PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Public health impact model estimating the impact of introducing an Adjuvanted Recombinant Zoster Vaccine into the UK universal mass vaccination programme.
AUTHORS	van Oorschot, Desiree; Hunjan, Manjit; Bracke, Benjamin; Lorenc, Stephane; Curran, Desmond; Starkie-Camejo, Helen

VERSION 1 - REVIEW

REVIEWER	Gabutti Giovanni University of Ferrara, Ferrara, Italy Giovanni Gabutti received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Seqirus, Sanofi Pasteur, Merck Italy, Pfizer and PaxVax for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.
REVIEW RETURNED	24-Aug-2018

GENERAL COMMENTS	The paper addresses a relevant topic such as the evaluation of the public health impact of introducing a new recombinant HZ vaccine in UK. The manuscript is interesting, well written and very clear. However, there are some points that should be addressed in order to make the paper even more complete. - last sentence in page 4 and first sentence in page 5. Probably it should be better to say "...conferring low protection against HZ beyond 8 years..." than "...no protection..." - page 5 lines 29-32 It seems that the sentence "RZV is administered in two doses 2 to 6 months apart and is not contraindicated in immunocompromised (IC) individuals as it is a non-live vaccine.22" is not completely correct and should be changed/integrated As a matter of fact the RCP of Shingrix states: 4.4 Systemic immunosuppressive medications and immunodeficiency OBJ OBJ OBJ OBJ Safety and immunogenicity data on a limited number of immunocompromised subjects with human immunodeficiency virus (HIV) or haematopoietic stem cell transplant (HCT) are available (see section 5.1). The use of Shingrix in subjects with other confirmed or suspected immunosuppressive or immunodeficient conditions is under investigation. As with other vaccines, an adequate immune response may not be elicited in these individuals. The administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks. 5.1 Immunocompromised subjects

	Two phase I/II clinical studies, Zoster-001 and Zoster-015, were conducted in subjects with autologous hematopoietic stem cell transplant or HIV infection. A total of 135 adults, of whom 73 were ≥50 years of age, received at least one dose of Shingrix, which was shown to be immunogenic and well-tolerated. - page 7 lines 29-31 and 49-50. These sentences are not clear as in the reference by Yawn is written: "RECURRENCE The overall recurrence rate was 1.4% within 3 years, with 11 of the 1669 patients with confirmed HZ having a recurrence within 1 year after the onset of the incident case; 11, between 1 and 2 years; and 2, between 2 and 3 years. No significant differences in recurrence rates were caused by age or sex." - Model The model and obtained results are interesting. However, it seems that the use of one dose is possible. Up to now Shingrix should be used adopting a two-dose schedule. For this reason, this point should be clearly stated and discussed. For the same reason it seems that all tables should be changed as the one-dose schedule is not applicable. - Limitations of the model have been clearly explained (page 19 lines 40-43). The same limitations do not seem to support the sentence in page 20 lines 37-42 "..clinical profile of RZV shows a different optimal vaccination strategy compared to ZVL..." - page 19 lines 50-53 and page 20 line 3 "For ZVL waning rates, we included both data from the SPS and the LTPS study 25; however, data from a recent observational study evaluating effectiveness of ZVL in the UK were not included as they were not available at the time of modelling.36" This point should be included also in the introduction section after the sentence in page 5 lines 3-5 - Focus on the patient (page 36) . The sentence on duration of protection with RVZ could be deleted - SI table 1 line 31 Any corticosteroid exposure? Please note that printing layout is not always correct. e.g. page 12 (as well as other pages) includes only one sentence Please note that a space is needed in page 4 line 15 (5HZ) Please note that, at least on my pc, sometimes it is written: (Error! Reference source not found.).

