

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Exploring the potential impact of rotavirus vaccination on work absenteeism amongst female administrative personnel of the City of Antwerp through a retrospective data-base analysis
<b>AUTHORS</b>	Standaert, Baudouin; Van de Mierop, Els; Nelen, Vera

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Renat Latipov Research Institute of Virology, Uzbekistan
<b>REVIEW RETURNED</b>	05-Feb-2015

<b>GENERAL COMMENTS</b>	<p>Rotavirus vaccination is particularly differ from others vaccines. It is aimed to reduce number of severe cases instead prevention of new ones. In the light of high price of the vaccine and absent of international support in vaccine introduction in many countries there were provided many economic studies to show benefits of vaccine introduction in routine practice. Now, after many countries in world have been introduced vaccination, became a new era of studies: to show real benefits and effect of rotavirus vaccination. While in developed countries (with low and middle income), which have ability of support from international organizations (mostly from GAVI), it have been enough to calculate benefits from reduction of direct medical and non-medical expenses, then for developed countries, it was calculation of reduction of non-direct expenses only allowed to provide economic benefits for national policy makers. Data provided by Baodouin S. et al. in "Reduction in work absenteeism after introduction of the rotavirus vaccine" is exactly sample of data or studies that we have to need to show economic effect of vaccination in developed countries. Data represents logical results of vaccine introduction that have been expected and now they are visible. The same results have to be obtained and I hope will be done on other countries.</p> <p>I would like to highlight the strengths (on my mind) of the study</p> <ol style="list-style-type: none"><li>1. Usage of database with huge number of persons (about 11000 per year)</li><li>2. Two 5-year comparative periods</li><li>3. Comparing epidemic and non-epidemic periods can discover role of rotaviruses.</li></ol> <p>But, there are few questions I would like to clarify. There were certain difficulties in the perception of description of the methodology used by the authors, may be so raised the following questions.</p> <p>As I understood, the authors were taken a database of absences working hours of women who fit the selection criteria (the presence of a child of a certain age) and compare their indicators for the two</p>
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	<p>periods. Is there evidence that these women were absent a) by reason of illness of a child, b) by reason of a child's illness of gastroenteritis in) by reason of illness of the child of rotavirus gastroenteritis.</p> <p>If, in cases of absence of women in the workplace is not were associated with rotavirus gastroenteritis, could, the presence of outbreaks of other diseases in the population Antwerp, which could also occur at the same age affect the results of the study?</p> <p>Does the economic upheavals affected on the employment rate of women and level of absenteeism? Has the average employment rate of women and level of absenteeism during the two periods being compared? In my opinion, the economic crisis of 2008 could have a significant impact on this indicator.</p> <p>I have encountered some difficulties in the interpretation of the methodology and results presented in Table 1. In my opinion, the submitted data is missing presentation of the confidence intervals, which would help to compare the presented data.</p>
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<b>REVIEWER</b>	Eyal Leshewm US Centers for Disease Control and Prevention
<b>REVIEW RETURNED</b>	12-Feb-2015

<b>GENERAL COMMENTS</b>	<p>Re: BMJOpen-2014-007453</p> <p>An interesting paper comparing a simple model of reduction in work absenteeism after introduction of the rotavirus vaccine with real life data from a very small cohort of working mothers in Belgium. Below are several comments:</p> <p>The main issues that needs to be addressed is the small size of the cohort and the short pre-vaccine follow-up period preventing proper assessment of secular trends (decrease in seasonal work absenteeism not related to rota vaccine introduction):</p> <ol style="list-style-type: none"> <li>1. The authors have data for 56-114women with relatively small number of work days missed – please provide 95%CI for your estimates and add the small size of your cohort to study limitations.</li> <li>2. Do you have data for the period before 2003? When looking at table 1 there is a small decrease in the number of short absences per month even before the vaccines were introduced (from 0.350 to 0.316). Secular trends may account for some (and with wide 95%CI for a lot) of the declines you observed. Please add prior data and model to account for secular trends if existent or discuss as study limitation.</li> <li>3. Previous assessments of rota vaccine effect showed a clear biennial patter of disease reductions – this is not evident in your data – possibly due to small cohort – please discuss or add to limitations.</li> </ol> <p>Minor comments:</p> <ol style="list-style-type: none"> <li>4. Is work absenteeism coded specifically by reason (child disease)?</li> <li>5. L53 – rota transmission occurs at all pediatric age groups. It is true that infants are major spreaders but giving the 10 month age is misleading – rephrase.</li> <li>6. L121-2 – is there a reference for vaccine cost and gross daily income estimates?</li> <li>7. L153-4 – move to discussion</li> <li>8. L209 – which modeled estimates? Please add references.</li> </ol>
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	9. L212-4 – not clear – please rephrase 10. L243 – do you mean specific indirect benefit effect?
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### VERSION 1 – AUTHOR RESPONSE

