Detecting influenza and emerging avian influenza virus by influenza and pneumonia surveillance systems in a large city in China, 2005 to 2016

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DOI: 10.21203/rs.2.1751/v1

SUBJECT AREAS
Internal Medicine Specialties

KEYWORDS
Avian influenza virus; Influenza surveillance system; Pneumonia surveillance system
Abstract

Background: Detecting avian influenza virus has become an important public health strategy for controlling the emerging infectious disease. This study aimed to analyze the efficiency of two surveillance systems in detecting the emerging avian influenza viruses. Methods: A modified influenza surveillance system (ISS) and a new built pneumonia surveillance system (PSS) have been used to monitor the viruses in Changsha City, China. The ISS is based on monitoring outpatients in two sentinel hospitals to detect mild influenza and avian influenza cases, and PSS is based on monitoring inpatients in all 49 hospitals to detect severe and death influenza cases. Results: During the study period, 3551917 outpatients were monitored by the ISS system, among which 126076 were influenza-like illness (ILI) cases, with the ILI% of 3.55%. Totally, 14913 throat swabs were collected by the ISS system, among which 2016 were tested positive of influenza or avian influenza virus. Among the positive results, 621 were H3N2, 135 were seasonal H1N1, 610 were influenza A/H1N1 (pandemic in 2009), 106 were untyped influenza A, 540 were B, 1 was H5N6, 1 was H7N9, and 2 were H9N2 virus. 5491560 inpatient people were monitored by the PSS system, among which 6.61% (362743/5491560) were pneumonia cases. 10.55% (38260/362743) of reported pneumonia was severe or death cases. 3401 throat swab or lower respiratory tract samples were collected, among which 2094 were tested positive of influenza or avian influenza virus. Among the positive results, 78 were H3N2, 17 were seasonal H1N1, 1871 were influenza A/H1N1, 103 were untyped influenza A, 16 were B, 1 was H5N6, and 8 were H7N9 virus. Of 15 avian influenza cases reported from January, 2005 to September, 2016, 26.7% (4/15) were mild cases detected by the ISS system, while 60.0% (9/15) were severe or death cases detected by the PSS system. Two H5N1 severe cases were missed by the ISS system in January, 2009 when the PSS system was not available. Conclusion: The two systems seem to be of high efficiency in detecting the emerging avian influenza viruses but need to be verified in other cities or countries.

Background

In these years, human cases infected with emerging avian influenza virus were reported more and more commonly[1-3]. Human infected H5N1 virus was firstly reported in 1997 in Hong Kong, China,
and then spread widely in China or even many other countries[4-6]. Then, human cases infected with other emerging influenza virus were reported in the following few years, especially in China. For example, H7N9 was reported in 2013[7], H5N6 in 2014[2, 8-11], H10N8 in 2013[1], and H9N2 in 2013 in Hunan province, China[12]. Finding ways to detect these emerging viruses have become an exceedingly important issue in and out of China.

There are two main surveillance systems focusing on the viruses in China. One is China’s national sentinel surveillance system for influenza-like illness based on sentinel hospitals across 31 provinces in mainland China, covering 2.5% of all hospitals in China[13]. The other one is national pneumonia surveillance system, which has been built by Chinese Center for Disease Control and Prevention (CDC) since 2004, based on monitoring pneumonia of unknown etiology (PUE) to facilitate timely detection of novel respiratory pathogens, such as severe acute respiratory syndrome (SARS) and avian influenza[14]. The two systems have played significant roles in monitoring the activity of influenza, controlling and preventing emerging avian influenza[13-15].

Traditionally, the influenza-like illness (ILI) cases were counted by influenza surveillance staff manually. However, hospital information system (HIS) has been used for recording and dealing with the outpatients in most hospitals in China[16, 17]. How to conduct the influenza surveillance by utilizing the HIS has become an essential issue in the national sentinel surveillance system. The PUE surveillance system was not (and still is not) used consistently, and most of community-acquired pneumonia cases met PUE criteria and should have been reported to the PUE system were missed[14]. In addition, the only two H5N1 cases were missed by the PUE surveillance system in Changsha city but were reported in another city in early 2009. These data revealed that the PUE surveillance system was not sensitive enough to detect the emerging avian influenza virus.

