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World Flu Day, Be Aware of the Unavoidable Enemy
— November 1, 2020
George F. Gao

World Flu Day, designated to be every November 1, was initiated in 2018 at the Asian-Pacific Centenary Spanish 1918-Flu Symposium to commemorate the 100 years that followed the Spanish Flu Pandemic in 1918 (1). In an article in Lancet, I laid out four major purposes for World Flu Day: 1) to commemorate the centenary of the 1918–1919 influenza pandemic; 2) to raise public awareness of influenza; 3) to accelerate scientific innovation and basic research efforts toward remaining challenges of influenza, particularly the development of a universal flu vaccine; and 4) to push for stronger global political will in continuing the support of influenza prevention and control (1).

At the conference, five expert scientists from around the world, including Drs. Yoshihiro Kawaoka of the University of Wisconsin, Mark von Itzstein of Griffith University, Lei Liu of Shenzhen Third People’s Hospital, and Kwok-Yung Yuen from Hong Kong University, together with me led the symposium and established this special day. Dr. Robert Webster, of St. Jude Children’s Research Hospital, delivered the keynote speech, calling for the world to wake up to the inevitability of a pandemic and reminding us to respect “Mother Nature” and to control influenza viruses. Dr. Tedros Ghebreyesus, Director-General of the World Health Organization (WHO) and Dr. Hesheng Wang, Deputy Minister of National Health Commission (NHC) of the People’s Republic of China stressed the importance of prioritizing highly influenza prevention and control, and emphasized the commitment of WHO and China to pandemic preparedness and response.

War against pathogens has been a constant event for mankind. Emerging and reemerging pathogens have been the most dangerous threats to humans, with coronavirus disease 2019 (COVID-19) a clear, recent example (2). Louis Pasteur, the famed French biologist, renowned for his contributions to vaccines and the invention of pasteurization, once remarked: “Gentlemen, it is the microbes who have the last word” (3); Nobel Laureate Joshua Lederburg said that: “The single biggest threat to man’s continued dominance on the planet is the virus” (4); and Bill Gates remarked that: “If anything kills over 10 million people in the next few decades it’s highly likely to be a highly-infectious virus rather than a war. Not missiles, microbes” (5). The relationship between mankind and microbes has become akin to cartoon characters Tom and Jerry of Warner Bros., where one constantly tries to outmaneuver the other. So far, mankind has managed to coexist with microbes, but the threat of pathogens will always remain.

The first mention of Spanish flu appeared in a weekly public health report on April 5, 1918, and described 18 severe cases and 3 deaths in Haskell, Kansas in the United States (6). Smith, Andrewes, and Laidlaw managed to isolate the influenza A virus in ferrets in 1933, which was then followed by Francis isolating influenza B virus in 1936 (7). Though we, as a global community, have experienced 4 influenza pandemics thus far (1918 H1N1, 1957–1958 H2N2, 1968 H3N2, and 2009 H1N1pdm09), together with the 1977 H1N1 recognized as a “pseudo pandemic”, our preparedness is still woefully lacking as evidenced by the rapid spread of COVID-19 (8). The global community needs to unite against this common enemy, as divisions serve only to weaken our ability to respond to and control microbes.

Evidence from previous pandemic influenza viruses indicates the animal origin of the gene segments involved in each pandemic before the virus circulation in humans. Meanwhile, considering the continuously emerging human-infecting avian influenza viruses, e.g. H5N1, H7N9 and swine influenza viruses, e.g. Eurasian avian-like H1N1, poultry, wild birds and swine may provide reservoirs for the development of the next influenza pandemic (9–10). Thus, the concept of One Health is essential to ensure continued safety of not just the public’s health, but of ecosystems and environments that reduce otherwise unbridled spread of dangerous microbes. Advocacy for One
Health involves multi-sectoral research, policy, legislation, and programs for surveilling, preventing, detecting, and responding to influenza pandemics (11).

A key purpose of World Flu Day is to gather political will to aggregate available resources and reduce the impact of influenza. The 2019 World Flu Day theme was “Know Flu, Prevent Flu, and Beat Flu” (12). This year’s theme is “Influenza Control and COVID-19 Pandemic Response”. In our landscape still being shaped by the COVID-19 pandemic, we must not forget the devastating impact of the influenza virus. We, as a global health community, have eradicated smallpox, and we can strive for victory over influenza by bolstering our combined research and surveillance efforts.

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Mark von Itzstein
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Fellow of the Australian Academy of Science
Wang sent a congratulatory letter to the inaugural World Influenza Day Conference:
Influenza is a public health issue of global concern. Since 2000, China has set up influenza surveillance network including 408 national influenza surveillance network laboratories and 554 sentinel surveillance hospitals, which cover all cities and key counties in the national influenza surveillance network. The Chinese National Influenza Center is also a WHO Collaborating Centre for Reference and Research on Influenza. China is ready to work under the WHO framework of the influenza pandemic prevention and control, actively participate in global health, and contribute Chinese experience and knowledge for public health.

Dr Tedros Adhanom Ghebreyesus
WHO Director-General

Dr Tedros sent a congratulatory video for the inaugural World Influenza Day Conference:
“WHO’s collaborating centers in China, the USA, UK and Australia, and Japan are the global connective tissue in continuously monitoring influenza around the world. Thank you for your commitment to pandemic preparedness and response, although another flu pandemic is inevitable, together we can make sure that the world is much better prepared and protected.”