Reviewer Name Renat Latipov

Institution and Country Research Institute of Virology, Uzbekistan

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Rotavirus vaccination is particularly differ from others vaccines. It is aimed to reduce number of severe cases instead prevention of new ones. In the light of high price of the vaccine and absent of international support in vaccine introduction in many countries there were provided many economic studies to show benefits of vaccine introduction in routine practice. Now, after many countries in world have been introduced vaccination, became a new era of studies: to show real benefits and effect of rotavirus vaccination. While in developed countries (with low and middle income), which have ability of support from international organizations (mostly from GAVI), it have been enough to calculate benefits from reduction of direct medical and non-medical expenses, then for developed countries, it was calculation of reduction of non-direct expenses only allowed to provide economic benefits for national policy makers.

Data provided by Baodouin S. et al. in "Reduction in work absenteeism after introduction of the rotavirus vaccine" is exactly sample of data or studies that we have to need to show economic effect of vaccination in developed countries. Data represents logical results of vaccine introduction that have been expected and now they are visible. The same results have to be obtained and I hope will be done on other countries.

I would like to highlight the strengths (on my mind) of the study

1. Usage of database with huge number of persons (about 11000 per year)
2. Two 5-year comparative periods
3. Comparing epidemic and non-epidemic periods can discover role of rotaviruses.

But, there are few questions I would like to clarify.

There were certain difficulties in the perception of description of the methodology used by the authors, may be so raised the following questions.

As I understood, the authors were taken a database of absences working hours of women who fit the selection criteria (the presence of a child of a certain age) and compare their indicators for the two periods. Is there evidence that these women were absent a) by reason of illness of a child, b) by reason of a child's illness of gastroenteritis in) by reason of illness of the child of rotavirus gastroenteritis.

The highest level of detailed information about the reason being absent that potentially could be linked to a child disease is 'Absence for urgent familial reasons'. This type of reason doesn't mean that the absence is related to a child disease, or a specific child disease such as gastro-enteritis. But there are many other short duration absence reasons in the database that could mask a child disease situation. So, selecting specific reasons of absenteeism would not help us in better identifying the change of absenteeism as we may observe a large level of underreporting. That is the main reason we selected the evaluation on duration instead of reason of absence.

If, in cases of absence of women in the workplace is not were associated with rotavirus gastroenteritis, could, the presence of outbreaks of other diseases in the population Antwerp, which could also occur at the same age affect the results of the study?

It could of course. However we are not saying that we have found the right cause-effect relationship of the reduction in work absenteeism amongst working mothers with a first child. We give at least 4 arguments why the reduction could be related to the vaccine introduction and we added a fifth one:

we selected a control group of women around the same age-group with no children that could have been vaccinated against rotavirus. In that control group we do not observe any reduction in absenteeism after 2008. We added that new information in the manuscript.

Does the economic upheavals affected on the employment rate of women and level of absenteeism? Has the average employment rate of women and level of absenteeism during the two periods being compared? In my opinion, the economic crisis of 2008 could have a significant impact on this indicator.

For this analysis here we specially selected working personnel in the administration as they have security of employment as soon as they sign a contract with the authorities in Belgium. (it could be with the City, the Province, the Region, and the Federal Authority). But you are right to ask that question as we first have tried to evaluate the situation in the private sector but first we couldn't obtain very detailed information and second there is a high turn-over of personnel so that we couldn't follow them for a long period. So, the selection of the work environment is critical to observe the effect of reduction in absenteeism. But we mention that in the paper in the discussion section.

I have encountered some difficulties in the interpretation of the methodology and results presented in Table 1.

We have tried to be more explicit in the calculations of Table 1.

In my opinion, the submitted data is missing presentation of the confidence intervals, which would help to compare the presented data.

