Indian Journal of Biotechnology and Pharmaceutical Research
Journal homepage : www.ijbpr.in
ISSN: 2347-3266
2019, 7(2): 1-10

Review Article

Anecdotes of Influenza virus (Swine flu) from chronic age till present

S.S. Kulkarni

Dr. D. Y. Patil Biotechnology and Bioinformatics Institute, Tathawade, Pune, Maharashtra – 411057

ABSTRACT

Influenza viruses, members of Orthomyxoviridae, the family which represents enveloped viruses the genome of which consists of segmented negative - sense single strand RNA segment. Till 20th century, three pandemics have been known, named Spanish flu, Asian flu and Hong Kong flu which caused infection by different strains. Recently another pandemic declared by WHO famously known as Swine flu caused by strain H1N1/2009, spread all over the world originating from Mexico. Influenza virus being enveloped virus is comparatively vulnerable to environmental impacts. Influenza has 4 genes: type A, B, C and Thogot viruses. However, in this article we have talked only about type A and B viruses because they are clinically relevant for humans. Influenza type A virus has one of the unique properties of rapid evolution leading to generation of various Influenza strain. Also, Influenza virus is the most unstable virus till known viruses and cause infection in newly births and children. This article will guide thorough the history of Influenza and the changes took place during the infection spread. This article is a proof that with change in time how the detection of influenza virus changed. Brief discussion about epidemiology and reasons behind generation of variety of strains of Influenza virus is been studied in this review article.

Keywords: Influenza virus; Antigenic shift; Antigenic drift; H1N1; Swine flu

Introduction

Influenza also called as flu is an acute viral respiratory infection transmitted by Influenza virus which has always been a threat to life since 15th century due to its pandemic nature on the basis of its geographical spread that has caused illness, death, and disruption for centuries. It has been known to cause disease in other animals besides humans as well. In recent years, however, globalization has driven many changes socially and economically that has enhanced the threat of disease emergence and had faster the spread of novel virus. Alternately, Globalization also helped by facilitating international support, boosting progress in disease investigation and understanding global surveillance.

Influenza viruses are named for the Latin word *Influentia,* or "influence" [5]. Influenza virus belongs to family Orthomyxoviridae and have a single stranded eight segmented RNA which together code for ten proteins. These viruses are classified into A, B and C; on the basis of their core proteins. The situation of Influenza virus is way different than other viruses like herpes and rhinoviruses which do not undergo the rapid changes that are observed in Influenza virus [42]. They differ significantly from other RNA or DNA viruses infecting eukaryotic cells, both in virion structure and mode of replication. All the members of Orthomyxoviridae appears to have a common architecture, with glycoprotein molecules on the surface of the particle, a lipid bilayer membrane and a core consisting of the matrix (M) protein layer and a

Received: 10.08.2019, Revised: 16.10.2019,
Accepted: 01.11.2019

✉ S.S. Kulkarni

E-mail: shivani.kulkarni22@gmail.com

ribonucleoprotein complex. The ribonucleoprotein complex is made up of segmented RNA genome, nucleoprotein (NP) molecules, and three different polymerase (P) protein.

Classification of Influenza virus

Influenza virus is been classified into three types due to major differences among them: type A, B and C. the type A virus share serologically cross-reactive M and NP proteins both of which differ from the internal proteins of type B and C strains [42]. The lengths of eight RNA segments of different type A strains are largely conserved, they are different in size from eight genomic RNA segments of Influenza B viruses and from the seven RNA segments of Influenza C strain. Whereas, in contrast, through nucleotide sequencing of 5' and 3'ends of the genomic RNA's of strains of type A, B and C it has been revealed that there is a high degree of conservation of the terminal 10 to 20 nucleotides, suggesting a common evolutionary progenitor [53].While type A and B are responsible for the majority of mortality and morbidity, type A is the only one potential for causing pandemics [62]. The reason behind this being type A is the only strain with an animal reservoir. Aquatic birds and Swine are important reservoirs for influenza A, presenting obstacles to eradication and providing opportunities for viral mutation and reassortment [33]. The strains of Influenza virus majorly differ due to Nucleoprotein (NP) and Hemagglutinin (HA).

