Peer-Review comments and authors responses

Reviewer 1:
Comments:
If you send it for review, please address all the comments before submitting your paper.

We thank the reviewer for pointing this out. All comments in the manuscript are now addressed.

a) **METHODS**: *The biggest issue, or rather concern, is the exclusion of non-English materials and information campaigns. This exclusion results in only considering information campaigns in the U.S., while the authors themselves state that the biggest problem occurs in other parts of the world. To draw conclusions about those areas where the need is greatest, it could be beneficial to take a broader approach to selecting source materials. When planning such work from scratch in a multinational team such as PPCR GP it could be beneficial to consider multiple language sources.*

We appreciate the reviewer's suggestion. We agree that the inclusion of multiple language sources would probably lead to the retrieval of articles from more regions in the world. However, in the last few years, a shift toward English language publications has been observed, even from non-native English countries and it has been stated that it is most likely not a cause of bias in systematic reviews (Dobrescu et a. 2021). As shown in Table 1 of our study, we did achieve representativeness from a variety of countries, even with the strict language criteria. Given the time and resources constraints in this project, we believe that the hypothetical gain in number of articles and representativeness would not justify a broader language inclusion criteria.

Restricting evidence syntheses of interventions to English-language publications is a viable methodological shortcut for most medical topics: a systematic review. Dobrescu AI et al., Journal of Clinical Epidemiology, Volume 137, 209 - 217, https://doi.org/10.1016/j.jclinepi.2021.04.012.

b) **DISCUSSION**: *A good discussion should include: A brief recap of your key results. Interpretations: What do your results mean? Implications: Why do your results matter? Limitations: What can't your results tell us?*
In recommendations, avenues for further studies or analyses. Please make sure you have it all covered in your discussion. The impression is you could say more about the limitations of your review.

We have updated the discussion to ensure that the aforementioned sections are included, with emphasis on the limitations.

It now reads:

- Interpretation: “Our findings indicate that digital approaches such as text messages, video content, web-based information, and social media platforms show some effectiveness when used to improve HPV vaccination intention and, to a lesser extent, immunization uptake.”

- Implication: “ These findings broaden the tools available to public health policy makers fighting against this prevalent cause of morbidity, worldwide.”

- Recommendation: “Future research should aim to overcome these limitations with a diverse socio-economic and ethnic representation, strategies for long-term behavioral change, and effective translation from intention into HPV vaccination uptake/”

- Limitations: “There were some limitations to our study. Several articles measured only vaccination intention, which is known to be biased by the questionnaire measuring this outcome (Fishman et al., 2024). Moreover, intention did not entirely translate into increased vaccination rates. Only a few studies included reported previous HPV vaccination rate and knowledge, which could clearly influence HPV intention or uptake outcomes. Finally, gaming intervention was not included by the search strategy of our systematic review and it could be explored in future research.

  The reviewed studies share common limitations that are potential sources of bias leading to effect size overestimation – lack of blinding and high attrition rates –, or underestimation – small sample sizes and short-term follow-ups. In addition, limitations to the external validity could arise from the exclusively female population and homogeneous middle to upper-middle-class economic backgrounds in some studies. It remains unclear whether digital media would have a different effect on these underrepresented populations.“

c) **RESULTS/DISCUSSION**: *The potential biases in the analyzed studies could impact the results of the mini-review. You could discuss the risk of bias in the included studies and explain how potential biases, such as the exclusion of non-English papers, may have influenced the findings. Additionally, provide recommendations for improving the design of future studies.*
A more extensive discussion on how the results could be influenced by the previously mentioned limitations was included. It now reads:
   - “The reviewed studies share common limitations that are potential sources of bias leading to effect size overestimation – lack of blinding and high attrition rates –, or underestimation – small sample sizes and short-term follow-ups. In addition, limitations to the external validity could arise from the exclusively female population and homogeneous middle to upper-middle-class economic backgrounds in some studies. It remains unclear whether digital media would have a different effect on these underrepresented populations.

     Future research should aim to overcome these limitations with a diverse socio-economic and ethnic representation, strategies for long-term behavioral change, and effective translation from intention into HPV vaccination uptake. “

Comments: *Please also ensure that the language used in the mini-review is clear and precise.*

Writing was reviewed and proofread to assure fluency, clarity and precision.

Reviewer 2:

I believe that the manuscript could benefit from some revisions to enhance its clarity and comprehensiveness.

We appreciate your comments and feedback. We have restructured the text and improved the information flow of some sections.