Robert G. Webster
St. Jude Children’s Research Hospital, USA
Member of National Academy of Sciences, USA

Robert gave a keynote speech for the inaugural World Influenza Day Conference:
It is my great honor to be invited to this very important meeting to celebrate the beginning of World Flu Day. This is really an important day. I congratulate those who are involved in arranging the World Flu Day. We have many questions still remaining for the next generation of young people for influenza.
Vital Surveillances

Characterization of Influenza Viruses — China, 2019−2020

Weijuan Huang; Yanhui Cheng; Tao Chen; Xiyan Li; Minju Tan; Hejiang Wei; Xiaoxu Zeng; Yiran Xie; Jia Liu; Ning Xiao; Lei Yang; Dayan Wang

ABSTRACT

Introduction: Influenza surveillance is necessary for detection of emerging variants of influenza viruses and determining their epidemiological and clinical significance. Vaccination and antiviral drugs remain the most useful ways to protect against seasonal influenza and its potentially severe consequences. This study describes the epidemiology, antigenic and genetic characteristics, and antiviral susceptibilities of influenza viruses isolated from the mainland of China during the April 1, 2019 through October 4, 2020.

Methods: All viruses analyzed were isolated and submitted by Chinese National Influenza Surveillance Network laboratories. The Chinese National Influenza Center performed antigenic analysis, sequencing, and antiviral resistance testing after propagation of the viruses. Antigenic characterizations were determined by hemagglutinin inhibition assay; next-generation sequencing was used for genetic analyses; phenotypic assay and next-generation sequencing were used for determining antiviral resistance.

Results: The influenza positivity rate declined significantly starting in late January 2020 and has remained low. There was no summer influenza peak season in south China. Influenza A(H3N2) and B/Victoria lineage viruses were the dominant subtype/lineage during April 1, 2019 through October 4, 2020. The majority of influenza viruses were antigenically and genetically similar to reference viruses representing components of vaccines for the 2020–2021 northern hemisphere influenza season. Nearly all seasonal influenza viruses were susceptible to oseltamivir and zanamivir.

Conclusions and Implications for Public Health Practice: Since the outbreak of COVID-19, the influenza positivity rate declined with implementation of strong COVID-19 control measures. The majority of circulating viruses are well matched with the current 2020–2021 northern hemisphere influenza vaccine viruses. Circulating seasonal influenza viruses were sensitive to neuraminidase inhibitors and Baloxvir marboxil. This study provided evidence for World Health Organization (WHO) recommendations for vaccine viruses, for prevention and control of influenza, and for clinical use of antiviral medications.

INTRODUCTION

Influenza viruses evolve rapidly and escape natural or vaccine-induced immune responses by accumulating mutations within the surface glycoprotein genes for hemagglutinin (HA) and neuraminidase (NA) (1). The emergence of coronavirus disease 2019 (COVID-19) has had a huge impact on the world by shifting public health challenges and changing behaviors that even affect influenza activity.

Between April 2019 and September 2020, influenza activity was reported in all global regions. However, since April 2020, low levels of influenza activity have been reported — including from countries in the southern hemisphere temperate zone. Although influenza A(H1N1)pdm09, A(H3N2), and influenza B viruses co-circulated, the predominant circulating viruses varied by country and region. Overall, influenza A viruses were detected more often than influenza B viruses. Globally, co-circulation of A(H1N1)pdm09 and A(H3N2) viruses was evident in most countries, areas, and territories, but influenza A(H1N1)pdm09 viruses circulated in higher proportion than A(H3N2) viruses beginning in mid-January 2020. The B/Victoria lineage circulated in higher proportion than the B/Yamagata lineage viruses worldwide (2–3).

Each year, the WHO recommends compositions for the northern hemisphere influenza vaccine in February and for the southern hemisphere in September. Vaccination remains the best way to protect against seasonal influenza and its potentially severe consequences.

Influenza A(H3N2) and B/Victoria lineage viruses were the dominant subtype/lineage in the mainland of China during 2019–2020. To understand the variation of circulating seasonal influenza viruses and their match with vaccine virus strains, we analyzed the
antigenic and genetic characteristics and antiviral susceptibilities of influenza viruses isolated from the mainland of China.

**METHODS**

The Chinese National Influenza Surveillance Network includes 410 laboratories and 554 sentinel hospitals. The influenza surveillance year typically starts on week 14, which is around April 1, and lasts for an entire year. Sentinel hospitals report influenza-like illness (ILI) cases to the Chinese National Influenza Surveillance Information System (CNISIS) and collect respiratory specimens. Network laboratories test the specimens with real-time reverse transcriptase polymerase chain reaction (RT-PCR). Influenza positive specimens are propagated in Madin-Darby canine kidney (MDCK) cells and/or embryonated chicken eggs. Viruses are submitted to the Chinese National Influenza Center (CNIC) for further characterization.

Antigenic characterizations were assessed with HA inhibition (HI) assays, and genetic characterization was performed with next-generation sequencing. Influenza virus testing for antiviral resistance was conducted at CNIC using next-generation sequencing analysis, phenotypic assays, or with both tests (4). The viruses evaluated were isolated from specimens collected between week 14 in 2019 (April 1, 2019) and week 40 in 2020 (October 4, 2020).

**RESULTS**

For virus surveillance during April 1, 2019 through October 4, 2020 (surveillance week 14 in 2019 to week 40 in 2020), the percentage of specimens testing positive for influenza each week ranged from 0% to 46.5% in southern China and ranged from 0% to 47.3% in northern China. The positivity rate of specimens collected from ILI cases increased starting in week 40 in 2019 reaching a peak (46.5% for southern China and 47.3% for northern China) during the first week of 2020 and decreasing substantially after that. During week 8, the positivity rate in southern China decreased to 2.0%, and by week 10 in northern China, the influenza-positive rate declined to 1.3%. The positivity rate since then has been lower than that of the same period in previous years (5) and has remained low ever since (Figures 1 and 2).

