VirusDis. (July–September 2017) 28(3):225–232
DOI 10.1007/s13337-017-0390-8

REVIEW ARTICLE

History and current trends in influenza virus infections with special reference to Sri Lanka

R. A. M. Rafeek[1] · M. V. M. Divarathna[1] · F. Noordeen[1]

Received: 2 March 2017 / Accepted: 20 June 2017 / Published online: 18 July 2017

Abstract The World Health Organization (WHO) estimates that approximately one billion people are infected and up to 500,000 people die from influenza each year in the world. Influenza is considered to be the greatest killer of the human populations, due to the 1918 Spanish flu, which killed millions around the world. Despite the effective treatment available against influenza, it still contributes to significant morbidity and mortality. Currently circulating influenza strains in humans include influenza A (H1N1)pdm09, influenza A (H3N2) and influenza B viruses, (B/Victoria and B/Yamagata). Influenza has been prevalent in Sri Lanka from 1969, since then it continued to cause morbidity and mortality in children and adults. The current global influenza surveillance network monitors the global influenza activity through WHO collaborating centres. The Medical Research Institute monitors and diagnoses influenza cases in the country as part of the WHO network laboratories. Vaccinations to high risk groups and antiviral therapy for the successful prevention of influenza have been practiced in Sri Lanka. This review highlights the impact of influenza on public health in Sri Lanka including the historical aspects, current diagnostic practices and prevention approaches in high risk individuals in the country.

Keywords Influenza · Morbidity · Mortality · Prevention · Public health · Sri Lanka

✉ F. Noordeen
faseehan@pdn.ac.lk; faseeha.noordeen12@gmail.com

[1] Department of Microbiology, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka

Introduction

Influenza viruses are important viral pathogens attacking infants, young children and elderly often causing morbidity, mortality and significant economic and social impact on communities [46]. Influenza is an acute respiratory tract infection (ARTI) also known as flu with an incubation period ranging from 1 to 4 days [14]. Influenza outbreaks have been reported globally and locally with an annual infection rate of ~5–10% in adults and 20–30% in children and thus influenza contributes to 3–5 million cases of severe ARTI and ~250,000–500,000 deaths annually [17, 27]. Although the seasonality of influenza differs between the tropical and temperate regions, the overall disease burden and mortality remains comparable [45].

Influenza viruses infect the upper respiratory tract including nose, throat and bronchi and rarely, the lungs. It poses a serious risk to the elderly, the very young, pregnant women, immunocompromised patients and those with underlying medical conditions such as lung, kidney or cardiac disorders, diabetes and cancer [11]. Symptoms of classical influenza usually appear abruptly and include chills, headache, coryza and dry cough followed by high fever, generalized myalgia, malaise and anorexia. Fever usually lasts for 3–5 days similar to the systemic symptoms [22]. Respiratory symptoms typically last for another 3–4 days. The cough and weakness may persist for 2–4 weeks after the major symptoms subside. During an outbreak mild or asymptomatic influenza viral infections may also occur [42]. Most of the infections caused by the influenza A, H1N1 subtypes seem to be mild and self-limiting and do not require hospitalisation. However, severe illness and deaths have also been reported in a small proportion of cases. In seasonal influenza, the

overwhelming majority of severe morbidity and mortality is noted to occur in people over the age of 65 years [6].

Properties of influenza viruses and transmission

The influenza viruses belong to the family *Orthomyxoviridae* and the genus *Orthomyxovirus*. Influenza viruses have an enveloped segmented RNA genome. The viruses are approximately 120 nm in diameter [31]. These viruses are classified based on the antigenic differences of their nucleocapsid and matrix proteins [12].

Influenza viruses, A and B are associated with significant seasonal morbidity and mortality. Influenza A and B viruses were first isolated in 1933 and 1940, respectively. Influenza A viruses can be subtyped according to the antigenic and genetic nature of their surface glycoproteins; 15 haemagglutinin (HA) and 9 neuraminidase (NA). Antigenic changes occur within the influenza A viruses and to a lesser degree in the influenza B viruses whereas the influenza C viruses appear to be antigenically stable [37]. Mutability and high frequency genetic re-assortment leading to antigenic changes in the viral surface glycoproteins make influenza viruses as formidable challenges to public health. Influenza A viruses are antigenically variable and responsible for the most epidemics; Influenza B viruses exhibit antigenic changes and sometimes cause epidemics; Influenza C virus is antigenically stable and causes only a mild respiratory illness [37].

