PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of papillomavirus in Brazil: a systematic review protocol.
AUTHORS	Colpani, Veronica; Bidinotto, Augusto; Falavigna, Maicon; Giozza, Silvana; Benzaken, Adele; Pimenta, Cristina; Maranhão, Ana; Domingues, Carla; Hammes, Luciano; WENDLAND, ELIANA

VERSION 1 - REVIEW

REVIEWER	Sarah Damery Institute of Applied Health Research, University of Birmingham, United Kingdom
REVIEW RETURNED	10-May-2016

GENERAL COMMENTS	This protocol outlines a proposed systematic review to assess the prevalence of HPV in Brazil. The protocol is in general quite well-written but rather brief and would benefit from some more detail being added to expand the authors' description of exactly what they intend to do. Detailed comments are below: 1. The protocol would benefit from review by a native English speaker. There are a number of spelling, grammatical and phrasing errors which an English reviewer would be able to correct. For example: Abstract (lines 46-48) "in Brazil there are no prevalence study considering a nationwide sample and has not been determined in many regions". This does not make sense in English and it would improve the comprehensibility of the manuscript if this and other sentences were rephrased. 2. How will the previously published review articles be identified? Do the authors assume that all such reviews will be returned by their searches, or will they attempt to identify existing reviews in another way? 3. It is not clear why the authors have chosen to use the GRADE criteria and an additional quality assessment tool when GRADE criteria encompass a measure of quality assessment (methodological rigour, risk of bias etc.) already. 4. The search strategy seems rather simplistic. This leads to a two-fold concern: first, the number of hits returned in each of the databases searched is likely to be very high and not very easy to screen given the lack of specific terms incorporated into the search. Second, the lack of specific terms may also mean that important studies are overlooked. Have the authors done any scoping searches to test this out? Are there important studies that the authors already know about that they can use to test whether their search is sensitive/specific enough? Even though the authors are not imposing language or date limits on their searches (which is

	beneficial), I am not confident that the search strategy will allow the authors to address their twin aims of establishing HPV prevalence in the general population and evaluating prevalence in individuals with premalignant and malignant lesions. 5. The authors recognise that a limitation may be variation between studies in terms of sample size, participants and sociodemographics and state that they will control the heterogeneity with statistical analyses, yet the methods do not adequately describe how such control of heterogeneity will be undertaken over and above assessing heterogeneity using the appropriate statistics. Assessing heterogeneity is different to controlling heterogeneity, so if the authors plan to do the latter rather than simply assessing the former, more information is needed as to how this will actually be done. 6. The statistics cited in the introduction appear to answer the authors' question: a review was undertaken in 2010 which assessed the prevalence of HPV infection in Brazil and the authors cite figures from this review when establishing the context for their study. If a review of prevalence was undertaken so recently, a) why are the authors not just performing an update of this recent review, and b) what do the authors feel their review will accomplish that has not already been established by Ayres et al in 2010? In other words, the protocol needs to make a more explicit case for why the present systematic review is a) needed and b) provides a useful addition to the literature or addresses gaps in the evidence base that have not yet been answered. The paragraph on page 10 that attempts to make the case for the originality of the current review (lines 199-203) is not convincing. For example, the assertion that the Ayres review was not broad enough because it searched few databases does not really stand up to scrutiny: the Ayres review included 4 databases, the current authors plan to search 5, the majority of which are exactly the same. 7. Is there any particular reason that the authors have chosen not to search the Cochrane library? 8. Can the authors say more about how they expect their systematic review to contribute to monitoring the impact of the national HPV vaccination programme? I can't see the link between this review and the national programme – and certainly the impact of the vaccination programme on national and regional prevalence will not be seen for many years, by which time the review will be well out of date. 9. The methods lack detail about how the review will be undertaken. Which specific grey literature sources will be searched? How many Brazilian specialists in the area will be contacted to help identify further studies? How will conference abstracts be included in the review (these do not really count as primary research unless the study that they report is also available in article form). 10. I am not clear about the significance of eligibility criterion number 3 – this does not seem to be about establishing HPV prevalence, so the importance of this eligibility criterion needs to be stated in more detail. 11. It's not clear what the authors mean in eligibility criterion 4 "the collection of material has occurred in cervical, penile, anal or oral region". This may be because of the slightly strange phrasing. How does this criterion differ from number 2, which states that prevalence

