the length and make it an easy read.

**Reviewer #2**

**(None)**

**Reviewer #3**

**(Refused to review again)**

**Reviewer #4**

**Reviewer Recommendation Term:** Accepted pending minor revisions

Are you willing to review the revision of this manuscript? Yes

Originality, novelty and significance of results: Good

Technical Quality of Work: Good

Comprehensibility and Presentation of Paper: Good

What is the overall impression: Good

Is the article significant to the field? [1-5] 4

Is the article appropriate for the journal? [1-5] 4

Is the work an original contribution? [1-5] 5

Are the conclusions adequately supported by the data? [1-5] 3

Is the research interesting and important? [1-5] 4

Is the level of English adequate? [1-5] 5

**Narrative (as sent to corresponding author):**

The revisions by the authors have dealt with my initial concerns but I have a few other issues that need to be addressed.

1. Page 9: The statement that Danish girls enrolled in the study believing that they were doing a public good needs a reference or else it should be deleted.

2. Page 16: The authors are taking the report from the 2013 workshop and assuming that the statement in the report reflects the collective position of regulatory authorities about why they regard adjuvants as inactive. The link that the authors draw may be correct but do they have any solid proof of what they are saying?

3. Page 16: The authors seem to be implying that the concerns voiced by Franklyn Judson are the consensus view of the ACIP meeting. Is there documentation that the other members at the meeting agreed with Judson?

4. Page 18: The authors have not voiced an opinion about the benefit to harm ratio of Gardasil in low- and middle-income countries. Do they think that their conclusions also apply in those countries where 90% of the deaths from cervical cancer occur?

**Author’s reply to the reviews:**

RESPONSE TO Reviewer #1:

This represents my second review of the manuscript titled "A Reactogenic "Placebo" and the Ethics of Informed Consent in the Gardasil Vaccine Clinical Trials: A Case Study from Denmark" submitted to the IJRSM. The authors have responded to my queries from the first review satisfactorily, except to the point that the manuscript is exceedingly long. In fact, after responding to reviewers comments, the manuscript has become even longer. I believe the authors should work on making the manuscript concise, focussing on the core aspect of safety of AAHS, and try to remove some points that do not directly contribute. Though the authors have included a section on 'benefits', they have in fact discussed further risks under this heading as well: as a result, I am not inclined to call this review as a 'balanced opinion'. This makes it even more important to specifically call for Merck for a rebuttal.

Backed by these points, I believe this is an interesting and timely article, but is very lengthy, and deserves a publication; it will be beneficial if the authors consider reducing the length and make it an easy read.

Answer: We appreciate the reviewer’s comments and welcome a response from Merck.

We substantially shortened the manuscript: our second revision is 621 words shorter than our original submission, and 1089 words shorter than the first revision. Total word count including manuscript title, abstract, keywords, main body, and declarations (COI, funding & Acknowledgments) is 7110 words (excluded from the word count are only list or References, Tables and Figures). We hope that this is acceptable. The IJRSM word limit for review articles is 7500 words according to the guidelines for authors; however, we are aware that most review manuscripts are much shorter than that.

The only way we can think of to further substantially reduce the word count would be to entirely remove section #4 Aluminum adjuvant safety: What are the facts? The authors are however very reluctant to do so (unless absolutely required by the reviewer and/or the editor) because the main reason why aluminum adjuvants have historically been permitted as placebos in vaccine trials is the mistaken assumption that they are only associated with transient injection site-related adverse reactions. Therefore, it is a regulatory problem. This section also shows that our grief is not simply with the vaccine manufacturer against whom we have a lawsuit, but the regulators as well. Foremost, it is the regulatory system that needs reformation in this and many other areas, because the vaccine manufacturers will not engage in proper safety assessment of their products unless compelled by the regulators. A clear example of this is the fact that Merck only included an aluminum-free prelicensure Gardasil trial (protocol 018) because the FDA ultimately insisted they do so.

Moreover, this entire section also contributes to the originality of the paper (and in one reviewer’s judgment our manuscript somewhat lacked originality since similar ground was covered in two prior publications).

Adding the discussion on Merck’s lack of transparency in referring to the AAHS adjuvant used in several of their vaccines licensed before Gardasil as “aluminum hydroxide”, is another element that contributed substantially to the word count. That section, however, not only further contributes to the originality of our paper, but it is also clearly directly relevant to one of our main points, which is that the safety of AAHS has not been as “well characterised” as claimed by Merck and the EMA.

The submitted manuscript does not contain track changes of the deletions we made, but for most part we removed unnecessary details, and found ways to say the same thing in a more concise way.

There are several parts that are highlighted in yellow: mainly a few sentences that we judged were necessary to insert to strengthen our argument that the use of the AAHS “placebo” in Gardasil clinical trials was totally unwarranted (even according to the guidelines of the WHO Expert Panel, reference #3 Rid et al.)

