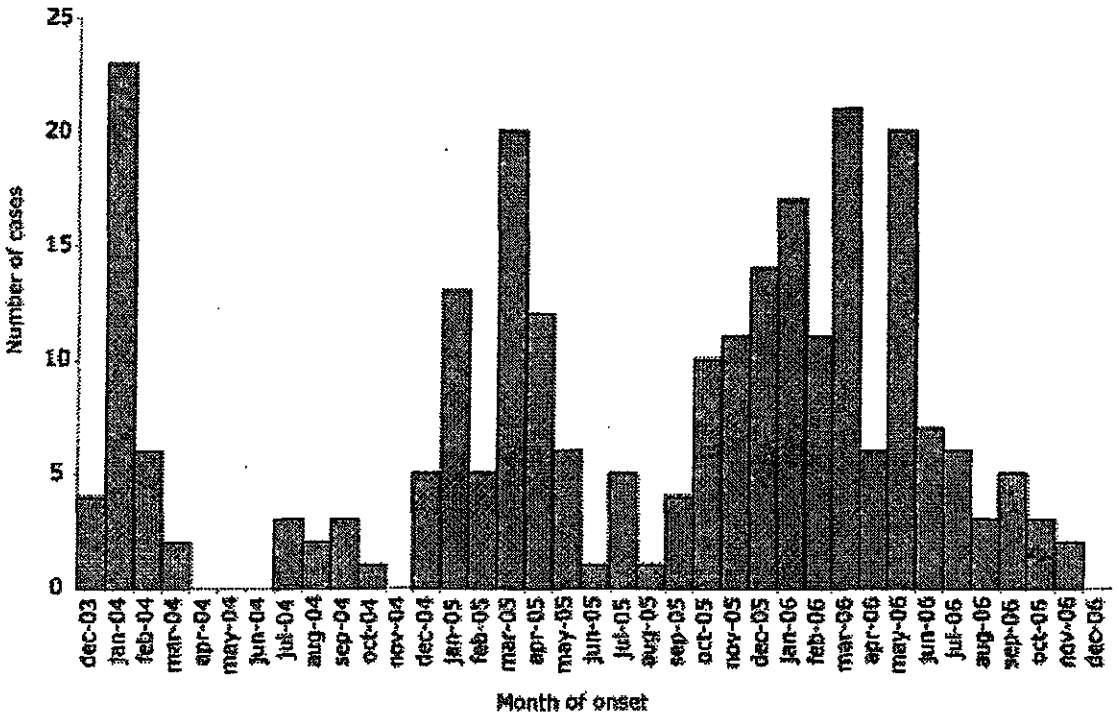


Based on reports to WHO published at http://www.who.int/csr/don/archive/disease/en/index.html using method used by WHO and descri[illegible]in Reference 2

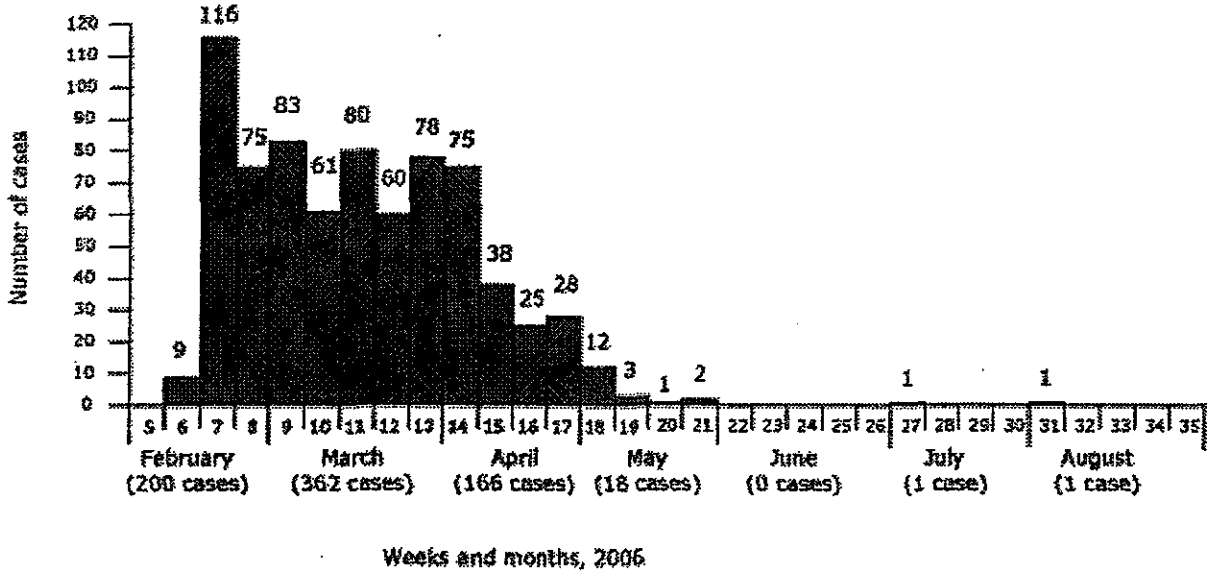
Animals still source of human infections