We have calculated the 95% CI-data as well but as Table 3 is showing we have quite skewed data in the numbers of days being absent before and after the introduction of the vaccine. We therefore reported the results of Table 3 with a non-parametric test result or rank-test to report whether there is a statistically significant difference pre- versus post-vaccination.

Reviewer Name Eyal Leshewm

Institution and Country US Centers for Disease Control and Prevention

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Re: BMJOpen-2014-007453

An interesting paper comparing a simple model of reduction in work absenteeism after introduction of the rotavirus vaccine with real life data from a very small cohort of working mothers in Belgium. Below are several comments:

The main issues that needs to be addressed is the small size of the cohort and the short pre-vaccine follow-up period preventing proper assessment of secular trends (decrease in seasonal work absenteeism not related to rota vaccine introduction):

The total number of women with a first child in this study as seen from Table 2 is 658 of whom 241 were in the pre-vaccination period and 417 in the post-vaccination period if the analysis is targeted towards a subgroup of mothers of whom their babies are around 10 months old during the epidemic period. Meanwhile we did an analysis in a second step where we included all the mothers with a first baby the year before the epidemic. The results were the same as from the targeted group, but the number of mothers enrolled in that second analysis was much higher. Unfortunately we could not obtain data prior 2003 because these data were not electronically available.

1. The authors have data for 56-114 women with relatively small number of work days missed – please provide 95%CI for your estimates and add the small size of your cohort to study limitations. Done, but we need to emphasize that first this group of mothers is a targeted or a sub-group of mothers with a first child. We however also looked at the whole group or full cohort of mothers with a 1st child over a one-year period instead of the targeted group (see Table 3). That group of mothers

was much larger than the targeted one (see Table 3). Also the number of absenteeism days less or equal to 5 days was larger than in the targeted group. Finally we calculated the 95% CI but from Table 3 one can observe that the change in number of days of absenteeism pre- versus post-vaccination is a very skewed distribution for which we prefer to use a rank-test for showing a statistical significant difference.

2. Do you have data for the period before 2003? When looking at table 1 there is a small decrease in the number of short absences per month even before the vaccines were introduced (from 0.350 to 0.316). Secular trends may account for some (and with wide 95%CI for a lot) of the declines you observed. Please add prior data and model to account for secular trends if existent or discuss as study limitation.

No data were electronically available before 2003 unfortunately. Not sure that we can talk about a secular trend with the variation observed. If you look at Table 2 and Table 3 we do not see a same secular decreasing trend in the early years amongst the targeted versus the full cohort group. In addition we added a control group in the analysis of females closed to the mothers with a 1st child. We do not observe a secular trend neither nor a decrease in absenteeism after 2008.

3. Previous assessments of rota vaccine effect showed a clear biennial patten of disease reductions – this is not evident in your data – possibly due to small cohort – please discuss or add to limitations. The biennial pattern is seen in real life and in models if the vaccine coverage rate is not optimal like in the US. In Belgium we reached a coverage rate above 85% -close to 90%- and that may explain why we do not see the biennial pattern instead of being a limitation in the study.

Minor comments:

4. Is work absenteeism coded specifically by reason (child disease)?

No, it is coded as 'absence for urgent familial reasons'. Many other reasons could mask the issue of absenteeism due to a child disease. We therefore selected duration instead of specific reasons reported in the data-base.

5. L53 – rota transmission occurs at all pediatric age groups. It is true that infants are major spreaders but giving the 10 month age is misleading – rephrase.

We adjusted, but would like to add that we did in the past an analysis by age of the children getting the disease during the epidemic period. As you know the highest frequency is around 10 to 12 months, the lower frequencies in younger and older age-groups and that during the peak of the epidemic period. We presented those data years ago at an ISPOR meeting in Europe, but didn't publish it in a journal. I suspect that this pattern is country specific depending how children are nurtured at young age. 10 months in Belgium is the period they go to day-care centre;s the ideal hup situation for spreading the disease.

6. L121-2 – is there a reference for vaccine cost and gross daily income estimates?

References added.