Among the many subtypes of influenza A viruses, currently influenza A (H1N1)pdm09 and A (H3N2) subtypes are circulating in humans [6]. Moreover, there are two types of influenza B viruses circulating and cause seasonal influenza outbreaks and influenza C occurs less frequently [19, 21]. Influenza A viruses infect mammals and birds. Influenza B viruses infect mammals only and Influenza C viruses infect humans and pigs. In addition to the influenza A virus, which causes respiratory disease in humans, some strains of influenza A are capable of causing respiratory tract infection in pigs referred to as swine flu. Swine influenza is very common in the mid-western United States, Mexico, Canada, South America and Europe including the United Kingdom, Sweden, Italy and East Asia [15]. Transmission of flu from pigs to humans, however, is not common, although there have been some suspected cases reported in farmers, who were in close contact with pigs [23]. Bird flu is a respiratory disease of birds caused by influenza A (H5N1), (H7N9) virus. Although this virus usually does not infect humans, there have been many suspected cases and deaths reported in humans in some countries like China and Indonesia [49, 50]. There have been no bird flu cases reported in Sri Lanka so far. Symptoms of avian influenza are similar to the symptoms of pandemic influenza but severe cases may develop serious respiratory complications. From a study carried out in China, 82% of the cases of bird flu are from patients, who had exposure to live animals such as poultry or swine. This raises the possibility of zoonotic transmission of certain strains of influenza A virus from poultry or swine to humans through direct or indirect exposure [9, 47].

Influenza virus may be transmitted to humans in three ways including (a) direct contact with infected individuals (b) indirect contact with contaminated fomites and (c) inhalation of virus-laden aerosols [32]. Phylogenic studies suggest that wild waterfowls are the natural reservoirs of influenza A viruses. Seasonal influenza spreads easily and can sweep through densely populated places such as schools, nursing homes or townships [24]. When an infected person coughs or sneezes, infected droplets disperse into the air and another person inhaling them can be exposed. The virus can also be spread through contact with hands infected with the virus. Influenza viruses are relatively hardy and survive on the surfaces for 2–8 h [36]. Influenza predominates in winter in temperate regions of the world and in the rainy season in the tropics, although many tropical and subtropical regions experience more complex seasonal patterns including semi-annual cycles and year-round activity [2, 43].

History of influenza pandemics

Influenza pandemics have been amongst the largest and the deadliest in the history of man and were observed since ancient times. The very first influenza outbreak occurred in 1580 in Asia and swept through Europe, Africa and the Americas [26]. In the last 100 years, four influenza pandemics had been reported including 1918 (Spanish Flu), 1957 (Asian Flu), 1968 (Hong Kong Flu) and 2009 (Mexican Flu) and these pandemics were caused by influenza A viruses H1N1, H2N2, H3N2 and A (H1N1)pdm09, respectively. The 1918 pandemic resulted in 20–50 million deaths worldwide and the other two resulted in 1–4 million deaths globally [26, 29]. The most recent pandemic influenza was experienced in 2009 by the novel influenza A virus, H1N1 [44]. Mexico and America were the first countries to be affected. The pandemic rapidly spread throughout the world to over 214 countries by the 1st of August 2009. Since it was a new strain of the virus to which humans had no immunity and thus it caused 18,449 deaths globally [1].

The 2009 pandemic influenza outbreak affected many of the South Asian regions, including India, Pakistan, Bangladesh, Nepal and Maldives. The first Indian pandemic influenza case was reported from Hyderabad in May 2009 [30]. An estimated 43 million episodes of ARTI occur annually in India and 4–12% of respiratory illnesses in the community are due to influenza [7]. The 2009 pandemic

influenza A (H1N1) virus caused approximately 6000 deaths in Bangladesh costing 6.1 million US dollars for medical costs [3, 38]. Nepal has started screening febrile travellers with respiratory symptoms from affected countries for the pandemic influenza A (H1N1) since April 2009 and the first case in that country was detected in June 2009 [1]. The Maldives did not detect any cases of swine influenza up to July 2009. Since then 6 cases of H1N1 was confirmed as imported cases and the first case of internal transmission was detected in November 2009 in that country (http://www.health.gov.mv/publications/Maldives%20Pandemic%20Preparedness%20Plan_%20November%202009%20update.pdf). Data on influenza burden in Southeast and East Asia is relatively limited, although influenza rates of 11–26% in outpatient fevers and 6–14% of hospitalised pneumonia cases have been reported from various Southeast and East Asian countries [41].

Sri Lanka was also affected by the 2009 pandemic influenza with 642 laboratory confirmed influenza A cases and 48 deaths in the country. A second wave of the disease occurred in 2010 and this resulted in 580 laboratory confirmed influenza A cases and 29 deaths (http://epid.gov.lk/web/attachments/article/161/Vol%2038%20NO%2003%20English.pdf). Influenza pandemics are unpredictable events that cause significant panic and thus negative impact on societies [28]. The impact of such an event could be worse in developing countries including Sri Lanka where stockpiling of antiviral drugs for treatment and vaccine for prevention are not done due to lack of resources and this contributes to the fear among the public [13].

Global surveillance

Global influenza surveillance has been conducted through the WHO Global Influenza Surveillance and Response System since 1948/1952 including Sri Lanka. This network monitors evolution of influenza viruses and provides recommendations on laboratory diagnostics, vaccines, antiviral susceptibility and risk assessment. It also serves as a global alert mechanism for the emergence of pandemic influenza A viruses. The network currently comprises 6 WHO Collaborating Centres, 4 Essential Regulatory Laboratories and 136 institutions in 106 WHO member states, which are recognized by the WHO as National Influenza Centres (NIC) [8].