During the study period, network laboratories in southern China tested 423,466 specimens for influenza; among these specimens, 49,147 (11.6%) tested positive including 23,234 (47.3%) for influenza A and 25,913 (52.7%) for influenza B. Most of the positive samples were collected before March 2020. Among the 23,208 seasonal influenza A positive specimens that were subtyped, 2,830 (12.2%) were influenza A(H1N1)pdm09 and 20,378 (87.8%) were influenza A(H3N2). Among the 25,627 influenza B viruses for which lineage was determined, 25,477 (99.4%) belonged to the B/Victoria lineage and 150 (0.6%) belonged to the B/Yamagata lineage (Figure 1).

Network laboratories in northern China tested 216,874 specimens between April 1, 2019 and October 4, 2020. Among these, 26,759 (12.3%) were positive for influenza viruses — influenza A and influenza B viruses were 20,203 (75.5%) and 6,556 (24.5%), respectively, of the tested viruses. Among the 20,199 seasonal influenza A viruses that were subtyped, 2,091 (10.4%) were influenza A(H1N1)pdm09 and 18,108 (89.6%) were influenza A(H3N2). Influenza B lineage information was available for 6,547 influenza B viruses; 6,460 (98.7%) were B/Victoria lineage and 87 (1.3%) were B/Yamagata lineage (Figure 2).

CNIC tested the antigenic and genetic characteristics of influenza viruses between April 1, 2019 and October 4, 2020. A total of 653 A(H1N1)pdm09 viruses were analyzed with HI tests, and 521 viruses were antigenically analyzed with A/Guangdong-Maonan/SWL1536/2019, and 98.3% (512/521) were well inhibited by ferret antisera raised against A/Guangdong-Maonan/SWL1536/2019, the egg-propagated reference virus representing the A(H1N1)pdm09 component for the upcoming 2020–2021 winter season’s northern hemisphere influenza vaccination (2). Among the 205 viruses sequenced, phylogenetic analysis of HA gene segments determined that 199 (97.1%) belonged to genetic clade 6B.1A (Figure 3); 161 (78.5%) belonged to subclade 6B.1A5A, which evolved from clade 6B.1A. Subclade 6B.1A5A HA genes fall into 3 genetic groups: a progenitor 6B.1A5A subclade (22.9%) and 2 recently designated groups, 5A-187A (46.3%), with additional amino acid substitutions D187A and Q189E, and 5A-156K (9.3%), with an additional amino acid substitution N156K.

Antigenic characterization of 1,410 A(H3N2) viruses were conducted using HI tests that used guinea pig red blood cells (RBCs) in the presence of oseltamivir, and 63 viruses underwent antigenic analysis with A/Hong Kong/2671/2019 where the
results showed that 79.4% (50/63) of virus isolates were well inhibited by ferret antisera raised against A/Hong Kong/2671/2019, the egg-propagated reference virus representing the A(H3N2) component for the 2020–2021 northern hemisphere influenza vaccine — a higher proportion than the last influenza season (6). Among the 502 viruses sequenced, phylogenetic analysis of the HA gene segments determined that 501 (99.8%) viruses belonged to genetic clade 3C.2a, and only 1 virus belonged to clade 3C.3a. Multiple subclades within the 3C.2a clade co-circulated with viruses belonging to subclade 3C.2a1b, the majority subclade. Subclade 3C.2a1b viruses includes viruses having either T135K or T131K amino acid substitutions in their HA protein; 406 (80.9%) belonged to 3C.2a1b+T135K and 90 (17.9%) belonged to 3C.2a1b+T131K (Figure 3).

A total of 2,070 B/Victoria lineage viruses were antigenically analyzed with the HI test. Overall, 1,012 viruses underwent antigenic analysis with B/Washington/02/2019, and 92.4% (935/1012) were similar to B/Washington/02/2019, the egg-propagated reference virus representing the B/Victoria lineage component for the 2020–2021 northern hemisphere influenza vaccine. Significant genetic diversity was seen in B/Victoria lineage cocirculating viruses. In the HA proteins, viruses with a 2 amino acid deletions (positions 162 and 163) belonged to subclade V1A.1, and viruses with a 3 amino acid deletions (positions 162–164) belonged to subclade V1A.2; subclade V1A.3 shared a triple amino acid deletion and had an additional substitution at K136E (2, 7). Among the 330 virus HA gene segments sequenced and phylogenetically analyzed, 44 (13.3%) belonged to genetic clade V1A, 7 (2.1%) belonged to subclade V1A.1, 2 (0.6%) belonged to subclade V1A.2, and 277 (83.9%) belonged to subclade V1A.3 (Figure 3).

Few B/Yamagata lineage viruses were detected
During the study period. Antigenic characterization of the 12 B/Yamagata lineage viruses by HI test indicated that 11 (91.7%) viruses were similar to the egg-propagated B/Phuket/3073/2013, the reference virus representing the B/Yamagata lineage component of quadrivalent vaccines for the northern hemisphere influenza season. Phylogenetic analysis of 9 (100%) influenza B/Yamagata lineage viruses determined that the HA gene segments belonged to clade Y3 (Figure 3).

CNIC then tested 41,667 influenza viruses collected in the mainland of China for resistance to oseltamivir and zanamivir, including 664 influenza A(H1N1)pdm09, 1,419 influenza A(H3N2), 2,071 influenza B/Victoria, and 12 influenza B/Yamagata viruses. Overall, 3 influenza A(H1N1)pdm09 viruses showed highly reduced inhibition by oseltamivir; 2 had a H275Y amino acid substitution and 1 had a H275H/Y mixed substitution in the NA protein. In addition, 1 influenza B/Victoria lineage virus had a G243D amino acid substitution and exhibited reduced inhibition by oseltamivir and highly reduced inhibition by zanamivir; 1 influenza B/Victoria lineage virus showed reduced susceptibility to zanamivir with substitution D198N in the NA protein. All sequenced seasonal influenza viruses do not carry any reported resistant mutations to Baloxavir marboxil. All sequenced influenza A(H1N1)pdm09 and influenza A(H3N2) viruses were resistant to adamantanes, which was consistent with the current recommendation to avoid use of these drugs against influenza.