7. L153-4 – move to discussion

We moved that to the discussion section

8. L209 – which modeled estimates? Please add references.

We add the reference

9. L212-4 – not clear – please rephrase

We rephrase that sentence

10. L243 – do you mean specific indirect benefit effect?

Yes, we do.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Renat Latipov Research Institute of Virology, Uzbekistan
<b>REVIEW RETURNED</b>	20-Mar-2015

<b>GENERAL COMMENTS</b>	<p>It was good idea to use control group. However, control group is just idea in presented paper. Did not presented comparative analysis between control and main groups as well as did not presented statistical analysis of main results. Main results</p> <p>Did not provided statistical comparison of the two main indicators (1.71 - 0.83) obtained by the authors. Is the difference in the 0.88 days caused by actually decline or is the result of statistical errors. It would be a clear relationship between these indicators if the authors have presented range and 95% CI.</p> <p>According to Table 3 it seems slight decreasing in number of days absent from work in the control group too. How is statistically correlated?</p>
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<b>REVIEWER</b>	<p>Eyal Leshem  Division of Viral Diseases  National Center for Immunization and Respiratory Diseases  Centers for Disease Control and Prevention</p>
<b>REVIEW RETURNED</b>	26-Mar-2015

<b>GENERAL COMMENTS</b>	<p>The manuscript was revised ; however, I still find it quite challenging to fully understand the methods and interpret the results. Several of my comments were not addressed and I will repeat those.</p> <p>The main issues that needs to be addressed is the small size of the cohort and the short pre-vaccine follow-up period. These limitations make it difficult to assess secular trends (decrease in seasonal work absenteeism not related to rotavirus vaccine introduction). The authors should mention either address these issues in their rebuttal letter or in the study limitations part of the manuscript:</p> <ol style="list-style-type: none"> <li>1. The authors have data for 56-114women with relatively small number of work days missed. The authors mention they have seen a substantial reduction in absenteeism (L155). They should perform and report a statistical test showing the rate of pre-vaccine absenteeism was higher. They should also add small size of your cohort to study limitations.</li> <li>2. Do you have data for the period before 2003? When looking at table 2 there is a small decrease in the number of short absences per month even before the vaccines were introduced (during 2003-2006 from 0.350 to 0.316). Secular trends may account for some (and with wide 95%CI for a lot) of the declines you observed. Please add prior data and model to account for secular trends if data is available or discuss as study limitation.</li> <li>3. Previous assessments of rota vaccine effect showed a clear biennial patter of disease reductions – this is not evident in your data – possibly due to small cohort – please discuss or add to limitations.</li> <li>4. The manuscript and especially the discussion are very long and should be shortened or simplified if possible to ease readability.</li> </ol> <p>Minor comments:</p> <ol style="list-style-type: none"> <li>5. L89 – what does overall reason mean? Is work absenteeism coded specifically by reason (family / child disease)?</li> <li>6. L129-130, L204-208 and L298 – This study was not designed as a cost-effectiveness evaluation and the use of reduction in absenteeism versus vaccine cost to demonstrate cost effectiveness does not provide useful data. Other factors in the benefit side are direct medical costs and other on the vaccine cost side are the costs of a national vaccine program (infrastructure and staffing).</li> <li>7. Table 1: Why did you choose 5 days for average number of days absent/women? Is this based on local data? Otherwise please</li> </ol>
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	<p>provide reference.</p> <p>8. Table 3: The table is difficult to read and interpret. The authors would like to show that post vaccine absenteeism rates are lower. Why show the frequency distribution. The test used (Mann-Whitney) only attests to a significant difference between the distributions but not necessarily a reduction in absenteeism. The test result cannot be <math>&lt;0.00</math> – please rephrase. Why not simply compare pre-vaccine rates (2003-2006) with post-vaccine rates (2008-12) and provide rate reductions with reference to confidence intervals? This will allow the reader to understand if rates were indeed lower after vaccine introduction.</p> <p>9. L196 – the assumption is that these are cumulative gains – this is unclear and should be substantiated.</p> <p>10. L201 – while this is not a cost effectiveness evaluation the authors choose to discuss cost effectiveness studies at the beginning of their discussion. This may be misleading. Please present your main findings at the beginning of your discussion.</p>
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### VERSION 2 – AUTHOR RESPONSE

Reviewer Name Renat Latipov

Institution and Country Research Institute of Virology, Uzbekistan

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below It was good idea to use control group. However, control group is just idea in presented paper. Did not presented comparative analysis between control and main groups as well as did not presented statistical analysis of main results. Main results Did not provided statistical comparison of the two main indicators (1.71 - 0.83) obtained by the authors. Is the difference in the 0.88 days caused by actually decline or is the result of statistical errors. It would be a clear relationship between these indicators if the authors have presented range and 95% CI.