REVIEWER	Alexander Doroshenko University of Alberta, Canada
REVIEW RETURNED	27-Aug-2018

GENERAL COMMENTS	This is an interesting mathematical modeling study to determine public health impact of potential introduction of newly licensed recombinant zoster vaccine in the UK immunization schedule. It

	utilizes UK demographic data, incidence of herpes zoster and its complications, hospitalization and general practitioners' visits and published vaccine efficacy as model inputs which may be of great interest to UK public health policy makers. However, in my opinion, the following issues related to methodology and manuscript presentation needs to be addressed before this manuscript may be suitable for publication. Major revisions: 1. The methodology described in this manuscript (and choice of analyses and even presentation of infographics) is very similar to a previously published paper by Curran et al (reference 25 in this manuscript) which used data from Germany. While UK policy makers may undoubtedly be interested in UK data, this manuscript is lacking methodological novelty which would have made a stronger argument for policy makers. The same VE and waning of immunity values used in both studies make results of this work somewhat predictable and limitations identified in Curran et al paper (e.g. problems with extrapolation of 1-dose VE for RZV and RZV waning estimation based on linear fitting based on only 4 year of data) were carried over to this manuscript. Despite similarities there are some differences between these papers (e.g. in Curran et al paper, HZ cases averted were computed for multiple age cohorts versus single year cohorts in this manuscript). As a minimum, authors should discuss comprehensively how this paper differs from Curran et al paper rather than just mentioning on line 40-44 on page 17 that it shows similar results. 2. What was the rationale for choosing static multi-cohort model for this study? There is no discussion or mentioning advantages and limitations of static models versus dynamic models. 3. Model Structure section (lines 15-28 on page 6) does not provide adequate description on how model was constructed. I appreciate that authors reference Curran et al paper for more information, but it is not sufficient. There are some elements that needs to be included in this section. Specifically, authors mentioned 5 different health states and transitions between them, but there is no single reference to how vaccination is "administered" in the model. Perhaps an updated diagram (similar to Figure 5 in Curran et al paper), but with inclusion of vaccination would be helpful. How does model handle individuals which are not RZV vaccinated because of vaccine coverage is not 100%; are these individuals then transitioned to RZV 1-dose VE cohort probability for HZ? This emphasizes the need for more comprehensive description of the model. 4. Under the Strength and Limitations of this study, authors state that "model structure and inputs have been validated by external experts" (line 15 page 3). This has not been mentioned anywhere in the main text. Considering confidentiality, authors should describe their expertise and broad affiliations. Also in the same section (line 18-19, page 3), authors state that "further analyses have to be performed once data becomes available on the duration of protection of RZV". This contradicts the statement in Figure 6 under "What is the impact" which states more categorically that "model suggests that the duration of protection with recombinant zoster vaccine lasts longer".

	5. There is overreliance on vaccine efficacy (from RCTs) data versus vaccine effectiveness (from observational but derived from real-life (versus experimental) settings in this study. While vaccine effectiveness studies for RZV are not available, they are available for ZVL. Authors mentioned one study from the UK (Walker et al 2018, reference 36), which was too recent to be included; however there are other studies, for example McDonald et al 2017 "The effectiveness of shingles vaccine among Albertans aged 50 years or older: a retrospective cohort study". Using vaccine effectiveness for ZVL but not for RZV may actually over-estimate benefits of RZV. These points need to be discussed. 6. Authors should indicate how they computed NNV in this study as depending how these values were derived, NNV can produce overestimation (Tuite AR 2013, Vaccine 2013). This may or may not be relevant to this study, but statement about NNV calculation method is warranted. How is NNV is different from NNV per 100,000 (mentioned on line 18 page 14)? 7. How was the number of 15,704 HZ cases averted for RZV as opposed to ZVL in sensitivity analysis on line 18 page 17 derived? It does not appear to be correct from Tornado Diagram. 8. While ethics approval may indeed not be required for this study (as authors only used publicly available data), statement that ethics approval is not applicable (line 41 page 25) to all modeling studies is overreaching. There are some modeling studies which may use individual data for model calibration or validation, which may require ethics approval. Consulting ethics board may still be necessary for this study. 9. In several section of the manuscript, there were "Error! Reference source not found" statements. These needs to be corrected. 10. Tornado Diagram, Figure 4: Text for the legend is truncated with some important content missing. Minor revisions 11. Line 38, page 2: "Compared to revaccination". Should it be "Compared to no vaccination"? 12. Remove blank spaces on pages 11-15. 13. Line 15, page 4: there should be space between 5 HZ. 14. Line 38, page 17: rephrase " …in those IC individuals who are not contraindicated" to "…in those IC individuals who have no contraindications…" 15. Line 12, page 19: "to prevent one case of ZVL" ZVL should be HZ.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments to Author:

