Author’s response to reviews

Title: Incidence and effects of Varicella Zoster Virus Infection on academic activities of medical undergraduates - a Five Year Follow-Up Study from Sri Lanka

Authors:

Suneth B Agampodi (sunethagampodi@yahoo.com)
Samath D Dharmaratne (samathd@pdn.ac.lk)
Vasanthi Thevanesam (vasanthithevanesam@yahoo.com)
Sameera Dassanayake (sdasanayake1981@yahoo.com)
Prabhashini Kumarihami (prabhashinikumarihamy@yahoo.com)
Ashani Rathnayaka (aashanirm@yahoo.com)

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Author's response to reviews: see over
Responses to reviewers comments

Thank you very much for all valuable comments made. These comments helped us to improve the manuscript considerably. We have given point by point explanations for your comments and also highlighted the revised section in the manuscript.

Corresponding author

Reviewer's report 1
Major compulsory Revisions:
The authors should discuss the following aspects:
1. The investigators did not perform a serological analysis at the end of the follow up. Would it be possible that some of the students had a subclinical VZV infection?
2. How reliable was the diagnosis varicella made? Could there be any recall bias?
Thanks for this point. There would definitely be a recall bias and subclinical infections, where the estimated incidence would be an underestimation of true incidence. I have included this in revised manuscript.

Minor Essential Revisions:
1. On page 7: it seems to me that the number 8,663 is wrong and should be corrected in 863 (i.e. 5.5 x 157).
This entered number was a mistake. I have included the months not the years. In the revised manuscript total person years are included. However, total exposure is less than 5.5x157, because once a student get infected, he is not considered as susceptible anymore and person years of exposure ends at that point.

Reviewer's report:2
Major Compussory Revisions:
1. How reliable of the study by using the information from self-administered structured questionnaire? Did the questionnaire have been validated before use?
This is a major limitation in our study. We include a separate section on these limitation in discussion

2. The authors show the effect of VZV infection on academc activities lost in Table 2 and elaborate details in text (Result section) by using mean without standard deviaiton. How much do the variations of those information have? The mean number might be higher than it should be due to some of them had severe symptoms. Mean may not be a good representation. How is about Mode or Median?
I also agree with you. Inrevides manuscript median and IQ range is presented.

3. Need clarification about the number of total person years of exposure (8,663) and the incidence desity per 1000 persons years of follow-up
This person years of exposure was wrong. I have entered the months, without dividing it by 12. This exposure period was calculated for actual susceptible period. If a student acquired the infection in the first month of his second year, his contribution to the total exposure was only 12 months, not 5.5 years. This explanation is given in the methods section, in revised manuscript.

4. Please recheck the number of susceptible follow-up (157 or 153) as well as the proportion lost (8.7%). The number does not correlate to the figure 1. There errors are corrected in the revised manuscript

Reviewer's report 3
SPECIFIC POINTS
Minor essential revisions
1. ABSTRACT - "Varicella" misspelt
Corrected

2. METHODS:
VZV antibody test - not specified (i.e. which assay/kit)
Details of assay is given in the previous paper and reference is given

3. RESULTS:
p8: Please explain what "clinical appointments" and "professorial appointments" are.
These explanations are included now

4. p8: "Four (9.3%) medical undergraduates reported that it affected their probability of obtaining a class at the examination."
The meaning of this sentence is unclear.
We changed the structure of this sentence

5. References:
No. 1 is incomplete

Major compulsory revisions
6. ABSTRACT
47/153=30.7% not 29.9%
Thanks. This is corrected in revised manuscript
377/47=8.02 working days lost, not 8.8
1927/47=41 hrs lost, not 44.8
(although it is apparent later on in the results that this "incorrect" figures were obtained using questionnaire answers given by only 43 students; this should be clarified in the abstract)
I have included this explanation in abstract in the revised manuscript.

