PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The "Reducing Delays In Vaccination" (REDIVAC) Trial: A protocol for a randomized controlled trial of a web-based, individually tailored, educational intervention to improve timeliness of infant vaccination
AUTHORS	Dempsey, Amanda; Wagner, Nicole; Narwaney, Komal; Pyrzanowski, Jennifer; Kwan, Bethany; Kraus, Courtney; Gleason, Kathy; Resnicow, Ken; sevick, carter; Cataldi, Jessica; Brewer, Sarah; Glanz, Jason M

VERSION 1 – REVIEW

REVIEWER	Arnaud Gagneur University of Sherbrooke, Quebec, Canada
REVIEW RETURNED	16-Dec-2018

GENERAL COMMENTS	The REDIVAC trial is a well-written protocol that aims to evaluate the effectiveness of a web-based individually tailored, educational intervention to increase timeless of infant vaccination. In fact timeless of infant vaccination is a major concern worldwide and intervention strategies are essential. Several improvements should be made to the protocol to facilitate its reproducibility; - Intervention: MI has recently been described as a promising tool to address vaccine hesitancy and increase vaccine coverage (missing references in the protocol). How were the principles of MI integrated into the educational intervention according to its spirit (compassion, altruism, non-judgement etc..) , processes and tools ? How were parents motivated to visit the website? Have they received specific message to stimulate them? Have the number of visit and the time spent on the website been collected and included in the analyses? if a mother visited one for 3 min on the website, was she in the intervention group ? This aspect is important to measure the quality of the intervention itself and not just the strategy as a whole. - Questionnaire: The questionnaire should be added as an appendix to improve the reproducibility of the protocol. Several vaccine hesitancy questionnaire are already available. Which one was use in this study? What cut-off value was used to determine parents as hesitant or non-hesitant? How was this threshold value determined? - Population: How was the 15% hypothesis of hesitant parents in recruitment determined? - Outcomes:

	Precision should be made on the calculation of the 200 days outcome. Investigators took into account 30 days after each dose of vaccine to determine the immunization status of the infant and 30 days after the 6 months vaccine is 210 days and not 200 days. The description of secondary outcomes must be more precise. Which aims? measures? outcomes? analysis?

REVIEWER	Dustin Gibson Assistant Scientist, Johns Hopkins Bloomberg School of Public Health, USA
REVIEW RETURNED	17-Dec-2018

GENERAL COMMENTS	Abstract: Include location of study Methods: study design and registration section- it seems out of place to discuss secondary outcomes and rationale in this section Methods: study setting- I know the trial has started, but it would have been preferred to send VISs to those in the intervention group too, particulary if this is usual practice…which would then show the added benefit of VAYB Methods- study setting- the authors spend most of this paragraph discussing the interventions, and their delivery, which should not be in study setting. Perhaps could combine study setting and participants section. Methods: assignment of interventions- would be helpful to provide more information on the stratified groups “hesitant” vs “non-hesitant”. How does the system classify participants? Summary score? Answered a few set of key questions? Methods-blinding-----first sentence needs to be revised for grammar Primary outcome- I am unclear what is the primary outcome. In the abstract, its listed as a dichotomous outcome “dichotomous outcome (up to date versus not) assessed at 200 days of age, reflecting the time when infants should have completed the first set of vaccine provided (at age 2, 4 and 6 months).” Where in methods section on page 9, it says, “The primary vaccination outcome to be assessed for the study (average number of days under vaccinated for all vaccinations in the recommended vaccine schedule) occurs when the infant is 200 days old.” Outcomes: given the uncertainty of outcomes and the multiple times they are defined throughout the paper, I would recommend including an “outcomes” sub-heading Methods- sample size calculation----I am confused by this section, it seems as if the sample size is being driven by a third primary outcome, “vaccine hesitant” or is this a rephrasing of the primary dichotomous outcome? Given this study is conducted within an EMR, I can assume that there is baseline data for underimmunization. If so, please include in this section. Also, unclear why the authors provide sample size for a range of effect size (odds ration from 2 to 3). Authors should indicate what precise sample size is (i.e. what they have IRB approval to study). There is also typically a justification for desired effect size in SS section