According to Table 3 it seems slight decreasing in number of days absent from work in the control group too. How is statistically correlated?

We are a little surprised by the comment about absence of 95% CI and no stats comparison in the previously submitted document. Table 2 in specific columns and Table 3 at the bottom in rows report the 95% CI of each average absenteeism days measured per year. Figure 1A also showed 95% CI. So, there is a significant difference seen if we consider the 95%CI levels that do not overlap between the periods before 2006 (pre-vaccination) and after vaccination (2009 and later). We also report a ranking test result for Table 3 (the comparison between the year 2004 and 2009 (2 years before and 2 years after the introduction of the vaccine) with a star). For us it makes sense to use that test with the categorical results (number of people with zero, one, two, three, four and five days of absence from work classified per specific period of observation). We have now added a statistical parametric test result about a significant difference for the mean result (average days absent from work per woman per period) over the period before the introduction of the vaccine (2004-2006) compared with the period after (2010-2012) and between the control group and the working mothers with potentially vaccinated children during the epidemic period. We agree with the reviewer that there could be a trend to a decrease in absenteeism seen in the control group in the period the vaccine is introduced, but in Table 3 it is clear that in 2009 there was a very high reduction in 5-day absences from work but also an overall decrease for that year across all day categories except the 1-day absence. The big difference in the number of people per category for zero and five days over time is more consistent in the target group for which the children move from unvaccinated to vaccinated condition. We have added a figure to better illustrate the issue (New Figure 1A). We conducted a regression analysis to identify whether the coefficients were significantly different for the control group versus the target group, which we now also report in the text. The difference is significant and therefore it may indicate

that another factor influences the decrease in absenteeism in the target group versus the control group which could be explained by the introduction of the vaccine. I hope that this additional statistical analysis is helpful.

Reviewer Name Eyal Leshem

Institution and Country Division of Viral Diseases

National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention

1600 Clifton Rd, MS A-34 Atlanta, GA 30333

Please state any competing interests or state 'None declared': None

The manuscript was revised ; however, I still find it quite challenging to fully understand the methods and interpret the results. Several of my comments were not addressed and I will repeat those.

The main issues that needs to be addressed is the small size of the cohort and the short pre-vaccine follow-up period. These limitations make it difficult to assess secular trends (decrease in seasonal work absenteeism not related to rotavirus vaccine introduction). The authors should mention either address these issues in their rebuttal letter or in the study limitations part of the manuscript:

1. The authors have data for 56-114 women with relatively small number of work days missed. The authors mention they have seen a substantial reduction in absenteeism (L155). They should perform and report a statistical test showing the rate of pre-vaccine absenteeism was higher. They should also add small size of your cohort to study limitations.

We reported the small sample size already in the previous text as a study limitation. We have now created a paragraph in the discussion specifically about study limitations to make this clearer. We have added a statistical parametric test analysis for Table 2 and 3. We are still not fully convinced that a parametric test is the right thing to do because the number of days of absence is not normally distributed per sample per year. Using a non-parametric test with the observation of reduction in average values over time should help to conclude that there is a significant reduction over time in absenteeism.

2. Do you have data for the period before 2003? When looking at table 2 there is a small decrease in the number of short absences per month even before the vaccines were introduced (during 2003-2006 from 0.350 to 0.316). Secular trends may account for some (and with wide 95%CI for a lot) of the declines you observed. Please add prior data and model to account for secular trends if data is available or discuss as study limitation.

We mentioned in the comments of the previous version that we did not have access to data before 2003 as they were not electronically available. We have added that information to the paragraph in the discussion about study limitations.

3. Previous assessments of rota vaccine effect showed a clear biennial patten of disease reductions – this is not evident in your data – possibly due to small cohort – please discuss or add to limitations.