Reviewer 3:

Comments:

a) **ABSTRACT**: *Please adjust the abstract according to the PPCR journal guidelines. The Maximum length is 250 words.*

We appreciate your feedback and thank you for bringing this to our attention. A thorough review of the abstract was performed. it now fits the PPCR journal guidelines and reads:

"Background: Human papillomavirus (HPV) is a preventable sexually transmitted infection and a leading cause of cervical cancer, with high global prevalence, especially in low- and mid-income countries (LMIC). Although HPV immunization has been shown to reduce cancer incidence, vaccination uptake remains insufficient. Digital media offers a promising avenue to address vaccine hesitancy and improve vaccination rates among adolescents and their parents.

Objective: To evaluate the effectiveness of digital media interventions on HPV vaccination rate and intention.

Methods: We undertook a comprehensive search for PubMed, Scopus, Web of Science, and Cochrane databases, through May 2024. After including Randomized Controlled Trials (RCTs) and observational studies (OS) focusing on adolescents, young adults (9-26 years) and their parents, we investigated the impact of digital interventions on HPV vaccination rate and intention. Quality assessment was conducted using the Cochrane Risk of Bias 2 tool for RCTs and an adapted Newcastle-Ottawa Scale for OS. Data extraction included study design, demographics, intervention types, and outcomes.

Results: From 2350 records, 23 studies (19 RCTs and 4 OSs) met the inclusion criteria. Digital interventions (SMS, mobile apps, video, and web-based platforms) increased HPV vaccination intention in 46% of studies – Odds Ratio up to 2.5 –, and uptake in 27% – Odds Ratio up to 1.82.

Conclusion: Digital interventions showed some potential in increasing short-term HPV vaccination intention, and less expressively, vaccination rates. Future research should focus on long-term strategies to improve HPV immunization uptake."

b) **METHODS**:

- *The inclusion criteria should be clear. Please revise this paragraph to describe each criterion.*

  A more concise and clear inclusion criteria was updated: “The inclusion criteria for participants was being either female or male early adolescents and young adults (9-26 years old) and/or their parents,(...)”

- *Please revise the following sentence for cohesion and comprehension "any or no digital intervention as defined by the World Health Organization to include a specific technology function designed to address a health system challenge, such as ensuring vaccinations or follow-up appointments.”*

  We have reviewed the wording of the sentence. It now reads: “We included studies with any or no digital intervention, as defined by the WHO – specific technology functions designed to address health system challenges, such as ensuring vaccinations or follow-up appointments (WHO, 2023)”

- *Also, “young adults” are currently not described in this section, however in the abstract and throughout the manuscript this group of studied population seem to be included. Please revise.*

  The updated inclusion criteria addresses your comment. It now reads: “The inclusion criteria (...) early adolescents and young adults (9-26 years old) (...)

- Please provide the reference used to define “early to late adolescents (9-26 years old)”. WHO defines adolescent from 10-19 years of age “

  The sentence was reformulated for better clarity. It now reads: “early adolescents and young adults (9-26 years old) and/or their parents, as this age range aligns with the primary target population for HPV vaccination recommended by the WHO (WHO, 2017).”

c) **RESULTS**: *Please consider summarizing the text presented in the Results section. Each subsection should have a summary of the papers main findings considering each selected variable. For example, a specific subsection entitled “HPV vaccination uptake or intention” could be more informative.”*

We appreciate your suggestion. We have included the subsections to further improve information flow and clarity. It now reads:

- “*Description of the studies”*
- *“Population”*
- *“Intervention/ Exposure and control characteristics”*
- *“Outcomes and main results”*

- *"Assessment of risk of bias in individual studies"*

d) **DISCUSSION/RESULTS**:

- *Intervention/ Exposure and Control Characteristics: There are some authors' comments in this section. This authors' discussion should have been settled before submission. Also, this mini review seems to be missing a final text review. Please address this.*

Thank you for bringing this issue to our attention. All comments were settled and a final text review was performed.

- *Consider including a specific section for confounders*.

It now reads: "The cross-sectional studies listed a variety of confounders, ranging from parental beliefs and knowledge to socio-demographic factors such as age, gender, education level, socioeconomic status, and ethnicity. Health access and patients' trust on healthcare or other sources, community type, health and media literacy, prior vaccination status, internet usage, parental health behaviors, and social media engagement were also listed as covariates."

- *In the paragraph: "Several factors, including employment status,(…) mentioned." It is not clear if this paragraph summarizes all four observational studies' results. It should be considering all the cross-sectional studies' results together. Please revise.*

After revision, it now reads: "Several factors, including employment status, political affiliation, education level, household income and Twitter (X) usage, were significantly associated with HPV vaccination intention/uptake but those effects were no longer significantly associated in the multivariate model, after adjustment (Manganello et al., 2023)."