Globally seasonal influenza has shown an increasing trend (Fig. 1). Temperate countries in the southern hemisphere, Northern Africa and northern hemisphere, north America and countries like China in the East Asia shows an increase in the influenza activity, but other countries in the southern hemisphere show an inter-seasonal activity. In Europe and Northern Asian regions, the influenza activity has been remarkably high with influenza A (H3N2) dominating. According to the WHO reports, apart from North America, Europe and Western Asian countries where influenza A (H3N2) virus activity is high, the other

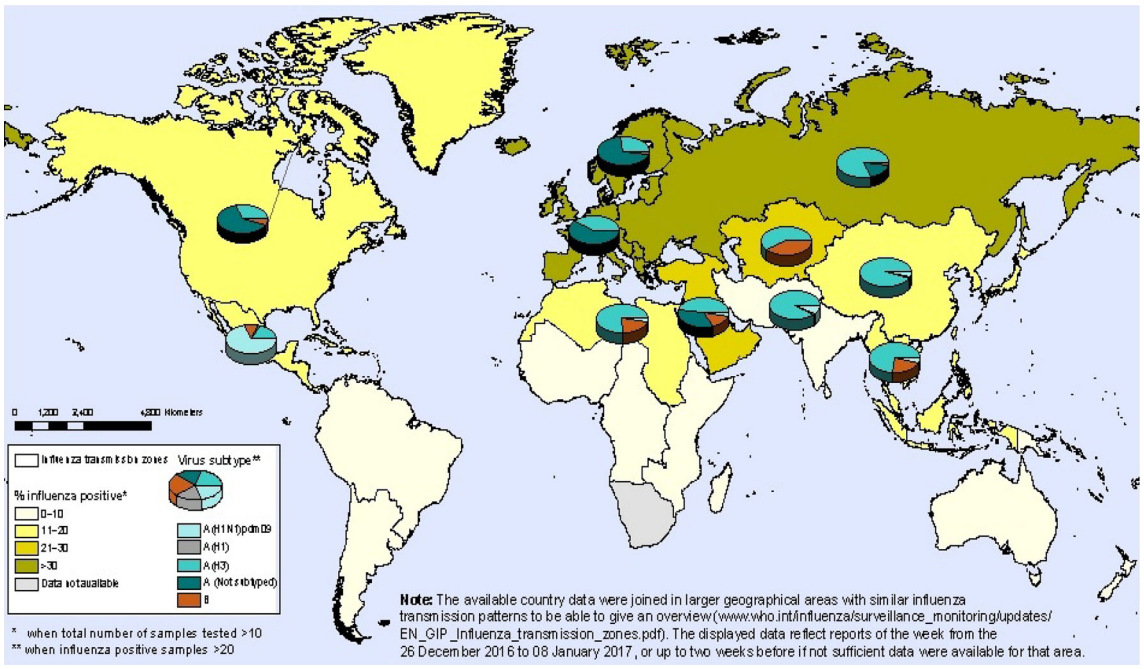

Fig. 1 Percentage of respiratory specimens tested positives for influenza by the influenza transmission zone as on the 25th December, 2016. *Source*: URL Adapted from WHO. http://www.who.int/influenza/surveillance_monitoring/updates/2017_01_23_influenza_update_281.jpg?ua=1

countries including China and Southeast Asian regions had reported influenza A (H1N1)pdm09 in high numbers with some untyped influenza A and B viruses.

Epidemiology of influenza in Sri Lanka

In tropical countries including Sri Lanka, influenza viruses circulate throughout the year with one or two peaks occurring during the rainy season. For the last few years, peaks have been generally observed during April to June and again in November to January. The influenza virus was first isolated in Sri Lanka during the pandemic "Hong Kong flu" H3N2 in 1969 [25]. The first confirmed case of pandemic influenza A/H1N1 in the country was reported in June 2009. Subsequently, influenza A viral strains (H1N1)pdm09 and (H3N2) and influenza B have been identified as the commonly circulating seasonal influenza viruses in Sri Lanka [8]. The epidemic in this season has been observed to cause severe disease (http://www.epid.gov.lk/web/images/pdf/Fact_Sheet/fact_sheet_seasonal_influenza.pdf). The annual incidence of influenza varies widely and depends on the virulence of the circulating strains and the susceptibility of the population to these viral strains.

