sciendo

Progress and current status of influenza researches in China

Tianyun Shi, Xintong Feng, Zhijun Jie

Department of Pulmonary and Critical Care Medicine, the Fifth People's Hospital of Shanghai, Fudan University, Shanghai, China

ABSTRACT

Influenza pandemics with different extent occur every year in the world. It can cause high morbidity and mortality, arouse fear panic in public, and attract extensive attention worldwide. This paper reviews the research progress in epidemiological characteristics, detection methods, pathogenesis, treatment and prophylactic measures of influenza in China. It will be helpful for us to understand the current situation of influenza.

Key words: influenza, epidemiology, H7N9

Address for Correspondence:
Prof. Zhijun Jie, Department of Pulmonary and Critical Care Medicine, the Fifth People's Hospital of Shanghai, Fudan University, Shanghai 200240, China
Email: jiezjlxh@163.com

Access this article online

Website: www.intern-med.com

DOI: 10.2478/jtim-2019-0012

Quick Response Code:

INTRODUCTION

Influenza (Flu) is a kind of acute respiratory infection caused by influenza virus (IVs). Influenza A Virus (IAV), Influenza B Virus (IBV) and Influenza C Virus (ICV) are three members of the Orthomyxoviridae family, which belongs to the RNA virus.[1] IVs can cause fever, cough, copious sputum, chest pain, dyspnea and other respiratory symptoms. Among these viruses, IAV can cause the most harm to people, and is the most prevalent in recent years. This review has summarized recent researches about the epidemiological characteristics, detection methods, pathogenesis, prevention and treatment of influenza in China.

EPIDEMIOLOGY OF COMMON INFLUENZA VIRUSES

H7N9

In 2013, human cases of new H7N9 avian influenza infection were first reported in Shanghai and Anhui.[2] Then H7N9 spread rapidly in China, leading to higher morbidity and mortality, causing public worries, panic and widespread concern on a global scale. This novel reassortant H7N9 virus is composed of six internal protein genes (PB2, PB1, PA, NP, MP, NS) from H9N2, hemagglutinin (HA) gene of H7N3 and neuraminidase (NA) gene of H7N9. The current studies indicate that the novel H7N9 virus was most likely transmitted from the secondary wholesale market to the retail live-animal market and then to the patient. These data showed that human infections with the novel H7N9 virus had an epidemiologic association with chickens from live-animal markets, but not contacting patients who were already infected with H7N9.[3]

Since the first human infection case with H7N9 avian influenza virus (AIVs) was identified in March 2013, five viral outbreak waves have been recorded in mainland China. Wang *et al.*[4] analyzed 1,220 laboratory-confirmed human infections with H7N9 virus in mainland China from 2013 to 2017, with 134 cases confirmed in the spring of 2013, 306 in 2013–2014, 219 in 2014–2015, 114 in 2015–2016, and 447 in 2016–2017. IAV infection occurred and prevalent in almost every winter and spring, but the 2016–2017 H7N9 epidemic began earlier, spread to more districts and counties in affected provinces, and had more confirmed cases than previous epidemics. Most cases are concentrated in the "Yangtze River Delta" region and Guangdong. Twenty provinces have reported H7N9 cases, and the most three provinces are: Zhejiang (294

cases), Guangdong (247 cases) and Jiangsu (232 cases). About 70% of the human cases of H7N9 virus infection reported exposure to poultry within the 10 days before the onset of symptoms across five epidemics. Visiting a live poultry market and contact with backyard poultry were the two major sources of poultry exposure. As of March 2, 2018, the World Health Organization (WHO) influenza surveillance reported a total of 1567 laboratory confirmed cases of human infection with H7N9 avian influenza, of which 615 died and the cumulative mortality rate was as high as 39.25%.

It was rational to speculate that H7N9 viruses in the "sixth wave" (October 2017 to September 2018) might be as aggressive as the fifth wave. Surprisingly, only three H7N9 human cases have been reported since 1st October, 2017. To control and eradicate both the H7N9 low and highly pathogenic viruses, a series of actions had been taken in China, such as closing live poultry markets, culling poultry, and establishing the platform for influenza research and early-warning and standard bioinformatics analyses for monitoring virus evolution.[5] Shi *et al.*[6] performed large-scale surveillance and evaluated the vaccine to H5/H7 influenza virus in laboratories and farmed poultry in September 2017. The results showed that this bivalent H5/H7 inactivated vaccine had controlled H7 influenza viruses efficiently. 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.