METHODS:
7. Data collected retrospectively only after final exams - i.e. 5.5 yrs later, highly
likely inaccurate recall of no. of lectures/practicals/etc missed. Could a more accurate picture have been obtained from e.g. attendance records? This is true and a major limitation in our study. Attendance records are difficult to obtain specially for clinical work. We discussed this as a major limitation in our study, in a separate section.

RESULTS:
8. No. followed up said to be 157 but in Fig 1 and abstract, the figure given is 153. This has led to the incorrect percentage figures given in the abstract. Thanks. It should be corrected as 153
9. The total person years of exposure were 8,663. Should this figure be person months? Only 157 were followed up for 5.5 years, giving a maximum possible total of 863.5 person years. This was a silly mistake. It is the number of months as you pointed out. We calculated the person years, which was 722 and included in the text in revised manuscript.

10. p7: "Of them, 38 (88.4%) were residing outside their homes (in a university hostel or a boarding place) when they acquired the disease. Five (11.6%) medical undergraduates acquired the infection while they were at home." Does this refer to development of symptomatic disease or actually site of initial exposure, taking into account the incubation period? Later on, in the discussion (p9), it says: "...at the time of the diagnosis 88% of the medical undergraduates were residing at hostels." This suggests that the authors are referring to development of symptoms, rather than place of exposure. This is actually the development of symptomatic disease. We corrected this in revised manuscript.

11. p7/8: "...the other had a severe secondary bacterial infection." But this patient was not hospitalised. What was the nature of this "severe" infection? the student who had widespread secondary bacterial infection was given only the oral drugs. In results section we change the expression to “moderate to severe in complications”

12. p7: "Only two (4.6%) were hospitalized during the illness, and both had VZV pneumonia." More detail should have been given on the 3 patients (7%) with severe disease, as 7% represents a notable proportion. Adding the clinical impact would have strengthened the authors’ support for immunisation. Eg. did these severe patients miss more academic activities? Impact on academic activities among these students were not different from others. We included this in results section in revised manuscript.

13. p8: "All but one stayed at the hostel during the total duration of the illness. Nine (20.9%) went home on the second or the third day of diagnosis and 27
(62.8%) went home on the same day of diagnosis."
These 2 sentences do not agree with each other. If "all but 1 stayed at the hostel during the total duration of illness", how could 36 have gone home before the 3rd day of diagnosis?
It should be “all but one went home” this is changed in revised manuscript

14. The 6 who reported "no effect on academic activities" - did they continue to attend all classes despite their illness?
This is according to their perceptions. Despite stayed away from classes they thought that it has not had an impact on their academic activities.

DISCUSSION
15. p9: "...went home on the same day of the diagnosis (27 – 62.8%)"
This 62.8% refers to 27/43 (total with VZV), but the denominator should not include the 5 who developed the disease at home.
This calculation is corrected in revised manuscript

16. p11: "...the authors believe (sic) that a cost effective analysis based on the data reported in this study may show that immunization is far more effective than wasting resources on those medical undergraduates who get the disease."
This assumption should not be made based on the study findings, as there was no information on the resources "wasted" on the students (e.g. clinic visits, hospital inpatient stay for the 2 admitted students, drug treatment, travel home for convalescence, etc).
We agree with reviewer and this comment was not based on our finding. we removed this statement and recommended a immunization policy.

17. The authors also did not point out the risk to pregnant/immunocompromised patients from medical students with chickenpox. For example, what proportion of VZV cases occurred during the students' clinical years, when they have contact with patients?
Thanks for this valuable comment and we included a paragraph on this aspect in the revised manuscript.

18. Fig 1: Should be "Followed up for 5.5 years" not 0.5 years
The figure given for "susceptible for VZV infection" is incorrect (153-47=106)
19. Fig 2: Cumulative proportion with VZV at the end of 5.5 years is >0.3, but is given at 29.9% in the results
It should be corrected as 30.7% (47/153). We corrected it in revised manuscript.