Sri Lanka started its influenza surveillance in 2006. The NIC monitors the influenza activity throughout the year and provides influenza surveillance information to the public (http://epid.gov.lk/web/pdf/wer_2009/vol_36_no_38_english.pdf). Influenza surveillance comprises of 2 components; Influenza like illness (ILI) surveillance and severe acute respiratory tract infections (SARI) surveillance. For the ILI surveillance, NIC screens 20 hospitals and informs each hospital to send at least 30 respiratory samples from the suspected patients with ILI and SARI to the NIC every month for testing to identify the circulating influenza A viruses in the country (http://epid.gov.lk/web/images/pdf/wer/2015/vol_42_no_25-english.pdf). These hospitals are expected to send weekly data returns of influenza patients to the Epidemiology Unit where the data are entered into a database for further analysis (http://epid.gov.lk/web/pdf/wer_2009/vol_36_no_38_english.pdf). SARI surveillance has been established in 3 hospitals in the country: Lady Ridgeway Children's Hospital (LRH), General Hospital, Matara and Teaching Hospital, Peradeniya. These hospitals are expected to send samples from all inward patients admitted with severe ARTI.

Based on the flu-net reports from 2006 to 2008, only 4 influenza types circulated in the country including influenza A (H1), influenza A (H3), influenza B and un-typed influenza A. Of these, influenza viruses A (H1) and (H3) were reported only in 2007 (http://epid.gov.lk/web/images/pdf/wer/2015/vol_42_no_25-english.pdf). In 2009, with the influence of pandemic influenza, a new influenza subtype, influenza A (H1N1)pdm09, circulated in the country (Table 1). On the other hand, the percentages of influenza A and B positive cases from 2006 to 2016 with all influenza cases are given in Fig. 4.

During the second wave in 2010, all districts except Mannar, Mullativu and Kilinochchi had confirmed cases of influenza. From the 812 confirmed cases, 30% were from the Colombo District and 9% each from Gampaha and Kandy Districts and 7% from the Galle and Matara Districts. The distribution of confirmed cases by Province in 2010 and 2014 is shown in Fig. 2 (http://epid.gov.lk/web/pdf/wer_2009/vol_36_no_38_english.pdf). In 2011 and 2012, the predominant influenza virus reported was influenza B, 235 and 358, respectively.

In 2013, NIC tested 4854 samples and of these 616 were positive for influenza A (H1pdm09 = 323, H3 = 126, not typed = 93) and 381 were positive for influenza B (http://

Table 1 Influenza subtypes circulated in Sri Lanka from 2006 to 2016 (WHO, Flu net reports)

Years	Number of influenza subtypes					
	Influenza A H5N1	Influenza A H1N1	Influenza A H1N1 2009	Influenza A H3N2	Influenza A not sub-typed	Influenza B
2006	0	0	0	0	18	3
2007	0	10	0	9	12	12
2008	0	0	0	0	24	4
2009	0	11	423	0	123	6
2010	0	4	541	29	129	109
2011	0	0	168	122	43	235
2012	0	0	129	168	51	358
2013	0	0	323	128	134	360
2014	0	0	17	113	76	26
2015	0	0	197	166	928	173
2016	0	13	49	122	3	240