H1N1 and H3N2

During October 2017 to 2018 winter, H1N1 became the main influenza virus type in mainland China once again. According to the China Center for Disease Control and Prevention (CDC), the number of influenza epidemics in the Chinese mainland in 2017 was 456,718, with an incidence rate of 33.1/100,000. The intensity of influenza activity caused by H1N1 was higher than recent years. The popular dominant viruses were mainly the Yamagata strain of influenza B and influenza A (including H3N2 and H1N1). There were differences in peak trends and epidemic durations between the regions. However, the monitoring results showed that there were no differences in the virus transmission, the severity of the disease and the variation of drug resistance compared with before.

In 2017 summer, H3N2 flu broke out in Hong Kong, China. The number of confirmed patients was over 10,000, particularly among very young babies and frail old man, while the majority of severe patients are young adults, obese people and pregnant women.[7]

Other Influenza Viruses

On November 30, 2013, the first case of human infection with H10N8 avian influenza virus was discovered in Nanchang City, China's Jiangxi Province.[8] The patient was a 73-year-old woman, who was diagnosed with severe pneumonia, accompanied by high blood pressure, heart disease, myasthenia gravis and other underlying diseases, with a low immunity level. A 55-year-old woman in Jiangxi Province was reported as the second human case of H10N8. Chinese CDC found that the risk of human infection and transmission of H10N8 avian influenza virus through personal contact was low.

In February 2014, a 5-year-old girl from Hunan Province was the first person diagnosed with H5N6 influenza virus infection in China.[9] In the following two years, H5N6 infection patients were reported in many places. H5N6 also broke out in poultry in Japan, South Korea and Taiwan, China.

INFLUENZA VIRUS DETECTION METHOD

The main detection methods of influenza virus mainly include viral nucleic acid detection, viral antigen detection, virus isolation culture and serological detection. The most common method is influenza virus nucleic acid, which is always detected by multiple reverse transcription polymerase chain reaction (RT-PCR) in respiratory specimens (throat swab, nasal swab, nasopharyngeal or tracheal extract, sputum). Viral nucleic acid detection is the most specific and sensitive method, and can distinguish between virus types and subtypes. In addition, some new virus detection technologies have been developed.

Biochip technique

Rapid identification of infections with specific subtypes of influenza virus is critical for treatment and pandemic control. Wang *et al.*[10] found that the application of RT-PCR coupled with membrane-based DNA biochip can detect and discriminate the type (A and B) and the subtype (human H1N1, human H3N2, avian H5N1 and avian H7N9) of influenza viruses in circulation in China. PCR products were analyzed by a membrane-based biochip. The clinical sensitivity and specificity were 95.5% and 100%, respectively. This method could allow a rapid, reliable and inexpensive detection and differentiation of human-infecting influenza viruses.

Gene Sequencing

In recent years, the sequencing of pathogenic microbial genomes has gradually become an important tool and means in the field of clinical microbiology. Applications

include: rapid identification of pathogens, pathogen genomic variation, pathogen drug resistance monitoring and so on. Next-generation gene sequencing (NGS) technology can be a useful tool to accurately identify virus subtypes from the clinical specimens. Seong *et al.*[11] used NGS technology in clinical specimens to investigate an influenza outbreak in hospitals. Nasopharyngeal swabs from patients were collected for molecular epidemiological analysis. Total of 7 to 12 million reads were obtained; however, 3–4% of reads originated from a non-human source. A BLAST search of the contigs revealed high sequence similarity to pandemic H1N1 virus sequences, and indicated that most contigs were originated from human and bacterial sources. Therefore, the application of NGS technology in clinic about viral infection will become more and more extensive.

INFLUENZA PATHOGENESIS

After infected with IVs, viral replication can directly cause damage to patient's cells and tissues. Most importantly, IVs can induce inflammatory factor storms, leading to systemic inflammatory reactions, which can cause acute respiratory distress syndrome (ARDS), shock and multiple organ failure. During viral replication in the host, viral RNA are recognized by pattern recognition receptors (PRRs), mainly Toll-like receptor (TLR)-3, TLR7/8 and RIG-I, triggering different pathways to induce production of a large amount of inflammatory cytokines. The higher level of proinflammatory cytokines has been documented to be associated with disease severity and lung damage. Patients infected with H5N1 could induce a strong cytokine response, with significantly elevated levels of interleukin IL-6, IL-10 and tumor necrosis factor (TNF)-α. However, patients infected with H7N9 are mainly expressing IL-6 and IL-8.[12]