Similarly, protein sequence data on the hemagglutinins of types A and B showed conserved stretches of amino acids in some areas of functional importance. For example, cleavage of hemagglutinin (HA) precursor of Influenza virus A and B viruses into HA1 and HA2 subunits results in HA2 molecules with common amino terminal sequences [35]. It also appears that the three influenzas' virus types may differ in their degree of variation. Although types B and C vary in their surface antigens, the B as well as C strains are generally believed to undergo less antigenic variation than the A strains. Also, according to past research it has been observed that B and C strains change less than A strain [41]. Influenza subtypes are strictly divided into two surface antigens based on its antigenic properties: Hemagglutinin (H) and Neuraminidase (N), which access and cooperate the host cell entry and exit, respectively. The United States for Centre for Disease Control and Prevention has identified 18H subtypes and 11N subtypes which altogether comprises a total of 198 various strains [9]. Only H1, H2 and H3 strains are known to have achieved substantial human to human transmission [61].

Antigenic shift and Antigenic drift

Influenza virus C is of minor concern to human because it infrequently spread disease to human, while type B is often associated with the human type disease but less than type A viruses, as A type virus is very important because they are known to cause pandemic influenza. It is very important to keep tracking the influenza virus gene composition only because of two reasons that the influenzas virus is very friendly to antigenic shift and drift. They can go for either of them, but there is not much difference in the severity of these changes by antigenic shift and drift.

Antigenic drift is one of the ways through which influenza virus change. It is a result of small changes in genes of Influenza virus that occur due to continuous replication. As an outcome, viruses are produced which are pretty closely related to one another. Hence, the immune system exposed to this type of change will usually recognize it and respond to it.

But these small changes can accumulate over time and result in the viruses that are antigenically different. However, the body's immune system cannot recognize this virus.

Antigenic shift is another type of change. It is a major and abrupt change in influenza A virus, resulting in new Hemagglutinin and/or new Hemagglutinin and Neuramidase proteins in Influenza viruses that infect humans. Antigenic shift results in new subtype of virus with change in hemagglutinin or neuramidase acquired from an animal population. Antigenic shift in Influenza virus changes the virus combination and as a result most people have very little or no protection against the new virus.

Antigenic drift occurs all the time, but antigenic shift happens exclusively (occasionally). Type A viruses

undergo both type of changes, but Influenza virus type b undergo only more gradual process of antigenic drift [10].

Epidemiology and Pandemics

Pandemics are epidemics that spread globally. Influenza epidemics and pandemics have been occurring from centuries. Greek writings from 412 BC describe what medical historians believe may have been an Influenza outbreak [31,45]. If the novel strain has the ability to infect humans and achieve human to human transmission, and possess virulence for humans, then as a result pandemic may arise and however the novel strain born from these cause a problem to human, as humans are unlikely to have appreciable immunity to this novel strains. However, because the virus was not sequestered and discovered till twentieth century, medical historians are confined to search for known signs and symptoms of Influenza infection. Within the past one hundred years, four pandemics have been resulted from the emergence of a novel Influenza strain for which human had little or no immunity. The pandemics were; The H1N1 Spanish flu (1918), the H2N2 Asian flu (1957), the H3N3 Hong Kong flu (1968) and the HIN1 Swine flu (2009), which has been summarized in table 1 [43].

Table 1 Key characteristics of Influenza pandemics from the past one hundred years

Pandemic name	Year	Strain	Suspected origin of outbreak	Approximate number of deaths
Spanish flu	1918-1920	H1N1	China	40-50 million
Asian flu	1957-1958	H2N2	China	1-2 million
Hong Kong flu	1968-1970	H3N2	China	500,000-2 million
Swine flu	2009-2010	H1N1	Mexico	Up to 575,000

Source: Patrick & Krewski, Daniel. (2016). Reviewing the History of Pandemic Influenza: Understanding Patterns of Emergence and Transmission. Pathogens. 5. 66. 10.3390/pathogens5040066

From Historic Age

Earlier arguments have reported that an outbreak in 1580 was the first Influenza pandemic [46,15]. It emerged in Asia and spread all the way to Asia minor and North Africa before moving across Europe and into North America [47]. Disruption, deaths and illness were ideally reported [3]. Hence, the first reference to "Influenza" in the form of scientific literature appeared in 1650 and since that year, history of pandemics is more readily documented [46]. The first pandemic of the eighteenth century began in the spring of 1729 in Russia, which later spared globally in the next three years [47,25,18]. In China, in the autumn of 1781, the second pandemic of that country occurred [47,18]. The outbreak spread over Russia and Europe within eight months with particular high attack rate on young adults [48]. The major pandemic of the nineteenth century began in the winter of 1830 in China [46]. Reports say that it was equally similar to that of 1918 Spanish flu pandemic as it spread over Southeast Asia, Russia and Europe by 1831 [47,3,44]. Compared with the attack rate, which was high, but mortality rate was low [46].