To explore a new way for monitoring influenza virus by using HIS and improve the sensitivity of detecting emerging avian influenza virus, we modified the influenza surveillance system (ISS) and built a new pneumonia surveillance system (PSS) in Changsha, China. In this study, we reported the roles of the ISS and the PSS systems in detecting influenza and emerging avian influenza virus.

Methods
Study area

Changsha (27°51’~28°41’ N, 111°53’~114°15’ E), a large city with 7.04 million people in central south China, is the capital city of Hunan province. It includes 6 districts and 3 counties. There are 4586 health departments including hospitals, clinics, and public health departments all over the city.

The modified influenza surveillance system

The ISS, based on two sentinel hospitals which locates in the south and the north of the city respectively, was set up in Changsha in September 2005. In 2006 and 2008, the system became a branch of Hunan and national influenza surveillance network respectively. In the 6th week in 2012, the HIS was adopted for the surveillance in one of the sentinel hospitals (hospital A), and was modified after the 25th week in 2013. Therefore, the ISS in Changsha underwent five stages (stage 1: week 39, 2005 to week 52, 2005; stage 2: week 1, 2006 to week 52, 2007; stage 3: week 1, 2008 to week 5, 2012; stage 4: week 6, 2012 to week 24, 2013; stage 5: week 25, 2013 to week 41, 2016.). During stage 1 to 3, two sentinel hospitals registered ILI cases manually in five outpatient departments which were outpatient and emergency departments of respiratory medicine, outpatient and emergency departments of pediatrics, fever clinic. During stage 4 to 5, hospital B remained the manual surveillance in the same outpatient departments. ILI case was defined as “fever (axillary temperature \( \geq 38^\circ C \) + cough or sore throat”[18, 19].

Differently, in hospital A, HIS was adopted into the ISS during stage 4 to 5 which was also named as “HIS (stage 1)” and “HIS (stage 2)” respectively. During stage 4, all outpatient departments of the hospital were enrolled into the ISS, and the computer would emerge a popup window by HIS with the question that “ILI or not” if physicians diagnosed one of the 108 influenza-associated diseases coded by International Classification of Diseases 10th Revision (ICD-10). The physician should answer the question to continue the later part to deal with the patients. But we found that some ILI cases would still be missed because of some reasons like the misremembering of the definition of ILI or the sense of the responsibility of the physician, especially if the physician was in the department which was not in the ISS system during stage 1 to 3. Therefore, during stage 5, the question was changed as three
options: a) fever (axillary temperature $\geq 38^\circ$C), b) cough, c) sore throat. The procedure of HIS would count the ILI automatically by computing the number of “a) + b)”, “a) + c)”, and “a) + b) + c)”. Therefore, patients visiting the outpatient departments of the two hospitals, among whom ILI cases were monitored, were calculated every week. At least 5-20 throat swab samples of ILI cases per hospital per week were collected for testing the influenza virus by reverse transcription polymerase chain reaction (RT-PCR) and/or cell culture in the laboratory of Changsha CDC. This system may monitor influenza and emerging avian influenza cases with mild symptoms or at the early stage of the infection (Figure 1). Data of the system from week 39, 2005 to week 41, 2016 were collected in our study.

**The new pneumonia surveillance system**

The PSS was built in Changsha in March, 2009. Pneumonia related inpatient departments of all 49 hospitals (excluding the primary health care centers and private clinics) in Changsha were enrolled into the system. This system monitors pneumonia cases among inpatient population. The public health staffs in the surveillance hospitals would count the total number of monitored inpatient people, pneumonia cases, severe or death pneumonia cases diagnosed by physicians and report the data to local CDC monthly. Throat swab or lower respiratory tract samples of suspicious patients were collected for testing avian influenza virus by RT-PCR in the laboratory of Changsha CDC. The PSS system may monitor influenza and emerging avian influenza cases with severe symptoms or death (Figure 1). In this study, we collected the data of the system from March, 2009 to September, 2016.