**DISCUSSION**

Unlike previous years, influenza activity began to decline sharply after the epidemic peaked in the first week of 2020. Lower levels of influenza activity have
also been reported globally during the April to September period in 2020 compared with recent years (3). This decrease in activity could be due to the COVID-19 pandemic response, as the government implemented a series of prevention and control measures, including home quarantine and wearing masks, to stop spread of COVID-19.

In late February 2020, the WHO issued its recommendations for the 2020–2021 northern hemisphere influenza vaccines. Egg-based influenza trivalent vaccines will use an A/Guangdong-Maonan/SWL1536/2019(H1N1)pdm09-like virus, an A/Hong Kong/2671/2019 (H3N2)-like virus, and a B/Washington/02/2019-like virus (B/Victoria lineage). For quadrivalent vaccines, an additional component, the B/Phuket/3073/2013-like virus (B/Yamagata lineage), was recommended (2). Except for the B/Yamagata lineage, all vaccine components were updated from the 2019–2020 northern hemisphere influenza vaccine formulation.

Most of these viruses belonged to subclade 6B.1A5A and contained amino acid substitutions D187A and Q189E (e.g. A/Guangdong-Maonan/SWL1536/2019) in their HA proteins. Although antigenic analyses do not detect all antigenic differences in these A(H1N1)pdm09 viruses, amino acid substitutions acquired in the circulating viruses were within the antigenic HA epitopes (8). Almost all influenza A(H1N1)pdm09 viruses were well inhibited by ferret antisera raised against A/Guangdong-Maonan/SWL 1536/2019, but group 5A-156K viruses reacted poorly with these antisera and were antigenically distinct, and the 5A-156K group has increased rapidly in many countries since December 2019 (3). The majority of circulating A(H3N2) viruses belonged to subclade 3C.2a1b. Among A(H3N2) viruses circulating globally, there were regional differences in the proportions of subclades circulating, and viruses with 2a1b+T135K subclade (e.g. A/Hong Kong/2671/2019) are the most prevalent in the mainland of China. Because most of the B/Victoria lineage viruses belonged to subclade V1A.3 (e.g. B/ Washington/02/2019), they were well inhibited by post-infection ferret antisera raised against B/Washington/02/2019 viruses. Most B/Yamagata lineage viruses were antigenically and genetically similar to the reference viruses representing the components of vaccines for the 2019–2021 northern hemisphere influenza season. It is worth noting that vaccine effectiveness cannot be determined solely based on similarity between circulating viruses and vaccine reference viruses because there are many other factors influencing vaccine effectiveness.

Based on our analysis, >99% of seasonal influenza viruses were susceptible to oseltamivir and zanamivir. Only 3 influenza A(H1N1)pdm09 viruses were resistant and included the H275Y or H275H/Y amino acid substitution in the NA protein that has previously been associated with highly reduced susceptibility to oseltamivir. The H275Y amino acid substitution in
A(H1N1)pdm09 viruses is considered clinically relevant and leads to reduced treatment efficacy (4). An influenza B/Victoria lineage virus showed reduced inhibition by oseltamivir and highly reduced inhibition by zanamivir; this virus had a G243D amino acid substitution in the NA protein, a substitution that has not been previously described. The G243S/G amino acid substitution, which was reported in B/Victoria-lineage viruses, is associated with reduced susceptibility to zanamivir (9). We should conduct additional evaluation to clarify the significance of this substitution. Anti-influenza drugs are effective as post-exposure prophylaxis and treatments for influenza virus infection. It is important to continuously monitor antiviral resistance of circulating influenza viruses.

The COVID-19 pandemic has changed lifestyles, improved public health preventative measures, and had an impact on other respiratory infectious diseases including influenza. Surveillance and research on influenza should be strengthened, including human infection with zoonotic influenza, to better predict and prepare for the next pandemic.

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Overview and Lessons Learned for Increasing Influenza Vaccination Coverage Among Healthcare Workers in the United States

Ying Song¹; Alexander J. Millman¹,#

BACKGROUND

Vaccinating healthcare workers (HCWs) annually against influenza is a key strategy for protecting HCWs, preventing nosocomial outbreaks and mortality (particularly among high-risk patient populations), and reducing work absenteeism during the influenza season (1–4). Vaccinated HCWs have also been shown to be more likely to recommend influenza vaccination to their patients (5–7).

US CDC’s official position has been recommending annual influenza vaccination to HCWs with direct patient contact since 1984 and for all HCWs since 1993 (8–10). In 2006, the CDC’s recommendation for influenza vaccination defined HCW to include physicians, nurses, nursing assistants, therapists, technicians, emergency medical service personnel, dental personnel, pharmacists, laboratory personnel, autopsy personnel, students and trainees, contractual staff not employed by the health-care facility, and persons (e.g., clerical, dietary, housekeeping, maintenance, and volunteers) not directly involved in patient care but potentially exposed to infectious agents (1). Since then, influenza vaccination coverage among HCWs in the United States increased from 10.0% in 1989 to 38.4% in 2002 (19).

However, during 1997–2002, vaccination coverage among HCWs plateaued around 40% (19). This indicated that while these voluntary programs were able generate modest gains, they were insufficient for increasing HCW influenza vaccination beyond a suboptimal level despite the allocation of substantial resources to support those programs (20).