Later, about one million people were killed globally due to the outbreak with estimated fatality rate of 0.1%-0.28% [57]. As this pandemic spread at faster rate, hence, this was an indication of the accelerated spread of emergent diseases as a result of progress in transportation technology. As per the data collected, it has been identified that either China, Russia or more broadly Asia are the point of origin [46].

Spanish flu 1918

After 1918 Spanish flu pandemic, there was progress in both public health practice and infectious disease

management, as they both became the priority. Several patterns emerged in examining early pandemic. The first pattern was an overall lack of quality, severity and cogency in the available evidence. Repugnance in the disease recognition and reporting makes it difficult to estimate the certainty and health burden of disease outbreak. Second pattern was the rate of disease spread and the transportation revolution of eighteenth and seventeenth century. However, these technological advances led to transport of disease along with the people to both within and across the country. As a result, it became one of the primary vectors of disease spread throughout the world [43].

In 1981, an H1N1 influenza strain emerged to cause the Spanish flu pandemic a disaster that has been called the "greatest medical holocaust in History" [60]. This flu had three waves whose timing was not consist globally: the spring of 1918, the fall of 1918, and the winter of 11918-1919 [27,29]. Where most of these deaths occurred in the autumn of 1918. After the calculation and recalculation in 1991, between 24.9 and 39.3 million deaths were recorded in the 1918 Spanish flu. In terms of overall illness Spanish flu is been recorded the most dangerous health disasters in history [60]. It was a result of highly pathogenic, transmissible strain of influenza that emerged in time when populations had limited contact with each other but apparently, they were brought together due to World War I. On the other hand, the trench warfare provided poor health facility, bad sanitation to the people which gave a chance to virus to become transmissible [58].

In 1918, experts still believed that influenza was caused due to *Bacillus influenzae* bacterium, though doubts were raised when physicians were unable to find any bacilli strain during autopsies [58]. Doctors also had a very difficult time in examining this disease as they often got confused it with common cold, cholera or bubonic plague [56]. However, they did recognize the routes of influenza virus was via infection respiratory droplets from nose and throat. Year of 1918 was still decades away from vaccines and antibiotics as well as antivirals. Because of World War I there was shortage in hospital bed supply. Meanwhile people turned their faces towards home remedies (mixture of water, salt and coal oil), also some doctors prescribed consumption of alcohol to prevent the infection, as a result there was a sudden surge in the liquor demand [2]. As a result, to control outbreak people during that time relied on non-pharmaceutical interventions (NPI) such as quarantine, school closure, banning public meetings, etc. which later proved to be the most successful remedy [37].

Story after 1918 Spanish flu pandemics

After the outbreak in the following year the H1N1 continued to circulate, though it did not emerge to cause illness and death on similar scale. With respect to pandemic influenza, three areas of progress might be highlighted: virus isolation and identification, development of vaccines and the advance of global health diplomacy [43]. In later 1930s and early 1940s, the first vaccine for Influenza was developed as a result of multiple research whose credit must go to Jonas Salt and Thomas Francis [19,20]. In 1947, an epidemic emerged as a result of antigenic drift resulted in changes to the hemagglutinin antigen such that the flu vaccine did not provide any protection against influenza to the humans [50]. The strain being not severe, and the pandemic did not occur [30].

Later many organizations and bodies were formed to take care of upcoming pandemics. The leagues of Nations, arguably the first global political system was founded in 1919, establishing the health organization in 1923 (replaced by World Health Organization in. 1948) [17,26]. With the passing time the size and responsibilities of local, states, provincial and federal health departments increased, hence, many more organizations were formed and expanded over upcoming decades. The world experienced massive growth in population, trade and travel in the interpandemic period between 1918 and 1957. Population has increased from 1.8 billion in 1918 to approximately 2.8 billion in 1957 [36,55]. With the increasing population there was simultaneous increase in providing leisure to the increasing population by

building international travelling facility for both business and leisure in 1950, which increased the number of passengers travelling inter country immediately. However, this again increased the threat of pandemics of Influenza virus.