In 2003, highly pathogenic avian influenza viruses type A/H5N1 (Asian strain) re-emerged and spread rapidly, infecting poultry and some humans in a number of southeast Asian countries, particularly Vietnam, Thailand, Cambodia and Indonesia [7]. The mechanism for this spread remains unclear although it is suspected that it was as much related to trade of poultry and poultry products as the movements of wild birds. An exceptional multi-species epizootic at Qinghai Lake in northwest China in May 2005 seemed to demonstrate a role of wild birds in the spread of the viruses beyond Asia [8]. From Qinghai, the virus spread to Central Asia, Europe and some African countries with human cases reported in Turkey, Iraq, Azerbaijan, Djibouti and Egypt [1,2,7]. Now, at the end of 2006, the virus has been confirmed in birds in over 50 countries, with birds (almost entirely domestic poultry) being the source of human infections in ten of these [2,7,9].

Some countries are facing up to endemic infection in their national poultry flock and consequent ongoing risks to humans with domestic poultry, while others are barely affected. At a recent world conference on avian influenza and pandemic preparedness [footnote], field reports on efforts to control avian influenza were presented by national and international authorities. There is evidence that H5N1 viruses have now become entrenched in backyard poultry in Indonesia, and perhaps also Egypt [10,11]. Large scale programmes of poultry immunisation have been underway in China and Vietnam where, since 2005 and until an outbreak in the Mekong Delta this week in Vietnam [12], poultry outbreaks had stopped being reported [9]. The scale of immunisation in China, with potentially 14 billion poultry needing to be vaccinated twice annually (in spring and autumn), is the largest immunisation programme against avian influenza ever attempted anywhere in the world.

In the European Union (EU), the virus has not become established in poultry nor have there been there any human infections even though the virus was found in wild birds in at least fifteen countries in the spring of 2006 (Figure 2). Some cats and a pine marten that fed on infected birds were also infected [13]. The bird movements to the EU may have been exceptional following an unusually cold spell of weather in Russia and Central Asia in early 2006. After the spring wave, there have only been confirmation of sporadic H5N1 infections in birds in Spain and Germany (Figure 2).

Figure 2. Highly pathogenic avian influenza cases in wild birds in the EU member states notified to the European Commission in 2006.



Based on reports through reports to the European Commission Animal Disease Notification System (ADNS) http://ec.europa.eu/food/animal/diseases/adns/adns_en.htm as cited in Reference 14. Cases are almost entirely due to A/H5N1.

The successful protection of domestic birds in EU countries was primarily due the robust and consistent application of veterinary measures directed under EU legislation. As a consequence, only five poultry outbreaks occurred in the EU and these were rapidly contained [14,15]. However, the continuing sporadic reports demonstrate that the virus may still sometimes be present and therefore, routine biosecurity measures and early warning systems cannot be relaxed. There were major outbreaks of infection in wild birds and domestic poultry in the Danube delta in 2005 and 2006, and the Romanian authorities successfully contained these. There will be an additional challenge for EU authorities if it occurs here again after Romania joins the European Union next month.

