

Virus-host interactions and the unusual age and sex distribution of human cases of influenza A(H7N9) in China, April 2013

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To the editor:

Over the past two weeks, *Eurosurveillance* has published several timely papers related to the emergence of a new influenza A(H7N9) virus affecting humans in China [1-3]. Genetic studies by Kageyama et al. [1] and Jongens et al. [2] assessed evidence in the genome for virus origin, adaptation and virulence, and a paper by Corman et al. [3] described real-time reverse-transcription PCR assays for specific virus diagnosis. While these are important aspects of novel virus characterisation and detection, the accrual of over 100 human cases now also affords opportunity to consider evolving epidemiologic patterns as part of population risk assessment.

Perhaps the most intriguing impression to date from available surveillance findings has been the unexpected age/sex distribution of reported influenza A(H7N9) cases. The age range spans from 2 to 91 years but two thirds of influenza A(H7N9) cases have been 50 years of age or older and two thirds have been

male (Table) [4,5]. Illness severity, with a substantial case fatality of 20%, shows a similar age/sex profile (Table) [4,5]. Unlike the pattern observed for influenza A(H5N1), children, both boys and girls and notably the school-aged, are under-represented among influenza A(H7N9) detections. Among the first 100 adult influenza A(H7N9) cases, men and women were equally represented in the youngest age category 20–34 years, but men were 2–3-fold more frequent than women in older age groups (Table). Furthermore, compared with women 20–34 years of age, women 50–64 and 65–79 years were each twice as frequent among influenza A(H7N9) detections. Conversely, men 50–64 and 65–79 years are each 4–5-fold more frequent among influenza A(H7N9) detections than men 20–34 years of age. While being careful not to over-interpret early surveillance data, what hypotheses might be invoked to explain that pattern?

Disease occurrence is the result of the classic interaction triad of agent–host–environment. Environmental

TABLE

Human cases of influenza A(H7N9) and deaths by age group and sex, China, as of 23 April 2013 (n=109)^a

	Age (years)										
	<2	2–4	5–9	10–14	15–19	20–34	35–49	50–64	65–79	≥80	Unknown
Total cases	0	3	1	0	0	9	16	30	36	12	2
Female	0	0	1	0	0	4	5	9	9	4	0
Male	0	2	0	0	0	5	11	21	27	8	0
Unknown	0	1	0	0	0	0	0	0	0	0	2
Deaths	0	0	0	0	0	1	3	6	7	3	1
Female	0	0	0	0	0	0	1	2	2	0	0
Male	0	0	0	0	0	1	2	4	5	3	0
Unknown	0	0	0	0	0	0	0	0	0	0	1

^a Data sources include the Chinese Center for Disease Control and Prevention and the World Health Organization.

factors such as differences in poultry exposure due to socio-cultural behaviours and host factors such as healthcare-seeking behaviour or underlying comorbid conditions have been postulated to explain these early influenza A(H7N9) surveillance signals [6,7]. However, hypotheses should also include the additional perspective of agent (i.e. virus)–host interactions. Immunological profiles by age likely reflect accumulated lifetime opportunities for influenza virus exposure, leaving intricate imprints that may positively or negatively modulate subsequent risk. We have illustrated this immunological complexity at the population level for influenza, showing variation in age-specific cross-reactive antibody levels to previously emerging influenza A(H1N1)pdm09 virus [8] and more recently to the emerging (swine-origin) influenza A(H3N2)v, probably reflecting complex cohort effects based on differential prime/boost exposures to influenza variants by age [9].

That pre-existing immunity can differentially modulate the infection process for novel pathogens may be relevant in understanding the differing age distributions of the emerging influenza A(H5N1) versus A(H7N9) viruses [6,7]. Anti-neuraminidase (N1) antibodies induced by cumulative influenza A(H1N1) lifetime exposures may have a role in mitigating risk and severity of influenza A(H5N1) infection [10–13] in older individuals accounting for its more youthful profile to date [4–7]. In contrast, for influenza A(H7N9) we may anticipate that anti-N9 antibodies would be less prevalent overall in the population. Other population immunological effects of the 2009 influenza A(H1N1) pandemic, which affected predominantly young people, such as cross-reactive T-cell responses to generally conserved internal virus proteins [14] or memory B cell responses to shared epitopes within group 1 (i.e. H1, H5) versus group 2 (i.e. H3, H7) subtypes [15] may also need to be considered as factors that influence influenza A(H5N1) and A(H7N9) age profiles.