**Statistical methods**

The sentinel hospitals A and B are in the same city, although they locate in the south and north respectively, we assumed that the outpatients came from a same age structure population. Therefore, three indicators ($d_1$, $d_2$ and $d_3$) were used to compare the difference between the two hospitals among the five stages. They were the differences of weekly number of monitored outpatients, ILI, and ILI% of the two hospitals, and were expressed as follows:

$$d_1 = x_A - x_B$$
\[ d_2 = y_A - y_B \]
\[ d_3 = z_A - z_B \]

\( x_A, x_B, y_A, y_B, z_A \) and \( z_B \) refer to weekly number of monitored outpatients of hospital A, weekly number of monitored outpatients of hospital B, weekly ILI of hospital A, weekly ILI of hospital B, weekly ILI\% of hospital A, and weekly ILI\% of hospital B.

Analysis of variance (ANOVA) was employed to show the \( d_1, d_2 \) and \( d_3 \) among the five surveillance stages of the two sentinel hospitals. If there is statistical significance, the Least Significant Difference (LSD) method will be adopted to conduct the multiple comparisons between any two stages. The difference is significant at the 0.05 level.

**Results**

**Influenza surveillance system**

From week 39 (from 26 September to 2 October) in 2005 to week 41 (from 10 October to 16 October) in 2016, 3551917 outpatients were monitored by the ISS system, among whom 126076 were ILI cases, with the ILI\% of 3.55\% (Table 1). The total monitored outpatients, ILI, and ILI\% of the two sentinel hospitals was 2178811 and 1373106; 96271 and 29805; 4.42\% and 2.17\%, respectively (Table 1).

The results of ANOVA showed that the \( d_1, d_2 \) and \( d_3 \) were significantly different among the five surveillance stages. The \( F \) and \( P \) values were 892.789 and 0.000, 206.246 and 0.000, and 75.594 and 0.000, respectively. The results of multiple comparisons by LSD method showed that the difference of weekly number of monitored outpatients between hospital A and B were significantly different between any two stages except between stage 1 and 3. The weekly numbers of ILI in hospital A during stage 4 and 5 were shown significance to hospital B, but no significance during the stages from 1 to 3. The weekly numbers of ILI\% in hospital A were shown significance to hospital B during almost all stages except between stage 3 and 4 (Table 2). These results indicated that HIS could improve the efficiency of ISS system in monitoring ILI and ILI\% significantly (Figure 2).

The seasonality of ILI in hospital A matched the activity of influenza virus better than hospital B after
the use of HIS (Figure 3). Two ILI peaks were almost recorded in each year from the ISS system during stages 4 and 5 in hospital A. One peak was recorded in the alternation of winter to spring, and the other one was in summer (Figures 3). However, the seasonality of ILI was not obvious in hospital B. Because of the employment of the HIS, the proportion of tested sample descended in hospital A. However, the proportion of positive samples almost had same tendency of the two hospitals (Figures 4). The inpatient of pneumonia cases ascended after “HIS (stage 1)” in hospital A (Figures 5).

Totally, 14913 throat swabs were collected from the two hospitals during the five surveillance stages, among which 2016 were tested positive of influenza or avian influenza virus. Among the positive results, 621 were H3N2, 135 were seasonal H1N1, 610 were influenza A/H1N1 (pandemic in 2009), 106 were untyped influenza A, 540 were B, 1 was H5N6, 1 was H7N9, and 2 were H9N2 virus. The results of influenza virus of the two hospitals were similar during the five stages. However, the outcomes of monitoring avian influenza virus were different between the two hospitals. In stage 4, one mild H7N9 case was captured in hospital A when the HIS was adopted at HIS (stage 1). In stage 5, one mild H5N6 case and two mild H7N9 cases were captured in hospital A when the HIS was adopted at HIS (stage 2) (Table 1).

**Pneumonia surveillance system**

From March, 2009 to September, 2016, 5491560 inpatient people were monitored by the PSS system, among which 362743 were pneumonia cases, with the rate of 6.61%. 10.55% (38260/362743) of reported pneumonia was severe or death cases. The incidence of pneumonia increased each year in Changsha.

