

<b>Institution: The University of Oxford</b>
<b>Unit of Assessment: 1</b>
<b>Title of case study:</b>  <p style="text-align: center;"><b>ON THE FRONT LINE: DEFINING THE CLINICAL FEATURES OF H5N1 IN VIETNAM</b></p>
<b>Summary of the impact:</b>  <p>The human influenza A (H5N1) infection emerged in China in 2003 and quickly spread throughout Asia, killing more than half of those infected. Researchers at the Oxford University Clinical Research Unit in Vietnam (OUCRU) provided rapid information to the World Health Organization (WHO) on the pathological and clinical features of H5N1 infection in humans, as it emerged in Vietnam. The WHO used this front line information to inform recommendations for the investigation, diagnosis, management, and treatment of H5N1 globally, ultimately reducing mortality by up to 19%.</p>
<b>Underpinning research:</b>  <p>H5N1, also known as “bird flu”, is a type of influenza virus that causes a highly infectious and deadly respiratory disease in birds. Initially identified in a farmed goose in China in 1996, the first human case of avian influenza was reported 12 months later, in Hong Kong. After a five-year hiatus, H5N1 infection was again reported in birds and humans in Hong Kong in February 2003, and quickly spread from China throughout Asia. The first human case of H5N1 was reported in Vietnam in January 2004.</p> <p>OUCRU researchers swiftly undertook studies on the initial 10 patients admitted to hospitals in Ho Chi Minh City and Hanoi, to gain a better understanding of this largely unknown and deadly virus. This research was significant in classifying the clinical and pathological features of H5N1 infection in and in identifying the preliminary epidemiologic findings<sup>1</sup>. The 2004 study showed that H5N1 infection resulted in fever, respiratory symptoms, and lymphopenia, and confirmed the high risk of death. It also confirmed that the virus was transmitted from infected poultry in all 10 cases<sup>1</sup>.</p> <p>In a further study conducted in 2005 OUCRU researchers investigated the use of antiviral treatment in the disease. They identified high-level resistance to antiviral influenza treatment with Oseltamivir in two of eight Vietnamese patients. While Oseltamivir treatment led to a rapid decline in viral loads among six patients (all of whom survived), the two resistant patients died of H5N1 infection, in spite of early treatment<sup>2</sup>. This study identified the effectiveness of existing antiviral treatments in some cases, whilst also highlighting the significant danger of resistance in the event of viral spread.</p> <p>As avian and human cases of H5N1 began to spread from Asia to Siberia in 2005 the WHO assembled a review panel of 13 clinicians and experts from around the world to identify key features of H5N1 infection in humans. <i>The Writing Committee of the World Health Organization Consultation on Human Influenza</i><sup>3</sup>, including four researchers from OUCRU, provided a comprehensive review of essential information on H5N1 transmission, clinical severity, diagnosis, pathogenesis, and responses to treatment. This review also exposed the urgent need for additional clinical and epidemiological research<sup>3</sup>.</p> <p>Accordingly, at the height of the outbreak in 2006, researchers from OUCRU performed further immunological and viral studies to better understand the virulence of H5N1 infection in humans. This study showed that an adverse outcome during human H5N1 infection was determined by high viral loads and inflammatory responses; it also emphasised the importance of early diagnosis and</p>

treatment<sup>4</sup>. This study provided *The Writing Committee of the Second World Health Organization Consultation on H5N1 Virus*, with key information on the virulence of the infection in humans<sup>5</sup>.

To better understand treatment options for human H5N1 infection, OUCRU researchers conducted a retrospective study of H5N1 management in Vietnam between 2004 and 2006. This study showed that while Oseltamivir treatment is indeed beneficial to patients, treatment with corticosteroids is associated with an increased risk in mortality<sup>6</sup>.

#### References to the research:

1. Tran, T. H. *et al.* Avian influenza A (H5N1) in 10 patients in Vietnam. *N. Engl. J. Med.* **350**, 1179–1188 (2004).  
  