Besides the innate immune response, evidences revealed that uncontrolled adaptive immune response was also involved in the disease pathogenesis. It has been found that, in patients infected with H1N1, the level of circulating influenza specific $CD4^+$ but not $CD8^+$T cells is positively correlated to the disease severity. [13,14] Xue *et al.*[15] found that in the lungs of mice infected with H1N1, IL-17A was predominantly secreted by γδT cells (especially the $V\gamma4^+\gamma\delta T$ subset), but not $CD4^+$Th and $CD8^+$Tc cells at the early stage of infection, and IL-1β and/or IL-23 were sufficient to induce IL-17A production by γδT cells. In addition to secreting IL-17A, γδT cells secreted interferon (IFN)-γ and expressed an activation-associated molecule, natural killer group 2, member D (NKG2D) and an apoptosis-associated molecule, FasL. These findings would play an important role in the prevention and treatment of influenza in the future.

TREATMENTS

Current Antiviral Drugs

At present, there are two main types of anti-influenza drugs. One is the neuraminidase inhibitors (NAIs), which were developed in the 1990s. NAIs are sialic acid analogs that competitively bind to active sites on the NA molecule to inhibit the release of influenza virus progeny from the cell surface. Three FDA-approved NAIs are oseltamivir, peramivir and zanamivir.[16] Wang *et al.*[17] performed a multicenter, retrospective study about 478 patients hospitalized with H7N9 infection during 2013–2017 in China. The results showed that the median duration of H7N9 RNA detection from onset was 15.5 days. Delayed NAI treatment after > 5 days of onset were independent risk factors for prolonged H7N9 RNA shedding. However, there was no significant difference in H7N9 RNA shedding duration between NAI combination treatment and monotherapy or between standard-dose and double-dose oseltamivir treatment.

Another antiviral drug is the adamantanes inhibitors, including adamantanes, rimantadine and amantadine. They target the M2 ion channel of IVA. IVAs have more than 99% resistance to adamantanes; therefore, they are no longer recommended for influenza treatment. NAIs are still the main antiviral drugs.[18]

Zou *et al.*[19] obtained 29 samples sequenced by NGS successfully from 11 patients diagnosed with H7N9 infection, and found that Neuraminidase (NA) R292K, basic polymerase 2 (PB2) E627K and D701N were the three most dynamic mutations. The NA R292K mutation is associated with oseltamivir resistance. Due to the constant variability of the virus and emergence of oseltamivir-resistant strains, it is very important and urgent for us to explore new antiviral drugs.

A Human Monoclonal Antibody Targets on HA: m826

The team of Professor Ying Tianlei from the School of Basic Medical Sciences, Fudan University, reported a human monoclonal antibody-m826, which could bind to H7 HA and protect against H7N9 infection. M826 binds to H7N9 HA with subnanomolar affinity at acidic pH and 10-fold lower affinity at neutral pH, which indicated that M826 is pH-dependent in combination with HA. M826 fully protects mice against lethal challenge with H7N9 virus through mechanisms likely to be involving antibody-dependent cell-mediated cytotoxicity (ADCC). M826 is a germline antibody, and m826-like sequences can be identified in H7N9-infected patients, healthy adults, and new born babies. These m826 properties can also offer a template for H7N9 vaccine.[20]

Peptidic inhibitors against HA

Kadam *et al.*[21] reported on design and structural characterization of potent peptidic inhibitors against influenza HA. The peptide design was based on complementarity determining region (CDR) loops of anti-HA human broadly neutralizing antibodies, FI6v3 and CR9114. The optimized peptides exhibit nanomolar affinity and neutralization against influenza A viruses including H1N1 and H5N1. These peptidic compounds and their advantageous biological properties should accelerate development of novel small molecule and peptide-based therapeutics against influenza virus.

A small molecule prodrug – Baloxavir marboxil

In February 2018, Xofluza (Baloxavir marboxil, previously known as S-033188), a new anti-influenza drug developed by Shionogi, was approved for sale in Japan. Barofavir is a small molecule prodrug that is a Cap-dependent endonuclease inhibitor.[21] Thereby, it can inhibit the process known as cap snatching, which is a mechanism exploited by viruses to hijack the host mRNA transcription system to allow synthesis of viral RNAs. Therefore, this is currently a new drug that can inhibit the proliferation of influenza virus. Recently, Koshimichi *et al.*[22] published a phase III clinical trial of Xofluza (CAPSTONE-1 study). The results of this study showed that the median time for alleviation of symptoms was significantly shorter in the baloxavir group than in the placebo group ($P < 0.001$). Baloxavir was associated with greater reductions in viral load 1 day after the initiation of the regimen than placebo or oseltamivir. The overall adverse events rate of baloxavir was lower (20.7%). On October 24, 2018, the U.S. FDA approved it for the treatment of uncomplicated acute influenza patients aged 12 years and older, who have been symptomatic for no more than 48 hours. This is the first anti-influenza drug with a new mechanism of action approved by the FDA in the past 20 years.