3401 throat swab or lower respiratory tract samples were collected, among which 2094 were tested positive of influenza or avian influenza virus. Among the positive results, 78 were H3N2, 17 were seasonal H1N1, 1871 were influenza A/H1N1, 103 were untyped influenza A, 16 were B, 1 was H5N6, and 8 were H7N9 virus (Table 3). The seasonality of pneumonia was obvious in spring (Figure 5).

**Emerging avian influenza cases**

15 avian influenza cases were reported from January, 2005 to September, 2016 (Table 4). Four of the cases were mild cases and were detected by the ISS system. Nine of the avian influenza cases were
severe or death cases and were detected by the PSS system. Two H5N1 severe cases were missed by the two systems in January, 2009 when the PSS system was not available. Two H5N6 cases, of which one was mild case reported by the ISS system in 2014 and the other was severe case reported by the PSS system in 2016, were detected in Changsha. Nine H7N9 cases were reported by the two systems. One of them was mild case and was detected by the ISS system in 2013 and the other eight severe / death cases were detected by the PSS system in 2014. Two H9N2 cases were mild cases and were detected by the PSS system in 2016.

Discussion
To our knowledge, it is the first study to research the role of HIS and a new pneumonia system in detecting influenza and emerging avian influenza virus in China. According to our results, we found that the efficiency of the ISS was improved for monitoring ILI and emerging avian influenza virus after the HIS was used in hospital A. The differences of ILI were significant between stages 1 to 3 and stages 4 to 5, and between hospital A and hospital B after the HIS was used. All the mild emerging avian influenza cases (H5N6, H7N9, H9N2) were detected in the hospital A where the HIS was adopted. These results would encourage a higher coverage of the HIS and the quality of the influenza surveillance in China. If the coverage of HIS is improved, the manual surveillance of ILI would be replaced by computer system and hundreds of doctors in sentinel hospitals would be released from the repetitive works on counting the ILI cases every week in each outpatient department, and the manual bias would be avoided. What's more, the probability in finding out influenza and avian influenza virus would be higher than the existing surveillance system because more ILI cases would be recorded by the higher coverage of HIS.

Because the ISS only focuses on the mild cases or the early stage of the infection, the surveillance of severe influenza or avian influenza cases depends on the PSS. The PSS is a new system built in Changsha city and covers all the hospitals which have inpatient departments. Because the PSS focuses on pneumonia cases instead of PUE cases, the system might be more sensitive in detecting influenza virus and emerging avian influenza virus. Since the PSS was built, the system had not only given us a way to estimate the disease burden of pneumonia cases in the city, but also played an
important role in controlling and preventing seasonal influenza each year, the pandemic of influenza A/H1N1 in 2009, and the emerging avian influenza such as H5N6 and H7N9 by dealing with the severe cases of the infection with these viruses.

From the data of emerging avian influenza cases, the ISS and the PSS systems seem to be highly efficient in detecting emerging avian influenza virus. However, although the two systems have run stably for a long time and covered a large population, the number of avian influenza cases was limited. It still needs a longer time to utilize the systems to assess the sensitivity and specificity of the systems. In addition, the ISS system only covers two sentinel hospitals, and the coverage of the system should be improved. The PSS system is a new system and firstly applied in Changsha, its efficiency needs to be verified in other cities or countries.

Conclusions
From the data of emerging avian influenza cases, the ISS and the PSS systems seem to be highly efficient in detecting emerging avian influenza virus but need to be verified in other cities or countries.

Abbreviations
ISS, influenza surveillance system; PSS, pneumonia surveillance system; ILI, influenza-like illness; CDC, Center for Disease Control and Prevention; PUE, pneumonia of unknown etiology; SARS, severe acute respiratory syndrome; HIS, hospital information system; ICD-10, International Classification of Diseases 10th Revision; RT-PCR, reverse transcription polymerase chain reaction; ANOVA, analysis of variance; LSD, the Least Significant Difference method.

Declarations
Ethics approval: This effort of disease control was part of CDC’s routine responsibility in Changsha City, China; therefore, institutional review and informed consent were not required for this study.