Reviewer: 1

Reviewer Name: Gabutti Giovanni

Institution and Country: University of Ferrara, Ferrara, Italy Please state any competing interests or state ‘None declared’: Giovanni Gabutti received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Seqirus, Sanofi Pasteur, Merck Italy, Pfizer and PaxVax for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.

The paper addresses a relevant topic such as the evaluation of the public health impact of introducing a new recombinant HZ vaccine in UK. The manuscript is interesting, well written and very clear.

However, there are some points that should be addressed in order to make the paper even more complete.

last sentence in page 4 and first sentence in page 5. Probably it should be better to say "...conferring low protection against HZ beyond 8 years..." than "...no protection..."

We have changed the wording in the text to “… conferring little or no protection against HZ beyond 8 years after vaccination” We have added also an extra sentence in the discussion section, to explain the various effectiveness studies.

page 5 lines 29-32 It seems that the sentence "RZV is administered in two doses 2 to 6 months apart and is not contraindicated in immunocompromised (IC) individuals as it is a non-live vaccine.22" is not completely correct and should be changed/integrated. As a matter of fact the RCP of Shingrix states: 4.4 Systemic immunosuppressive medications and immunodeficiency Safety and immunogenicity data on a limited number of immunocompromised subjects with human immunodeficiency virus (HIV) or haematopoietic stem cell transplant (HCT) are available (see section 5.1). The use of Shingrix in subjects with other confirmed or suspected immunosuppressive or immunodeficient conditions is under investigation. As with other vaccines, an adequate immune response may not be elicited in these individuals. The administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks. 5.1 Immunocompromised subjects - Two phase I/II clinical studies, Zoster-001 and Zoster-015, were conducted in subjects with autologous hematopoietic stem cell transplant or HIV infection. A total of 135 adults, of whom 73 were ≥50 years of age, received at least one dose of Shingrix, which was shown to be immunogenic and well-tolerated.

Because RZV is a non-live vaccine, it is not contra-indicated in an immunocompromised population as per the label of EMA and FDA. The zoster vaccine live (ZVL, Zostavax) is for that reason contra-indicated. A clinical trial has been performed in a very severe IC condition (HSCT patients) to demonstrate that RZV is safe and efficient to use in this population. The only contra-indication in the USPI is “Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.” Indeed some immunocompromised individuals may be on therapy containing the excipients listed in 6.1. As such we have added this sentence in the section discussed: “As with other vaccines, the administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks.

page 7 lines 29-31 and 49-50. These sentences are not clear as in the reference by Yawn is written: "RECURRENCE The overall recurrence rate was 1.4% within 3 years, with 11 of the 1669 patients with confirmed HZ having a recurrence within 1 year after the onset of the incident case; 11, between

1 and 2 years; and 2, between 2 and 3 years. No significant differences in recurrence rates were caused by age or sex."

Yawn reported that the recurrence rates was 6.2% with a median follow-up of 8 years. Assuming an exponential distribution the recurrence rate per year is approximately 8 per 1000 person years, which is similar to the initial incidence of HZ.