Corticosteroids

The application of corticosteroids in influenza virus pneumonia has always been controversial. A multicenter, retrospective study about 478 patients performed by Wang *et al.*[17] found that corticosteroid therapy was associated with prolonged H7N9 RNA shedding. Early corticosteroids therapy appeared more strongly associated with mortality than late administration. More patients receiving steroids had acquired pneumonia and a trend to a longer duration of ventilation.[23] The steroid group was more likely to have superinfection such as secondary bacterial pneumonia or invasive fungal infection, and had more prolonged intensive care unit (ICU) stays than the no-steroid group.[24,25] However, Martin-Loeches *et al.*[26] had performed a study on 220 patients admitted to an ICU and had got different results. Cox regression analysis adjusted for severity and potential confounding factors indicated that early use of corticosteroids was not significantly associated with mortality but was associated with an increased rate of HAP.

Cao *et al.*[27] found that high-dose corticosteroid therapy (> 150 mg/d methylprednisolone or equivalent) significantly increased both 30-day and 60-day mortality, whereas no significant impact was observed for low-to-moderate doses of corticosteroids (25–150 mg/d methylprednisolone or equivalent). Li *et al.*[28] found that patients with PaO2/FiO2 < 300 mm Hg, low-to-moderate-dose corticosteroid treatment significantly reduced both 30-day mortality and 60-day mortality. For patients with PaO2/FiO2 ≥ 300 mm Hg, corticosteroids (irrespective of dose) showed no benefits and even increased 60-day mortality.

Therefore, the timing, dosage, and course of corticosteroids in patients with influenza virus pneumonia are still the focus of controversy.

Extracorporeal membrane oxygenation (ECMO)

ECMO is the ultimate respiratory support method and can directly improve the oxygenation and ventilation of patients. ECMO was the breakthrough treatment for the severe avian influenza A (H1N1) outbreak of 2009 and reduced mortality from this outbreak. A multicenter retrospective cohort study was conducted by Huang *et al.*[29] In this study, 23 patients with an average PaO2/FiO2 of 78 ± 23 mmHg had undergone invasive positive pressure ventilation (IPPV). After 48 hr on ECMO, PaO2 improved from 56 ± 21 mmHg to 90 ± 24 mmHg and PaCO2 declined from 52 ± 24 mmHg to 38 ± 24 mmHg. Therefore, ECMO is effective at improving oxygenation and ventilation of patients with avian influenza A (H7N9) induced severe ARDS. Early initiation of ECMO with appropriate IPPV settings and anticoagulation strategies are necessary to reduce complications.

Chinese medicine treatment

Traditional Chinese medicine also plays an important role in fighting against influenza virus. Chinese herbal medicines are commonly used for anti-influenza viruses mainly include heat-clearing drugs, drug-solving drugs and tonic drugs. The main ways of Chinese medicine against influenza virus are as follows: (1) Banlangen, Honeysuckle, Forsythia, Guanzhong inhibit viruses directly by killing the virus, inhibiting the adsorption, infection and replication of influenza virus. Among them, baicalin[30] and silybin inhibit the virus replication by inhibiting autophagy; miRNA-microRNA2911 extracted from plants such as honeysuckle, matrine, chamomile, violet, ginseng and tea can directly act on virus and inhibit the replication of H5N1, H7N9 and H1N1 virus.[31] Yamagicin inhibits viral

replication by inhibiting the v-ATPase pathway.[32] (2) Drugs such as Astragalus, Codonopsis, Angelica, Epimedium, Scorpion, Houttuynia and Salvia can inhibit viruses indirectly by adjusting the body's inflammatory response and improving the body's immunity through various ways to alleviate the symptoms and prevent complications. In a word, combination of traditional Chinese medicine and Western medicine against influenza virus is a direction worth exploring.