We were also told by the Publisher to revise the Abstract and make it a structured Abstract with Background, Objective, Methods, Results and Conclusion sections. The necessary revisions made the abstract somewhat longer than the original but still within the Journal’s word limit for Abstracts of 300 words.

RESPONSE TO Reviewer #4: The revisions by the authors have dealt with my initial concerns but I have a few other issues that need to be addressed.

1. Page 9: The statement that Danish girls enrolled in the study believing that they were doing a public good needs a reference or else it should be deleted.

Answer: We deleted this sentence.

2. Page 16: The authors are taking the report from the 2013 workshop and assuming that the statement in the report reflects the collective position of regulatory authorities about why they regard adjuvants as inactive. The link that the authors draw may be correct but do they have any solid proof of what they are saying?

Answer: the cited article (reference #69) actually gives a solid proof that this is the position of the regulators:

“Whereas adjuvants are considered as an active component of an adjuvanted vaccine from an immunological viewpoint, the question has been raised as to whether adjuvants should be considered as active ingredients, or as excipients, with ensuing differential impact on regulatory requirements.

Marion Gruber (FDA, Rockville, Maryland, USA) discussed the regulatory pathways supporting the development and approval of vaccines formulated with novel adjuvants in the United States. There is a rigorous review of laboratory and clinical data to ensure vaccine safety, efficacy, purity and potency prior to marketing [74]. She drew attention to the fact that under the US regulatory considerations, adjuvants are considered as inactive ingredients, as described in the Code of Federal Regulations (CFR). Based on this classification, adjuvants are not licensed on their own but rather as a constituent material of vaccine formulations (21CFR 610.15).

…

Pieter Neels (EMA, United Kingdom) noted that whilst adjuvants are highly heterogeneous in their mechanisms of action, they are generally classified as excipients for regulatory purposes in the European Union.”

Marion Gruber was until very recently (2021) the director of the Office of Vaccines Research and Review at FDA’s Center for Biologics Evaluation and Research.

Pieter Neels, at the time of the 2013 workshop was a member of the Committee for Human Medicinal Products, in Belgium; Vice-Chair of the Committee for Human Medicinal Products, Vaccines Working Party; EU representative at various meetings and conferences including the World Health Organization; a General Practitioner, and Belgian Regulatory Agency member. One of his key area of expertise is detailed knowledge of the European approval system including the European Medicines Agency. Reference: https://ndareg.com/our-experts/dr-pieter-neels/

Therefore, it is hard to imagine that these two highly qualified experts in regulatory processes involved in licensing of vaccines would have been mistaken on such a basic issue.

To back up our statement further, we added another reference in the manuscript (reference #118) which is Marion Gruber’s and Valerie Marshall’s chapter in Stanley Plotkin’s book Vaccines, entitled Regulation and Testing of Vaccines. In this article Gruber and Marshall write:

“From a regulatory perspective, adjuvants are not considered active ingredients as defined in 21 CFR §210.3(b)(7) and vaccine adjuvants are not licensed separately.”

The related statement in our manuscript\*, therefore remains unchanged as we believe that it is an accurate presentation of facts, and is now backed up by the two references from which the excerpts cited above originate.

\*Another glaring inconsistency is that even though vaccine adjuvants are recognized and regarded as active components of a vaccine formulation from an immunological standpoint, for regulatory purposes they are regarded as inactive ingredients or excipients by both the U.S. FDA and the EMA [69, 118].

3. Page 16: The authors seem to be implying that the concerns voiced by Franklyn Judson are the consensus view of the ACIP meeting. Is there documentation that the other members at the meeting agreed with Judson?

Answer: We rephrased this sentence to make it clear that F. Judson’s comment does not necessarily represent ACIP consensus:

“Finally, during the discussion on HPV vaccines at the U.S. CDC ACIP meeting in October 24-25, 2007, one ACIP member (Franklyn Judson) commented that, “experience over the years with hepatitis B and other protein-alum combinations indicates that the reactogenic part is predominantly the alum and that studies that use alum minus the active protein are not really placebos in terms of reactogenicity” [118].

In the same paragraph we cited the WHO’s and EMA’s statements that affirm that adjuvants can have their own pharmacological and immunotoxic properties so that evaluation of pharmacokinetics and safety of the adjuvant alone are sometimes warranted. And from that we drew the conclusion that in view of such statements it is difficult to understand why vaccine manufacturers are still permitted to use adjuvants as placebos in clinical trials.

4. Page 18: The authors have not voiced an opinion about the benefit to harm ratio of Gardasil in low- and middle-income countries. Do they think that their conclusions also apply in those countries where 90% of the deaths from cervical cancer occur?

Answer: We limited our discussion to developed countries because that is where the Gardasil vaccine is most used, as most developing countries still cannot afford it. To properly address the risk versus benefit balance in developing countries would require a separate manuscript. Nonetheless, it is worth noting that highly reputable Indian oncology experts have voiced their opposition to implementation of mass HPV vaccination programs in India. One of their arguments is that in lower income countries where Pap screening practices are almost non-existent, the already limited funds should actually be used to establish these screening procedures because these interventions, unlike HPV vaccination, have a long established and proven record in reducing the burden of cervical cancer. They also pointed out that for any population coverage cervical screening will always detect more pre-cancers and cancers than vaccination can prevent.