	of cervical, penile and anal HPV infection are the conditions of interest? 12. After the eligibility criteria, the text jumps straight to how data extraction will be performed. This misses out the important detail of how title and abstract screening will be performed, and how full text screening will be carried out. The authors need to add detail about this. 13. The data synthesis section is not very clear – this seems to depend on whether various types of analysis are possible given the nature of the studies returned. Whilst I appreciate that a detailed approach to data synthesis cannot always be pre-specified before the nature of the search results and their study designs are known, there are still too many uncertainties and unknowns in the data synthesis section to give me confidence that the authors will a) be able to extract the kind of data that they would like, b) that they will be able to perform a coherent analysis, and most importantly, c) that they will be able to robustly answer their research question(s) from the findings of the review. 14. How will meta-regression be undertaken when the authors assume that they will be providing a narrative synthesis of study findings? The analysis section appears to propose the use of some fairly sophisticated statistical analyses, yet the likelihood that the included studies will be amenable to such analyses is extremely low given that they are focusing on prevalence studies that will be largely observational rather than interventional. 15. I would assume that the number of prevalence studies about HPV in Brazil is fairly small. In including relevant reviews as well, the authors risk potentially counting the same primary studies more than once if they appear in multiple reviews and/or in their own right as individual papers. How are the authors going to ensure that they do not calculate inflated prevalence estimates as a result of some studies possibly being included more than once?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sarah Damery
Institution and Country: Institute of Applied Health Research, University of Birmingham, United Kingdom
Please state any competing interests or state ‘None declared’:None declared.

This protocol outlines a proposed systematic review to assess the prevalence of HPV in Brazil. The protocol is in general quite well-written but rather brief and would benefit from some more detail being added to expand the authors’ description of exactly what they intend to do. Detailed comments are below:

1. The protocol would benefit from review by a native English speaker. There are a number of spelling, grammatical and phrasing errors which an English reviewer would be able to correct. For example: Abstract (lines 46-48) “in Brazil there are no prevalence study considering a nationwide sample and has not been determined in many regions”. This does not make sense in English and it would improve the comprehensibility of the manuscript if this and other sentences were rephrased.
Answer: Although the manuscript was already sent to a professional language editing service (http://www.scientific.com.br/), we agree with your suggestion to send this article to be edit by a native

speaker and we are sending this Protocol Study for the editorial company suggested by BMJ. The reviewed text will be uploaded as soon as we receive an answer from https://secure.aje.com .
The sentence highlighted above was corrected: “In Brazil, there are no prevalence study considering a nationwide sample and the HPV prevalence has not been determined in many regions.”
2. How will the previously published review articles be identified? Do the authors assume that all such reviews will be returned by their searches, or will they attempt to identify existing reviews in another way?
Answer: It’s a very important aspect. Yes, we assume our literature search will identify existing reviews. Our search strategy is comprehensive and will result in a large amount of studies. In addition, we will scan the reference lists of identified publications in order to identify additional studies; is very likely that these studies cite other reviews.

3. It is not clear why the authors have chosen to use the GRADE criteria and an additional quality assessment tool when GRADE criteria encompass a measure of quality assessment (methodological rigour, risk of bias etc.) already.
Answer: There are two levels of quality of evidence. The first one is the individual study level, that we will evaluate the risk of bias for each study; for this aim we will use the NIH ‘Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies’. GRADE evaluate the quality of evidence across studies, rating the overall quality for the body of evidence. Risk of bias (methodological rigour) is one of the domains assessed with GRADE and it will be related to the quality of evidence of each study. Furthermore, GRADE evaluate additional domains that are not included at individual study level, such as inconsistency (heterogeneity across studies), indirectness and publication bias. Although GRADE is not commonly used for the evaluation of prevalence evidence, the use of GRADE domains may apply also to this kind of evidence. We will use an approach similar to the method used for evaluating baseline risk, as explained in the paper: “Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients, BMJ. 2015 Mar 16;350:h870”. Of note, one of the co-authors of this review is member of the GRADE working group and was co-author of the mentioned paper.