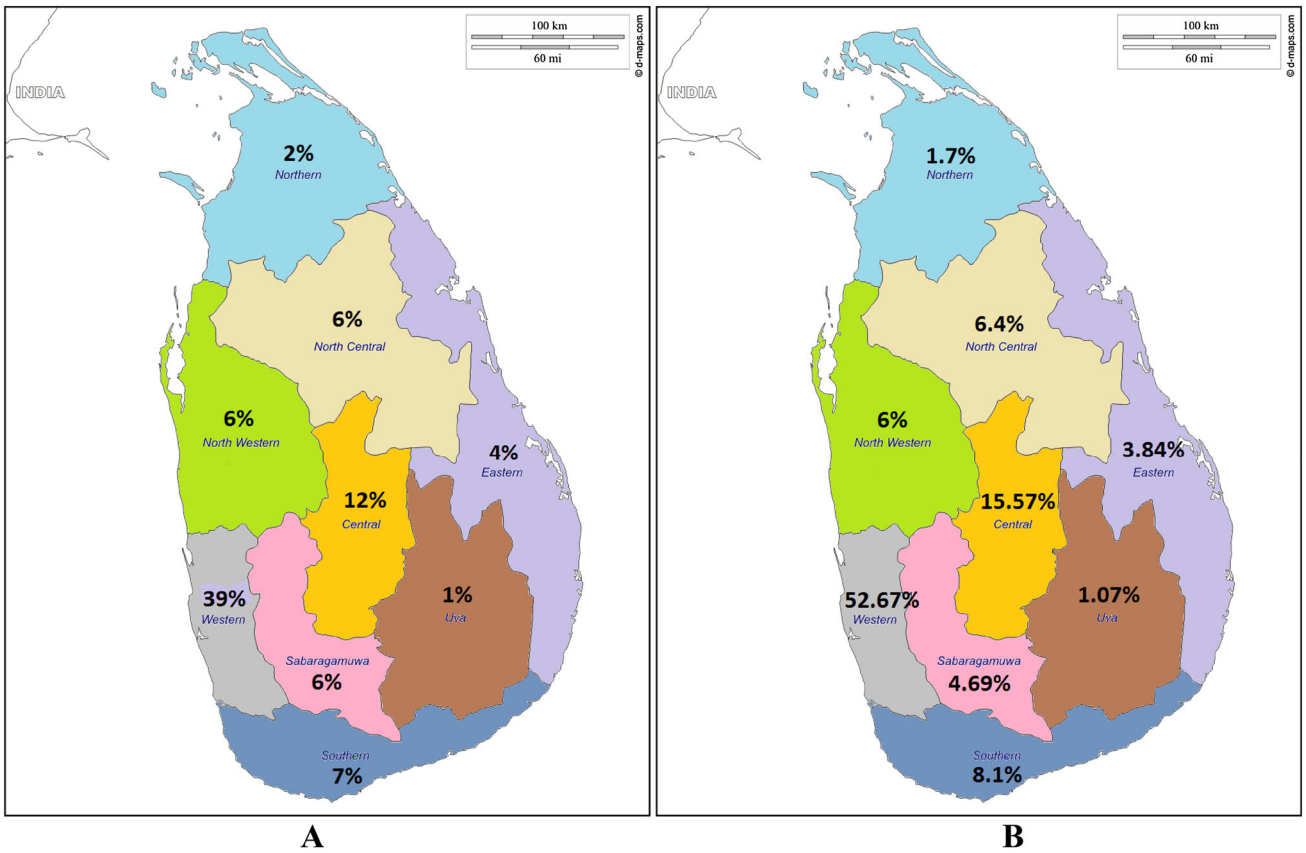

Fig. 2 Distribution of influenza in Sri Lanka by provinces in 2010 (**a**) and 2014 (**b**)

www.mri.gov.lk/departments/virology/influenza-2/). In 2014, NIC tested 2015 respiratory samples, of these 232 were positive for influenza viruses. Based on the 2014 report from the NIC, the predominant strain was influenza A (H3N2) in addition to influenza A (H1N1) pdm09 and influenza B. The most complicated influenza year in the history of Sri Lanka was 2015 as many new types of influenza viruses including highly infectious strains were detected in that year. These 2015 influenza virus strains were similar to what are normally found in birds capable of infecting people with high lethality.

In 2015, more than 5324 ILI patients and 303 SARI patients were reported from the island from the selected hospitals. This number consisted of 1.04 and 2.39% of the total out patients' department (OPD) visits and total hospital admissions, respectively (http://www.mri.gov.lk/departments/virology/influenza-2/). In 2015, MRI detected 1464 influenza virus positive patients having 291 influenza A and 173 influenza B viruses. Seven deaths have been attributed to influenza in 2015 including 4 pregnant mothers from Tissamaharama (Fig. 3). However, these cases were found to be scattered on further investigations (http://www.mri.gov.lk/departments/virology/influenza-2/). In 2016, MRI has tested 2762 respiratory samples, of these 427 were positive for influenza viruses including 187 influenza A and 240 influenza B viruses (Fig. 4).

Apart from these national surveillance data, there have been a few studies on influenza in the last two decades in Sri Lanka. According to a study carried out by Perera et al. on influenza virus infections in a sample of hospital attendees in Ragama, influenza viruses were found to circulate at different times of the year and were responsible for 11% of all ARTI in their study cohort. The largest peak of influenza A virus activity occurred from May to June in 2004 and it is the rainy season in the country. Influenza B virus activity occurred from September to December 2003 at low levels without a major peak in virus activity [35].

Subsequently, a different study conducted by Perera et al. on the isolation and characterization of influenza viruses circulating among avian, swine and human populations in Sri Lanka in 2007, tested 300 NPA samples. Of these, 138 were positive for multiple viruses: 24/138 were influenza A and 9/138 were influenza B viruses and these influenza viruses were characterized as influenza A Panama/2000/99 (H3N2) and influenza B/Sichuan/379/99-like virus [35].

Animal influenza virus surveillance is carried out by the Department of Animal Production and Health (DAPH) of

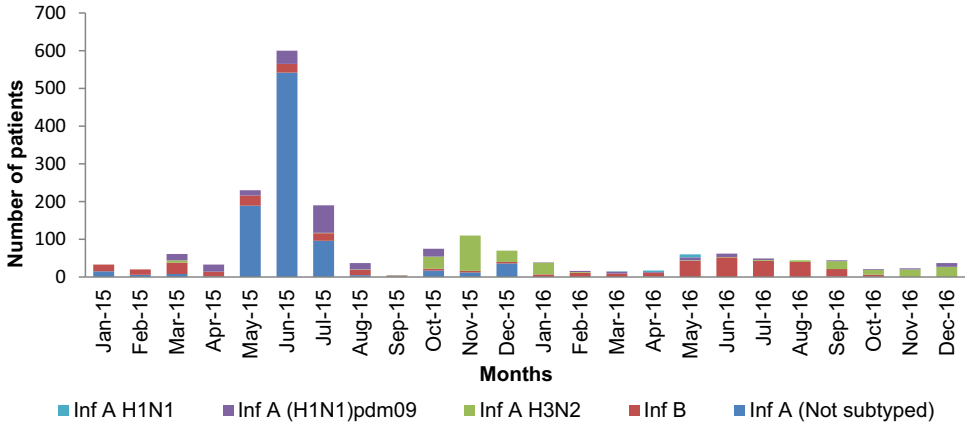

Fig. 3 Number of specimens positive for influenza virus by subtypes in Sri Lanka from January 2015 to December 2016 (WHO, Flu net reports)