At this stage, we should also stay open to the possibility that pre-existing cross-reactive antibodies may actually facilitate the viral infection process, a phenomenon best recognised for dengue through the mechanism of antibody dependent enhancement (ADE) [16,17]. ADE is thought to occur when low-levels of weakly heterotypic, cross-reactive but not cross-protective, antibodies generated by past exposure to virus antigen, e.g. through prior infection or immunisation, form bridging complexes to facilitate uptake and replication of related but non-identical variants [16–18]. The possibility of ADE in influenza has long been and remains the subject of intense interest among experts [19,20], for which there may recently be indirect evidence. Early during the 2009 influenza pandemic, we described a potentially important interaction between seasonal and novel emerging influenza virus, notably an approximate doubling of the likelihood of medically-attended pandemic influenza A(H1N1) illness among people previously administered seasonal influenza

vaccine that contained virus antigenically related but distant from the emerging influenza A(H1N1)pdm09 strain [18]. In a follow-up experiment, vaccinated ferrets showed higher lung virus titres and greater illness severity after influenza A(H1N1)pdm09 challenge than influenza-naïve animals [21]. In swine, disease exacerbation has also been observed following heterologous challenge [22–24]. ADE was one of the proposed (but unproven) hypotheses to explain the unexpected findings from Canada during the 2009 pandemic [18]. The possible relevance of weakly cross-reactive antibodies in facilitating infection due to other emerging influenza viruses with pandemic potential may therefore warrant further consideration.

In that regard, older Chinese men may not only have a greater likelihood of current poultry/bird exposure, to explain their disproportionate representation among influenza A(H7N9) cases, but also a greater total sum of lifetime avian influenza exposures potentially contributing to cross-reactive H7 antibody. Few serosurveys to assess H7 antibodies in the population of China are available in the English language, and none has yet been sufficiently powered to compare this by age or sex [25–28]. In a serosurvey conducted 20 years ago in central China (Nanchang), 25% of 100 samples collected from women who raised pigs were found by ELISA to have antibodies to purified H7 antigen [25]. In a more recent serosurvey conducted in 2006–08 in northern China, 5–10% of ca. 1,000 farmer families and poultry workers aged 5–87 years had detectable but low-level antibodies (titre of at least 1:20 but not exceeding 1:40) to influenza (H7N1) in a modified haemagglutination inhibition (HI) assay using horse erythrocytes [26]. In 2011, none of >1,500 duck-related workers in Beijing aged 14–71 years had influenza (H7N2) or (H5N1) titres exceeding 1:40 by modified HI, although seropositivity to influenza (H9N2) was more prevalent, particularly among adults older than 50 years of age in whom the rate of seropositivity was four-fold higher than among younger participants [28].

Although the detection of antibodies to H7 subtype viruses has proved challenging even among culture-confirmed cases [29–35], serosurveys to compare cross-reactive antibodies and neutralising effects by multiple assays and by age group could be important, not only to inform possible protection, but also to explore patterns of enhanced risk in influenza A(H7N9) affected areas and more broadly elsewhere to inform risk assessment. Certain immunological effects, including ADE as it pertains to influenza, may yet be speculative. At this early stage of trying to understand the unexpected epidemiological patterns of an emerging pathogen, however, it is prudent for the global scientific and public health community to consider all possibilities within the full virus–host–environment paradigm.

Authors' contributions

All authors contributed to the writing, review and final approval of this letter.

Conflict of interest

GDS has received research grants from GlaxoSmithKline (GSK) and Sanofi Pasteur and participated in an ad hoc GSK advisory board meeting for an unrelated issue for which travel expenses were reimbursed. No other authors have competing interests to declare.

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