We added one extra reference from a follow-up paper of Yawn (2011), in which they state: “Indeed, after adjustment for age and sex, the rate of recurrent episodes was similar to the incidence rate of HZ episodes in the same population, suggesting that the risk of having another episode of HZ in people with a history of HZ is about the same as the risk of having a first HZ episode in the general population.”

Sensitivity analyses were performed to explore the impact of this parameter on outcomes.

Model

The model and obtained results are interesting. However, it seems that the use of one dose is possible. Up to now Shingrix should be used adopting a two-dose schedule. For this reason, this point should be clearly stated and discussed. For the same reason it seems that all tables should be changed as the one-dose schedule is not applicable.

We have tried to reflect the real-life situation in the UK as realistic as possible. In this setting, it is likely that not everyone is compliant with the RZV dosing schedule, therefore we have set the second dose compliance to 70%. This means that 30% of the vaccinated cohort will only receive one dose, therefore we include also the vaccine efficacy for one dose only.

We have changed the text in the method section under “Efficacy”: VE for RZV is based on a 2-dose schedule given 2 months apart. However, compliance with 2nd dose RZV is likely to be lower than 100%, as such there is a cohort of individuals who are only vaccinated with one dose.

Limitations of the model have been clearly explained (page 19 lines 40-43). The same limitations do not seem to support the sentence in page 20 lines 37-42 "...clinical profile of RZV shows a different optimal vaccination strategy compared to ZVL..."

Changed the concluding statement into the following: “The model projects for RZV a longer duration of protection and the VE remains high in older age groups compared to ZVL. Therefore, the results of this model show that the difference in clinical profile of RZV leads to a different optimal age of vaccination. Vaccinating the UK population with RZV at 60 YOA or 65 YOA is the optimal vaccination strategy in terms of public health impact, while being superior to ZVL in all age cohorts studied.”

page 19 lines 50-53 and page 20 line 3 "For ZVL waning rates, we included both data from the SPS and the LTPS study 25; however, data from a recent observational study evaluating effectiveness of ZVL in the UK were not included as they were not available at the time of modelling.36" This point should be included also in the introduction section after the sentence in page 5 lines 3-5

We have changed the bullet point under “Strengths and limitations on this study”:

Further analyses have to be performed once long term effectiveness data becomes available on the duration of protection of RZV.

Furthermore there is some extra explanation in the discussion section on the use of RCT data versus effectiveness data, see comment 5 of the second reviewer.

Focus on the patient (page 36). The sentence on duration of protection with RVZ could be deleted.

We deleted this sentence.

SI table 1 line 31 Any corticosteroid exposure?

Yes, Corticosteroid exposure is included I this list: “The immunocompromised (IC) population was identified as individuals presenting one of the following conditions: Hematopoietic stem cell transplantation, solid organ transplantation, solid organ malignancies, haematological malignancies, human immunodeficiency virus, end-stage renal disease, corticosteroid exposure, other immunosuppressive therapy, other immunodeficiency conditions and autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, psoriasis, multiple sclerosis, polymyalgia rheumatica and autoimmune thyroiditis).”

We have also added the reference related to the CPRD study [doi:10.1136/bmjopen-2017-020528], which was not available at time of submission.

Please note that printing layout is not always correct. e.g. page 12 (as well as other pages) includes only one sentence

We do not have the same problem in the word document but to be sure we reapplied the style again.

Please note that a space is needed in page 4 line 15 (5HZ)

Thank you for spotting the error. This is corrected now.

Please note that, at least on my pc, sometimes it is written: (Error! Reference source not found.).

We could not find the same error in the word document, to be sure we changed the dynamic links and switched these to plain text removing the links.

Reviewer: 2

Reviewer Name: Alexander Doroshenko

Institution and Country: University of Alberta, Canada Please state any competing interests or state ‘None declared’: None declared

This is an interesting mathematical modeling study to determine public health impact of potential introduction of newly licensed recombinant zoster vaccine in the UK immunization schedule. It utilizes UK demographic data, incidence of herpes zoster and its complications, hospitalization and general practitioners’ visits and published vaccine efficacy as model inputs which may be of great interest to UK public health policy makers. However, in my opinion, the following issues related to methodology and manuscript presentation needs to be addressed before this manuscript may be suitable for publication.

