

The medical community should insist that we invest the resources needed to do trials that ascertain the effect of interventions on patient-important outcomes. This policy will prevent the premature dissemination of therapies that ultimately prove harmful, facilitate patients' participation in decisionmaking, and speed the day when we can confidently offer treatments that will provide long-term benefit to patients with diabetes.

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We declare that we have no conflict of interest.

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## Pathology of human H5N1 infection: new findings

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Human cases of the highly pathogenic avian influenza virus H5N1 were first documented in Hong Kong in 1997. From late 2003, this disease became endemic in Asia, often but not invariably associated with an outbreak in poultry. According to WHO, the total number of cases reported from 12 countries until July 25, 2007, was 319, with a fatality rate of 60%.<sup>1</sup> Sporadic cases of person-to-person transmission have been reported and a pandemic outbreak poses a serious threat. The table summarises the results of the few postmortem studies after human H5N1 infection. In today's *Lancet*, Jiang Gu and colleagues report new findings from two postmortem studies in people who had H5N1, including a rare case of a pregnant woman and her fetus.<sup>2</sup>

In birds, H5N1 affects multiple organs. In human beings, H5N1 infection mainly affects the lower respiratory tract, causing diffuse alveolar damage and respiratory failure, by contrast with human influenza infection, which mainly affects the upper respiratory tract. Diarrhoea is also a common presenting feature of H5N1, occurring in up to 70% of patients. Viral RNA was detected in seven of nine faecal samples tested.<sup>9</sup> Positive and negative strands of viral RNA in the intestine in case 5 (table) and in Gu and colleagues' two cases

suggest viral replication occurred in the intestine. This finding could have important implications for infection control. The virus was also cultured from cerebrospinal fluid and faecal, throat, and serum specimens from a child who presented with diarrhoea before developing coma.<sup>10</sup> Cases 1 and 5, both children, had brain lesions, although the role of H5N1 in these lesions remained unclear. Gu detected viral genomes in the neurons of an adult brain without pathological changes. The neurotropism of H5N1 in human beings needs further study. Gu also showed viral replication in T cells in lymph nodes. Whether this infection is related to the commonly reported lymphoid depletion is unclear. Viral replication in the placenta, lung, and circulating mononuclear cells of the fetus supports the possibility of vertical transmission. The absence of pathological changes in the immunologically incompetent fetus is taken as evidence that viral replication itself is not pathogenic. Speculation about the fate of the fetus if the mother survived the infection is interesting. With the development of antibodies in the mother and their transplacental crossing into the fetus, pathological lesions in the fetus may result. Thus data are accumulating in support of extrapulmonary infection at many sites in the body.

In the respiratory tract, the receptor for human-adapted influenza viruses,  $\alpha$ 2,6-linked sialic acid, is mostly expressed in the upper airways; the cells in the alveoli and terminal bronchiole express  $\alpha$ 2,3-linked sialic acid, the receptor for avian influenza viruses.<sup>11</sup> Viral replication has been detected in type II pneumocytes in the lung, but also in ciliated and non-ciliated epithelial cells of the trachea in Gu and colleagues' study, which contrasts with a previous report (case 5).<sup>7</sup> Receptor affinity is believed to be a major factor that prevents efficient person-to-person transmission.<sup>12</sup> Successful infection of the epithelial cells in the trachea by H5N1 virus has two implications. First, other mechanisms that mediate virus entry might exist. Second, the virus might develop mechanisms to overcome respiratory-tract defences. However, Gu and co-workers implied that infection in both ciliated and non-ciliated epithelial cells of the

trachea was not related to substantial changes in the receptor-binding sites of the virus. Information about receptor affinity in the nasal mucosa and other sites of the upper respiratory tract was not available. The clinical significance of such findings needs further assessment.

The pathogenic mechanisms of this highly fatal infection remain unclear. The concentrations of inflammatory mediators related to an innate immune response in fatal cases were higher than in non-fatal cases. High concentrations of cytokines in the blood and the innate immune responses might contribute to pathogenesis.<sup>3,4,9</sup> In the adult patient who died on day 9 of disease in Gu and colleagues' report, the finding of sparse infected pneumocytes in the lungs contrasted with the severe and widespread histopathological changes of diffuse alveolar damage, which is consistent with a late phase of viral eradication in an immunocompetent host.