PREVENTION

Isolation of patients, elimination of diseased poultry, cutting off routes of transmission and vaccination to protect susceptible populations are effective measures to prevent IVA. Wu *et al.*[33] compared the detection frequency of avian influenza H7 subtypes at live poultry markets in Guangdong Province, China, before and after the introduction of a bivalent H5/H7 vaccine in poultry. The study found that the vaccine was associated with a 92% reduction in H7 positivity rates among poultry and a 98% reduction in human H7N9 cases. So, vaccination is still an effective way to prevent influenza. Most of the current vaccines are trivalent vaccines or tetravalent vaccines, including inactivated whole virus vaccines, split vaccines, subunit vaccines and live attenuated vaccines. The vaccines currently under development are divided into the following categories: (1) Vaccines that respond to antibodies in the conserved regions of HA and M2e structures, mainly to prevent infection; (2) Vaccines that produce cross-protective T cell responses to internal proteins such as NP and M1, mainly to reduce the severity of the disease.

SUMMARY

At present, the situation of the Flu is still very serious. In the Flu season, we should still be vigilant and take defensive measures to detect, diagnose and treat it earlier, more accurately and more quickly. It is hoped that the Flu will no longer be a threat to human health in the near future.

Source of Foundation

Key Medical Specialty funded by The Fifth People's Hospital of Shanghai, Fudan University (No.2017WYZDZK07); Scientific Research Project Funded by the Fifth People's Hospital of Shanghai, Fudan University (No.2018WYFY01)

Conflict of Interest

None declared.

REFERENCES

1. Peiris JS, Tu WW, Yen HL. A novel H1N1 virus causes the first pandemic of the 21st century. Eur J Immunol 2009; 39: 2946–54.
2. Gao R, Cao B, Hu Y, Feng Z, Wang D, Hu W, *et al.* Human infection with a novel avian-origin influenza A (H7N9) virus. N Engl J Med 2013; 368: 1888–97.
3. Bao CJ, Cui LB, Zhou MH, Hong L, Gao GF, Wang H. Live animal markets and influenza A (H7N9) virus infection. N Engl J Med 2013; 368: 2337–9.
4. Wang X, Jiang H, Wu P, Uyeki TM, Feng L, Lai S, *et al.* Epidemiology of avian influenza A H7N9 virus in human beings across five epidemics in mainland China, 2013-17: an epidemiological study of laboratory-confirmed case series. Lancet Infect Dis 2017; 17: 822–32.
5. Wei X, Cui J. Why were so few people infected with H7N9 influenza A viruses in China from late 2017 to 2018? Sci China Life Sci 2018; 61: 1442–4.
6. Shi J, Deng G, Ma S, Zeng X, Yin X, Li M, *et al.* Rapid Evolution of H7N9 Highly Pathogenic Viruses that Emerged in China in 2017. Cell Host Microbe 2018; 24: 558–68.
7. Zhu H, Lee ACY, Li C, Mak WWN, Chen YY, Chan KH, *et al.* Low population serum microneutralization antibody titer against the predominating influenza A(H3N2) N121K virus during the severe influenza summer peak of Hong Kong in 2017. Emerg Microbes Infect 2018; 7: 23.
8. Wan J, Zhang J, Tao W, Jiang G, Zhou W, Pan J, *et al.* A report of first fatal case of H10N8 avian influenza virus pneumonia in the world. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2014; 26:120–2.
9. Zhang R, Chen T, Ou X, Liu R, Yang Y, Ye W, *et al.* Clinical, epidemiological and virological characteristics of the first detected human case of avian influenza A(H5N6) virus. Infect Genet Evol 2016; 40: 236–42.
10. Wang Y, Qu J, Ba Q, Dong J, Zhang L, Zhang H, *et al.* Detection and typing of human-infecting influenza viruses in China by using a multiplex DNA biochip assay. J Virol Methods 2016; 234: 178–85.
11. Seong MW, Cho SI, Park H, Seo SH, Lee SJ, Kim EC, *et al.* Genotyping influenza virus by next-generation deep sequencing in clinical specimens. Ann Lab Med 2016; 36: 255–8.
12. Li H, Cao B. Pandemic and avian influenza A viruses in humans: epidemiology, virology, clinical characteristics, and treatment strategy. Clin Chest Med 2017; 38: 59-70.
13. Horman WSJ, Nguyen THO, Kedzierska K, Bean AGD, Layton DS. The drivers of pathology in zoonotic avian influenza: the interplay between host and pathogen. Front Immunol 2018; 9: 1812.
14. Zhao Y, Zhang YH, Denney L, Young D, Powell TJ, Peng YC, *et al.* High levels of virus-specific $CD4^+$ T cells predict severe pandemic influenza A virus infection. Am J Respir Crit Care Med 2012; 186: 1292–7.
15. Xue C, Wen M, Bao L, Li H, Li F, Liu M, *et al.* Vγ4+γδT cells aggravate severe H1N1 influenza virus infection-induced acute pulmonary immunopathological injury via secreting interleukin-17A. Front Immunol 2017; 8: 1054.
16. Nicholson EG, Munoz FM. A review of therapeutics in clinical development for respiratory syncytial virus and influenza in children. Clin Ther 2018; 40: 1268-81.
17. Wang Y, Guo Q, Yan Z, Zhou D, Zhang W, Zhou S, *et al.* Factors associated with prolonged viral shedding in patients with avian influenza A(H7N9) virus infection. J Infect Dis 2018; 217: 1708–17.
18. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices-united states, 2018-19 influenza season. MMWR Recomm Rep 2018; 67: 1–20.
19. Zou X, Guo Q, Zhang W, Chen H, Bai W, Lu B, *et al.* Dynamic variation and reversion in the signature amino acids of H7N9 virus during human infection. J Infect Dis 2018; 218: 586–94.
20. Yu F, Song H, Wu Y, Chang SY, Wang L, Li W, *et al.* A potent germline-like human monoclonal antibody targets a ph-sensitive epitope on H7N9 influenza hemagglutinin. Cell Host Microbe 2017; 22: 471–83.