- *For the following sentence: "In the adjusted model for HPV vaccine uptake intention, only HPV vaccine confidence remained significantly associated with HPV vaccine intention". The mini review is aimed at digital interventions/exposures, thus the association to be studied should be between social media use and vaccine intention. Please clarify why vaccine confidence and intention was described here.*

We agree with your observation. The results were removed from the manuscript since it was not relevant for the study objectives.

- *Please check this statement: "The specific covariates used for adjustment were not mentioned" for the Manganello et al. 2023 study. This study clearly shows a table with unadjusted and adjusted variables."*

We thank the reviewer for bringing this to our attention. After proofreading the manuscript and double checking the data extracted from the articles, we have found the source of the error and promptly corrected it. It now reads: "Several factors, including employment status, political affiliation, education level, household income and Twitter (X) usage, were significantly associated with HPV vaccination intention/uptake but those effects were no longer significantly associated in the multivariate model, after adjustment (Manganello et al., 2023)."

- *"Our findings indicate that digital approaches such as text messages, video content, web-based information, and social media platforms might represent great tools when used to improve HPV vaccination intention."*
  Consider revising this statement. According to the mini review results, nearly 50% of the RCTs saw no significant improvement in any outcome.

Based on the reviewer comment, the sentence was updated to better reflect the results of the mini-review. It now reads*: "*Our findings indicate that digital approaches such as text messages, video content, web-based information, and social media platforms show some effectiveness when used to improve HPV vaccination intention and, to a lesser extent, immunization uptake."

- *"Finally, several studies measured only vaccination intention, which, as noted above, did not entirely translate into increased vaccination rates."*
  Have you considered narrowing it down the outcome to only vaccination uptake? There was too much heterogeneity in the interventions/exposures and the measured outcomes, considering only vaccination uptake can contribute to a more concise and coherent mini review.

We agree with the reviewer questioning on the heterogeneity in interventions/exposures in the selected articles. However, a considerable proportion of vaccination campaigns and government policies measure its effectiveness based on intention alone. We, therefore, decided to include both uptake and intention outcomes exactly to highlight the contrast between both outcomes. We have aimed to bring to the reader's attention to the fact that intention rarely translates to uptake after interventions, and that this ubiquitous "quality measure" may be inappropriate for public-health monitoring.

- *"In addition, a variety of world regions and ethnicities were represented". This statement is contrasting with the previous paragraph.*

The following sentence was included for better clarity: "In addition, limitations to the external validity could arise from the exclusively female population and homogeneous middle to upper-middle-class economic backgrounds in some studies. It remains unclear whether digital media would have a different effect on these underrepresented populations.

- *"Digital interventions have shown great potential in increasing HPV vaccination intentions". As described above, consider revising this statement. According to the*

mini review results, nearly 50% of the RCTs saw no significant improvement in any outcome.

"Digital interventions have shown some potential in increasing HPV vaccination intention, influencing vaccination rates to a lesser extent."

e) **FORMAT**:

- *Please check your reference format, the PPCR journal uses the APA system (author's last name followed by the date of publication).*

All references were updated to the APA system, as required by the PPCR journal guidelines.

- *Please consider removing the PICOS.*

We appreciate your suggestion. PICOS were removed from the supplementary material.

- *Please check the word count limit after adjusting the references. This mini review is excessively long, it should be no longer than 1500 words.*

We thank you for the suggestion. We have updated the text to improve the flow of information making it lighter for the reader. We have rechecked the literature and believe a 3000 word count is in-line with most journals for mini-reviews.

- *To improve clarity, please consider defining the terms 'vaccine intention' and describing how this outcome was measured in the studies.*

Addressing your comment, we have included the following sentence in methods section: "Intention to vaccinate was measured by different questions in each study." and the following sentence in the limitations section: "There were some limitations to our study. Several articles measured only vaccination intention, which is known to be biased by the questionnaire measuring this outcome (Fishman et al., 2024)."

Fishman, J., Schaefer, K.A., Scheitrum, D. et al. Common measures of vaccination intention generate substantially different estimates that can reduce predictive validity. Sci Rep 14, 22843 (2024). https://doi.org/10.1038/s41598-024-69129-5

Reviewer 4

Comments:

a) **ABSTRACT**:

The abstract could be more specific in reporting numerical results (e.g., percentage improvement in vaccination rates). This would provide a clearer understanding of the magnitude of the effect of digital interventions.