Major revisions:

The methodology described in this manuscript (and choice of analyses and even presentation of infographics) is very similar to a previously published paper by Curran et al (reference 25 in this manuscript) which used data from Germany. While UK policy makers may undoubtedly be interested in UK data, this manuscript is lacking methodological novelty which would have made a stronger argument for policy makers. The same VE and waning of immunity values used in both studies make results of this work somewhat predictable and limitations identified in Curran et al paper (e.g. problems with extrapolation of 1-dose VE for RZV and RZV waning estimation based on linear fitting based on only 4 year of data) were carried over to this manuscript. Despite similarities there are some

differences between these papers (e.g. in Curran et al paper, HZ cases averted were computed for multiple age cohorts versus single year cohorts in this manuscript). As a minimum, authors should discuss comprehensively how this paper differs from Curran et al paper rather than just mentioning on line 40-44 on page 17 that it shows similar results.

It is well noticed from the reviewer that there are similarities between both papers, especially regarding the vaccine efficacy and waning applied. This is mainly due to the fact that these come from clinical trials were there is no distinction between countries. The differences can be explained more clearly, as we aimed to do in the discussion section:

“Although results are in line with the German study, this UK model adaptation has some different methodological considerations that are of importance to potential decision-making bodies. Firstly, this model assesses single year cohorts versus multiple year cohorts. This was chosen to reflect the current HZ vaccination programme in the UK where people get vaccinated with ZVL at 70 YOA and 79 YOA as a catch-up programme. Secondly, the HZ incidence is calculated based upon a weighting method of IC-free and IC populations using the prevalence of IC in the different age groups. This is important to estimate the actual HZ incidence in the general population.”

What was the rationale for choosing static multi-cohort model for this study? There is no discussion or mentioning advantages and limitations of static models versus dynamic models.

We choose a static multi cohort model because this reflects the disease pathway of herpes zoster. The risk of transmission of disease from a subject with HZ is minimal and as such no herd-effect is expected because of vaccination. Therefore a static model was sufficient to demonstrate the impact of HZ vaccination in various age groups.

Model Structure section (lines 15-28 on page 6) does not provide adequate description on how model was constructed. I appreciate that authors reference Curran et al paper for more information, but it is not sufficient. There are some elements that needs to be included in this section. Specifically, authors mentioned 5 different health states and transitions between them, but there is no single reference to how vaccination is “administered” in the model. Perhaps an updated diagram (similar to Figure 5 in Curran et al paper), but with inclusion of vaccination would be helpful. How does model handle individuals which are not RZV vaccinated because of vaccine coverage is not 100%; are these individuals then transitioned to RZV 1-dose VE cohort probability for HZ? This emphasizes the need for more comprehensive description of the model.

Thank you for this clear explanation. We have updated the text in the method section so that it becomes clearer on how we handle different vaccination strategies in the model:

“The ZOster ecoNomic Analysis (ZONA), a static multi-cohort Markov model previously developed using Microsoft Excel, was adapted to the UK setting. The economic model considers up to five various age cohorts that can transition between different health states, including no HZ, HZ, health states associated with complications of HZ (PHN and non-PHN complications) and death from HZ or natural causes.25 Cycle length is set to one year and a life-long time horizon is assumed. follows all subjects from the year of intervention over their remaining life-time. The model has three different arms, having the same yearly model structure: No vaccination, vaccination with RZV and vaccination with ZVL. Within the vaccine strategy, individuals can be fully compliant with the vaccine dosing schedule, only partially or not vaccinated at all (depending on the compliance rate). The model allows evaluation of three different HZ vaccination strategies: vaccination with RZV, vaccination with ZVL and no vaccination, using single cohorts. Further details regarding the model structure are reported in Curran et al, 2017.25”

Under the Strength and Limitations of this study, authors state that “model structure and inputs have been validated by external experts” (line 15 page 3). This has not been mentioned anywhere in the

main text. Considering confidentiality, authors should describe their expertise and broad affiliations. Also in the same section (line 18-19, page 3), authors state that “further analyses have to be performed once data becomes available on the duration of protection of RZV”. This contradicts the statement in Figure 6 under “What is the impact” which states more categorically that “model suggests that the duration of protection with recombinant zoster vaccine lasts longer”.