***Early study reporting clinical features and preliminary epidemiologic findings in 10 patients with confirmed cases of human H5N1. Referred to as (Hien et al. 2004) in WHO guidelines.***
2. de Jong, M. D. *et al.* Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N. Engl. J. Med.* **353**, 2667–2672 (2005).  
  
***Study showing that while Oseltamivir treatment is successful, resistance may occur in a small percentage of patients, highlighting the need for alternative or combination antiviral therapy.***
3. Beigel, J. H. *et al.* Avian influenza A (H5N1) infection in humans. *N. Engl. J. Med.* **353**, 1374–1385 (2005).  
  
***Review from ‘The Writing Committee of the World Health Organization Consultation on Human Influenza’, providing essential information on human H5N1.***
4. de Jong, M. D. *et al.* Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nat. Med.* **12**, 1203–1207 (2006).  
  
***A study showing that high viral load and inflammatory responses are key outcomes of H5N1 infection in humans, emphasising the importance of early diagnosis and treatment.***
5. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus Abdel-Ghafar, A.N. *et al.* Update on avian influenza A (H5N1) virus infection in humans. *N. Engl. J. Med.* **358**, 261–273 (2008). doi:10.1056/NEJMra0707279  
  
***WHO Writing Committee Report citing (de Jong, M.D. et al. 2006) in regards to the virulence of H5N1 infection in humans. de Jong was also listed as an author on this report.***
6. Liem, N. T. *et al.* Clinical features of human influenza A (H5N1) infection in Vietnam: 2004-2006. *Clin. Infect. Dis.* **48**, 1639–1646 (2009). doi:10.1086/599031  
  
***Study showing that treatment with corticosteroids is associated with an increased risk in mortality.***

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### Details of the impact:

The rapid spread of avian and human H5N1 infection throughout Asia in 2004 occurred less than 12 months after the global SARS outbreak, which almost reached pandemic proportions (8,273 cases worldwide, 9.6% fatality) in 2003. Not surprisingly the unknown and significantly more deadly human H5N1 virus, with a fatality rate of 60%, became a high priority concern to the WHO. Fortunately, unlike SARS, first responders soon realised that human cases of H5N1 were mostly contracted through direct contact with birds, reducing the frightening possibility of human-to-human infection. As a result, containment of H5N1 in humans has been relatively successful. The WHO recently reported a total of 608 confirmed human cases of H5N1 and 359 deaths between 2003 and 2012.

As Vietnam faced the third largest number of all cases worldwide (after Egypt and Indonesia) the University of Oxford's OUCRU researchers in Vietnam were at the frontline of the global investigation into H5N1. As a result, Oxford's research into the epidemiological and pathological features of human H5N1 infection provided the WHO with key evidence for rapid clinical guidelines for the management and investigation of H5N1 infection globally during the period from 2006-2013.

### **WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus**<sup>7</sup>

In early 2006, as mortality rates rose and infection spread throughout the world, the WHO assembled an international panel of experts and clinicians, including Professor Jeremy Farrar (Director of OUCRU Vietnam), to assist in developing rapid advice for the pharmacological management of patients with human H5N1 infection.

The early research from OUCRU<sup>1</sup> provided the panel with key data on the clinical features of H5N1 infection in humans, as well as preliminary epidemiologic findings. Research from OUCRU Vietnam directly led to the WHO's strong recommendations for the use of Oseltamivir antiviral drugs in patients with, "confirmed or strongly suspected H5N1 infection"<sup>2,3</sup>.

The 2006 guidelines also included a clinical algorithm adapted from an algorithm used at the Hospital for Tropical Diseases, in Ho Chi Minh City, by OUCRU's Dr Tran Tinh Hien<sup>7</sup>. The WHO guidelines for the management of H5N1 have remained in place since 2006 and have been the major instrument for the treatment of cases in the period 2006-2013.