	For outcomes section, in your example of RV due at 2 months, are all participants who receive vaccination between 61 days and 92 days given 0 days of immunization or are they given a "negative" number of days. I ask, because it seems like summing the days undervaccinated may be unnecessary given that its dichotomized at <1 and >=1 days underimmunized. Couldn't the authors just state that for any child who received a vaccination late, they were considered not-up-to date? Statistical methods- Did the authors consider conducting risk ratios or risk differences, which would make the results more interpretable to clinicians and the general public? Dissemination section. Please add reference for CONSORT (although SPIRIT guidelines are included)

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers

Reviewer: 1
Reviewer Name: Arnaud Gagneur
The REDIVAC trial is a well-written protocol that aims to evaluate the effectiveness of a web-based individually tailored, educational intervention to increase timeless of infant vaccination. In fact timeless of infant vaccination is a major concern worldwide and intervention strategies are essential.
Several improvements should be made to the protocol to facilitate its reproducibility;
- Intervention:
1. MI has recently been described as a promising tool to address vaccine hesitancy and increase vaccine coverage (missing references in the protocol). How were the principles of MI integrated into the educational intervention according to its spirit (compassion, altruism, non-judgement etc..) , processes and tools ?

We did not "do MI" in the intervention, but rather used certain MI principles when crafting the tailored messages. MI is based on 4 tenets – empathy, collaboration, evocation and support for autonomy. As mentioned in the initial manuscript we "addressed autonomy" in the messages. By the nature of the project (mothers answer a survey and messages are based on their responses) we demonstrate evocation and provide a sense of collaboration. We also tried to use non-judgmental and empathetic language. To make this clearer the description of MI in the "conceptual model" part of the manuscript now reads

> "By affirming individual patient values and identity, using non-judgmental and empathetic language, emphasizing autonomy (i.e. adding tenets from Motivational interviewing and Self Determination Theory)[21,23] and constructing controlling tones of messages, this can minimize reactance and counterarguments."

Regarding missing references, we have now added the original book by Miller and Rollnick as a reference for MI.

2. How were parents motivated to visit the website? Have they received specific message to stimulate them? Have the number of visit and the time spent on the website been collected and included in the analyses? if a mother visited one for 3 min on the website, was she in the intervention group ? This aspect is important to measure the quality of the intervention itself and not just the strategy as a whole.

Mothers access the website as part of the study. They are informed at study recruitment that they are being recruited for a study that examines the impact of web-based information regarding childhood

vaccines. Mothers are taken directly to the website automatically at the time they finish their baseline or interim questionnaires. Prompts for completing these questionnaires are sent via email, with multiple prompts for non-responders. This is likely the main way they will see the website, though participants are made aware that they can log back in to the study and view the website at any time. Since study incentives are tied to completing the questionnaires, and because finishing an questionnaire automatically brings you to the website, we expect that essentially all mothers who finish a questionnaire will spend at least some time on the website. We plan to assess website utilization and engagement (time spent, number of pages, etc) as part of the study and to examine as exploratory secondary outcomes its relationship to study arm and to vaccine attitudes and utilization. However, because both the control and intervention arms receive a website (though they differ) we expect any variability in engagement with the websites to be distributed similarly between arms. Thus, for the primary analysis, website use will not be factored in. To clarify this, we have added the following text to Study Setting and Overview:

> "Participants in all arms complete surveys at baseline, and three additional time points (Table 2). Participants are reminded to take the survey at these intervals via a series of emails. Following survey completion, participants are taken automatically to the website that contains either tailored or untailored information, depending on study arm."

The paper already included the text:

> "Upon completion of the pre-intervention questionnaire where initial tailoring information is obtained, participants are automatically directed to the VAYB website which is individually customized based on their responses."

In the Outcomes section in the paragraph describing secondary outcomes we have added the following missing text:

> "Also included [in the secondary analyses] will be metrics measuring website engagement (VAYB and Untailored arms only) including time spent on the website, number of times viewing website, number and order of pages viewed, and match between stated concerns and website material viewed (VAYB arm only)."

3. - Questionnaire:
The questionnaire should be added as an appendix to improve the reproducibility of the protocol. Several vaccine hesitancy questionnaire are already available. Which one was use in this study? What cut-off value was used to determine parents as hesitant or non-hesitant? How was this threshold value determined?

We feel providing all the questionnaires would likely be confusing as there are actually four different questionnaires provided throughout the study. Instead, we have provided the pre-intervention questionnaire as an Appendix. This includes the vaccine hesitancy questions. As was already stated in the original manuscript, we used a validated, unpublished, 5-item version of the PACV questionnaire with cutoff measures as per the validation protocol.