We can agree with the statement made about biennial pattern of disease reduction in conditions when the vaccine coverage is not optimal, but this was/is not the case in Belgium. Belgium had a very high uptake from the start of introducing the vaccine in November 2006, as mentioned in the text. It may be helpful to read the other material we have already published on the Belgium rota-disease situation and the impact of the vaccine (Raes et al. 2011, PIDJ, 30: e120-e125; Standaert et al. 2013, Plos One, 8(1), e53864). We have one of the longest follow-up periods of hospital impact data recorded in the developed world using a standard approach over the years (8 years post-vaccination). The latest analysis is now submitted to another journal for review (Standaert et al. 2015, BMC Health Services Research) and that latest analysis is showing no biennial pattern of disease reduction. Furthermore, modelling exercises conducted with our dynamic model do not show such a shift if the vaccine uptake is very high, as is the case in Belgium. Our understanding of the working of the vaccine is that it stops disease transmission between children, besides protecting those who are vaccinated, and the vaccine does this reduction very well (indicated by a large herd effect in the early years). But there is another source of infection that the vaccine does not touch by vaccinating the children only, and that could be

the reason why rotavirus vaccination will not lead so easily to elimination in a short time period if the vaccination program is not optimal.

4. The manuscript and especially the discussion are very long and should be shortened or simplified if possible to ease readability.

We have edited the text to shorten the manuscript where possible.

Minor comments:

5. L89 – what does overall reason mean? Is work absenteeism coded specifically by reason (family / child disease)? Unfortunately not. The reason mentioned is for urgent familial reasons in general, as we explained in the previous comments. The lack of a specific reason for absence has now been added to the new paragraph about the study limitations in the discussion.

6. L129-130, L204-208 and L298 – This study was not designed as a cost-effectiveness evaluation and the use of reduction in absenteeism versus vaccine cost to demonstrate cost effectiveness does not provide useful data. Other factors in the benefit side are direct medical costs and other on the vaccine cost side are the costs of a national vaccine program (infrastructure and staffing). We have deleted references to cost-effectiveness evaluation, although we think it is a little strange to delete a possible application for these data.

7. Table 1: Why did you choose 5 days for average number of days absent/women? Is this based on local data? Otherwise please provide reference.

We explained in previous comments that we selected the cut-off point of 5 days taking into account that mild disease on average has an average duration of 5 days maximum and mild disease is the most frequent event that will occur. If the frequency was not so high we could not have detected a reduction in work absenteeism. If we had selected a higher cut-off point in number of days of absenteeism, such as 7 or 10 days, that could be related to more severe disease, the frequency of occurrence of such absences is much lower and it could have interfered with holiday periods. The latter would then have become an important confounding factor in the analysis, and it is likely that therefore we would not have been able to measure any significant reduction. At the start of our analysis we considered all days of absenteeism. The result was that we could not identify a reduction because the long periods of absenteeism due to holidays were masking the effects of short period absenteeism. I hope this better clarifies the issue. Also, developing the simple model helped us to better understand what we had to look for.

8. Table 3: The table is difficult to read and interpret. The authors would like to show that post vaccine absenteeism rates are lower. Why show the frequency distribution. The test used (Mann-Whitney) only attests to a significant difference between the distributions but not necessarily a reduction in absenteeism. The test result cannot be <0.00 – please rephrase. Why not simply compare pre-vaccine rates (2003-2006) with post-vaccine rates (2008-12) and provide rate reductions with reference to confidence intervals? This will allow the reader to understand if rates were indeed lower after vaccine introduction.

We thought we are working with categorical variables and that it was interesting to demonstrate the important shift from 5 days being absent of work to the growth of zero days being absent of work with the introduction of the vaccine. We have now added the other test results as well as a new graph to better illustrate the overall issue (Figure 2).

9. L196 – the assumption is that these are cumulative gains – this is unclear and should be substantiated. We have reworded the title of Table 4 to specify that these are ‘Estimated cumulative gains...’

10. L201 – while this is not a cost effectiveness evaluation the authors choose to discuss cost effectiveness studies at the beginning of their discussion. This may be misleading. Please present your main findings at the beginning of your discussion. We have changed that.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Eyal Leshem Division of Viral Diseases
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	National Center for Immunization and Respiratory Diseases Centers for Disease Control and Prevention Atlanta, GA, United States of America
<b>REVIEW RETURNED</b>	11-May-2015

<b>GENERAL COMMENTS</b>	The manuscript was revised and most of my comments addressed. I still think it is challenging to understand the methodology and that the manuscript would benefit from language editing and clarification of the groups compared but would leave these comments to the editor.
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