Author's response to reviews

Title: Influenza A H5N1 and HIV co-infection: Case Report

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Author's response to reviews: see over
Authors response to comments

Reviewer 1:

- Regarding name admitting hospital
  
  *The name and location of the hospital is not mentioned to protect the privacy of the patient given the presence of HIV co-infection. There are few patients with H5N1 and their details are often reported in the local papers such that the patient’s identity could easily be deduced.*

- Regarding health condition before admission

  *It is correct that the patient did not know his HIV status and didn’t report any prior chronic condition and therefore had not had any prior investigation of CD4 counts.*

- Regarding role corticosteroids

  *Corticosteroid administration may have contributed to the presumed development of invasive pulmonary aspergillosis and this is now mentioned along with the possibility that it was related purely to the influenza A/H5 infection. This is based on case reports of invasive pulmonary aspergillosis in influenza, for which some references have been included in the manuscript.*

  Additional reports are here:

  1. Fischer JJ, Walker DH. Invasive pulmonary aspergillosis associated with influenza. JAMA 1979;241:1493-4

- Regarding follow up CD4 counts

  *The patient was not admitted into a study and therefore we were only able to perform tests if blood was made available as part of the clinical investigation. We have presented all CD4/CD8 counts that were performed.*

- Regarding including X-rays

  *Chest x-rays have been provided as a supplementary online figure.*

Reviewer 2

- Regarding what antibiotics were started?

  *The antibiotics given are now listed in an additional table that can be made available online.*
• Regarding what bacterial cultures were requested and what were their results? Laboratory investigations that were performed to identify suspected bacterial or fungal co-infection have been listed in an additional table that can be made available online. The only potentially pathogenic organisms identified were Candida albicans and Aspergillus fumigatus.

• Regarding *P. jiroveci* diagnosis in this patient and the presence of another AIDS-defining illness (TB/MAC) at presentation? *P. jirovecii* diagnostics were not in place and treatment commenced presumptively. We can not exclude the possibility of *P. jiroveci* infection but the patient had reportedly been healthy and admitted 7 days after exposure to sick poultry with symptoms typical of severe influenza A/H5N1 including rapid onset pneumonia and productive cough. In contrast, *Pneumocystis pneumonia* infections generally have a slower course with patients presenting several weeks after symptom onset with a dry cough. It is similarly unlikely that the presenting signs and symptoms were due to mycobacterial infection although again we can not rule out the possibility of infection. Acid fast bacilli were not detected in sputum smears and the Mantoux/PPD skin test was negative and we did not detect TNF-α, a cytokine that has been found at elevated levels in patients with mycobacterial infection. We believe that the patient presented with symptoms attributable to highly pathogenic influenza H5N1 with no evidence of an AIDS-defining illness at admission.

• Regarding “Also, although the rising CRP, neutrophilia and return of the patient’s fever is mentioned, only the findings related to Aspergillus are mentioned. Here the (presumably) negative findings for other secondary bacterial pathogens should be mentioned. Are these clinical findings explained by the Aspergillus alone?“ The inclusion of Additional Table 1 should help to clarify that *A. fumigatus* was the only organism that we could identify as a possible cause of the patient’s clinical deterioration with rising CRP, neutrophil counts and recrudescence of fever.

• Regarding “it is unlikely that the oseltamivir contributed much to this patient’s clearance of H5N1 - the authors should briefly mention this - again for less specialised readers” We have noted that the contribution of Oseltamivir to virus clearance may have been negligible.

• Please would the authors add the presenting CD4 cell count in the case history. We have included the CD4 count at admission in the text.

• Regarding “low presenting viral load for a new HIV diagnosis - is this typical of the patients presenting with newly diagnosed HIV infection in Vietnam? Most newly diagnosed cases of HIV elsewhere would have much higher viral loads. For the purposes of this report, would this be an unusual case? Can the authors speculate on the possible difference in presentation and outcomes for patients with H5N1-HIV co-infection in patients with higher (more typical?) HIV loads at diagnosis? We have noted that the patients HIV viral load is low and that it is difficult to determine whether there had been any progression to AIDS before H5N1 infection because lymphopenia is also a consequence of severe influenza A. We do not want to speculate about the outcome in patients that have documented progression to AIDS because we can not know where to place our patient. We
believe that our comment regarding CD4 and control of H5N1 viremia would hold for patient’s presenting with higher loads.

- Regarding “Could they expand on this by describing and comparing how such cytokines behave in HIV-infected patients? How do the authors know that these cytokine profiles are not a result of the HIV-infection, or at least have not been influenced in anyway by the HIV-co-infection? There should be some additional discussion about this.

We have noted the possible contribution of HIV to the patient’s cytokine profile and have provided reasons why we believe that the cytokines detected are principally produced in response to H5N1.