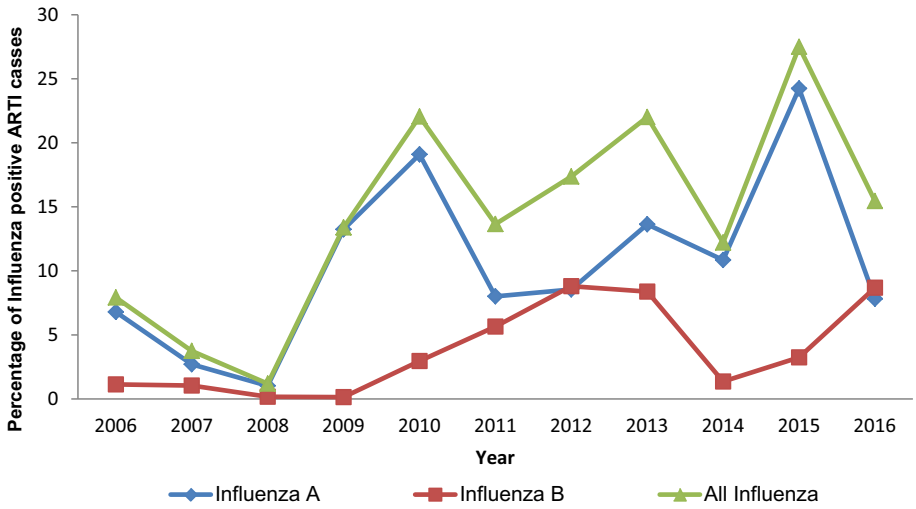

Fig. 4 Percentage of influenza A and B positive cases from 2006 to 2016 with all influenza cases (compiled using the data from the WHO, Flu net reports). The percentages were calculated using the data given for influenza A and B in Table 1

the Ministry of Livestock Development, Sri Lanka partnered with the Ministry of Health, Sri Lanka in Avian/Pandemic preparedness activities.

Laboratory diagnosis of influenza

Respiratory illnesses caused by influenza viruses are difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of clinical symptoms alone [20]. The symptoms of ARTI caused by influenza viruses mimic a large variety of other respiratory illnesses and thus the definitive diagnosis of the influenzavirus infection and strain typing is mandatory [4]. Diagnosis of influenza is done through isolation, identification of viral antigens or viral nucleic acid using the patients' samples [39]. Rapid influenza antigen detection has been in use in several countries including in Sri Lanka.

Ideally samples should be obtained within 3 days after the onset of symptoms. The isolates are identified by viral culture, IFA and RT-PCR. According to a study carried out by Noordeen et al. [33] viral antigen detection rate is higher in nasopharyngeal aspirates than that of nasal swabs or nasal washings. In the study of Perera et al. higher number of influenza A positive cases were identified via RT-PCR than viral culture. Hence, the detection of the virus or viral antigen or nucleic acid depends on the appropriate specimen collected at the right time of the illness and the methods used to identify and thus these conditions must be optimal for a better detection of the virus for the diagnosis.

Treatment, prevention and protection against influenza

Although the prevention of the spread of virus from the infected individuals and the removal of virus in transit could contribute to the control of influenza, the effective control also requires the optimal use of vaccines and antiviral drugs. Anti-influenza drugs are effective to treat the infected patients minimizing the spread to others. There are two classes of antiviral drugs, the inhibitors of M2 protein, amantadine and remantadine and inhibitors of

neuraminidase, oseltamivir and zanamivir. Amantadine and remantadine are not in use due to the emergence of antiviral resistance [48]. Oseltamivir and zanamivir are available and used for influenza associated respiratory illness in many countries and are also stockpiled for pandemic preparedness. Antiviral treatment is most effective when it is initiated within 48 h after the onset of illness. Any individual who is compromised should be treated with anti-influenza agents based on the recommendations [10]. Antiviral therapy with oseltamivir or zanamiviris only administered to hospitalized patients with severe respiratory illness [18].

Vaccination against influenza

Vaccination is the most effective means of reducing the influenza burden including morbidity and mortality. About 50 countries have government-funded national immunisation programmes. About 234 million individuals of the world's population of 6 billion were vaccinated in 2000. Safe split-product formulations and those containing purified surface antigen are available now and in use in many countries.