Asian flu 1957

Almost after 40 years of H1N1, only being Influenza strain in circulation, a new strain emerged to cause another influenza pandemic. In February 1957, the new Influenza strain H2N2 emerged in the Yunnan Province of China [47]. There was no immunity towards H2N2 strain in the humans under 65, suggesting prior viral circulation and exposure at some point in the late 19th century. Virus had spread to Hong Kong in April, then to Singapore, Taiwan and Japan throughout the summer of 1957 [54]. The strain was known as the Asian flu, it caused between one to two million deaths worldwide, hence was comparatively mild influenza pandemic [52].

The Asian flu was the first pandemic to occur in an environment with the global surveillance systems and laboratory place to study it. In 1957, all the laboratories worldwide were connected to the Influenza research center based in London and it became easier for the investigators from Melbourne to Washington to study strain after it emerged [28]. Beside research, it was also the first chance to study the response of an immunological population to Influenza vaccination campaigns [30]. The development and distribution of vaccines was a bit slow [28]. Antivirals had not yet developed. Physicians used various antibiotics to cause the cases and seriously ill patients as at least these antibiotics were preventing bacterial infection which might take place along with Influenza. Also, there was use of non-pharmaceutical interventions (NPI) such as school closure, travel restrictions, banning of mass gatherings or quarantine [52]. Quarantine, in particular was considered inappropriate due to the wild nature of symptoms and due to large number of infections as quarantine was a bit weak source. Though it was a mild influenza pandemic, the Asian flu had put the reminder for all of the persisting threat of the global spread of emergent disease.

Hong Kong flu 1968

Hong Kong flu started in 1968 and lasted till 1970. It was the first virus to exhibit an accelerated spread due to extensive air travel [12.34]. Ten years down the Asian flu strain underwent an antigenic shift introducing to new strain H3N2, known as Hong Kong flu. This strain was more transmissible and less mild than Asian flu. Estimates suggests that Spanish flu had a mortality rate of 598 deaths per 100000 people/year, Asian flu was only 40.6 and Hong Kong was 16.9, though their method of calculations varied [39]. H3N2 strain was first reported in Hong Kong in July 1968, spreading to United States. A unique feature of this pandemic was that the majority of Influenza related deaths in United States (70%) and Canada (54%) occurred in the first pandemic wave whereas countries in Europe and Asia experienced 70% deaths associated with the pandemic during second wave [59]. This was due to different geographical areas having different environment leading to antigenic drift chance in various time intervals.

Asian flu strain was H2N2, whereas Hong Kong flu strain was H3N2 however, the reason behind less mortality rate could be the preexisting immunity towards the neuramidase in humans. There were various scenarios as well that took up and lead a lesson from Hong Kong flu, as in most countries, vaccines were not available till the pandemic peaked up [49]. Also, hospitalization facilities were not at all improved as hospitalizations of patients became hard as the hospital bed capacity was neither increased nor decreased but it was not sufficient to keep pace with the population growth rate, as a result there were not enough beds available during outbreak [22]. The lesson and indication that got from Hong Kong flu was, there was lack in the progress in public health and medical science between 1957 and 1968 pandemics. 1977, was the year of re-emergence of H1N1for the first time since 1918 to cause “pseudo pandemics”

known as Russian flu [63]. Re-emergence of H1N1 is not clear but it is suspected to have arisen from a laboratory accident. H1N1 and H3N2 influenza strains produce persistent coordination and they were not displaced [40]. Year 1977 would mark the first case of human infection with H5N1 avian influenza, discharging fears of another pandemic from a pathogenic influenza strain [15]. For past 20 years of its emergence, H5N1 virus has failed to transmit itself from human to human. The reason being as the virus attaches to and replicates in cells of the lower respiratory tract, in contrast to most influenzas strains which attach and replicate in the upper respiratory tract [15]. A momentous development of that time was the availability of computer technology. In late 20th century there were improvements in two important medical advances: the purification of vaccines and the development of anti-viral.