Case: year, place	Sex (age)	Time from onset of disease to death (days)	Main extrapulmonary findings	H5N1	Influenza virus
1: 1997, Hong Kong <sup>3</sup>	Female (13 years)	30	Reactive haemophagocytic syndrome, lymphoid depletion, microglial nodule in cerebral white matter	Negative: bone marrow, brain, heart, intestine, liver, lung, lymph node, spleen, kidney*†	Negative: tissues as listed on left (H5 antigen‡)
2: 1997, Hong Kong <sup>3</sup>	Male (25 years)	30	Reactive haemophagocytic syndrome, lymphoid depletion	Negative: bone marrow, brain, heart, intestine, liver, lung, lymph node, spleen, kidney*†	Negative: tissues as listed on left (H5 antigen‡)
3: 2003, Hong Kong <sup>4</sup>	Male (33 years)	10	Reactive haemophagocytic syndrome, lymphoid depletion	Positive: lung† Negative: bone marrow, brain, kidney, liver, spleen†	..
4: 2004, Thailand <sup>5</sup>	Male (26 years)	10	Reactive haemophagocytic syndrome, lymphoid depletion	Positive: lung*	Positive: epithelial cells of lung (influenza A nucleoprotein‡)
5: 2004, Thailand <sup>6,7</sup>	Male (6 years)	17	No reactive haemophagocytic syndrome, small foci of necrosis in brain	Positive: lung, small and large intestine (positive and negative strands of RNA),* spleen (negative strands of RNA)* Negative: adrenal glands, brain, bone marrow, kidneys, liver, pancreas, plasma,* spleen (positive strands of RNA)*	Positive: pneumocytes (influenza A nucleoprotein‡) Negative: small and large intestines, trachea (influenza A nucleoprotein‡)
6-8: 2004, Thailand <sup>8</sup>	..	..	Examination of lung and spleen only: atypical lymphocytes in spleen	..	..
9: 2005, China <sup>2</sup>	Pregnant female (24 years)	9	Reactive haemophagocytic syndrome, lymphoid depletion	Positive: lung, intestines, heart, spleen, liver, kidney, placenta*¶	Positive: trachea, pneumocytes, cytotrophoblasts, Hofbauer cells (nucleoprotein and haemagglutinin‡), lymph node (T cells), small intestine§ Negative: bronchi, spleen, heart, endothelial cells, hepatocytes, Kupffer cells, kidney, syncytiotrophoblasts, circulating mononuclear cells‡§ small intestine‡
9: 2005, China <sup>2</sup>	Fetus (4 months)	..	No specific changes	Positive: lung, liver ¶** Negative: intestines, heart, kidneys*¶	Positive: bronchi, pneumocytes, circulating mononuclear cells,‡§ Kupffer cells§ Negative: heart, endothelial cells,‡§ hepatocytes, kidney, small intestine§
10: 2005, China <sup>2</sup>	Male (35 years)	27	Reactive haemophagocytic syndrome, lymphoid depletion	Positive: lung, trachea, intestines, brain, heart, spleen, liver, kidneys*¶ Negative: lymph node*¶	Positive: trachea, lymph node (T-cells), brain,‡§ small intestine,§ circulating mononuclear cells‡ Negative: bronchi, pneumocytes, spleen heart, endothelial cells, hepatocytes, Kupffer cells, kidney,‡§ small intestine,‡§ circulating mononuclear cells§

All cases had diffuse alveolar damage. For cases 9 and 10, see reference for strand-specific reverse-transcriptase PCR results.<sup>2</sup> \*Detected by reverse-transcriptase PCR. †Detected by culture. ‡Detected by immunohistochemistry. §Detected by in-situ hybridisation. ¶Formalin-fixed tissue PCR. \*\*Real-time reverse-transcriptase PCR.

**Table: Summary of postmortem case-reports on H5N1 by year, location, and distribution of viral genomes and antigens**

Gu and colleagues' successful use of newly developed molecular techniques on paraffin-embedded tissues enables broad use outside level III biological laboratories, and also makes review of previous material possible. These molecular techniques have pitfalls, including cross-contamination, operator dependence, and other technical issues. Correlation with viral culture to confirm productive viral replication is needed and is absent from Gu's report. Reproduction of these studies, including experimental models, is awaited.

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- 1 Cumulative number of confirmed human cases of avian influenza A/ (H5N1) reported to WHO. July 25, 2007. [http://www.who.int/csr/disease/avian\\_influenza/country/cases\\_table\\_2007\\_07\\_25/en/index.html](http://www.who.int/csr/disease/avian_influenza/country/cases_table_2007_07_25/en/index.html) (accessed July 25, 2007).
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## Supported employment for people with severe mental illness



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All countries can do more to improve the employment of people with severe mental illness, and facilitating access to the competitive labour market offers one way to achieve this goal. In today's *Lancet*,<sup>1</sup> Tom Burns and colleagues report a randomised trial in six European countries of supported employment (an evidence-based job-placement programme) versus the typical and dominant alternative vocational rehabilitation service available locally for people with severe mental illness. The investigators looked at competitive employment and clinical outcomes. Supported employment programmes assist adults with severe mental illness to enter jobs that meet their personal preferences, thereby achieving social inclusion, relief from poverty, and diminished reliance on governmental welfare assistance.

Over an 18-month intervention period, Burns and colleagues observed that more participants in the supported employment programme (55%) obtained competitive employment compared with participants in traditional services (28%), without increased admissions to hospital for illness relapse. These outcomes closely resemble those of randomised trials in the USA<sup>2,3</sup> and Canada,<sup>4</sup> confirming an effective way to improve employment prospects of people with severe mental illness across widely differing

cultural, health, welfare, and labour-market contexts.

In the USA, most researchers and policymakers describe competitive employment in terms of jobs open to anyone, located in typical business environments, and staffed by workers recruited on the basis of qualifications, not disabilities.<sup>5</sup> In Burns and colleagues' study, most jobs obtained by study participants were in unskilled or support positions (eg, warehouse or catering work). The primary study outcome was the number of participants who worked for at least 1 day over the 18-month intervention period: for those who might not have worked in decades, 1 day marks a real accomplishment. Evaluation periods of 18–24 months are typical for randomised trials in this field, yet are insufficient to capture the career trajectories of participants.

In supported employment programmes, participants typically obtain unskilled and semi-skilled entry-level competitive jobs, paying wages at or near the local minimum and earning an average US\$3000–5000 over 10–20 full-time-equivalent weeks per year.<sup>2,3</sup> These low wages rarely lead to economic independence, do not markedly reduce reliance on governmental income support, and do not lead to career development. Moreover, few competitive jobs acquired by people in supported