From 2350 records, 23 studies (19 RCTs and 4 OSs) met the inclusion criteria. Digital

interventions (SMS, mobile apps, video, and web-based platforms) increased HPV vaccination intention in 46% of studies – Odds Ratio up to 2.5 –, and uptake in 27% – Odds Ratio up to 1.82."

b) **INTRODUCTION**: *The introduction is supported by precise citations; however, it would be helpful to briefly summarize the findings from the cited sources.*

We have included the relevant findings to the text. It now reads: "Despite these HPV vaccination programs being initiated in 2006, between 2008-2020, HPV vaccination coverage in high-income countries declined from 89% to 41%, while in low- and middle-income countries, increased from 0.8% to 5.2%, remaining insufficient (Dorji et al., 2021). In addition, competing health priorities may be inferred from WHO'S data on HPV vaccination coverage of 2018 – it was missing from over half of members' reports."

- *The introduction is well structured, and it provides the necessary background information, however a "bridge sentence" would help to move from the concept of global HPV prevalence to discussing the impact of digital media interventions in a smoother manner.*

The following bridge sentence was included, based on your suggestion. "Given the widespread prevalence of HPV and the persistent challenges in achieving adequate vaccination coverage, it is crucial to explore innovative approaches to overcome known barriers of vaccination uptake, including digital intervention (Spayne et al., 2021)."

- *The research gap is identified but it could be made more explicit by stating why it is important to study digital media interventions in various global settings, not just focusing on previous studies' limitations.*

We have made the research gap more explicit. It now reads: "Therefore, it is essential to investigate the broader effectiveness of diverse digital interventions on HPV immunization across distinct cultural and socioeconomic contexts."

- *The first sentence could be rephrased. Suggestion for improvement:*

"This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines."

We thank you for your suggestion and we reformulated the sentence accordingly.

c) **METHODS**:

- This sentence could be simplified for readability. “The quality assessments were assessed using the Cochrane Risk of Bias 2 tool and an adapted Newcastle-Ottawa Scale for RCTs and observational studies respectively, while data extraction focused on study design, demographics, intervention types, and outcomes.”

We have updated the sentence for readability as you suggested. It now reads: “Quality assessment was conducted using the Cochrane Risk of Bias 2 tool for RCTs and an adapted Newcastle-Ottawa Scale for OS. Data extraction included study design, demographics, intervention types, and outcomes.”

- *The Inclusion and exclusion criteria could be simplified for readability*

Based on the reviewer’s comments, we have updated the inclusion and exclusion criteria. It now reads: “The inclusion criteria for participants was being either female or male early adolescents and young adults (9-26 years old) and/or their parents, as this age range aligns with the primary target population for HPV vaccination recommended by the WHO (WHO, 2017). We included studies with any or no digital intervention, as defined by the WHO – specific technology functions designed to address health system challenges, such as ensuring vaccinations or follow-up appointments (WHO, 2023). The primary outcomes of interest were vaccination intention and vaccination rates. Intention to vaccinate was measured by different questions in each study. Eligible study designs included randomized controlled trials (RCTs) and observational studies.

We excluded trials that lacked control groups, involved participants outside the specified age range, did not obtain proper consent, were published in languages other than English or with unavailable full texts.

- *What was the rationale behind choosing the age range of 9-26 years for adolescents?*

We have included sources justifying the age range of our study. It now reads: “The inclusion criteria for participants was being either female or male early adolescents and young adults (9-26 years old) and/or their parents, as this age range aligns with the primary target population for HPV vaccination recommended by the WHO (WHO, 2017).”

WHO, W. H. O. (2017). Human papillomavirus vaccines: WHO position paper, May 2017–Recommendations. Vaccine, 35(43), 5753–5755. https://doi.org/10.1016/j.vaccine.2017.05.069

- *Regarding studies in languages other than English, did you consider using translation services, or was this exclusion deliberate? If it was deliberate, could you explain the reasoning behind this choice?*

We appreciate your comments and questions. We indeed considered using translation services, since including multiple language sources would probably lead to more articles included from more world regions – increasing representativity. However, in the last few years, a shift toward

English language publications has been observed even from non-native English countries and it has been stated that it is most likely not a cause of bias in systematic reviews (Dobrescu et a. 2021). As shown in Table 1 of our study, we did achieve representativeness from a variety of countries, even with the strict language criteria. Given the time and resources constraints in this project, we believe that the small hypothetical gain in number of articles and representativeness would not justify a broader language inclusion criteria.

> Restricting evidence syntheses of interventions to English-language publications is a viable methodological shortcut for most medical topics: a systematic review. Dobrescu AI et al., Journal of Clinical Epidemiology, Volume 137, 209 - 217, https://doi.org/10.1016/j.jclinepi.2021.04.012.