Amantadine was reported as an inhibitor of influenza in 1946 [16]. This class of drug is susceptible to viral development of drug resistance, it also provides a basis for more recent development of neuraminidase inhibitors, which can be effective in preventive influenza infection as well as reducing the duration of the infection particularly if administered within 48 hours of symptoms on set [32]. Neuraminidase inhibitors are the class of anti-viral most commonly used today, their development is an important milestone in treating the symptoms of influenza.

With the passing time swine flu again emerged in 2009 as that was the when global connectivity was well developed. This would have crucial entailment for disease outgrowth, spread, wallop and survival.

Swine Flu 2009

The pH1N1/09 virus, also known as swine flu, Mexican flu, new flu and A(H1N1) emerged from Mexico in April 2009 [6,4]. Swine flu is the result of Antigenic shift H1N1 like bird flu H1N5. It was first recorded simultaneous outbreaks in Mexico and the United Stated [54]. The disease had spread across 30 countries in weeks [51]. On 11 June 2009, the WHO declared it as global influenza pandemic. By July, the infection was reported in 122 countries with 1,34,000 laboratory confirmed cases and 800 deaths [24]. This strain has been emerged from pigs and had been circulating in them for years [51]. With the pandemics of 20th century, this swine flue pandemic exhibited wave behavior with wave timings varying according to geographical area. For example, in Mexico it showed three pandemic profile with spring, summer and fall wave [11]. While in North America it showed two wave profile with spring and summer [13]. India experienced 3 wave peaks in September, December 2009 and August 2010 [38]. The WHO declared the pandemic officially over in August 2010 [1]. Again, pandemic infection showed a shift in mortality towards younger population and majorly affecting children, young adults and pregnant women [21]. The pandemic also caused societal disruption and economic burden which was documented more comprehensively than for past influenza pandemics. Containment efforts employed a combination of pharmaceutical and non-pharmaceutical interventions which eventually helped to control the outbreak until more information could be gathered. During this year the non-pharmaceutical measures were changed to hand hygiene and voluntary isolation of symptomatic individuals [8]. Another important change that was observed was on public health, hospital and human resources during pandemic peaks [7]. Health systems were generally able to accommodate surges in patience demand. Doctors started prescribing anti-viral and distributing authority was given to pharmacists.

Overall the 2009 pandemic was a mild, albeit costly, global virus. While internet and globalization did help in controlling the outbreak majorly through the non-pharmaceutical measures, the same also led people to confuse this outbreak with normal seasonal flu as well. Due this anyone with flu like symptoms assumed it to be H1N1 and rushed to the medical care. This while unnecessarily increased the number of patients in medical care but also made people extra cautious. While epidemics of seasonal flow occurs across the

whole world and throughout the year but is not life threatening and can be cured with anti-viral drugs.

Conclusions

Influenza virus (Swine flu since 2009), belonging to family Orthomyxoviridae is vulnerable to environmental impacts which leads to sudden and drastic change in its gene segment leading to evolution of new Influenza strain. From the study it was found that economical and geographical changes resulted change in human immunity as well. Earlier when there was relatively y low population and less advance technology, the threat of infection spread was less, which resulted in poor medication and handling towards the virus. With increase in population there was faster spread and due to globalization, there is geographical spread throughout the world. But technological advancement and research with time helped in controlling the spread and better medical facilities. This study showed that how flexible and strong Influenza virus is that with every changing phase it is able to develop new strain affecting humans, birds, etc. Many factors may contribute to control Influenza virus but the major factor that limits the ability to control the disease is the capacity of influenza virus to rapidly vary and undergo antigenic structure that outsmart the protective effect of a patient's immune system and its response [14]. Due to change in strain the existing immunity has not been able to fight against the exposure. Though some of them were mild influenza pandemic, they had put the reminder for all of the persisting threat of the global spread of emergent disease.

