Author's response to reviews

Title: An outbreak of coxsackievirus A6 hand, foot, and mouth disease associated with onychomadesis in Taiwan, 2010

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Author's response to reviews: see over
Dear Editor,

Thank you so much for giving us an opportunity to revise this paper. We are grateful for the detailed comments and suggestions provided by each of the reviewers and we believe that their input has greatly improved our manuscript. We have considered comments from reviewers carefully and have made revisions to address their concerns. The changes are underlined and the revised manuscript conforms to the journal style. The item by item response to the reviewer's comment is in the following pages.

Thank you for your sincere consideration and assistance.

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For reviewer 1 (1084906655610268_comment)

1. Methods of VP1 sequence analysis should be explained in little more details

Response: Methods of VP1 sequence analysis is amended on pages 7-8 to provide details of RNA extraction, sequencing, and data prepare and alignment in the study.

2. The specimen type for the diagnosis and typing should be presented. The best specimen type for HFMD diagnosis is vesicular fluid. Unusual virus types (not belonging to enterovirus species A) found in stool or throat samples of HFMD patients can not be taken as a direct proof of causality.

Response: The specimen type for the diagnosis and typing in the study is provided on page 9. Of the 275 enrolled cases, enterovirus was isolated from the pharyngeal swabs of 274 patients and the rectal swab of 1 patient. We also add a discussion on the crucial role of specimen in the study on page 13-14.

3. The timing of the specimen collection in relation to the symptoms should be reported. Although enteroviruses can be excreted into the stool even for months, virus found after the HFMD symptoms have gone may not be the one that caused the disease.

Response: The timing of the specimen collection in relation to the symptoms was reported on page 9. Of the 275 patients, 252 (92%) were requested to submit the specimens within three days of clinical presentation (median duration, 1 day; range, 0
to 8 days). In addition, we introduce the virology reference laboratories network on pages 5-6 to provide more details of obtaining specimen in the study.
For reviewer 2 (1407020492617139_comment)

1. “…typical presentation of skin eruptions on the hands, feet and mouths.” In fact, periungual oval blisters belong to the typical skin lesions.

Response: The reviewer’s comment is essential and very interesting. We also observed periungual oval blisters in patients with HFMD. However, we did not request the information of periungual oval blisters during the telephone interview and the detail of this symptom is not described in the study.

2. “…or onychomadesis, nail separation from the nail bed beginning at the proximal portion.” More precision is needed: onychomadesis starts at the matrix and later grows distal to the proximal portion of the nail bed. Matrix and nail bed MUST not be confused.

Response: We have carefully amended the description of onychomadesis on page 5, 7 and 18 as following, “…onychomadesis, defined as nail separation starting at the matrix and later extending distally to the proximal portion of the nail bed….”

3. “Sixty-six (51%) patients with CA 6 infection experienced desquamation of palms and soles after the infection episode.” And “Nail abnormalities were found in 48 (37%) of 130 patients with CA6 infection.” As one might assume that onychomadesis might be an analogue to desquamation it would be interesting to know whether there was an association of the two.
Response: The association of desquamation and onychomadesis is supplemented on page 10 as following, “Among the 48 patients, 33 (69%) also had desquamation before or during the nail abnormality presentation; presentation of nail abnormality was significantly associated with presentation of desquamation (p=0.002)”.

4. To be discussed: Coxsackie A6 HFMD apparently caused more widespread skin lesions, see table, this would also explain the difference in the percentage of nail alterations in CA6 and non-CA6 HFMD.

Response: we add some discuss on what the reviewer concerns in the second paragraph of the discussion section on page 12. “The fact that HFMD patients with CA6 infection had more widespread skin lesions also explains the difference in the percentage of nail alterations in CA6 and non-CA6 HFMD. Expended skin sites involvement in our study implicated a broad spectrum of direct cell infection by CA6 virus….”

5. “.. skin eruption at unusual skin targets “ would be better .. skin eruption at unusual skin sites.

Response: “skin eruption at unusual skin sites.” is a more appropriate and accurate description and we have amended it according to the reviewer’s kind advice on page 6 and 14.