Consent for publication: Not applicable.

Availability of data and material: Extra data is available by emailing to the first author (Ruchun Liu, lrc8180@126.com) on reasonable request.

Competing interests: No authors declare a conflict of interest.

Funding: Not applicable.
Authors’ contributions: TC and BZ designed the study. DY, RL, YL, YeL, HZ, and XZ collected the data. TC, XG, QH, XM, and BZ analyzed the data. TC and QH wrote the first draft of this paper. All authors contributed to the writing of the manuscript.

Acknowledgments: We thank the staff members at the hospitals, local health departments, and municipal- and county-level CDCs for their valuable assistance in coordinating data collection.

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Tables
Table 1. Outcomes during different surveilled stages of influenza surveillance system in Changsha, China.
### Sentinel hospitals

| Stages | Surveilled patients | ILI | ILI% | Number of tested specimens |
|--------|---------------------|-----|------|-----------------------------|
|        |                     |     |      | H3N2 | H1N1 | H1 |

**Hospital A**

| Stages | ILI | ILI% | Number of tested specimens |
|--------|-----|------|-----------------------------|
| 1      | 188 | 2.29 | 30                          |
| 2      | 2100| 1.70 | 721                         |
| 3      | 17190| 3.41 | 2692                       |
| 4      | 10014| 2.64 | 641                        |
| 5      | 66779| 5.74 | 3534                       |
| Total  | 96271| 4.42 | 7618                       |

**Hospital B**

| Stages | ILI | ILI% | Number of tested specimens |
|--------|-----|------|-----------------------------|
| 1      | 452 | 5.83 | 29                          |
| 2      | 2089| 1.18 | 596                         |
| 3      | 13045| 2.72 | 2626                       |
| 4      | 2382| 1.37 | 651                        |
| 5      | 11837| 2.21 | 3393                       |
| Total  | 29805| 2.17 | 7295                       |

**Total**

| Stages | ILI | ILI% | Number of tested specimens |
|--------|-----|------|-----------------------------|
| 1      | 640 | 8.12 | 59                          |
| 2      | 4189| 2.87 | 1317                       |
| 3      | 30235| 6.13 | 5318                       |
| 4      | 12396| 4.01 | 1292                       |
| 5      | 78616| 7.95 | 6927                       |
| Total  | 126076| 3.55 | 14913                      |

| Stages | ILI | ILI% | Number of tested specimens |
|--------|-----|------|-----------------------------|
| 1      | 3551917| 126076| 14913                      |
| 2      | 15957| 8.12 | 59                          |
| 3      | 301191| 4189 | 1317                       |
| 4      | 982921| 30235| 5318                       |
| 5      | 553786| 12396| 1292                       |
| Total  | 1373106| 29805| 7295                       |

ILI, influenza-like illness.

### Table 2. Multiple comparisons of surveilled patients, ILI and ILI% among different stages between two sentinel hospitals based on Least Significant Difference method.