Continuing evolution of the viruses

There remains the risk of emergence of a human pandemic strain through either mutation of the H5N1 virus or incorporation of part of its genome, through recombination, into a human influenza virus [7,16]. As well as extending their range geographically the H5N1 viruses have diversified genetically into clades and sub-clades. Clade 1 dominated in 2003-2004, then clade 2 became more important. Clade 2 has subsequently developed into three distinct sub-clades [7,17,18]. The balance between the types of virus continues to change, for reasons that are not clear. For example, since 2005, the Fujian-like virus (clade 2, sub-clade 3) has become the dominant type found in surveillance of market poultry across southern China [17]. Fortunately, despite genetic changes, there has been no evidence of significant change in the viruses' effects on humans. The genetic differences and the fact that the virus is continuing to change are, however, important considerations since the clades have different antiviral resistance profiles and continuing genetic change will alter the necessary composition of human H5N1 vaccines referred to as 'pre-pandemic vaccines' [7,18]. Two countries have already committed to purchasing these vaccines and others are considering to do so, although it is by no means clear that an H5 based pandemic is inevitable[7,16].

Discussion

There are many important unknown factors relating to the spread of H5N1, including the current distribution of the viruses. The pattern of H5N1 infection in Africa remains elusive because surveillance is especially weak there, apart from Egypt and some parts of Nigeria [11,19]. The picture is also incomplete in eastern Asia - following two human cases in summer 2006, the situation has improved in Thailand, but the risk remains [20]

A good picture of the zoonotic situation in China is currently not available and it is also still unclear whether the H5N1 vaccination programmes in China and Vietnam have been successful in eliminating or just reducing the level of infection in poultry, and whether low levels of circulating viruses pose a significant human risk [7,21] One negative consequence of any success of vaccination programmes is that surveillance for sporadic human cases is made more difficult, since now, when atypical pneumonias occur, there is rarely the marker of local poultry deaths to inform decisions on whether to test the patient for H5N1 virus.

The relative role of the commercial movement of animals and wild birds in the international spread and local distribution of H5N1 viruses remains controversial. However, it is local preparedness and response that are most crucial in determining the outcome in terms of domestic animal and human health when countries are challenged by the virus. Nationally organised veterinary services, which would enable effective surveillance/early warning and biosecurity systems, are crucial so that authorities can respond promptly when

infections are first suspected in either birds or humans. Where biosecurity is poor and veterinary services ineffective, viruses can become endemic and the situation can be complicated by the virus cycling between poultry and wild birds [10,11,17].

One challenge developing countries face is a lack of financial support for the veterinary services and biosecurity measures, even though avian influenza has demonstrated that it is truly an international problem. There has been some progress towards a solution for the financial issues by the involvement of the World Bank, the European Commission and the United Nations System Influenza Coordinator (http://www.undg.org/content.cfm?id=1482), which have mobilised and released donations that had been pledged by national and international donors [22].

The data indicate that H5N1 avian viruses remain poorly adapted to humans. With a high enough viral challenge and perhaps some genetic host susceptibility the viruses can infect humans, in which case they are then often lethally pathogenic, although they are still unable to transmit efficiently between humans [2-5,16]. The H5N1 viruses have been around for nearly a decade and it might be tempting to conclude that if they were going to proceed to form or contribute to a pandemic strain, they would have done so by now. However, it should be remembered that it is thought that the avian influenza virus which contributed to the 1918-19 'Spanish Influenza' H1N1 pandemic strain had been around for some years before it became part of a virus that could efficiently transmit between humans and so be a successful pandemic strain [23].

Apart from the threat from H5N1 there are still many issues around influenza pandemic preparedness (irrespective of the virus type) which need urgent attention. One key area is how authorities in developing countries should best focus their efforts with preparedness, given often very limited resources and many more immediate competing priorities. So far, most discussion, ideas and research have been more suited to settings in better resourced nations. This area needs a multi-sector approach as medical services will not have the most to offer in poorer countries when it comes to preparing for a pandemic. It is hoped that the next world meeting, planned for New Delhi in late 2007 (and intervening technical meetings), will provide opportunities to tackle preparedness in developing nations as well as dealing with avian influenza.