References

1. Amato-Gauci, A.; Zucs, P.; Snacken, R.; Ciancio, B.C.; Lopez, V.; Broberg, E.; Penttinen, P.; Nicoll, A. Surveillance trends of the 2009 influenza a(H1N1) pandemic in europe. Infektionsepidemiologie 2011, 16, 4.
2. Barry, J. The site of origin of the 1918 influenza pandemic and ints public health implications. J. Transl. Med. 2004, 2, 3. [CrossRef] [PubMed]
3. Beveridge, W. The chronicle of influenza epidemics. Hist. Philos. Life Sci. 1991, 13, 223–235. [PubMed]
4. Bijl, D.; Schellekens, H. The sponsored pandemic of the mexican flu. Int. J. Risk Saf. Med. 2011, 23, 73–79. [PubMed]
5. Broxmeyer, L. Bird flu, influenza and 1918: The case for mutant avian tuberculosis. Med. Hypotheses 2006, 67, 1006–1015. [CrossRef] [PubMed]
6. Bults, M.; Beaujean, D.J.; Zwart, O.; Kok, G.; Empelen, P.; Steenbergen, J.E.; Richardus, J.H.; Voeten, H.A. Mexican flu: Risk perception in the general public, precautionary measures and trust in information provided by the government. Ned. Tijdschr. Geneeskd. 2010, 154, A1686. [PubMed]
7. Canadian Institute for Health Information (CIHI).The Impact of the H1N1 Pandemic on Canadian Hospitals; CIHI: Ottawa, ON, Canada, 2010.
8. Cantey, P.T.; Chuk, M.G.; Kohl, K.S.; Herrmann, J.; Weiss, P.; Graffunder, C.M.; Averhoff, F.; Kahn, E.B.; Painter, J. Public health emergency preparedness: Lessons learned about monitoring of interventions from the national association of county and city health official's survey of nonpharmaceutical interventions for pandemic H1N1. J. Public Health Manag. Pract. 2013, 19, 70–76. [CrossRef] [PubMed]
9. Centers for Disease Control and Prevention. Types of Influenza Viruses. 2014. Available online: http://www.cdc.gov/flu/about/viruses/types.htm (accessed on 2 March 2016).
10. Centre for disease control and preventions, National centre for Immunization and respiratory disease.
11. Chowell, G.; Echevarría-Zuno, S.; Viboud, C.; Simonsen, L.; Tamerius, J.; Miller, M.A.; Borja-Aburto, V.H. Characterizing the epidemiology of the 2009 influenza a/H1N1 pandemic in mexico. PLoS Med. 2011, 8, e1000436. [CrossRef] [PubMed]