| Dependent variables | Stages (I) | Stages (J) | Mean difference (I-J) |
|---------------------|------------|------------|-----------------------|
| Surveilled patients | Stage 1    | Stage 2    | 548.69643(*)          |
|                     | Stage 3    |            | -83.5781              |
|                     | Stage 4    |            | -2856.60463(*)        |
|                     | Stage 5    |            | -3583.67570(*)        |
|                     | Stage 2    | Stage 1    | -548.69643(*)         |
|                     | Stage 3    | Stage 1    | -632.27453(*)         |
|                     | Stage 4    | Stage 1    | -3405.30106(*)        |
|                     | Stage 5    | Stage 1    | -4132.37213(*)        |
|                     | Stage 3    | Stage 1    | 83.5781               |
|                     | Stage 2    | Stage 1    | 632.27453(*)          |
|                     | Stage 4    | Stage 1    | -2773.02652(*)        |
|                     | Stage 5    | Stage 1    | -3500.09759(*)        |
|                     | Stage 4    | Stage 1    | 2856.60463(*)         |
|                     | Stage 2    | Stage 1    | 3405.30106(*)         |
|                     | Stage 3    | Stage 1    | 2773.02652(*)         |
|                     | Stage 5    | Stage 1    | -727.07107(*)         |
|                     | Stage 5    | Stage 1    | 3583.67570(*)         |
|                     | Stage 4    | Stage 1    | 4132.37213(*)         |
|                     | Stage 3    | Stage 1    | 3500.09759(*)         |
|                     | Stage 4    | Stage 1    | 727.07107(*)          |
| ILI                 | Stage 1    | Stage 2    | -18.96291             |
|                     | Stage 3    | Stage 2    | -38.2263              |
|                     | Stage 4    | Stage 2    | -126.35010(*)         |
|                     | Stage 5    | Stage 2    | -334.61576(*)         |
|                     | Stage 2    | Stage 1    | 18.96291              |
| Year | Surveilled patients | Number of pneumonia cases | Number of severe / death cases | Number of tested specimens |
|------|---------------------|---------------------------|-------------------------------|----------------------------|
|      |                     |                           |                               | H3N2 | H1N1 | H1N1 r |
| 2009 | 394683              | 27388                     | 1892                          | 2944 | 69   | 17     | 1     |
| 2010 | 650244              | 30503                     | 3431                          | 136  | 1    | 0      |
| 2011 | 748361              | 34602                     | 4537                          | 142  | 0    | 0      |
| 2012 | 820482              | 39831                     | 4890                          | 10   | 3    | 0      |
| 2013 | 883769              | 47283                     | 6250                          | 29   | 0    | 0      |
| 2014 | 798792              | 62726                     | 7041                          | 81   | 5    | 0      |
| 2015 | 672289              | 67205                     | 5765                          | 16   | 0    | 0      |
| 2016 | 522940              | 53205                     | 4454                          | 43   | 0    | 0      |
| Total| 5491560             | 362743                    | 38260                         | 3401 | 78   | 17     | 1     |

* The mean difference is significant at the 0.05 level. ILI, influenza-like illness.

Table 3. Outcomes of pneumonia surveillance system in Changsha, China.
Table 4. Avian influenza cases detected by different ways in Changsha, China.

| Avian influenza virus | Category of cases | Detected by ISS system | Detected by PSS system |
|-----------------------|-------------------|------------------------|------------------------|
| H5N1                  | Mild cases        | 0                      | 0                      |
|                       | Severe / death cases | 0                      | 0                      |
| H5N6                  | Mild cases        | 1                      | 0                      |
|                       | Severe / death cases | 0                      | 1                      |
| H7N9                  | Mild cases        | 1                      | 0                      |
|                       | Severe / death cases | 0                      | 8                      |
| H9N2                  | Mild cases        | 2                      | 0                      |
|                       | Severe / death cases | 0                      | 0                      |
| **Total**             | Mild cases        | 4                      | 0                      |
|                       | Severe / death cases | 0                      | 9                      |

ISS, influenza surveillance system; PSS, pneumonia surveillance system.

Figures

Figure 1

Flowchart of detecting influenza and avian influenza virus by influenza surveillance system and pneumonia surveillance system in Changsha. PSS, pneumonia surveillance system; ISS, influenza surveillance system; ILI, influenza-like illness; PCR, polymerase chain reaction.
Figure 2

Temporal distributions of weekly monitored outpatients, ILI and ILI% of two sentinel hospitals in Changsha, week 39, 2005 to week 41, 2016. A, temporal distributions of weekly monitored outpatients; B, temporal distributions of weekly ILI; C, temporal distributions of weekly ILI%.
Figure 3

Temporal distributions of weekly ILI and weekly number of influenza cases in two sentinel hospitals in Changsha, week 39, 2005 to week 41, 2016. A, temporal distributions of weekly ILI and influenza cases in hospital A; B, temporal distributions of weekly ILI and influenza cases in hospital B.
Temporal distributions of weekly proportion of tested samples and weekly proportion of positive samples in two sentinel hospitals in Changsha, week 39, 2005 to week 41, 2016.
Figure 5

Temporal distributions of pneumonia cases in 49 hospitals and two influenza surveillance sentinel hospitals in Changsha, March, 2009 to September, 2016.