Footnote. The Bamako conference organised by the African Union, the Interafrican Bureau for Animal Resources and the European Union. International Conference on Avian and Human Pandemic Influenza, (Ministerial Meeting and Pledging Conference) 6-8 December 2006, Bamako.
Documentation and presentations at the conference are viewable at : http://www.avianinfluenzaconference4.org/index.php?id=61

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別紙様式第2-1

No. 15

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2006. 12. 5	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況	ProMED 20061201-3394, 2006 Dec 1. 情報源:CIDRAP News, 2006 Nov 29.	公表国 WHO
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			

研究報告の概要

○WHOがH5N1ヒト症例の診断ガイドラインを発表

WHOは、ウイルスにより光を当て、パンデミック株への変異の検出を容易にするために、H5N1鳥インフルエンザのヒト症例診断のためのガイドラインを発表した。

14ページのガイドラインは、患者の問診、周辺で他の症例を捜索することによる接触歴の調査、ヒトーヒト感染の何らかの徴候を発見するためのデータのふるいわけなど、各症例の徹底的な調査を求めている。ガイドラインでは、臨床検査の結果が出る前に疑い症例の調査を行うことを要請している。

症例診断の目的は、(1)H5N1の診断確定(2)早期発見、治療、予防による疾病と死亡の削減(3)感染源の早期特定と予防策実施による拡大防止(4)ヒトーヒト感染がより効率的になってきているかどうかの確定(5)各症例の疫学的、臨床的、ウイルス学的特徴の識別(6)臨床医、調査担当者、行政の間で常に情報を交換し、適切な対応を可能とすることである。

患者の接触歴の調査に当たって、WHOは患者は発症前1週間、治癒後2週間感染能を持つとみなすべきであるとしている。接触歴調査に加えて、調査担当者は家々の訪問や、医療機関や開業医、研究所への電話調査を行い、他のH5N1可能性例を積極的に探すべきであると勧告している。検査については、「商用の迅速診断検査の性能は不明であり、サブタイプの判別は出来ないため確認検査が必要である」としている。

ガイダンスでは、ウイルスのヒト間の伝播性における変化の手がかり、症例のクラスターを評価する上での注意点についても述べている。また、感染地域内の職業上リスクがある人の血清学検査、感染リスク要因を評価するための症例対照研究などの補足的研究の実施を提案している。

報告企業の意見	今後の対応
WHOがH5N1型トリインフルエンザのヒト症例の診断ガイドラインを発表したとの報告である。	H5N1型トリインフルエンザは日本でも鶏から検出されており、新型インフルエンザが流行した場合、献血者減少につながることも予想される。今後も引き続き情報の収集に努める。

使用上の注意記載状況・その他参考事項等

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合成血-LR「日赤」
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血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

57

Archive Number 20061201.3394
Published Date 01-DEC-2006
Subject PRO/AH> Avian influenza, human (185): WHO investigation guidelines

AVIAN INFLUENZA, HUMAN (185): WHO INVESTIGATION GUIDELINES
****
A ProMED-mail post
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ProMED-mail is a program of the
International Society for Infectious Diseases
<http://www.isid.org>

Date: Thu 30 Nov 2006
From: Brent Barrett <salbrent@sbcglobal.net>
Source: CIDRAP News, Wed 29 Nov 2006 [edited]
<http://www.cidrap.umn.edu/cidrap/content/influenza/avianflu/news/nov2906inves

The World Health Organization (WHO) this week released guidelines for investigating human cases of H5N1 avian influenza in an effort to shed more light on the virus and improve the chances of detecting changes that could turn it into a pandemic strain.

The 14-page document calls for a thorough probe of each case, from interviewing the patient and searching for contacts through hunting for other cases nearby and sifting data for any signs of human-to-human transmission. It calls for investigating suspected cases before laboratory test results are available.

The new guidance comes less than a month after the WHO issued a report on how much remains unknown about the H5N1 virus. Written by a group of leading flu experts, that report, issued Nov 2, said H5N1 illness is fundamentally different from ordinary flu in its severity and range of manifestations. Among other things, the panel called for research to determine why children and young adults seem especially susceptible and whether genetic factors increase the risk of infection or transmission among blood relatives.

The introduction to the new guidance says, "The document reflects and incorporates the practical field experience gained by investigators working at international, national, and sub-national levels during investigations of A(H5N1)."