To address this continued gap in coverage, Healthy People 2010 (a 10-year initiative released by the United States Department of Health and Human Services to guide national health promotion and disease prevention efforts) included a target influenza vaccination coverage goal for HCWs of 60% (21). Given the plateau in vaccination coverage among HCWs, organizations began considering new approaches to increase coverage and exceed the Healthy People 2010 target (22).
2005–2020

In 2005, the Society for Healthcare Epidemiology of America (SHEA), a professional society dedicated to the prevention of healthcare-associated infections, published a position paper stating that “all HCWs should receive influenza vaccine annually unless they have a contraindication to the vaccine or actively decline vaccination” citing evidence of reducing healthcare-associated influenza transmission and having a positive effect on HCW and patient safety (10). To support this, SHEA endorsed a multifaceted program to increase influenza vaccination among HCWs including targeted education, provision of no cost vaccination at convenient locations and times, the use of an annual active declination procedure for those refusing vaccination either for personal preference or medical contraindication, and performance of surveillance of vaccine uptake by medical unit and monitoring of healthcare-associated influenza to assess the impact of the program (10).

In 2006, US CDC’s Hospital Infection Control Practices Advisory Committee (HICPAC) and ACIP issued a joint recommendation for immunization of HCWs (including those in acute care hospitals, nursing homes, skilled nursing facilities, physician’s offices, urgent care centers, and outpatient clinics; and to those providing home health care and emergency medical services), reemphasizing that all HCWs should be vaccinated annually against influenza (1). In 2007, the Joint Commission on Accreditation of Healthcare Organizations (Joint Commission) issued an accreditation standard for hospitals and long-term care facilities to establish an influenza vaccination program to educate and provide influenza vaccination to HCWs (23). The Joint Commission further extended this to include all accredited healthcare organizations in 2012 (24).

Although HICPAC/ACIP and the Joint Commission did not include mandates among their recommendations, some professional organizations have encouraged mandatory influenza vaccination of HCWs, and some healthcare systems and state and local governments have implemented mandatory vaccination policies. In 2010, SHEA revised its position paper to recommend that annual influenza vaccination be made a condition of employment for HCWs citing continued evidence of the benefits of vaccination but suboptimal performance of voluntary programs at increasing coverage among HCWs (25), even during the 2009 H1N1 pandemic (26). In addition to SHEA, some of the largest US medical professional societies including the American Academy of Pediatrics, the American College of Physicians, the American Academy of Family Physicians, American Hospital Association, and the American Public Health Association similarly recommended mandatory influenza vaccination for HCWs (27). Although not without controversy, several major healthcare systems also implemented requirements for HCW influenza vaccinations as a condition of employment, which resulted in coverage rates of >90% (16–17,28). In 2004, Virginia Mason Medical Center in Seattle was the first healthcare system in the United States to mandate influenza vaccination for all hospital personnel resulting in coverage levels of 97.5% following the first year of the program, which were sustained at more than 98% in the subsequent 4 years (17). In 2009, New York became the first state to require influenza vaccination for all general hospitals, home health, home care, and hospice HCWs (25).

Prior to discussions of mandatory influenza vaccination policies, efforts to improve reporting of HCW influenza vaccination coverage also occurred following recommendations from HICPAC to monitor vaccination coverage by healthcare facility area (29). In fact, public reporting of HCW vaccination rates were found to result in significant facility level increases in influenza vaccination coverage by as much as 20% over three seasons (30). The 2007 Joint Commission accreditation standard required that healthcare facilities measure HCW influenza vaccination coverage among staff and independent practitioners (23), and in 2008, CDC proposed a standardized measure [National Quality Forum (NQF) #0431] for assessing HCW influenza vaccination coverage in healthcare facilities (31). Beginning in 2013, the Centers for Medicare and Medicaid Services (CMS) began requiring acute care hospitals to report HCW influenza vaccination rates through CDC’s National Healthcare Safety Network (NHSN) using the NQF measure (32). In 2015, CMS began publicly reporting these data (33). In addition to national-level reporting, some state health departments also made public voluntarily reported HCW influenza vaccination coverage for healthcare facilities on their websites and, in some cases, provided public recognition for facilities that achieved HCW vaccination coverage levels above 90% (34–35).

The Healthy People 2020 HCW influenza vaccination coverage goal was 90% (36). HCW influenza vaccination coverage remained at less than 50% until the 2009–2010 season when an estimated 61.9% received seasonal influenza vaccination by mid-January 2010 during the pandemic (26). HCW
vaccination coverage steadily increased, and in the 2018–2019 season, 81.1% of surveyed HCWs reported receiving an influenza vaccination, which was similar to the reported coverage in the previous 4 seasons (18). In the 2018–2019 season, vaccination coverage was highest (97.7%) among HCWs working in settings where vaccination was required. Among those working in settings without a vaccination requirement, coverage was 83.2% when vaccination was available at the worksite at no cost for >1 day. Vaccination coverage was lowest (42.1%) among those working in settings where vaccination was not required, promoted, or offered on-site (18).

**CHALLENGES FOR MANDATORY INFLUENZA VACCINATION AND REPORTING OF INFLUENZA VACCINATION COVERAGE**

The implementation of mandatory influenza vaccination policies for HCWs has not been universally accepted. Supporters of mandatory influenza vaccination cite evidence for reductions in healthcare-associated transmission and HCWs’ absenteeism, the favorable safety profile of the vaccination, professional duties to protect vulnerable patients, vaccination mandates for other infectious diseases, lack of efficacy of voluntary programs, and strengthening health systems familiarity with vaccination management to enhance pandemic preparedness (10,25,37–38). Critics of mandatory vaccination for influenza argue that such policies deprive HCWs of their decision-making autonomy, force an intervention with only moderate effectiveness, and do not provide sufficient prevention benefits to justify termination of employment (39–40). In some cases, HCWs have initiated legal challenges to employer-imposed influenza vaccination mandates (41). Other challenges for mandatory influenza vaccination programs include costs and staff–time associated with implementing the program including providing vaccination services, tracking and reporting data, and following up with healthcare workers and, if applicable, collecting declination information and evaluating exemption policies (42). In response to concerns of mandatory influenza programs, some proposed an alternative strategy that restricted mandatory vaccination to HCWs working in high risk areas such as intensive care units, oncology departments, and geriatric departments while offering HCWs unwilling to be vaccinated the option of transferring to alternative non-high risk departments in lieu of employment termination (20,43).