Thank you for noting this. The advisory board was referred to in the previous paper. We have updated the text under “model inputs parameters” with the following sentence: “Both model structure and global inputs such as VE and waning were validated with an external expert panel (epidemiologists, clinicians and health economists with a background in HZ) in September 2016.”

Regarding the duration of protection of RZV, for now these are the most adequate data inputs as validated by experts in the field and based on the clinical trial data. For now, the duration of protection over the life of the population is extrapolated based on a model, so as soon as we have more data available we will update this, also from the real-world setting. Therefore, we have changed the bullet point under “Strengths and limitations on this study”:

Further analyses have to be performed once long term effectiveness data becomes available on the duration of protection of RZV.

There is overreliance on vaccine efficacy (from RCTs) data versus vaccine effectiveness (from observational but derived from real-life (versus experimental) settings in this study. While vaccine effectiveness studies for RZV are not available, they are available for ZVL. Authors mentioned one study from the UK (Walker et al 2018, reference 36), which was too recent to be included; however there are other studies, for example McDonald et al 2017 “The effectiveness of shingles vaccine among Albertans aged 50 years or older: a retrospective cohort study”. Using vaccine effectiveness for ZVL but not for RZV may actually over-estimate benefits of RZV. These points need to be discussed.

We have carefully considered the different available studies reflecting the ZVL efficacy and effectiveness. The effectiveness study as described in Alberta, and the other ones, either in the UK or US all come to the same conclusion: ZVL wanes rapidly with little to no protection against HZ left at year 8. If we want to compare both vaccines in a health economic model it is the preferred option to use RCT data for both vaccines (also presented as gold standard by the Centers for Disease Control in the US.)

We have addressed this now in the discussion section:

“For ZVL waning rates, we included both data from the SPS and the LTPS study (25) to ensure that we could compare ZVL and RZV in the ZONA model. Recent observational studies looking into the vaccine effectiveness of ZVL show that the vaccine wanes rapidly and has little to no protection left beyond year 8 after vaccination.”

Authors should indicate how they computed NNV in this study as depending how these values were derived, NNV can produce overestimation (Tuite AR 2013, Vaccine 2013). This may or may not be relevant to this study, but statement about NNV calculation method is warranted. How is NNV is different from NNV per 100,000 (mentioned on line 18 page 14)?

Thank you for noticing this. The analyses were performed per 100,000 subjects. In this way we could compare the difference in case avoidance between age groups (as the size of age groups differs, this might give different, skewed, results). This actually does not implicate anything on the NNV.

We have excluded the “NNV per 100,000 people” in the results section and included the following in the method section to demonstrate how the NNV is calculated:

The number needed to vaccinate (NNV) to avert one case of HZ and PHN was also evaluated by applying the following calculation:.

NNV= 1/(((control cases)/(vaccinated persons))-((vaccinated cases)/(vaccinated persons)))

How was the number of 15,704 HZ cases averted for RZV as opposed to ZVL in sensitivity analysis on line 18 page 17 derived? It does not appear to be correct from Tornado Diagram.

Thank you very much for spotting this error. We had to re-run the tornado diagram before submitting the manuscript but we missed one update in the text because of that. Now we have updated the text as well in the discussion section: "…with an annual waning rate of 6.6%, RZV would prevent an additional 13,816 HZ cases as compared to ZVL"

While ethics approval may indeed not be required for this study (as authors only used publicly available data), statement that ethics approval is not applicable (line 41 page 25) to all modeling studies is overreaching. There are some modeling studies which may use individual data for model calibration or validation, which may require ethics approval. Consulting ethics board may still be necessary for this study.