References:

Gupta S, Kerkar RA, Dikshit R, Badwe RA. Is human papillomavirus vaccination likely to be a useful strategy in India? South Asian J Cancer. 2013;2(4):193-7.

Gupta S, Kerkar RA, Dikshit R, Badwe RA. HPV vaccination in India [Author's reply]. South Asian J Cancer. 2014;3(1):94-5.

**Reviewers’ response to the revision 2:**

**Reviewer #1**

**Reviewer Recommendation Term:** Accept as is

Are you willing to review the revision of this manuscript? Yes

Originality, novelty and significance of results: Good

Technical Quality of Work: Good

Comprehensibility and Presentation of Paper: Good

What is the overall impression: Good

Is the article significant to the field? [1-5] 5

Is the article appropriate for the journal? [1-5] 5

Is the work an original contribution? [1-5] 4

Are the conclusions adequately supported by the data? [1-5] 4

Is the research interesting and important? [1-5] 4

Is the level of English adequate? [1-5] 4

**Narrative (as sent to corresponding author):**

1. Is the paper logical with a concise ordering of ideas? Yes

2. Does the paper describe sound research methods, analysis & interpretation? Are limitations to the study included and discussed? Yes

3. In case the authors used established methodology, are the results of all previous studies been searched for and presented in a concise form? Has the current work had impact on the local practice and policies? Not applicable

4. Is the paper well referenced and using the Vancouver format? Are the majority of references within the last 3-5 years? Main findings should be traced back to their origin. yes; authors have provided rationale for using old references

5. Is the paper consistent with the purpose and scope of JRS? Does the paper discuss risk AND benefit? Risks are highlighted; benefits are mentioned in brief

6. What is the quality of the readability of the paper in English? Is the presentation/layout clear? Have the author guidelines been followed? Readability is good

7. Are the ideas in the paper original and the significance of the research described? Are the results of likely interest to an international audience? Yes

8. Is the content timely? Yes

9. Does the paper build on and advance the knowledge of papers published in JRS and other international journals? If the paper describes methodology and results of original / experimental clinical (health) research, does it build on the existing knowledge, coming from systematic reviews? Have the searches for the rationale been rigorously done? Appears so

**Reviewer #2**

**(None)**

**Reviewer #3**

**(None)**

**Reviewer #4**

**Reviewer Recommendation Term:** Accepted pending minor decisions

Are you willing to review the revision of this manuscript? Yes

Originality, novelty and significance of results: Good

Technical Quality of Work: Good

Comprehensibility and Presentation of Paper: Good

What is the overall impression: Good

Is the article significant to the field? [1-5] 4

Is the article appropriate for the journal? [1-5] 4

Is the work an original contribution? [1-5] 5

Are the conclusions adequately supported by the data? [1-5] 3

Is the research interesting and important? [1-5] 4

Is the level of English adequate? [1-5] 5

**Narrative (as sent to corresponding author):**

I think that this manuscript makes important points and that publication would start a meaningful review about the safety of aluminum based adjuvants, but there are a number of details that need to be dealt with before publication.

1. Page 3: While trials should be controlled, the control does not necessarily have to be a placebo, e.g., if the aim is to establish the superiority of one medicine over another.
2. Page 3: I agree that Pap smear screening is an effective way of detecting cervical cancer at an early stage but that is secondary prevention as opposed to vaccination which is primary prevention. Furthermore, even in high income countries only 63% of women receive effective Pap smear coverage (Gakidou et al. PLoS Med 2008;5(6): e132.) (This comment is not to imply that vaccination rates would be higher than screening rates.)
3. Page 7: I believe that the way that the authors use the term "dirty little secret" is misleading as it can imply to the reader that immunologists are deceptively keeping some knowledge secret from the wider community rather than trying to uncover the basis for the effect of aluminum adjuvants.
4. Page 8: On page 8 the authors refer to disclosures about why adjuvant toxicity is poorly understood and state that one of those reasons is the lack of "validated animal models that can adequately predict the health risks associated with adjuvants intended for human use". But in other places in the manuscript, they cite literature about animal studies to make the case for potential harms in humans from aluminum adjuvants, e.g., on page 4 where they use evidence from mice (references 20 and 23).
5. Page 14: The summary of the meeting in reference 69 does state that the FDA considers adjuvants as inactive ingredients and that in the EU they are considered excipients. However, it should be made clear that it is the authors' interpretation that this way of designating adjuvants is to spare manufacturers from conducting further clinical trials.
6. Page 17: In their response to reviewer 1 the authors state that they have an ongoing lawsuit against Merck and this should be acknowledged in the Conflict of Interest statement.

**THE ASSOCIATE EDITOR DECIDED TO ACCEPT THE PAPER**