- *You mentioned that duplicates were excluded, but how did you identify and manage duplicate records during the review process?*

We recognize the need for extensive and exhaustive description of the methods used, as suggested by the reviewer. However, since we have stated that we have used a specialized systematic review software (COVIDENCE) for data selection and extraction, we believe that it should be clear for the reader that duplications were automatically excluded by the software.

d) **RESULTS**:

- *Your results section is detailed and provides a comprehensive overview of the studies included in your systematic review. You can find some minor suggestions in the attached document (track change mode)*

We appreciate you bringing these minor suggestions to our attention. All corrections were made in the final manuscript.

- *Why were gaming-based interventions not included, and is there a possibility that emerging research might suggest a different role for them? Would it be beneficial to mention that future reviews should consider including these interventions?*

We have reorganized the sentence flow and included some justification on why gaming-based interventions were not mentioned in our review. It now reads: "Finally, gaming intervention was not included by the search strategy of our systematic review and it could be explored in future research."

e) **DISCUSSION***:*

- *Could you delve deeper into how these limitations might have specifically impacted the findings? For example, how might the exclusion of males and lower socio-economic groups skew the results? Could this have influenced the apparent effectiveness of certain digital interventions?. The section on the limitations of generalizability due to the homogeneity of study participants is important but could*

be expanded. The impact of excluding diverse populations, particularly from underrepresented regions like Africa, is briefly mentioned but not fully explored.

We share the uncertainty raised by the reviewer, and make it more explicit in the text. It now reads: "The reviewed studies share common limitations that are potential sources of bias leading to effect size overestimation – lack of blinding and high attrition rates –, or underestimation – small sample sizes and short-term follow-ups. In addition, limitations to the external validity could arise from the exclusively female population and homogeneous middle to upper-middle-class economic backgrounds in some studies. It remains unclear whether digital media would have a different effect on these underrepresented populations."

- *The call for future studies to ensure diverse representation is important but somewhat general. More specific recommendations could strengthen this section. Could you specify which populations or regions should be prioritized in future research? Additionally, how might future studies be designed to better assess long-term outcomes and actual vaccination uptake?*

More specific strategies were included. It now reads: "Digital interventions have shown some potential in increasing HPV vaccination intention, influencing vaccination rates to a lesser extent. However, low-income countries, and male patients were not extensively studied. Policies and funding should be directed to research focusing on these populations, not just as a matter of equity but also of public health necessity, given the high burden of HPV-related diseases in these groups."

- *The discussion makes a case for the potential impact of digital interventions but could more explicitly address the practical implications for public health strategies*

Practical implications of digital interventions on public health were included in the text. It now reads "Healthcare access and geographic regions, trusted sources of information and trust in the medical provider are associated with vaccine behavior and decisions (McRee AL et al., 2012) (Manganello et al., 2023). In addition, specific internet usage patterns, engagement with social media content, and peer influence, especially how information is framed and shared are also important factors to be considered when analyzing immunization behaviors (Sommariva et al., 2023; McRee AL et al., 2012). Finally, the cross-sectional studies listed a variety of confounders, highlighting the multifaceted nature of vaccination decision-making and the wide range of factors to be considered before considering public health policies aimed at vaccination uptake and intention."

- *How might the findings influence future public health campaigns or policies? Are there specific recommendations for how digital interventions could be implemented or improved in practice?*

We included one specific successful strategy: "One interesting strategy to address these issues could be the one used by Dixon et al., 2019, offering the video intervention in a setting with readily

available vaccines, such as at the health facility waiting-room, substantially improving HPV immunization rates."

f) **CONCLUSION**: *The conclusion could make a stronger case for the urgent need to address these gaps in research. For instance, the paper could argue that increasing HPV vaccination rates in underrepresented populations is not just a matter of equity but also of public health necessity, given the high burden of HPV-related diseases in these groups. This could lead to a call for more funding and resources to be directed towards research and interventions in low-income countries and among male patients.*

Conclusion was restructured to emphasize the urgent need to address the gaps found in the study. It now reads: "Digital interventions have shown some potential in increasing HPV vaccination intention, influencing vaccination rates to a lesser extent. However, low-income countries, and male patients were not extensively studied. Policies and funding should be directed to research focusing on these populations, not just as a matter of equity but also of public health necessity, given the high burden of HPV-related diseases in these groups. "

Reviewer 5:
Comments:

a) *Please fill the affiliations.*
All affiliations were filled.

b) *That's the main idea of GP, but please be careful with such statements. It's important to recognize when someone has made a greater effort. For example, someone may be the lead or the first author, etc.*
all authors satisfy the ICMJE's criteria for authorship.

https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

c) **METHODS**: *Quality assessments were conducted using the Cochrane Risk of Bias 2 tool for RCTs and an adapted Newcastle-Ottawa Scale for observational studies. Data extraction focused on study design, demographics, intervention types, and outcomes.*
It now reads: "Quality assessment was conducted using the Cochrane Risk of Bias 2 tool for RCTs and an adapted Newcastle-Ottawa Scale for OS. Data extraction included study design, demographics, intervention types, and outcomes."