This study is only using publicly available literature and does not include any individual (patient) data. We have changed the text to: "Ethical approval is not applicable for this public health impact modelling analysis."

In several section of the manuscript, there were "Error! Reference source not found" statements. These needs to be corrected.

We could not find the same error in the word document, to be sure we changed the dynamic links and switched these to plain text removing the links.

Tornado Diagram, Figure 4: Text for the legend is truncated with some important content missing.

We re-exported the figure as labels were indeed truncated, the legend is now updated as well.

Minor revisions

Line 38, page 2: "Compared to revaccination". Should it be "Compared to no vaccination"?

Thank you for spotting this error, changed now.

Remove blank spaces on pages 11-15.

Line 15, page 4: there should be space between 5 HZ.

Changed.

Line 38, page 17: rephrase " …in those IC individuals who are not contraindicated" to "…in those IC individuals who have no contraindications…"

Changed upon suggestion.

Line 12, page 19: "to prevent one case of ZVL" ZVL should be HZ.

Changed accordingly, thank you for spotting this mistake.

VERSION 2 – REVIEW

REVIEWER	Giovanni Gabutti University of Ferrara Italy I have the following potential conflicts of interest to report: grants from Sanofi Pasteur MSD, GSK Biologicals SA, Novartis, Crucell/Janssen, Pfizer, Sanofi Pasteur, MSD Italy, Seqirus and PaxVax for taking part to advisory boards, expert meetings, for acting as speaker and/or organizer of meetings/congresses and as principal investigator and chief of O.U. in RCTs.
REVIEW RETURNED	20-Nov-2018

GENERAL COMMENTS	The paper addresses a relevant topic, is interesting and well written. The Authors have addressed most of the points previously raised. However, in my opinion, few relevant points have not been completely clarified. Taking into account the response letter, the points are the following: 2. As in the SCP of RVZ is written "4.4 Systemic immunosuppressive medications and immunodeficiency Safety and immunogenicity data on a limited number of immunocompromised subjects with human immunodeficiency virus (HIV) or haematopoietic stem cell transplant (HCT) are available (see section 5.1). The use of Shingrix in subjects with other confirmed or suspected immunosuppressive or immunodeficient conditions is under investigation", I continue to believe that the sentence in page 5 "RZV is administered in two doses 2 to 6 months apart and is not contraindicated in immunocompromised (IC) individuals as it is a non-live vaccine. As with other vaccines, the administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks 22" is not enough 3. I take into account the two references provided to suggest the high rate of recurrence. However, to the best of my knowledge, the reported risk of recurrence is not available in any other publication. 4. I continue to believe that RVZ should be used following a two-dose schedule (as included in SCP). For this reason, any evaluation/estimate of efficacy/effectiveness of one dose is only speculative. If this point was not clearly defined, the results provided by some tables/figures could be misleading

REVIEWER	Alexander Doroshenko University of Alberta, Canada
REVIEW RETURNED	20-Nov-2018

GENERAL COMMENTS	Authors have adequately addressed my concerns identified in the previous round of review. Although I would have preferred if a

	model diagram was included in this article (item 3 in my comments to authors), I would leave it to the discretion of editorial team.

VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 2

Authors have adequately addressed my concerns identified in the previous round of review. Although I would have preferred if a model diagram was included in this article (item 3 in my comments to authors), I would leave it to the discretion of editorial team.