4. The search strategy seems rather simplistic. This leads to a two-fold concern: first, the number of hits returned in each of the databases searched is likely to be very high and not very easy to screen given the lack of specific terms incorporated into the search. Second, the lack of specific terms may also mean that important studies are overlooked. Have the authors done any scoping searches to test this out? Are there important studies that the authors already know about that they can use to test whether their search is sensitive/specific enough? Even though the authors are not imposing language or date limits on their searches (which is beneficial), I am not confident that the search strategy will allow the authors to address their twin aims of establishing HPV prevalence in the general population and evaluating prevalence in individuals with premalignant and malignant lesions.
Answer: We agree that our search strategy is very broad, not using many limits, what makes it looks like simplistic. Indeed, a broad strategy is usually more sensitive and we will result in a larger number of abstracts to review, increasing the workload of our researchers. Our strategy was designed to retrieve any publication about HPV in Brazil, not using any limit such as “prevalence studies”, “body region” or “study design”. In our preliminary search we identified about 1.500 abstracts, that may be considered a large amount for a meta-analysis focused in a single country. In this preliminary search strategy, previous known studies that met the inclusion criteria appear in the search strategy proposed here.

5. The authors recognize that a limitation may be variation between studies in terms of sample size,

participants and sociodemographic and state that they will control the heterogeneity with statistical analyses, yet the methods do not adequately describe how such control of heterogeneity will be undertaken over and above assessing heterogeneity using the appropriate statistics. Assessing heterogeneity is different to controlling heterogeneity, so if the authors plan to do the latter rather than simply assessing the former, more information is needed as to how this will actually be done.
Answer: We will perform subgroup analysis for some factors that can possible explain heterogeneity. Our pre-specified subgroup analysis are: geographic area (Brazilian region), body region (cervical, penile, anal and oral region), method for HPV assessment, HIV co-infection and the presence of premalignant or malignant lesions, presence of risk factors and study quality. Additional exploratory sensitive analysis may be performed.

6. The statistics cited in the introduction appear to answer the authors' question: a review was undertaken in 2010 which assessed the prevalence of HPV infection in Brazil and the authors cite figures from this review when establishing the context for their study. If a review of prevalence was undertaken so recently, a) why are the authors not just performing an update of this recent review, and b) what do the authors feel their review will accomplish that has not already been established by Ayres et al in 2010? In other words, the protocol needs to make a more explicit case for why the present systematic review is a) needed and b) provides a useful addition to the literature or addresses gaps in the evidence base that have not yet been answered. The paragraph on page 10 that attempts to make the case for the originality of the current review (lines 199-203) is not convincing. For example, the assertion that the Ayres review was not broad enough because it searched few databases does not really stand up to scrutiny: the Ayres review included 4 databases, the current authors plan to search 5, the majority of which are exactly the same.
Answer: The SR conducted by Ayres and Silva was a well conducted systematic review, proposing a narrower scope. The authors evaluated qualitative results for HPV prevalence in uterine cervix, presenting data for each HPV type.
We are conducting a more comprehensive SR, including other body sites and additional subgroup analysis, in special geographic region. Additionally, we are proposing the quantitative synthesis of results.
Although Ayres and Silva search similar databases, their search strategy probably was less comprehensive, ending with 155 abstracts (as mentioned before, we are expecting to review figures 10 times higher). Thus, we judged that a SR update wouldn't meet our needs and we decided to conduct a new one. However, Ayres reference list will be scanned and we will include all studies identified in this review in our analysis.

7. Is there any particular reason that the authors have chosen not to search the Cochrane library?
Answer: CENTRAL only include Randomized Controlled trials and is very important for intervention reviews. For our research question, is unlike that CENTRAL add us additional studies not covered in the other databases.