Ensuring accurate and standardized measurement and reporting of influenza vaccination coverage is essential for evaluating the implementation of HCW influenza vaccination programs and increasing vaccination. A study reporting on data from the year prior to the 2007 Joint Commission requirements found that nearly one-third of surveyed hospitals did not measure staff vaccination coverage, and that even among hospitals that did measure vaccination coverage, there was variability in the methods used for measurement (44). For example, hospitals reporting vaccination coverage had differing approaches in whether certain types of HCWs such as contract staff or trainees would be included in the population denominator for vaccination coverage (44). Similarly, the study identified differing practices in counting employees who were vaccinated off site or who declined vaccination (44). Standardized measurements of HCW influenza vaccination coverage are essential for enabling comparisons between different types of healthcare facilities and for evaluating the validity of reported data. In the case of measuring influenza vaccination among HCWs, the NQF #0431 measure provided a standard reporting mechanism to enable calculation of comparable vaccination coverage among diverse healthcare facilities (32). Data collected through standardized reporting measures could then be used to facilitate the development of programs aimed at increasing HCW vaccination coverage in settings or groups reporting suboptimal coverage. For example, during the 2018–2019 season, coverage was highest among HCWs in hospital settings (95.2%) and lowest in long-term care settings (67.9%) (18). Based on these findings, healthcare systems could identify tools such as CDC’s long-term care web-based toolkit to increase influenza vaccination among HCWs using a tailored approach (18).

**CONCLUSION**

Annual vaccination of healthcare workers (HCWs) against influenza is a key prevention strategy and an integral part of healthcare systems’ comprehensive infection control program. In the United States, influenza vaccination coverage among HCWs has increased from 10% in 1984 to 81% by 2018–2019. National level policy recommendations coupled with state government, regulatory organization, professional society, and healthcare institution policies and
multicomponent interventions including provider education, occupational programs offering free, onsite vaccination, and institutional vaccination requirements have been critical to increasing influenza vaccination coverage in HCWs. Although not without controversy, healthcare facilities with mandatory HCW influenza vaccination programs have reached the highest influenza vaccination coverage; however, healthcare facilities without mandates have also achieved high levels of vaccination coverage with free, onsite vaccination. In addition, public reporting of HCW influenza vaccination coverage has the potential to improve HCW vaccination uptake but requires a standardized and validated reporting methodology. Finally, increasing influenza vaccination coverage among HCWs requires developing appropriate and achievable goals and targeted interventions that are appropriate and acceptable for the healthcare facility.

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Battling COVID-19 Using Lessons Learned from 100 Years of Fighting Against Influenza

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In 1918, a letter from a doctor at an USA Army camp read:

“These men start with what appears to be an ordinary attack of LaGrippe or Influenza, and when brought to the Hosp, they very rapidly develop the most vicious type of pneumonia that has ever been seen… and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face until it is hard to distinguish the colored men from the white. It is only a matter of a few hours then until death comes… It is horrible. One can stand it to see one, two or twenty men die, but to see these poor devils dropping like flies … We have been averaging about 100 deaths per day … Pneumonia means in about all cases death … We have lost an outrageous number of Nurses and Drs. It takes special trains to carry away the dead. For several days there were no coffins and the bodies piled up something fierce… It beats any sight they ever had in France after a battle. An extra long barracks has been vacated for the use of the Morgue, and it would make any man sit up and take notice to walk down the long lines of dead soldiers all dressed and laid out in double rows … Good By old Pal, God be with you till we meet again.” (1)

This letter shed some light on the scenario of the 1918 influenza pandemic. What the physician had not foreseen was that this disease would cause 50 million people to die in the following year — many more deaths than those caused by the two World Wars. The 1918 “Spanish Flu” was the first influenza pandemic in the 20th century and also the most lethal one. Following this one, 3 more influenza pandemics have occurred as of 2020, including the 1957 H1N1, 1968 H3N2, and the 2009 H1N1, though the 1977 “Russian Flu” caused by H1N1 has also led to concentrated epidemics around the world. Compared with the 1918 pandemic, the later influenza viruses showed lower morbidity and mortality, but 100 years after the 1918 “Spanish Flu”, we confronted a second severe pandemic disease caused by the coronavirus disease 2019 (COVID-19) (2–3). Up to October 28, 2020, this virus has caused 43,906,632 cases in the world with over 1 million deaths (4). Unlike the highly genetically related SARS-CoV virus that causes severe acute respiratory syndrome (SARS), which abated quickly because of aggressive containment procedures and relatively lower transmission capacity, COVID-19 continues spreading globally and is expected to circulate in the population in the near future. Using lessons learned from combating influenza pandemics over the past 100 years, we can use this historical perspective in our battle against COVID-19.

As stated by John Barry, the most important lesson from the 1918 influenza is to “tell the truth” (5). In 1918, due to the pressure to maintain wartime morale, neither national nor local government officials told the truth to the public. However, Spain was neutral in the First World War, and newspapers there could report on the disease so it was generally perceived that the pandemic had originated from Spain and led to the misnaming of the disease as the “Spanish Flu” (6–7). In countries that silenced the press, trust in authority deteriorated as the death toll increased, and this led to increased vulnerability amongst the population.

Because effective pharmaceuticals either did not exist or were not readily available, most cities suffered a tremendous death toll during the 1918 pandemic. However, cities that had imposed multiple social containment measures within a few days of detecting the first local cases had peak deaths rates of up to 50% lower than other cities that waited weeks to respond (8). Early implementation of some interventions, including the closure of schools, churches, and theater, was associated with lower peak death rates, but no single intervention showed an association with improved outcomes (8). In addition, the benefit of these multiple interventions was extremely limited if implemented too late or lifted too early, which indicated that proper timing of the response is crucial to curbing the effects of a pandemic (9).