Reviewer: 1

The paper addresses a relevant topic, is interesting and well written. The Authors have addressed most of the points previously raised. However, in my opinion, few relevant points have not been completely clarified. Taking into account the response letter, the points are the following:

2. As in the SCP of RVZ is written "4.4 Systemic immunosuppressive medications and immunodeficiency Safety and immunogenicity data on a limited number of immunocompromised subjects with human immunodeficiency virus (HIV) or haematopoietic stem cell transplant (HCT) are available (see section 5.1). The use of Shingrix in subjects with other confirmed or suspected immunosuppressive or immunodeficient conditions is under investigation", I continue to believe that the sentence in page 5 "RZV is administered in two doses 2 to 6 months apart and is not contraindicated in immunocompromised (IC) individuals as it is a non-live vaccine. As with other vaccines, the administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks 22" is not enough

The reviewer is correct to state that the sentence as stated in the manuscript might be misinterpreted by thinking the vaccine is not contra-indicated to anyone or effective to use in the immunocompromised population. Concerning contra-indication, the SPC states: “Hypersensitivity to the active substances or to any of the excipients listed in section 6.1” (https://www.ema.europa.eu/documents/product-information/shingrix-epar-product-information_en.pdf), this is the case for immunocompetent and immunosuppressed patients. To clarify that there is limited data available on immunocompromised populations, we added the following sentence:

“RZV is administered in two doses 2 to 6 months apart. Because RZV is a non-live vaccine, it is not contra-indicated in immunocompromised (IC) individuals. While at this point in time there is only limited data available regarding the use of Shingrix in subjects with confirmed or suspected immunosuppressive or immunodeficient conditions, further studies are ongoing. As with other vaccines, the administration of Shingrix to immunocompromised subjects should be based on careful consideration of potential benefits and risks. [22]”

3. I take into account the two references provided to suggest the high rate of recurrence. However, to the best of my knowledge, the reported risk of recurrence is not available in any other publication.

Within this manuscript, we refer to the two most cited papers. However, there are more papers looking into the recurrence rate of herpes zoster. In 2014, Kawai et al. performed a review looking into (among others) the HZ recurrence rates, there were 9 papers at the time that reported these, noting that there were different with respect to in- and exclusion criteria. Kawai et al. stated in their

manuscript: “Several prior studies with a long-term follow-up found that recurrence of HZ is frequent, with a rate of 5–6%, which is comparable to rates of first occurrence of HZ.”

For completeness, we have added this reference to the section on recurrence rates.

4. I continue to believe that RVZ should be used following a two-dose schedule (as included in SCP). For this reason, any evaluation/estimate of efficacy/effectiveness of one dose is only speculative. If this point was not clearly defined, the results provided by some tables/figures could be misleading.

We completely agree with the reviewer that RZV should be used following the SPC, two doses given 2-6 months apart. However, within this modeling exercise, we try to reflect the real world setting, i.e. what might happen in real life. Therefore, we have to make assumptions. We know that not every individual will come back for the second dose of RZV, therefore we model this based on a 70% second-dose compliance assumption. A similar approach has also been taken by an independent research group, modeling the effects of RZV in the US population (Le et al 2018). They assumed, 56% second dose compliance, this was also presented by CDC to the open ACIP meeting in June 2017. We agree with the reviewer that there is limited data regarding one-dose vaccine efficacy and waning, and therefore we take into account a wide confidence interval for our sensitivity and scenario analyses.

To avoid confusion by interpreting the results in the tables and figures, we have included extra footnotes to address the coverage and compliance of HZ vaccination.

VERSION 3 – REVIEW

REVIEWER	Gabutti Giovanni University of Ferrara, Ferrara, Italy I confirm that I received grants from GlaxoSmithKline Biologicals SA, Sanofi Pasteur MSD, Novartis, Crucell/Janssen, Seqirus, Sanofi Pasteur, Merck Italy, Pfizer and PaxVax for being consultant or taking part in advisory board, expert meetings, being a speaker or an organizer of congresses/conferences, and acting as investigator in clinical trials.
REVIEW RETURNED	23-Jan-2019

GENERAL COMMENTS	The Authors have addressed my previously raised points.