Constant structural changes occurring in the influenza viruses make the vaccines virus composition to be adjusted annually to include the most recent circulating influenza viruses to induce protection [16]. Currently available vaccines against influenza do not induce long-lasting immunity against many different strains of influenza viruses. Thus new vaccines are re-formulated for every flu season based on the global human influenza surveillance data [40]. Such vaccines generally contain two influenza A subtypes H1N1 and H3N2 and one influenza B virus lineage [5]. Pandemic H1N1 vaccine was used as a disease control strategy from mid-2010. Vaccination for the susceptible group are recommended by the treatment guidelines issued by the Ministry of Health, Sri Lanka too to minimize the influenza associated panic and burden in the country [34].

Concluding remarks

Influenza infections are prevalent throughout the year in Sri Lanka with slight variations in the type of the circulating virus. Sri Lanka has a complete directory of information on influenza activity in the last 2 decades as NIC regularly monitors the influenza situation in the country as part of the pandemic preparedness programme. A few studies have been carried out on influenza infections in the country but the seasonality of occurrence of influenza is not well documented. Thus the continuous monitoring of seasonal influenza subtypes in both ILI and SARI cases would help determine the seasonal trends and assess the disease burden. Prospective long term multicentre influenza surveillance would help to predict seasonality and fortify pandemic preparedness initiatives. Moreover, such surveillance would help to define seasonal patterns and regional differences in seasonality if any and to determine optimal periods to implement influenza vaccination to high risk populations.

Author contributions RR: compiled data and drafted the manuscript. MD: contributed to the drafting of the manuscript. FN: contributed to the design and critically corrected the manuscript.

References

1. Adhikari BR, Shakya G, Upadhyay BP, et al. Outbreak of pandemic influenza A/H1N1 2009 in Nepal. Virol J. 2011;8(1):133.
2. Azziz Baumgartner E, Dao CN, Nasreen S, et al. Seasonality, timing, and climate drivers of influenza activity worldwide. J Infect Dis. 2012;206:838–46.
3. Azziz-Baumgartner E, Alamgir ASM, Rahman M, et al. Incidence of influenza-like illness and severe acute respiratory infection during three influenza seasons in Bangladesh, 2008–2010. Bull World Health Organ. 2012;90:12–9.
4. Barenfanger J, Drake C, Leon N, et al. Clinical and financial benefits of rapid detection of respiratory viruses: an outcomes study. J Clin Microbiol. 2000;38:2824–8.
5. Barr IG, McCauley J, Cox N, et al. Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009–2010 Northern Hemisphere season. Vaccine. 2010;28:1156–67.
6. Bellei N, Carraro E, Perosa A, Granato C. Patterns of influenza infections among different risk groups in Brazil. Braz J Infect Dis. 2007;11(4):399-02.
7. Chadha MS, Broor S, Gunasekaran P, et al. Multisite virological influenza surveillance in India: 2004–2008. Influenza Other Respir Viruses. 2012;6:196-03.
8. Chadha MS, Hirve S, Dawood FS, et al. Burden of seasonal and pandemic influenza-associated hospitalization during and after 2009 A (H1N1)pdm09 pandemic in a rural community in India. PLoS ONE. 2013;8(5):e55918.
9. Chaudhary S, Pahwa VK. Avian influenza. J Univers Coll Med Sci. 2013;1(3):11.
10. Couch RB. Prevention and treatment of influenza. N Engl J Med. 2000;343:1778–87.
11. Couch RB, Kasel JA, Glezen WP, et al. Influenza: its control in persons and populations. J Infect Dis. 1986;153:431–40.
12. Cox NJ, Subbarao K. Global epidemiology of influenza: past and Present. Annu Rev Med. 2000;51:407–21.
13. Esposito S, Molteni CG, Daleno C, et al. Clinical and socioeconomic impact of different types and subtypes of seasonal influenza viruses in children during influenza seasons 2007/2008 and 2008/2009. BMC Infect Dis. 2011;11:271.
14. Finkelstein SN, Larson RC, Nigmatulina K, Teytelman A. Engineering effective responses to influenza outbreaks. Serv Sci. 2015;7(2):119–31.
15. Gao R, Cao B, Hu Y, et al. Human infection with a novel avian-origin influenza A(H7N9) virus. N Engl J Med. 2013;368:1888–97.
16. Gerdil C. The annual production cycle for influenza vaccine. Vaccine. 2003;21:1776–9.