- KEYWORDS. *Maybe you could consider adding here telemedical solution?*

We appreciate your suggestion. Since keywords are limited to a number of six, we believe the current keywords would better represent the study.

- *Nevertheless, 95% (n=18) of the trials were conducted in the United States and the majority of the studies could not be conclusively considered low risk regarding methodological bias". Wasn't it because of choice English material only?*

The great number of studies performed in the United States could be certainly explained by the English language of the material. However, the bias (and, thus, the research gap) persists, even if we understand the reason for it happening

- *suggestion: The inclusion criteria targeted early to late adolescents (9-26 years old) and/or their parents. We included studies with any or no digital intervention, as defined by the World Health Organization, which includes specific technology functions designed to address health system challenges, such as ensuring vaccinations or follow-up appointments.11 The primary outcomes of interest were vaccination intentions and vaccination rates. Eligible study types included randomized controlled trials (RCTs) and observational studies*. We excluded studies that lacked control groups, involved participants outside the specified age range, did not obtain proper consent, or were published in languages other than English.

We've updated the text taking all reviewers suggestion into account: "The inclusion criteria for participants was being either female or male early adolescents and young adults (9-26 years old) and/or their parents, as this age range aligns with the primary target population for HPV vaccination recommended by the WHO (WHO, 2017). We included studies with any or no digital intervention, as defined by the WHO – specific technology functions designed to address health system challenges, such as ensuring vaccinations or follow-up appointments (WHO, 2023). The primary outcomes of interest were vaccination intention and vaccination rates. Intention to vaccinate was measured by different questions in each study. Eligible study designs included randomized controlled trials (RCTs) and observational studies.

We excluded trials that lacked control groups, involved participants outside the specified age range, did not obtain proper consent, were published in languages other than English or with unavailable full texts."

- *"languages other than English". In this particular case, it might be worth considering the inclusion of other languages. As the PPCR group, you have a unique opportunity to ask friends around the world if they know of, or can check if, similar campaigns were conducted in their countries."*

We appreciate the reviewer's suggestion. We agree that the inclusion of multiple language sources would probably lead to the retrieval of articles from more regions in the world. However, in the last few years, a shift toward English language publications has been observed, even from non-native English countries and it has been stated that it is most likely not a cause of bias in systematic reviews (Dobrescu et a. 2021). As shown in Table 1 of our study, we did achieve representativeness from a variety of countries, even with the strict language criteria. Given the time and resources constraints in this project, we believe that the hypothetical gain in number of articles and representativeness would not justify a broader language inclusion criteria.

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- Suggestion: Four cross-sectional studies were conducted, three in the USA and one in Italy, involving a total of 2,658 participants."

Four cross-sectional studies were retrieved, three in the USA and one in Italy, involving a total of 2,658 participants

- *"and independent variables that were statistically significant. suggestion: statistically significant independent variables"*

This paragraph was reformulated to improve readability: Several factors, including employment status, political affiliation, education level, household income and Twitter (X) usage, were significantly associated with HPV vaccination intention/uptake but those effects were no longer significantly associated in the multivariate model, after adjustment (Manganello et al., 2023)."

- *Negative content seemed to hinder exposure to positive content influence in parent's decisions. All models were adjusted for child's sex, child's age group, parent's race/ethnicity, parent's education, and parent's age group" Suggestion: "Negative content appeared to reduce the impact of positive content on parents' decision-making. All models were adjusted for the child's sex and age group, as well as the parent's race/ethnicity, education, and age group."*

Taking into account the editor's comments, this paragraph now reads: Social media comments' valence (positive vs. negative) or format (narrative vs. descriptive) played a role in parents' decision: negative narrative comments, by sharing personal stories about risks and concerns, increased vaccination intention (Zhang et al., 2019)

- *"high percentage of non-responders and failed to report adjustment for confounders" Suggestion: "high non-response rate and did not report adjustments for confounding factors."*

Updated.