8. Can the authors say more about how they expect their systematic review to contribute to monitoring the impact of the national HPV vaccination programme? I can't see the link between this review and the national programme – and certainly the impact of the vaccination programme on national and regional prevalence will not be seen for many years, by which time the review will be well out of date.
Answer: One of our objective in do this systematic review is to evaluate the necessity of nationwide surveys to evaluate the HPV prevalence and identify gaps in information across Brazilian regions. We are developing a nationwide HPV prevalence study (POP-Brazil study) in order to meet Brazilians Ministry of Health needs, such as to evaluate the impact of the national HPV vaccination program in

Brazil. The systematic review will help in study designing (i.e., data for samples size calculation, identification of bias in previous studies, regions with lack of information) and will identify the necessity of a time-series cross-sectional data. The POP-Brazil study is under development and it is expected that its results will be able to fulfill the lack of epidemiological information that may be detected in this review.

9. The methods lack detail about how the review will be undertaken. Which specific grey literature sources will be searched? How many Brazilian specialists in the area will be contacted to help identify further studies? How will conference abstracts be included in the review (these do not really count as primary research unless the study that they report is also available in article form).
Answer: We will use the website “bancodeteses.capes.gov.br” for identification of thesis in the area and websites such as Grey Literature Report (www.greylit.org) will be searched as grey literature. In addition, The Department of IST/HIV have an extensive scientific network and personal information from experts in the area will be gathered personally. Data from conference proceedings will be included, even without answer from authors, if the abstract provide us enough information to assess its eligibility and to abstract, at least, the overall prevalence and number of participants. See page 7.

10. I am not clear about the significance of eligibility criterion number 3 – this does not seem to be about establishing HPV prevalence, so the importance of this eligibility criterion needs to be stated in more detail.
Answer: We want to evaluate the prevalence of HPV and its types. Therefore, it is important that the studies use a HPV stablished detection and typing process. We are not interested in clinical diagnosis of HPV related outcomes as genital warts.

11. It’s not clear what the authors mean in eligibility criterion 4 “the collection of material has occurred in cervical, penile, anal or oral region”. This may be because of the slightly strange phrasing. How does this criterion differ from number 2, which states that prevalence of cervical, penile and anal HPV infection are the conditions of interest?
Answer: We rephrased the “Eligibility Criteria”, excluding the information cited in the 4th criteria, that was already stated in the 2nd criteria and added the statement that studies that analyzed material such as blood, sperm and urine will not be included. See page 7-8

12. After the eligibility criteria, the text jumps straight to how data extraction will be performed. This misses out the important detail of how title and abstract screening will be performed, and how full text screening will be carried out. The authors need to add detail about this.
Answer: Thank you for the input, in the paper we were not clear enough. This sentence has been re-written: “Two independent reviewers will screen the titles and abstracts of all studies initially identified, according to the selection criteria. The same researchers will independently perform data extraction for full text review using standardized forms.” See page 8.

13. The data synthesis section is not very clear – this seems to depend on whether various types of analysis are possible given the nature of the studies returned. Whilst I appreciate that a detailed approach to data synthesis cannot always be pre-specified before the nature of the search results and their study designs are known, there are still too many uncertainties and unknowns in the data synthesis section to give me confidence that the authors will a) be able to extract the kind of data that they would like, b) that they will be able to perform a coherent analysis, and most importantly, c) that they will be able to robustly answer their research question(s) from the findings of the review.

Answer: Thank you for the input. We added in the manuscript the following sentences:
“We will provide a clear narrative synthesis and summary tables of the findings from the included studies, structured around the HPV prevalence”. See page 9
“Studies in which the HPV type (high or low risk) was not assessed or was not reported were excluded from the HPV type-specific analyses.” See page 9

14. How will meta-regression be undertaken when the authors assume that they will be providing a narrative synthesis of study findings? The analysis section appears to propose the use of some fairly sophisticated statistical analyses, yet the likelihood that the included studies will be amenable to such analyses is extremely low given that they are focusing on prevalence studies that will be largely observational rather than interventional.
Answer: Meta-regression probably will not be performed because all variables considered for sensitivity analysis are categorical. For these situations, we will perform subgroup analysis in order to assess the heterogeneity.
Meta-regression may be used for additional exploratory analysis, not specified in the protocol. For instance, if during the review process we expect that there are a correlation of publication year and HPV prevalence, meta-regression may be performed and results will be presented, highlighting that it was not a pre-specified sensitivity analysis. For the Answer: analysis, we will use the software R, package meta (command metareg).

