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Why were so few people infected with H7N9 influenza A viruses in China from late 2017 to 2018?

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Since the first human infection case with H7N9 avian influenza virus (AIVs) was identified in March 2013, there has six viral outbreak waves recorded in China as of September 2018. In total, there have been 1,567 confirmed cases of human H7N9 infection and 615 deaths, the fatality rate is around 40% (http://www.who.int/csr/don/05-september-2018-ah7n9-china/en/). In general, the H7N9 virus has posed a great threat in avian and human health. According to molecular characteristics of the virus and the ability to cause disease and mortality in chickens, the AIVs are designated as highly pathogenic avian influenza virus (HPAIV) or low pathogenicity avian influenza virus (LPAIV) (https://www.cdc.gov/flu/avianflu/influenza-a-virus-subtypes.htm).

Initially, many studies indicated that these H7N9 viruses isolated from birds in 2013 were low pathogenic, especially for mice, and barely replicable in ducks (Pantin-Jackwood et al., 2014; Zhang et al., 2013). However, some H7N9 variants firstly isolated from chickens in live poultry markets in early 2017 (Shi et al., 2017) and then in humans (Zhang et al., 2017; Zhou et al., 2017b) in Guangdong Province, China, possessed an insertion of 4 amino acids at the cleavage site of the HA protein, regarded as a molecular marker of HPAIV. Animal experiment supported that these variants were indeed highly pathogenic in chickens and lethal to mice (Qi et al., 2018). As of 5th September, 2018, the H7N9 HPAIVs have been reported in birds or the environment from at least 14 provinces, municipalities or autonomous regions in China (http://www.fao.org/ag/againfo/programmes/en/empres/H7N9/situation_update.html). And compared with the previous four waves, the fifth wave (October 2016–Septmber 2017) of H7N9 virus started earlier, distributed wider, and infected more people (Huo et al., 2017; Zhou et al., 2017a). All of that suggested that the H7N9 HPAIVs were not only disastrous to poultry but also increased threat to humans.

Based on the above, it was rational to speculate that H7N9 viruses in the "sixth wave" (October 2017–Septmber 2018) might be as aggressive as the fifth wave. Surprisingly, however, only three H7N9 human cases have been reported since 1st October, 2017. Currently, a study performed by Shi et al. who have long been committed to the basic and preventive research of influenza viruses unveiled this answer (Shi et al., 2018). To control and eradicate both the H7N9 low and highly pathogenic viruses, a series of actions had been taken such as the live poultry markets closing and poultry culling (Liu et al., 2014), the establishment of the platform for influenza research and early-warning (Bi et al., 2017) and standard bioinformatics analyses for monitoring virus evolution (Wei et al., 2017). Shi et al. also fully evaluated a bivalent H5/H7 inactivated vaccine in laboratories and farmed poultry in Guangxi autonomous region, Guangdong and Heilongjiang provinces before they are administered to poultry (mainly chicken) throughout China in

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To reveal the distribution and molecular evolutionary characteristics of H7N9 viruses in China, they performed two significant rounds of large-scale surveillance in poultry markets and farms before (February 2017–May 2017) and after (October 2017–January 2018) inoculation of the H7N9 vaccine. Shi et al. collected a total of 30,201 samples in which 10 different HA subtypes and 306 H7N9 viruses (250 LPAIVs and 56 HPAIVs) were isolated in the first round of surveillance. However, in the second round of surveillance, they isolated only 15 H7N9 viruses (2 LPAIVs and 13 HPAIVs) and one H7N2 HPAIV virus among 23,683 samples including 9 different HA subtypes; beyond this, compared with the previous five waves, only three human cases have been reported since October 2017. And the H5/H7 bivalent inactivated vaccine was fully evaluated by testing the protective efficacy in chickens and ducks against the representative H7 viruses. The results of experiments in chickens or ducks both showed that the birds vaccinated with this vaccine were not detected with virus shedding and all of them remained healthy and survived; on the contrary, those birds not being vaccinated were detected with virus shedding more or less and died in some day except for those being infected with LPAIVs. The obvious decreased prevalence of the H7N9 viruses in poultry and human suggested that the vaccination of poultry had played a main role in preventing the H7N9 virus infection in poultry, not only in chicken but also in duck and even eliminated the "sixth wave" H7N9 virus infection in human.

Nevertheless, two criterions for successes of this vaccination strategy should be met. One is that the vaccine is antigenically well matched with the target viruses, and another one is that the vaccination coverage reaches at least 70% population (van der Goot et al., 2005). In this study, beyond 70% chickens were vaccinated with this H5/H7 bivalent inactivated vaccine but not enough in ducks, because of the main prevalence in chickens and limited replication in ducks of the H7N9 viruses. Hence, it's necessary to applicate this vaccine to duck immediately to speed the process of prevention and deracination of the lethal H7N9 and H7N2 viruses.

In addition to evaluating the efficiency of this vaccine in chickens and ducks, they also found that there are 5 different motifs in the HA cleavage sites and 9 different genotypes of these H7N9 HPAIVs, which were all traced back to earlier Guangdong H7N9 HPAIVs rather than local low pathogenic H7N9 viruses.

To identify the pathotypes of these HPAIVs including 16 H7N9 viruses and one H7N2 virus in mammals, they tested the replications and virulence of these strains in four different organs of mice and which indicated that all of the strains replicated in turbinate and lung of the mice, while replicated less in spleen and brain, and no replication in kidney. By testing the virulence, they found the H7N9 HPAIVs have become more virulence in mice, which indicated that those mouse-lethal H7N9 strains may also be more lethal in humans. In the meanwhile, they also found there were two viruses with different 50% mouse-lethal dose (MLD_{50}) had 1000-fold different virulence in mice, however, those two viruses beared the same motif in HA cleavage, belonged to the same genotype and possessed the same amino acids at position associated with the virulence of AIVs in mice based on previous reports, which implied that same H7N9 HPAIVs could have become virulent in mice after circulating in poultry for only a few months. Therefore, these two viruses might be used as models to explore the unidentified molecular markers associated with the virulence of AIVs.

Strikingly, there were two strains (one H7N9 and one H7N2 viruses) replicated systemically and were lethal in ducks. And these two strains were the result of the chicken H7N9 virus reassorted with other unknown duck viruses, which was indicative of the H7N9 HPAIs had extended their host range by acquiring genes from duck viruses. In consequence, Shi et al. warned that even if these duck-lethal viruses were only found in ducks in Fujian province, they might soon spread more widely through the live poultry market which would pose more challenges to the control of influenza in China.

To sum up, Shi et al. performed large-scale surveillance and evaluated the vaccine to H5/H7 influenza virus in laboratories and farmed poultry, results of which showed that this bivalent H5/H7 inactivated vaccine had controlled H7 influenza viruses efficiently. This study has important guiding significance for controlling the variation and spread of AIV and preventing the avian influenza virus from spreading in the population.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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