- *"Overall, one study had a high risk of bias[38] and the remaining (n=3), some concerns[35–37]" Suggestion: Overall, one study was judged to have a high risk of bias, while the remaining three (n=3) raised some concerns.*

Updated

d) **DISCUSSION**: *By Anna Skotny: A good discussion should include: A brief recap of your key results. Interpretations: What do your results mean? Implications: Why do your results matter? Limitations: What can't your results tell us? And recommendations: Avenues for further studies or analyses. Please make sure you have it all cover in your discussion.*

We have reformulated the discussion section. It now addresses the results recap and its interpretations with implications. In addition the limitations and recommendations were updated.

Reviewer 6:

Comments**:**

This sentence is hard to read, please rewrite providing better clarity.

"The quality assessments were assessed using the Cochrane Risk of Bias 2 tool and an adapted Newcastle-Ottawa Scale for RCTs and observational studies respectively, while data extraction focused on study design, demographics, intervention types, and outcomes."

We appreciate the feedback and comments directed to the manuscript. After thoroughly considering your suggestions, we have made the following updates in text:

- It now reads: "Quality assessment was conducted using the Cochrane Risk of Bias 2 tool for RCTs and an adapted Newcastle-Ottawa Scale for OS. Data extraction included study design, demographics, intervention types, and outcomes."

"Moreover, data for HPV vaccination coverage in 2018 was missing for over half of WHO members' reports. 5" why was it missing and what does it mean in the context of this mini review? I advise you to add a comment/conclusion to this sentence or delete it.

- The sentence was reformulated. It now reads: " In addition, competing health priorities may be inferred from WHO'S data on HPV vaccination coverage of 2018 – it was missing from over half of members' reports."

INTRODUCTION: *Show the existing gap and the aim of the mini-review more clearly (e.g., this part is confusing "regardless of the setting or device[…]").*

- Reformulated. It now reads: "A recent systematic review published in 2023, included experimental trials and found a variety of digital interventions including video-games. Nevertheless, it measured narrow outcomes such as HPV knowledge, instead of HPV vaccination rate; and populations were not described in detail, thus limiting the external validity of the results (Choi et al., 2023)."

I suggest adding very brief information about gender and age in the context of HPV vaccination in the introduction. This can give a better background for whom digital technologies are addressed, especially since there are some significant gender differences, e.g., you report that 52.6 % of the analyzed RCTs included exclusively females.

- We have included the differences in HPV immunization recommendations, by gender. It now reads "Although cervical cancer prevention in reproductive age females has traditionally been the focus of such campaigns, since 2006, the World Health Organization (WHO) has expanded recommendations to include females up to 45 years old in certain circumstances, and males as a secondary target for HPV vaccination (WHO, 2017). Female-only programs have limitations as they overlook the spread of HPV through bisexual, same-sex contact, and digital or oral transmission, highlighting the need for a pan-gender approach to HPV vaccination (Dykens et al., 2023)."

METHODS: *Provide outcomes measured in previous studies (HPV knowledge, vaccination rate, or intention?)*

- Included accordingly. It now reads "The potential of social-media for HPV vaccination awareness and uptake has previously been reviewed, assessing a variety of outcomes such as immunization rates, intention, information/knowledge, motivation, and behavioral skills regarding HPV vaccination."

This sentence is very confusing: "The inclusion criteria included early to late adolescents (9-26 years old) and/or their parents, any or no digital intervention as defined by the World Health Organization to include a specific technology function designed to address a health system challenge, such as ensuring vaccinations or follow-up appointments.11"

- We have updated flow of information and clarity of sentence: "The inclusion criteria for participants was being either female or male early adolescents and young adults (9-26 years old) and/or their parents, as this age range aligns with the primary target population for HPV vaccination recommended by the WHO (WHO, 2017). We included studies with any or no digital intervention, as defined by the WHO – specific technology functions designed to address health system challenges, such as ensuring vaccinations or follow-up appointments (WHO, 2023). The primary outcomes of interest were vaccination intention and vaccination rates. Intention to vaccinate was measured by different questions in each study. Eligible study designs included randomized controlled trials (RCTs) and observational studies."

Table 1 - age has to be reported consequently in one unified way.

- Thank you for bringing this to our attention. It is now corrected.

AGE
N/A
45 (M)
N/A
18-46 (R)
13.19 (M)
11-18 (R)
16.47 (M)
11-17 (R)
30-59 (R)
43.64 (M)
24-62 (R)
35.39 (M)
40.8 (M)
12.2 (M)

AGE
Parents: 31-51 (R), Adolescents: 12.4 (M) 11-16 (R)
Parents 35.18 (M) Young adults: 23.9 (M)
Parents: 23 (M) Young adults: 12 (M)
15.35 (M)
19.12 (M) 18-22 (R) 18+ (R)
18-26 (R) 19.83 (M)

All used abbreviations have to be described under each table, this includes terms like Mean or Standard deviation.