15. I would assume that the number of prevalence studies about HPV in Brazil is fairly small. In including relevant reviews as well, the authors risk potentially counting the same primary studies more than once if they appear in multiple reviews and/or in their own right as individual papers. How are the authors going to ensure that they do not calculate inflated prevalence estimates as a result of some studies possibly being included more than once?
Answer: We explained in the subheading Study selection and data extraction that if the study is reported in duplication, the study published earlier or the one that provides more detailed information (e.g. largest sample size or completed data) will be included. We can check the duplication using data as authors, samples size and characteristics of the population. We also plan to send an email to the authors of eligible duplicated studies to ask more details about these articles. See page 8.

VERSION 2 – REVIEW

REVIEWER	Sarah Damery University of Birmingham, United Kingdom
REVIEW RETURNED	15-Aug-2016

GENERAL COMMENTS	The authors have in general addressed the concerns I expressed in my earlier review, albeit with minimal changes to the text of the protocol itself, so the manuscript remains largely unchanged. I am glad to see that the authors intend to have the manuscript professionally reviewed for language, as it is still rife with language and grammatical inaccuracies that really need to be corrected before publication. I do not feel that the authors responded adequately to one of my previous comments (my apologies if my meaning was not clear), so I am reiterating it here and asking the reviewers to respond as a minor revision: Previously, I asked the authors what they would do in the event that (because they include reviews), the same primary

	studies appear in several reviews and possibly on their own as well. Counting the same study more than once could lead to inflated estimates of prevalence. In making this point, I do NOT mean, what would happen if different versions of the same paper/review came up in the searches - the authors had already explained what they would do in these circumstances. What I mean is, what would happen if the same PRIMARY study was cited in multiple reviews. For example, you may include reviews by Smith (2010), Jones (2009), Lopez (2011). Each of those reviews may itself include the same primary study e.g. Evans (2008). If you include all three reviews, you are also including Evans three times. It is good practice to have a plan to deal with this, particularly in a prevalence review where accurate prevalence estimates are required.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sarah Damery
Institution and Country: University of Birmingham, United Kingdom
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The authors have in general addressed the concerns I expressed in my earlier review, albeit with minimal changes to the text of the protocol itself, so the manuscript remains largely unchanged.
I am glad to see that the authors intend to have the manuscript professionally reviewed for language, as it is still rife with language and grammatical inaccuracies that really need to be corrected before publication.
I do not feel that the authors responded adequately to one of my previous comments (my apologies if my meaning was not clear), so I am reiterating it here and asking the reviewers to respond as a minor revision: Previously, I asked the authors what they would do in the event that (because they include reviews), the same primary studies appear in several reviews and possibly on their own as well. Counting the same study more than once could lead to inflated estimates of prevalence. In making this point, I do NOT mean, what would happen if different versions of the same paper/review came up in the searches - the authors had already explained what they would do in these circumstances. What I mean is, what would happen if the same PRIMARY study was cited in multiple reviews. For example, you may include reviews by Smith (2010), Jones (2009), Lopez (2011). Each of those reviews may itself include the same primary study e.g. Evans (2008). If you include all three reviews, you are also including Evans three times. It is good practice to have a plan to deal with this, particularly in a prevalence review where accurate prevalence estimates are required.

Answer: Thank you for the input. As we can see in line 146-150, we are including the following studies design in this systematic review: randomized controlled trials, cohort studies, cross-sectional studies and prevalence studies. We are not including reviews. Please, see lines 166-168. For systematic reviews, we will only scan the reference lists of these reviews for search for additional studies. If the study is reported in duplication, the study published earlier or the one that provide more information will be included.
In addition, you can find in attach a review version of the manuscript after submitted to American Journal Experts to English review (a clean copy and a copy with highlighted changes).

VERSION 3 – REVIEW

REVIEWER	Sarah Damery University of Birmingham, United Kingdom
REVIEW RETURNED	21-Sep-2016

GENERAL COMMENTS	The authors have responded to my comments satisfactorily and the language checking has greatly improved the clarity of expression within the manuscript.