The intention is that local health agencies will use the guidelines to build their own investigative plans and procedures, the WHO says. The purposes of case investigation, according to the guidelines, include:

(1) Confirming the diagnosis of H5N1;
(2) Reducing illness and death by rapidly identifying cases and starting appropriate treatment and precautions;
(3) Reducing further spread by identifying possible sources of exposure and implementing prevention and control measures;
(4) Determining if human-to-human transmission is becoming more efficient;
(5) Identifying the key epidemiologic, clinical, and virologic characteristics of each case;
(6) Ensuring timely exchange of information among clinicians, health investigators, and government officials to facilitate appropriate responses.

In advice on searching for patients' contacts, the WHO says investigators should assume that patients are infectious for 1 week before onset of illness and 2 weeks afterward, even though the

infectious period for treatment, depending on their risk of exposure, as defined in other WHO guidance.

Besides tracing contacts, investigators should search actively for other possible H5N1 cases by going from house to house and possibly conducting telephone surveys of healthcare facilities, practitioners, and labs, the WHO advises.

The agency recommends against using rapid diagnostic tests for the H5N1 virus. "The diagnostic accuracy of commercially available rapid tests is unknown, and if the test result is positive, differentiation between influenza A subtypes is not possible and confirmatory tests must be done," the document says.

In its 2 Nov 2006 report, the WHO said a rapid, reliable diagnostic test for H5N1 infection was urgently needed.

The guidance document discusses potential clues to a change in the virus's human transmissibility and what to look for in evaluating clusters of cases. It also suggests doing complementary studies, such as seroprevalence surveys of people with possible occupational risk in affected areas and case-control studies to evaluate risk factors for infection.

[As of 30 Nov 2006, the full report: "WHO guidelines for investigation of human cases of avian influenza A(H5N1) - October 2006" at
<http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_6
is currently under revision. - Mod.CP]

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Brent Barrett
<salbrent@sbcglobal.net>

[These guidelines reflect concern that human cases of H5N1 virus may be escaping detection because of some difficulties encountered in diagnosis, as expressed recently in 2 papers published in the New England Journal of Medicine (see ProMED-mail post entitled: "Avian influenza, human (181): Indonesia, Turkey 20061124.3337" for detailed discussion).

See also Influenza research at the human and animal interface. Report of a WHO working group. Geneva, Switzerland. 21-22 Sep 2006. WHO/CDS/EPR/GIP/2006.3
<http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_
- Mod.CP]

[see also:
Avian influenza, human (181): Indonesia, Turkey 20061124.3337
Avian influenza, human (178): receptor mutations 20061116.3279
Avian influenza, human (175): new sub-lineage 20061108.3201
Avian influenza, human (173): new sub-lineage 20061102.3144
Avian influenza, human (172): genetic disposition 20061102.3140
Avian influenza, human (140): atypical infections 20060905.2522
Avian influenza, human (133): WHO case definitions 20060830.2467
Avian influenza, human (91): WHO epidemiology analysis 20060630.1812]
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INFLUENZA >> AVIAN INFLUENZA >> NEWS >>

WHO urges careful investigation of H5N1 cases

Editor's Note: Shortly after publication of this article, the guidelines referred to were removed from the WHO Web site pending further peer review. They will be republished soon, according to the agency.

Nov 29, 2006 (CIDRAP News) – The World Health Organization (WHO) this week released guidelines for investigating human cases of H5N1 avian influenza in an effort to shed more light on the mysterious virus and improve the chances of detecting changes that could turn it into a pandemic strain.

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- Determining if human-to-human transmission is becoming more efficient
- Identifying the key epidemiologic, clinical, and virologic characteristics of each case
- Ensuring timely exchange of information among clinicians, health investigators, and government officials to facilitate appropriate responses

In advice on searching for patients' contacts, the WHO says investigators should assume that patients are infectious for 1 week before onset of illness and 2 weeks afterward, even though the infectious period for the virus has not been determined. Healthy contacts should be monitored and given preventive antiviral treatment, depending on their risk of exposure, as defined in other WHO guidance.

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See also:

WHO guidelines for investigation of human cases of avian influenza A(H5N1)
http://www.who.int/csr/resources/publications/influenza/WHO_CDS_EPR_GIP_2006_4/en/index

Nov 2 CIDRAP News story "WHO report calls H5N1 vaccine stockpiling premature"