> "Hesitancy status is assessed using a 5-item validated measure developed by (Opel, personal communication) and participants are categorized based on the measure's suggested (but unpublished) cutoffs."

4. - Population: How was the 15% hypothesis of hesitant parents in recruitment determined?

This was based on several prior studies of vaccine hesitancy in the KPCO pregnant mothers population. We have clarified this in the methods and also added a reference. The text now states:

> "This sample size is based on an assumption of 15% of the recruited population being vaccine hesitant (as has been the case in prior studies in this population)[35]…"

5. - Outcomes:

Precision should be made on the calculation of the 200 days outcome. Investigators took into account 30 days after each dose of vaccine to determine the immunization status of the infant and 30 days after the 6 months vaccine is 210 days and not 200 days.

We agree that as it is written, this was confusing. The 200 day window is meant to capture vaccination at 2 and 4 months, not at 6 months, which the reviewer correctly points out would bring us to 210 days. This has been clarified in the "outcomes" portion of the text which now reads:

> "To categorize vaccination status we will first assess the number of days under-vaccinated for the 2- and 4-month vaccines (combined),..."

6. The description of secondary outcomes must be more precise. Which aims? measures? outcomes? analysis?
There are many secondary outcomes for a project this large and these cannot be described in any detail given the page limitations for the journal. To circumvent this, we have provided references to previously developed scales and measures we are using to provide a resource for those wanting this additional detail on the outcomes being assessed. We are not clear on what is meant by "aims" in the reviewer's comment. These secondary outcomes did not have specific aims that were conceptualized at the beginning of the study. These outcomes, because they are secondary, address new questions that arose about potential relationships between different influential factors in the study that arose after the study materials were made. We have tried to add some additional detail to the analysis section to address this reviewer's concern, recognizing that we do not have the space to describe all these secondary analyses in detail. The analysis section for secondary outcomes now reads:

> "For survey measures, descriptive statistics will be assessed and changes in vaccination attitudes and intention over time will be calculated. All measures are assessed using Likert scales and will be analyzed as linear measures. Repeated measures ANOVA will be used to assess the intervention's impact on average change by arm for each of these outcomes. Mixed linear models will be used to assess the "difference in difference" over time in these means, by arm, controlling for the covariates described above. Website utilization data will be measured primarily using linear measures (time spent on the website in minutes, number of times logging in, number of web pages viewed etc.) and may be included in the mixed linear models. ANOVA will be used to assess the association between each of these website utilization measures and study arm."

Reviewer: 2
Reviewer Name: Dustin Gibson
Institution and Country: Assistant Scientist, Johns Hopkins Bloomberg School of Public Health, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
7. Abstract: Include location of study

This has now been added.

8. Methods: study design and registration section- it seems out of place to discuss secondary outcomes and rationale in this section

We agree and have moved this to the "Study Overview and Population" section.

9. Methods: study setting- I know the trial has started, but it would have been preferred to send VISs to those in the intervention group too, particulary if this is usual practice…which would then show the added benefit of VAYB.

There does not appear to be a response needed for this comment. The study is ongoing and can't be changed, and the reviewer indicates.

10. Methods- study setting- the authors spend most of this paragraph discussing the interventions, and their delivery, which should not be in study setting. Perhaps could combine study setting and participants section.

We agree and have rearranged this section of the manuscript to place this information where it makes more sense, per the reviewer's suggestion. We have created a combined "Study Overview and Setting" category that includes this information.

11. Methods: assignment of interventions- would be helpful to provide more information on the stratified groups "hesitant" vs "non-hesitant". How does the system classify participants? Summary score? Answered a few set of key questions?

See response # 3 above.

12. Methods-blinding-----first sentence needs to be revised for grammar Primary outcome- I am unclear what is the primary outcome. In the abstract, its listed as a dichotomous outcome "dichotomous outcome (up to date versus not) assessed at 200 days of age, reflecting the time when infants should have completed the first set of vaccine provided (at age 2, 4 and 6 months)." Where in methods section on page 9, it says, "The primary vaccination outcome to be assessed for the study (average number of days under vaccinated for all vaccinations in the recommended vaccine schedule) occurs when the infant is 200 days old."