21. Kadam RU, Juraszek J, Brandenburg B, Buyck C, Schepens WBG, Kesteleyn B, *et al*. Potent peptidic fusion inhibitors of influenza virus. Science 2017; 358: 496–502.
22. Koshimichi H, Ishibashi T, Kawaguchi N, Sato C, Kawasaki A, Wajima T. Safety, tolerability, and pharmacokinetics of the novel anti-influenza agent baloxavir marboxil in healthy adults: phase I study findings. Clin Drug Investig 2018; 38: 1189–96.
23. Hayden FG, Sugaya N, Hirotsu N, Lee N, de Jong MD, Hurt AC, *et al*. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. N Engl J Med 2018; 379: 913–23.
24. Brun-Buisson C, Richard JC, Mercat A, Thiébaut AC, Brochard L; REVA-SRLF A/H1N1v 2009 Registry Group. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med 2011; 183: 1200–6.
25. Kim SH, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, *et al*. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med 2011; 183: 1207–14.
26. Martin-Loeches I, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, *et al*. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic(H1N1)v influenza A infection. Intensive Care Med 2011; 37: 272–83.
27. Cao B, Gao H, Zhou B, Deng X, Hu C, Deng C, *et al*. Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. Crit Care Med 2016; 44: e318-e328.
28. Li H, Yang SG, Gu L, Zhang Y, Yan XX, Liang ZA, *et al*. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1) pdm09 viral pneumonia. Influenza Other Respir Viruses 2017; 11: 345–54.
29. Huang L, Zhang W, Yang Y, Wu W, Lu W, Xue H, *et al*. Application of extracorporeal membrane oxygenation in patients with severe acute respiratory distress syndrome induced by avian influenza A (H7N9) viral pneumonia: national data from the Chinese multicentre collaboration. BMC Infect Dis 2018; 18: 23.
30. Zhu HY, Han L, Shi XL, Wang BL, Huang H, Wang X, *et al*. Baicalin inhibits autophagy induced by influenza A virus H3N2. Antiviral Res 2015, 113: 62–70.
31. Zhou Z, Li X, Liu J, Dong L, Chen Q, Liu J, *et al*. Honeysuckle-encoded atypical microRNA2911 directly targets influenza A viruses. Cell Res 2015; 25: 39–49.
32. Chen HW, Cheng JX, Liu MT, King K, Peng JY, Zhang XQ, *et al*. Inhibitory and combinatorial effect of diphyllin, a v-ATPase blocker, on influenza viruses. Antiviral Res 2013; 99: 371–82.
33. Wu J, Ke C, Lau EHY, Song Y, Cheng KL, Zou L, *et al*. Influenza H5/H7 virus vaccination in poultry and reduction of zoonotic infections,guangdong province, China, 2017-18. Emerg Infect Dis 2019; 25: 116–8.

How to cite this article: Shi T, Feng X, Jie Z. Progress and current status of influenza researches in China. J Transl Int Med 2019; 7: 53-8.