San Francisco, St. Louis, Milwaukee, and Kansas City had the most effective public health interventions as they were able to reduce transmission rates by up to
The first official preventive measures were implemented in August 1918 and included obligatory notification of suspected cases and community surveillance. As the disease spread, closure of public places, banning gathering in crowds, cleaning streets, disinfecting the environment, and limiting the numbers of passengers on public transport, were applied in these three cities (7).

Besides the implementation of preventive measures, a worldwide network was established during the 1957 “Asian Flu” pandemic to study the strain soon after it emerged and involved investigators from London, Melbourne, and Washington DC. It was also the first time that vaccinations were implemented to protect high-risk individuals (10). Due to the low disease severity and low mortality rates, costly control measures such as school closures or quarantines were thought to be unnecessary in both the 1957 and 1968 pandemic. However, the 1968 “Hong Kong Flu” emphasized the importance of a combination of vaccinations, hospitalizations for complicated cases, and antibiotics to treat secondary infections. Hand hygiene and voluntary isolation of symptomatic individuals were further recommended in the 2009 H1N1 pandemic (11). These measures that were applied in response to past influenza pandemics were again widely implemented to help contain the COVID-19 pandemic.

Like the influenza virus, COVID-19 mainly spread via respiratory droplets that are transmitted during close contact (12) and the direct contact of the infectious surface through hands and other body parts, which means that social distancing strategies designed to block influenza transmission are also effective against COVID-19. Many countries have observed influenza incidence plunging as positive consequence of the public health response to COVID-19 during the 2019–2020 influenza season (13–14). The $R_0$ (reproductive number) for the SARS outbreak in 2003 was estimated to be between 2.0 and 3.0 in the early stage and quickly declined to 1.1 after stringent control measures (15). Studies have estimated the $R_0$ of COVID-19 to be 2.2 (95% CI*: 1.4–3.9) and 2.7 (2.5–2.9) (16–17), though another study has calculated a median $R_0$ value of up to 5.7 (95% CI: 3.8–8.9) (18). By comparison, the initial $R_0$ estimate for the H1N1 influenza pandemic in 2009 was 1.7 and later estimated between 0.17 and 1.3 after control measures were started (15). Because of the higher $R_0$ and fatality rate of COVID-19 compared to the influenza virus, more rigorous policies including active surveillance, contact tracing, mass samples testing, quarantining, and strong social distancing efforts have been needed to stop further transmission of the virus.

China and other Asian countries have been successful in controlling the spread of COVID-19 through their rigorous and early action. Following the SARS epidemic in 2003, China has prioritized developing its early response systems to public health emergencies, and in the 2009 response to H1N1, Richard Stone stated: “No country has taken stricter measures than China to protect residents from pandemic swine flu” (19). As the COVID-19 emerged and spread, China has applied rapid and rigorous containment efforts to block disease transmission, including locking down major cities and reducing transport between affected regions. This strategy also included rigorous social distancing, universal temperature monitoring, ubiquitous face masks wearing, and hand washing (20). Similarly, other Asian countries such as Republic of Korea and Vietnam also took aggressive action such as mass testing, movement restriction, and mandatory mask wearing (21) and have also succeeded in disrupting transmission.

When faced with a novel influenza virus that is rapidly spreading in the human population, an investigation must be conducted to uncover the origin of the virus, the intermediate host, the transmission route, and the clinical features it causes (22). This knowledge could help alert people to take proactive measures to prevent uptake of the virus and its spread. As a consequence, global cooperation for information sharing and virology research is needed to face the challenges continuously posed by influenza, and the Global Influenza Surveillance and Response System (GISRS) exemplified such cooperative efforts to combat infectious disease (23). The GISRS currently comprises 142 national influenza centers, 6 World Health Organization (WHO) Collaborating Centres, 4 essential regulatory laboratories, and 13 WHO H5 Reference Laboratories. GISRS aims at surveillance and monitoring of seasonal and emerging influenza viruses; recommendations for laboratory diagnostics, vaccines, and antiviral susceptibility; risk assessment for seasonal and pandemic influenza; and detection and response to influenza outbreaks (24). During the 2009 H1N1 pandemic and 2013 avian H7N9 endemic, China cooperated with other countries by sharing virus

* CI = Confidence Interval.
strains, sequences, and clinical trial information, which greatly contributed to the containment of the disease. Thus, a global platform and network similar to GISRS should be established for COVID-19 research and surveillance to integrate the global efforts against COVID-19 worldwide. In the struggle against COVID-19, we need stronger global cooperation and solidarity than any time before.

Humanity has been repeatedly endangered by infectious diseases and, each time so far, has won the fight. More infectious diseases are certain to come, though when and where they will emerge cannot be predicted. The knowledge accumulated in these battles will prepare us to overcome the crises caused by infectious diseases in the future.

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The possible dual epidemic of coronavirus disease 2019 (COVID-19) and influenza in the coming winter raises serious concerns for the northern hemisphere as it will likely result in an expanded disease burden and overloading of public health institutions and clinical capacities as a result of continued increasing mental stress for the public and depletion of public resources. Several questions remain regarding how the flu season might affect the COVID-19 pandemic and vice versa.