17. Glezen WP. Prevention and treatment of seasonal influenza. N Engl J Med. 2008;359:2579–85.
18. Halloran ME, Hayden FG, Yang Y, et al. Antiviral effects on influenza viral transmission and pathogencity: observations from household based trials. Am J Epidemiol. 2007;165:212–21.
19. Horthongkham N, Athipanyasilp N, Pattama A, et al. Epidemiological, clinical and virological characteristics of influenza B virus from patients at the tertiary care units in Bangkok during 2011–2014. PLoS ONE. 2016;11(7):e0158244.
20. Jayaweera JAAS, Noordeen F, Morel A, et al. Viral burden in acute respiratory tract infections in hospitalized children in the wet and dry zones of Sri Lanka. 17th international congress on infectious diseases. Int J Infect Dis. 2016;45S:463.
21. Kitler ME, Gavinio P, Lavanchy D. Influenza and the work of the World Health Organization. Vaccine. 2002;20:5–14.
22. Lahti E, Peltola V, Virkki R, et al. Influenza pneumonia. Pediatr Infect Dis J. 2006;25:160–4.
23. Li Q, Zhou L, Zhou M, et al. Epidemiology of human infections with avian influenza A(H7N9) virus in China. N Engl J Med. 2014;370:520–32.
24. Lipsitch M, Viboud C. Influenza seasonality: lifting the fog. Proc Nat Acad Sci USA. 2009;106(10):3645.
25. Mendis NM, Maheswaran K, Mendis O, et al. Epidemic of influenza in Ceylon. Ceylon Med J. 1970;15:195-06.
26. Miller MA, Viboud C, Balinska M, Simonsen L. The signature features of influenza pandemics: implications for policy. N Engl J Med. 2009;360:2595–8.
27. Mishra AC, Chadha MS, Choudhary ML, Potdar VA. Pandemic influenza (H1N1) 2009 is associated with severe disease in India. PLoS ONE. 2010;5(5):e10540.
28. Murray JL, Lopez AD, Chin B, et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. Lancet. 2006;368(9554):2211–8.
29. Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011;378(9807):1917–30.
30. Nandhini G, Sujatha S. Epidemiology of influenza viruses from 2009 to 2013: a sentinel surveillance report from Union territory of Puducherry, India. Asian Pac J Trop Med. 2015;8(9):718–23.
31. Nayak DP, Balogun RA, Yamada H, et al. Influenza virus morphogenesis and budding. Virus Res. 2009;143(2):147–61.
32. Nicholson KG, Wood JM, Zambon M. Influenza. Lancet. 2003;362:1733–45.
33. Noordeen F, Pandithasundara H, Senavirathna SK, et al. Suspicion vs. reality: influenza A and B associated acute respiratory tract infection in a group of children in Sri Lanka. Sri Lankan J Infect Dis. 2014;4(1):48–50.
34. Perera HKK, Peiris JSM. Influenza viruses. Ceylon Med J. 2015;60(1):1.
35. Perera KVHKK, Chan KH, Ma E, Peiris JSM. Influenza virus infections among a sample of hospital attendees in Ragama, Sri Lanka. Ceylon Med J. 2010;55(2):45–8.
36. Playford EG, Dwyer DE. Laboratory diagnosis of influenza virus infection. Pathology. 2002;34:115–25.
37. Poehling KA, Edwards KM, Weinberg GA, et al. The under recognized burden of influenza in young children. N Eng J Med. 2006;355:31–40.
38. Rasul CH, Bakar MA, Mamun AA, et al. Burden and outcome of human influenza in a tertiary care hospital of Bangladesh. Asian Pac J Trop Med. 2011;1:478–81.
39. Rodriguez WJ, Schwartz RH, Thorne MM. Evaluation of diagnostic tests for influenza in a pediatric practice. Pediatr Infect Dis J. 2002;21:193–6.
40. Ropero-Alvarez AM, Kurtis HJ, Danovaro-Holliday MC, et al. Expansion of seasonal influenza vaccination in the Americas. BMC Public Health. 2009;9:361.
41. Sam JIC. The burden of human influenza in Malaysia. Med J Malays. 2015;70(3):127–30.
42. Samransamruajkit R, Hiranrat T, Chieochansin T, et al. Prevalence, clinical presentations and complications among hospitalized children with influenza pneumonia. Jpn J Infect Dis. 2008;61:446–9.
43. Tamerius J, Nelson MI, Zhou SZ, et al. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environ Health Perspect. 2011;119:439–45.
44. Tang JWT, Lee CK, Lee HK, et al. Tracking the Emergence of pandemic influenza A/H1N1/2009 and its interaction with seasonal Influenza viruses in Singapore. Ann Acad Med Singap. 2010;39:291–4.
45. Thomson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. J Infect Dis. 2006;194:82–91.
46. Turner D, Wailoo A, Nicholson K et al. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. Health Technol Assess. 2003; 7(35). http://www.nice.org.uk/pdf/influenzaassrep.pdf. Accessed 15 Oct 2003.
47. Wang C, Wang J, Su W, et al. Relationship between domestic and wild birds inlive poultry market and a novel human H7N9 virus in China. J Infect Dis. 2014;209:34–7.
48. Whitley RJ, Monto AS. Prevention and treatment of influenza in high-risk groups: children, pregnant women, immunocompromised hosts, and nursing home residents. J Infect Dis. 2006;194(2):133–8.
49. Xu C, Havers F, Wang L, et al. Monitoring avian influenza A(H7N9) virus through national influenza-like illness surveillance, China. Emerg Infect Dis. 2013;19:1289–92.
50. Zhou L, Liao QH, Dong LB, et al. Risk factors for human illness with avian influenza A (H5N1) virus infection in China. J Infect Dis. 2009;199:1726–34.