12. Cockburn, W.C.; Delon, P.J.; Ferreira, W. Origin and progress of the 1968–69 hong kong influenza epidemic. Bull. World Health Organ. 1969, 41, 345–348. [PubMed]
13. Cook, S.; Conrad, C.; Fowlkes, A.L.; Mohebbi, M.H. Assessing google flu trends performance in the united states during the 2009 influenza virus a (H1N1) pandemic. PLoS ONE 2011, 6, e23610. [CrossRef] [PubMed]
14. D. Kilbourne, Ed.,The Influenza Viruses and Influenza (Academic press New York; 1975 C. H. Stuart-Harris and G. C. Schild, Influenza, the Viruses and the Disease (Publishing Sciences Group, Littleton, Mass., 1976); D. A. J. Tyrrell and H. G. Pereira, Eds.,Influenza (Royal Society of London,Lon- don, 1980); G. C. Schild, Ed., "Influenza," Br. Med. Bull. 35, (1979), entire issue; C. Scholtis- sek, Adv. Genet. 20, 1 (1979)
15. Daly, P.; Gustafson, R.; Kendall, P. Introduction to pandemic influenza. BC Med. J. 2007, 49, 240–244.
16. Dawkins, A.; Gallager, L.R.; togo, Y.; Hornick, R.B.; Harris, B.A. Studies on induced influenza in man ii: Double-blind study designed to access the prophylactic efficacy of an analogue of amantadine hydrochloride. JAMA 1968, 203, 1095–1099. [CrossRef] [PubMed]
17. Fidler, D. The globalization of public health the first 100 years of international health diplomacy. Bull. World Health Organ. 2001, 79, 842–849. [PubMed]
18. Finkler, D. Influenza in twentieth century practice. In An International Encyclopaedia of Modern Medical Science; Shipman, T.L., Ed.; Sampson Law & Marston: London, UK, 1899; pp. 21–32.
19. Francis, T.; Salk, J.E. A simplified procedure for the concentration and purification of influenza virus. Science 1942, 96, 499–500. [CrossRef] [PubMed]
20. Francis, T.; Salk, J.E. Protective effect of vaccination against induced influenza a. J. Clin. Investig. 1945, 24, 536–546. [CrossRef] [PubMed]
21. Girard,M.P.;Tam,J.S.;Assossou,O.M.;Kieny,M. P.The2009a(H1N1)influenzaviruspandmeic:Arev iew. Vaccine 2010, 31, 4895–4902. [CrossRef] [PubMed]
22. Glaser, C.A.; Gilliam, S.; Thompson, W.W. Medical care capacity for influenza outbreaks in los angeles. Emerg. Infect. Dis. 2002, 8, 569–574. [CrossRef] [PubMed]
23. Guan, Y.; Yikaykrishna, D.; Bahl, J.; Zhu, H.; Wang, J.; Smith, G.J. The emergence of pandemic influenza viruses. Protein Cell 2010, 1, 9–13. [CrossRef] [PubMed]
24. Henderson, D.; Courtney, B.; Inglesby, T.; Toner, E.; Nuzzo, J. Public health and medical responses to the 1957–58 influenza pandemic. Biosecur. Bioterror. 2009, 7, 265–273. [CrossRef] [PubMed]
25. Hirsh. Handbook of Geographic and Historical Pathology; New Sydenham Society: London, UK, 1883.
26. Holton, R.J. Globalization and the Nation-State; Macmillan Press: New York, NY, USA, 1998.
27. Humphries, M. Paths of infection: The first world war and the origins of the 1918 influenza pandemic. War Hist. 2013, 21, 55–81. [CrossRef]
28. Jackson, C. History lessons: The asian flu pandemic. Br. J. Gen. Pract. 2009, 59, 622–623. [CrossRef] [PubMed]
29. Johnson, N.; Mueller, J. Updating the accounts: Global mortality of the 1918–1920 "spanish" influenza pandemic. Bull. Hist. Med. 2002, 76, 105–115. [CrossRef] [PubMed]
30. Kilbourne, E. Influenza pandemics of the 20th century. Emerg. Infect. Dis. 2006, 12, 9–14. [CrossRef] [PubMed]
31. Kuszewski, K.; Brydak, L. The epidemiology and history of influenza. Biomed. Pharmacother. 2000, 54, 188–195. [CrossRef]
32. Littler, E.; Oberg, B. Achievements and challenges in antiviral drug discovery. Antivir. Chem. Chemother. 2005, 16, 155–168. [CrossRef] [PubMed]