We have reworded the first sentence to improve clarity. Thank you for pointing it out. We have also fixed the wrong description pointed out on page 9. It now reads

> "The primary vaccination outcome to be assessed is a dichotomous outcome of vaccination status (up-to-date versus not) that is based on the average number of days under vaccinated for all vaccinations in the recommended vaccine schedule."

13. Outcomes: given the uncertainty of outcomes and the multiple times they are defined throughout the paper, I would recommend including an "outcomes" sub-heading

As in the original manuscript, "outcomes" exists as a subheading, found on page 18. We have read through the manuscript again and tried to ensure that all descriptions of the outcomes are consistent throughout.

14. Methods- sample size calculation----I am confused by this section, it seems as if the sample size is being driven by a third primary outcome, "vaccine hesitant" or is this a rephrasing of the primary dichotomous outcome? Given this study is conducted within an EMR, I can assume that there is baseline data for underimmunization. If so, please include in this section. Also, unclear why the authors provide sample size for a range of effect size (odds ration from 2 to 3). Authors should indicate what precise sample size is (i.e. what they have IRB approval to study). There is also typically a justification for desired effect size in SS section

We agree this was confusing and have reworded the sample size explanation for clarity and also included a reference to baseline vaccination rates. It now says:

> "This sample size is based on an assumption of 15% of the recruited population being vaccine hesitant (as has been the case in prior studies in this population)[35] and therefore not up to date in their infant's vaccination, a 1:1:1 randomization allocation ratio, two-sided tests of statistical significance, 80% statistical power, and a 5% type I error rate.

Since the study is ongoing we are not sure how many people we will be able to enroll in the time period available, based on the funding period. If we enroll more people, we will have the power to detect smaller odds ratios between groups. If less enroll, then we can only detect larger differences. It is not uncommon to present a range of sample size calculations when planning for a study, as is the case here. But based on prior literature, an Odds ratio of 2 to 3 is likely to provide clinically meaningful differences in the level of vaccination. To clarify this we have reworded the section to now read:

"We considered, based on prior studies,[3,35] an odds ratio (OR) between 2.0 and 3.0 for up-to-date vaccination status between the intervention study arms and usual care to be clinically meaningful. For this, we estimate a needed sample size of 477 (OR = 3.0) to 1002 (OR=2.0) participants. This sample size is based on an assumption of 15% of the recruited population being vaccine hesitant (as has been the case in prior studies in this population)[35] and therefore not up to date in their infant's vaccination, a 1:1:1 randomization allocation ratio, two-sided tests of statistical significance, 80% statistical power, and a 5% type I error rate. Accounting for an attrition of 15%, we need to enroll 561 to 1179 participants."

15. For outcomes section, in your example of RV due at 2 months, are all participants who receive vaccination between 61 days and 92 days given 0 days of immunization or are they given a "negative" number of days. I ask, because it seems like summing the days undervaccinated may be unnecessary
given that its dichotomized at <1 and >=1 days underimmunized. Couldn't the authors just state that for any child who received a vaccination late, they were considered not-up-to date?

All participants are given a score of "days under immunized" = 0 if they received their 2 month vaccines between 62 and 91 days. The reviewer is correct in that we could just avoid the summing and calculate immunization status in an easier way. However, as we describe, we also plan to look at underimmunization as a linear measure, which requires the described calculation. This measure can provide more meaningful insight into vaccination delays by allowing one to compare the relative impact on absolute number of days underimmunized in response to different interventions.

16. Statistical methods- Did the authors consider conducting risk ratios or risk differences, which would make the results more interpretable to clinicians and the general public?

We did not plan for this as our outcome assessment method so as to be consistent with ours, and others, studies of vaccine implementation interventions. However, we agree that for the general public, risk ratios or differences are easier to interpret. Should our intervention prove useful, resulting in plans to disseminate it more widely, we would plan to calculate the outcomes in this way so as to more easily convey the impact of the intervention to lay audiences.

17. Dissemination section. Please add reference for CONSORT (although SPIRIT guidelines are included)

This has been added.

VERSION 2 – REVIEW

REVIEWER	Arnaud Gagneur University of Sherbrooke, Québec, Canada
REVIEW RETURNED	18-Mar-2019

GENERAL COMMENTS	Just one correction in the abstract. Remove "and 6 months" line 40 as it's explain in the outcome section (ie To categorize vaccination status we will first assess the number of days undervaccinated for the 2- and 4-month vaccines (combined)