**DECREASED INFLUENZA ACTIVITY AND POTENTIAL CONTRIBUTORS**

Some signs of the interaction between the flu and COVID-19 were shown in the past flu season in the southern hemisphere. Australia, Chile, and South Africa recorded not only much lower influenza activity compared with usual seasons, but fewer positive test results of influenza viruses — 51 influenza positive specimens out of 83,307 samples, or 0.06% [95% confidence interval (95% CI): 0.04–0.08] (1). In the northern hemisphere, the United States, Republic of Korea, and Singapore reported an interruption to the then ongoing influenza circulation of the 2019–2020 season and a historically low interseasonal level of influenza incidence (1–3). Reduced activity was also observed for other common respiratory viral agents (4).

Non-pharmaceutical interventions (NPI) aimed against COVID-19 were supposed to be responsible for reducing transmission of influenza. A range of mitigation measures focusing on social distancing, including bans on mass gatherings, school closures, teleworking, and national or regional lockdowns, have been widely implemented for COVID-19 and whose effectiveness has been demonstrated by the corresponding incidence curves of many countries across the world, such as China, Germany, Australia, and South Africa (5). These community measures, in addition to recommended or mandatory individual measures against COVID-19 such as mask wearing and hand hygiene, can also curb the transmission of the seasonal influenza virus that shares same transmission routes with COVID-19 (6) but is less contagious (R0=1.28 for the flu compared to R0=2–3.5 for COVID-19) (7). Among these mitigation measures, school closures may have played an additional role in reducing transmission in children, who are important drivers of influenza virus transmission in the community (6).

Viral interference could also be at play (8–9) as infection with a virus can prevent or partially inhibit infection with another virus within the same host (9). The interference is variable between virus-pairs and could be modified by the time interval from primary to secondary viral exposure (8,10). In COVID-19 patients, the infection rate with non-COVID-19 respiratory viral pathogens was much lower than that in non-COVID-19 patients during the same time period (2.99% vs. 13.1%), which suggested a competitive advantage of COVID-19 in the interaction with other respiratory viruses including influenza (11).

**COINFECTION AND PRIOR INFECTION WITH INFLUENZA**

The coinfection rate of COVID-19 with other respiratory viral pathogens was reported vary widely between 0% to 25%, with a pooled estimate of 3% (12). The variety of virus targeted, the detection method used, and the seasonality of other respiratory viral pathogens during the research period (13) may contribute to heterogeneity among studies. Among the identified coinfeated viral pathogens, influenza virus was among the most common (12).

Coinfection with influenza virus has been reported in Middle East respiratory syndrome (MERS) cases (14). The coinfection rate with influenza virus was generally low in confirmed COVID-19 patients with a combination of different clinical severities (0.1%–2.7%), according to studies using PCR-based testing methods across the world, from Switzerland (4), Brazil
(15), the United States (16–17), Spain (18), and China (19–20). Although the clinical impact of coinfection has not been conclusive, some evidence has suggested that coinfection with influenza virus may worsen the clinical outcome of COVID-19 patients. In coinfected patients, substantially higher neutrophils and inflammatory markers and higher incidence of acute cardiac injury were observed (21), and the risk of ventilator use and death was elevated (22), in which the provoked hyperinflammatory state and the up-regulated pulmonary angiotensin-converting enzyme 2 (ACE2) receptors induced by influenza virus infection might play a role (23–24). In a study conducted in Iran, 22.3% of the dead COVID-19 patients were coinfected with influenza virus (25).

In contrast, the rate of recent influenza infection was high in COVID-19 patients (26). Over a half of the confirmed COVID-19 patients in a hospital in Wuhan, China tested positive for the influenza immunoglobulin M (IgM) antibody test (26). A study in Italy observed that 63.6% of COVID-19 patients reported a recent (1–3 weeks) influenza-like illness prior to the appearance of COVID-19-related symptoms (27). Thus, the upper airway mucosal damage and local immune impairment triggered by prior infection may predispose individuals for subsequent COVID-19 infection (27).

THE ROLE OF INFLUENZA VACCINATION

To reduce the public health, economic, and societal hardship associated with long-term stringent lockdown measures, many countries have been relieving public health and social measures against COVID-19, but a resurgence of COVID-19 cases has been observed to follow in many countries and areas (28). The transmission activity of other respiratory viruses, particularly influenza, could also spike along with the relief of NPI against COVID-19 in the coming winter of the northern hemisphere, challenging the already stressed public health and healthcare capacities. This spike may be more obvious in countries or territories where society has returned to a certain level of normalcy.

To reduce the epidemiological noise of influenza in the context of COVID-19, mass influenza vaccinations are strongly recommended. However, this would be tricky given the tampered routine immunization services as manufacturing capacity is diverted to COVID-19 and other vaccines. In that case, the elderly, healthcare workers, etc., could be targeted as priority groups for influenza vaccination due to risks of elevated mortality and exposure and the importance of maintaining healthcare services.

In addition to the potential of avoiding complicated coinfections, the influenza vaccination was found to be associated with lower risk of infection, severe clinical manifestation, and death with COVID-19 at the individual level (29–31). At the population level, an ecological study also showed that the coverage rate of the influenza vaccination in people aged 65 or over was associated with a reduced spread and a less severe clinical presentation of COVID-19 (32). It is possible that influenza vaccination could act as a non-specific immune stimulator leading to earlier activation of the immune system to combat COVID-19 (33).

Nevertheless, the effectiveness of influenza vaccine is generally modest and even lower in individuals aged 65 years or older, who are at higher risk of severe infection for both the influenza virus and COVID-19. Mismatch between the circulating influenza strains and the vaccine influenza strains would further jeopardize the vaccine’s effectiveness. This is more likely to happen in the next influenza season of southern hemisphere, as very few isolates of influenza virus were able to be collected in the past flu season making it especially difficult to predict the upcoming circulating strains. Thus, faster and more widely available testing is needed to distinguish between the influenza virus and COVID-19, which cause similar symptoms but requires different treatments and emergency response strategies. In addition, some NPI including wearing mask and social distance should be preserved as the new standard until a valid COVID-19 vaccine is available.

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