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expert reaction to model of emergence of avian flu in bird populations

A study in *PNAS* reported an alternative model for the emergence of new strains of bird flu, looking at the immunity of bird populations rather than the ability of viruses to acquire the necessary mutations.

Dr Jeremy Rossman, Lecturer in Virology, University of Kent, said:

"The recent study by Wikramaratna, Pybus and Gupta provides a novel explanation for the emergence of highly pathogenic strains of avian influenza virus (HPAI or Highly Pathogenic Avian Influenza, frequently referred to as H5N1). The emergence of HPAI strains is of great concern as they have devastating consequences to farmed poultry and can have up to 60 % case-fatality-rates in humans, though current strains do not appear to be capable of spreading through the human population. Previous studies have focused on the unique genetic attributes of HPAI strains in the hope of understanding the reasons for their pathogenicity and the genetic changes that are necessary to create new HPAI strains.

"Gupta and colleagues take a novel calculation-based approach, examining the ecological factors that contribute to novel HPAI strain emergence. The authors discover that there is a direct correlation between the longevity of bird species and the prevalence of influenza virus in the population. It is also suggested that HPAI strains are more likely to emerge in short-lived bird species, as they lack the immunity to influenza viruses present in long-lived species. This suggests that influenza virus infections in long-lived birds may be similar to human infections and may explain why highly pathogenic influenza viruses rarely emerge directly in humans. The authors also make the important observation that interaction between birds of different life-spans can enhance the emergence and persistence of HPAI in both bird populations. This observation is important for understanding HPAI emergence; however, it is unlikely that it will impact farming practice as the infection risk of wild birds on domestic poultry is already known and all infected flocks are currently culled.

"The conclusions of this paper are interesting and significant, though limited by the study methodology. The authors make several assumptions on the behavior of high and low pathogenicity viruses. This is necessary for the calculation-based approach, however, we know that the behavior of influenza viruses can vary with only small changes and thus the actual behavior of the high and low pathogenicity viruses may significantly differ from that calculated. In addition, it will be very difficult to

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experimentally validate these results as the authors calculated hypothetical influenza virus prevalence in bird populations over a 200 year time frame and saw only limited emergence events. This contrasts with the relatively consistent emergence of HPAI viruses that we have seen since 1997, though perhaps this difference stems from the constant interaction between different avian species seen in nature which may facilitate HPAI emergence and persistence, as Gupta has suggested."

Dr John McCauley, Director of the WHO Collaborating Centre for Influenza, MRC National Institute for Medical Research (NIMR), said:

"Highly pathogenic avian influenza viruses, like the H5N1 bird flu viruses that have caused so much concern for 10 years, evolve from avian influenza viruses of low pathogenicity – the evolutionary drive for this change in pathogenicity is unknown. The work from Wikramaratna presents a theoretical consideration of some of the events that could lead to low pathogenicity avian influenza viruses evolving into highly pathogenic ones.

"The work highlights several elements that need to be considered in the evolutionary change of low to high pathogenicity. The hypotheses generate some very interesting questions that will need to be addressed. Firstly, the model proposes that a key element is that in long-lived species of birds the circulating influenza viruses will show increased change in antigenicity – this might well be the case. Second, the model proposes that low-pathogenicity strains can out-compete an emerging highly pathogenic variant in some species due to a higher transmission potential of low-pathogenicity viruses – this might also be the case. The model predicts, thirdly, it is the intermingling of birds of with a long life-span with those of a short life-span that can lead to emergence of highly pathogenic avian influenza viruses.

"The importance of the work is that it provides a theoretical framework in which to address important questions about the evolution of highly pathogenic avian influenza viruses. Usually the direct evolutionary precursor low pathogenicity viruses circulate undetected. To test the model more of the evolutionary events leading to the generation of any unique high pathogenicity bird flu virus need to be examined in detail. However, in the past these evolutionary transitions have been rare. This model suggests these transitions could occur more frequently if there is increased degree of species mixing, perhaps due to ecological change."

Dr Colin Butter, Research Leader, Avian Viral Immunology Group, The Pirbright Institute, said:

"The paper from Professor Gupta's laboratory provides new insights into the evolution of influenza viruses that threaten avian and human populations. Their work challenges the orthodox scientific focus on the innate ability of viruses to evolve changes that contribute to pathogenicity and intra-species transmission and rather explores the role of the immunoecology of host species; domesticated poultry, waterfowl and humans. Whilst the need to separate poultry from wildfowl has long been understood on simple biosecurity grounds, this study concludes that contact between host species of different lifespans may actually promote the emergence of more virulent viruses.

"The study points to the requirement to test experimentally some predictions of their work and it is to be hoped that the laboratories able to do this take up the challenge. The effect of vaccination of host species has not been included in their analysis and it would be particularly interesting, in the era of the "one health" agenda, to model the effects of vaccinating different host species in ways that drive antigenic variation in similar or different directions. Can one vaccine serve safely to protect different

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species? The power of the ideas presented is clear and it will be intriguing to see them applied further."

Prof Jonathan Ball, Professor of Molecular Virology, University of Nottingham, said:

"Most often we think that emergence of new strains of influenza arise through a process of virus mutation which allows the virus to infect new species and develop more pathogenic traits. This study seems to turn that thinking on its head and argues that the host rather than the virus is more important.

"It's a thought-provoking study but worth remembering that the conclusion hinge on mathematical modelling – whether or not the findings would play out in the real world is not certain.

"If nothing else, what this paper reminds us is that emergence of deadly influenza in birds, or indeed any virus in any host, relies on a complex interplay between the virus and host: the virus' ability to infect and spread and the host's inherent resistance to that virus – both elements are important."

Prof Ira Longini, Professor of Biostatistics, Emerging Pathogens Institute, University of Florida, said:

"As the authors point out, much of the current research on potential for the emergence of pandemic influenza is concentrated on the intrinsic mutability of avian influenza virus (AIV). This includes the controversial gain of function (GOF) ferret passage studies for H5N1. Many argue that these experiments are dangerous and that they are not focused on the important predictors of emergence. This paper does focus on potential predictors that involve the passage of AIV between long-lived bird species and shorter-lived bird species. This is an ecological approach that attempts to explain how the re-assorted viruses emerge as a function of the immunity gained and virulence multiplied by the passage of the AIV among species with different lifespans.

"The paper presents some plausible scenarios by comparing output from mathematical models to qualitative observed trends, the most important being that species with longer lifespans tend to have higher prevalence of AIV. Although the authors of this work are really just propagating a theory at this time, the results of the paper indicate that more research should be centered on the measurement and phylodynamics of AIV among the different bird species, so that we can begin to build a theory of how these viruses gain transmissibility and virulence. In order to be really useful, the work should be extended to the avian-mammal interfaces as well. We should not forget, for example, that pandemic influenza H1N1 in 2009 was a triple re-assortant with avian, human and swine genes."

'Contact between bird species of different lifespans can promote the emergence of highly pathogenic avian influenza strains' by Paul S. Wikramaratna *et al.* published in *PNAS* on Monday 23 June 2014.

Declared interests

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