### **WHO guidelines for investigation of human cases of avian influenza A(H5N1)**<sup>8</sup>

The WHO's 2007 guidelines provide a framework for public health authorities and researchers to investigate H5N1 infection in humans. Based on research from OUCRU the guidelines recommend that clinicians investigating patients with possible H5N1 infection should obtain background information on the patients family and household, including all people who have come into contact with the patient within two weeks of the onset of symptoms. This information directly cites research from OUCRU, which shows that H5N1 virus is mostly detected in respiratory specimens within two weeks of symptomatic illness<sup>2-4</sup>. Studies from OUCRU also underpin recommendations for the collection of specimens (for laboratory testing) in patients with fever or respiratory symptoms, followed by appropriate medical management, including antiviral therapy (Oseltamivir)<sup>8</sup>. The WHO guidelines for the investigation of H5N1 have been used continuously for the investigation of sporadic cases since 2007 without modification.

### **WHO guidelines for pharmacological management of pandemic influenza A(H1N1) 2009 and other influenza viruses. Part II – review of evidence**<sup>9</sup>

OUCRU's research on H5N1 has additionally had important impact on the management of other forms of influenza since 2008. H1N1 influenza or "Swine Flu" was first identified in April 2009, claiming the lives of over 294,500 people globally in just 12 months. After declaring H1N1 a pandemic in June 2009, the WHO published recommendations for the *Pharmacological*

*Management of Pandemic Influenza A (H1N1) in August 2009.* In the absence of any systematic reviews for the treatment of H1N1, the WHO used OUCRU Vietnam's 2009 study of H5N1 to provide key evidence regarding safety concerns for corticosteroid treatment in influenza A viruses<sup>6</sup>. As a result of this research routine use of corticosteroids is no longer recommended in patients suffering from influenza A viruses<sup>9</sup>.

### **Reduction in mortality**

Cases of H5N1 infection have slowly been decreasing since the height of the outbreak in 2006, when a reported 115 cases resulted in 79 deaths worldwide<sup>10</sup>. In 2012 these numbers had reduced significantly, down to just 30 cases and 19 related deaths worldwide. Although the reduction in mortality is in line with the reduction of cases, a small decrease can be seen in mortality rates from 68.6% in 2006 to 63.3% in 2012. In Vietnam these rates have fallen even further from 69% mortality in 2006 to 50% in 2012<sup>10</sup>. While there are many factors involved in the reduction in human cases of H5N1, improved clinical management (particularly in Vietnam) has been a key determinant of increased survival.

### **Sources to corroborate the impact:**

7. *World Health Organization WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus* [online]. Geneva: WHO Press. (2006). Available at: [http://whqlibdoc.who.int/hq/2006/WHO\\_PSM\\_PAR\\_2006.6\\_eng.pdf](http://whqlibdoc.who.int/hq/2006/WHO_PSM_PAR_2006.6_eng.pdf) [Accessed 2013]  
***WHO rapid advice guidelines for pharmacological management of H5N1 citing several papers from OUCRU Vietnam.***
8. *World Health Organization WHO guidelines for investigation of human cases of avian influenza A(H5N1)* [online]. (2007). Available at: [http://www.who.int/influenza/resources/documents/WHO\\_CDS\\_EPR\\_GIP\\_2006\\_4r1.pdf](http://www.who.int/influenza/resources/documents/WHO_CDS_EPR_GIP_2006_4r1.pdf) [Accessed 2013]  
***WHO guidelines for investigation of H5N1 citing several papers from OUCRU Vietnam.***
9. *World Health Organization WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses* [online]. (2010). Available at: [http://www.who.int/csr/resources/publications/swineflu/h1n1\\_guidelines\\_pharmaceutical\\_mngt.pdf](http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf) [Accessed 2013]  
***WHO guidelines for pharmacological management of H1N1, and other influenza viruses, citing OUCRU Vietnam paper on H5N1 treatment.***
10. *World Health Organization Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2012* [online]. (2012). Available at: [http://www.who.int/influenza/human\\_animal\\_interface/EN\\_GIP\\_20120810CumulativeNumberH5N1cases.pdf](http://www.who.int/influenza/human_animal_interface/EN_GIP_20120810CumulativeNumberH5N1cases.pdf) [Accessed 2013]  
***WHO report on number of cases and deaths related to H5N1 between 2003 and 2012.***