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On the Case Fatality Rate: H7N9 Influenza Resurgence in China in 2017

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China experienced a large-scale H7N9 influenza outbreak during 2013–2014. Within 2 months after the first report, 132 patients were infected and 37 died. The case fatality (CF) rate was ~25% (1). The log-log plot of cases versus fatality on the x- and y-axes, however, yielded a slope of 0.66, indicating that the CF rate gradually decreased during the epidemic. The plot was approximated by postulating that the epidemic consisted of the original H7N9 strain with a high-virulence variant (HVV) and attenuated low-virulence variant (LVV) that spread much more rapidly than the former (2). The faster spread of LVV was expected because lower virulence allows for higher mobility of the patients that spread the virus (3). The second waves in Shanghai/Zhejiang/Jiangsu/Anhui and in Guangdong/Fujian/Hunan were reconstituted. The plots were well approximated by postulating that the LVV had a CF rate of 14% and spread twice as rapidly as did the HVV with the CF rate 80% (4).

Three years later in 2017, China experienced resurgence of H7N9. The available information is ProMed data distributed by umin.ac.jp <tani-kkr@umin.ac.jp> (Table 1). The number of the patients and that of deaths were plotted in Fig. 1. The slope was 45° suggesting homogeneous virus population and CF rate of the 2017 H7N9 epidemic obtained by extrapolating the plots to the x-axis was 17% ($= [1/6] \times 100$). It was close to the CF rate, 14%, estimated for the LVV (by simulation) in the second wave of 2013–2014 epidemics. Had the virus continuously spread in the human communities since 2013–2014, a much lower CF rate could have been reached in comparison to 2009 with AH1pdm2009 (3). It was as if H7N9 stopped adaptation to human community since 2014.

Several pieces of data, however, indicated that a low-virulence H7N9 variant had arisen and spread among human communities by 2017 without being noticed. On the basis of serological data between December 2013 and April 2014, Lin et al. found that in Guangzhou in China, the overall age-standardized cumulative infection rate was 0.50%, corresponding to 64,000 H7N9 human infections, and the infection fatality risk was 3.6 deaths

per 10,000 cases (5). Yang et al. found that, whereas none of 1,129 of the general population was seropositive, >6% of 396 apparently healthy poultry workers were HI antibody positive ($HI \geq 80$), indicating the presence of a subclinical infection with H7N9 among poultry workers (6). Subclinical spread of H7N9 throughout the human population was already suggested by Watanabe et al. (7). A similar observation was made regarding H5N1: Shimizu et al. found that 84% of the serum samples obtained from workers in a live poultry market in Indonesia were A (H5N1) HI antibody positive although none of them had experienced an acute respiratory illness in previous years (8).

The plot for the 2017 H7N9 epidemic in Fig. 1 is thus compatible with the notion that the overwhelming presence of asymptomatic or subclinical H7N9 human infections went unnoticed and only the symptomatic infections were reported. This observation is consistent with the first simulation in 2013, under the assumption that the LVV with the CF rate 0.1% spread 5-fold faster than did the HVV with the CF rate 50% (2). The symptomatic infection with H7N9 in China in 2017 was due to direct exposure to birds (see the bottom of Table 1). HVV H7N9 will be maintained among the birds without being noticed because natural infections with H7N9 in chickens, ducks, and other birds are asymptomatic (1).

The sequence of events proposed above is hypothetical. The issue may be clarified by close monitoring of virus genomes (which will become more and more heterogeneous as the epidemic advances) and, if possible, by isolation of the HVV and LVV.

In this regard, it is important to note that body temperatures of birds, pigs, and men were respectively 42°C, 39°C, and 36°C. Avian influenza virus grown in birds or pigs, when infecting men, will find replication niche at higher temperature in the lower respiratory tract causing fatal pneumonia. Their repeated replication in human body, however, will select for mutants that replicate better at human body temperature; among such mutants, those replicating in the upper respiratory tract will spread more efficiently. Temperature-sensitive attenuated influenza virus mutants have actually been reported (9). It has been also known that avian-derived viruses preferentially recognize $\alpha 2,3$ receptors found in lower respiratory tract in humans, while human-derived viruses recognize $\alpha 2,6$ receptors found in the upper respiratory tract of humans (10). The high optimum replication temperature of the avian virus and localization of its receptors in the lower respiratory tract of humans may explain the limited spread of the avian influenza virus among humans and rarity so far of the bird influenza pandemic. Comparative genomics of clinical isolates from the upper and lower

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Table 1. Data used for plots of 2017 H7N9 epidemics in Fig. 1.

Time span	Patients	Deaths	ProMed References
1-Jan~31-Jan China	192	79	Avian influenza, human (20): China (SC, YN, BJ), H7N9, death tol l 20170215.4841682
19-Jan~14-Feb China	304	36	Avian influenza, human (22): China (GX, SD), H7N9, WHO updates, vaccine 20170222.4852285
Jan~22-Feb	270	87	Avian influenza, human (24): China (JX), H7N9, control measures 20170224.4861044
19-Feb~4-Mar China	26	3	Avian influenza, human (35): China, H7N9, WHO updates 20170317.4905430
28-Feb~13-Mar China	22	3	Avian influenza, human (37): China, H7N9, WHO update, control, genetics 20170324.4923674
10-Mar~16-Mar China	21	4	Avian influenza, human (38): China, H7N9 20170327.4926547
2-Mar~23-Mar China	18	2	Avian influenza, human (38): China, H7N9 20170327.4926547
2017 till Mar 28 Guangxi	7	2	Avian influenza, human (39): China, H7N9 20170331.4935953
17~23-Mar Hunan	5	1	Avian influenza, human (39): China, H7N9 20170331.4935953
6~24-Apr China	35	5	Avian influenza, human (41): China, H7N9, WHO 20170406.4945768
week 14 Fujian	10	1	Avian influenza, human (43): China, H7N9 20170412.4962707
March China	96	47	Avian influenza, human (50): China, H7N9 20170509.5019418
since 2017 Guangxi	25	11	Avian influenza, human (50): China, H7N9 20170509.5019418
16-Mar~6-May China	1,393	534	World Health Organization Influenza at the human-animal interface Summary and assessment, 16 March to 20 April 2017
11-Apr~6-May China	23	7	Avian influenza, human (54): CHINA, H7N9, WHO 20170530.5069791
2017 as of June 13 Beijing	27	6	Avian influenza, human (63): China, H7N9, WHO update 20170720.5190748

Time span	Patients	Exposed	
19-Jan~14-Feb China	304	144	Avian influenza, human (22): China (GX, SD), H7N9, WHO updates, vaccine 20170222.4852285
19-Feb~4-Mar China	26	22	Avian influenza, human (35): China, H7N9, WHO updates 20170317.4905430
28-Feb~13-Mar China	22	19	Avian influenza, human (37): China, H7N9, WHO update, control, genetics 20170324.4923674

The upper panel: time span, number of patients, number of deaths, and data source. The lower panel: Number of patients having exposed to poultry among the total number of the patients

Fig. 1. Log-log plot of cases versus deaths for 2017 H7N9 epidemic. Number of deaths was plotted in the y-axis and that of patients in the x-axis. The time span applicable to each plot and plot's information source are shown respectively in the first and the last column of Table 1.

respiratory tracts of the influenza patients may shed light on this issue.

If selective propagation of the LVV in the human population is the rule, then the best countermeasures against

the coming influenza pandemic will be to increase the transmission barrier against the HVV, as was done by the WHO in 2009.

Conflict of interest None to declare.

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