- Thank you for this remark. We included all abbreviations as follows.
  - ***Table 1 -*** *Characteristics of the included studies.*
    M = mean; R = range; N/A = missing data.
    CNY, RMB = Chinese Yuan; USD = United States Dollars; JPY = Japanese Yen.

  - ***Table 2*****:** *Intervention, outcomes and risk of bias in RCTs.*

    HR = Hazard Ratio, OR = Odds Ratio, CI= Confidence Interval, MD= Mean Difference, t = student's t-statistic, p = p-value.

  - ***Table 3***: *Exposure, outcomes and risk of bias in Observational Studies.*

    M = Mean, OR = Adjusted Odds Ratio, MD = Mean difference, p = p-value.
    ** Segments classified by parental perception of digital feature importance 1 (Highest importance image-high text), 2 (highest image-high source/popularity, 8*

(highest image), 3 (highest text) , 4 (highest source), 5 (highest source-high text), 6 (highest text-highest source/popularity), 7 (high popularity-high source).

"mean age ranged from 11 to 26 years old for early-to-late adolescents and 22 to 62 for parents" is not correctly worded. The term mean refers to a single average value, not a range of values.

- The sentence was reworded for more clarity – referring to the range of each mean, found on each study. It now reads "The mean age of participants in each study ranged from 11 to 26 years-old for early-to-late adolescents and 22 to 62 for parents."

"Social media comments' valence (positive vs negative) or presentation (narrative vs descriptive) played a role in parents' decision and exposure to narrative comments appeared to increase perceived HPV risk, which was associated with vaccination intention34." - it would be better to specify these results, e.g., positive or negative valence was more effective?

- Results were specified. It now reads: "Social media comments' valence (positive vs. negative) or format (narrative vs. descriptive) played a role in parents' decision: negative narrative comments, by sharing personal stories about risks and concerns, increased vaccination intention (Zhang et al., 2019)."

DISCUSSION: *This section provides many interesting insights on digital interventions, however, the information should be provided with a better flow and clear transitions between paragraphs. It is advised to present limitations from most to least important ones.*

- The discussion section was reformulated aiming for a better flow of information with clear transitions between paragraphs. The paragraph on limitations was reworded according to the Editor's suggestion. It now reads:

- "There were some limitations to our study. Several articles measured only vaccination intention, which is known to be biased by the questionnaire measuring this outcome (Fishman et al., 2024). Moreover, intention did not entirely translate into increased vaccination rates. Only a few studies included reported previous HPV vaccination rate and knowledge, which could clearly influence HPV intention or uptake outcomes. Finally, gaming intervention was not included by the search strategy of our systematic review and it could be explored in future research.
  The reviewed studies share common limitations that are potential sources of bias leading to effect size overestimation – lack of blinding and high attrition rates –, or underestimation – small sample sizes and short-term follow-ups. In addition, limitations to the external validity could arise from the exclusively female population and homogeneous middle to upper-middle-class economic backgrounds in some studies. It remains unclear whether digital media would have a different effect on these underrepresented populations."

CONCLUSIONS: *Please present more precise and practical conclusions — why and what types of digital interventions should be used or investigated more? The last sentence is confusing.*

- We have rewritten the conclusion to reflect the Editor's comment, adding practical conclusions and improving clarity. It now reads: "Digital interventions have shown some potential in increasing HPV vaccination intention, influencing vaccination rates to a lesser extent. However, low-income countries, and male patients were not extensively studied. Policies and funding should be directed to research focusing on these populations, not just as a matter of equity but also of public health necessity, given the high burden of HPV-related diseases in these groups. "

A significant number of authors' affiliations is missing.

- corrected.

REFERENCES: *Please verify if all given references are correct — this is very important. Also, some comments have been left in the comments section of the document, what raised my concerns on that.*
References presents the wrong format, please take a look at the journal's guidelines.

- All references were updated according to PPCR journal guidelines. All references were double checked and comments were settled and solved. We apologize for the oversight.

GRAMMAR/FORMAT: *There are language, grammar, and punctuation errors in the text. It requires very careful revision.*

- The manuscript was thoroughly reviewed and proofread to correct the errors in text, including the ones pointed out by the Editor and reviewers.

We hope the updated manuscript will fit the Journal's highest standards. Kindly find it enclosed in this message.
We thank you again for considering our submission for publication in the Principles and Practice of Clinical Research Journal. We look forward to hearing from you soon.
Yours sincerely,

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