33. Lofgren, E.; Fefferman, N.; Naumov, Y.; Gorski, J.; Naumova, E. Influenza seasonality: Underlying causes and modeling theories. J. Virol. 2007, 81, 5429–5436. [CrossRef] [PubMed]
34. Longini, I.; Fine, P.; Thacker, S.T. Predicting the global spread of new infectious agents. Am. J. Epidemiol. 1986, 123, 383–391. [PubMed]
35. M. D. Waterfield, K. Espelie, K. Elder, J. J.Skehel, Br. Med. Bull. 35, 57 (1979); H. D. Klenk,R.Rott,M.Orlich,J.Blodorn,Virology 68, 426 (1975); S. G. Lazarowitz and P. W. Choppin,ibid.,p.440.
36. Madhav, N. Modelling a Modern-Day Spanish Flu Pandemic. 2013. Available online: http://www.air-worldwide.com/publications/air-currents/2013/modeling-a-modern-day-spanish-flu-pandemic/(accessed on 10 March 2016).
37. Markel, H.; Stern, A.M.; Navarro, J.A.; Michalsen, J.R.; Monto, A.S.; DiGiovanni, C., Jr. Nonpharmaceutical influenza mitigation strategies, us communities, 1918–1920 pandemic. Emerg. Infect. Dis. 2006, 12, 1961–1964. [CrossRef] [PubMed]
38. Mishra, B. 2015 resurgence of influenza a (H1N1) 09: Smoldering pandemic in india? J. Glob. Infect. Dis. 2015, 7, 56–59. [CrossRef] [PubMed]
39. Morens, D.; Taubenberger, J.; Fauci, A.S. The persistent legacy of the 1918 influenza virus. N. Engl. J. Med. 2009, 361, 225–229. [CrossRef] [PubMed]
40. Nguyen-Van-Tam, J.S.; Hampson, A.W. The epidemiology and clinical impact of pandemic influenza. Vaccine 2003, 21, 1762–1768. [CrossRef]
41. P.Chakraverty,Bull.WHO 45,755(1972);R.L. Curry, J. D. Brown, F. A. Baker, D. Hobson, J.Hyg.72,197(1974);P.Chakraverty,Arch. Virol. 58, 341 (1978); P. Palese, C. Brand, J. F. Young,M. Baez,H. R. Six,J.A. Kasel,Per- spect. Virol. 11, 115 (1981); P. Palese, R. M. Eliot,M. Baez, J.J.Zazra, J.F.Young,in(2), p.127.
42. Palese, P. & Young, J. F. Variation of influenza A, B, and C viruses. Science 215, 1468–1474 (1982)
43. Patrick & Krewski, Daniel. (2016). Reviewing the History of Pandemic Influenza: Understanding Patterns of Emergence and Transmission. Pathogens. 5. 66. 10.3390/pathogens5040066
44. Patterson, K.D. Pandemic Influenza 1700–1900: A Study in Historical Epidemiology; Rowan & Littlefield: Totowa, NJ, USA, 1987.
45. Potter, C. Chronicle of influenza pandemics. In Textbook of Influenza; Nicholson, K.G., Webster, R.F., Hay, A.J., Eds.; Blackwell Science LTD: Oxford, UK, 1998.
46. Potter, C. A history of influenza. J. Appl. Microbiol. 2001, 91, 572–579. [CrossRef] [PubMed]
47. Pyle, G.F. The Diffusion of Influenza: Patterns and Paradigms; Rowan & Littlefield: Totowa, NJ, USA, 1986.
48. Pyle, G.F.; Patterson, K.D. Influenza diffusion in european history: Patterns and paradigms. Ecol. Dis. 1984, 2, 173–184.
49. Rogers, K. Hong Kong Flu of 1968. Available online: http://www.britannica.com/event/Hong-Kong-flu-of-1968 (accessed on 16 March 2016).
50. Salk, J.E.; Suriano, P.C. Importance of antigenic composition of influenza virus vaccine in protecting against the natural disease. Am. J. Public Health 1949, 39, 345–355. [CrossRef]
51. Smith, G.J.; Vijaykrishna, D.; Bahl, J.; Lycett, S.; Worobey, M.; Pybus, O.G.; Ma, S.K.; Cheung, C.L.; Raghwani, J.; Bhatt, S.; et al. Origins and evolutionary genomics of the 2009 swine-origin H1N1 influenza a epidemic. Nat. Med. 2009, 459, 1122–1125. [CrossRef] [PubMed]
52. Trotter, Y.; Dunn, F.L.; Drachmann, R.H. Asian influenza in the united states. Am. J. Hyg. 1959, 70, 34–50. [PubMed]
53. U. Desselberger, V. R. Racaniello, J. J. Zazra, P. Palese, Gene 8, 315 (1980).
54. ukumi, H. Summary report of the asian influenza epidemic in japan, 1957. Bull. World Health Organ. 1959, 20, 187–198. [PubMed]
55. United Nations Department of Economic and Social Affairs (UNDESA). World Population

Prospects: The 2012 Revision; United Nations Department of Economic and Social Affairs, Population Division: New York, NY, USA, 2013.
56. USDHHS. The Great Pandemic: The United States in 1918–1919. Available online: http://www.flu.gov/pandemic/history/1918/index.html (accessed on 9 March 2016).
57. Valeron, A.J.; Cori, A.; Waltat, S.; Meurisse, S.; Carrat, F.; Boelle, P.Y. Transmissibility and geographic spread of the 1889 influenza pandemic. Proc. Natl. Acad. Sci. USA 2010, 107, 8778–8781. [CrossRef] [PubMed]
58. VanEpps, H.L. Influenza: Exposing the true killer. J. Exp. Med. 2006, 203, 803. [CrossRef]
59. Viboud, C.; Grais, R.; Lafont, B.; Miller, M.; Simonsen, L. Multinational impact of hong kong influenza pandemic: Evidence for a smoldering pandemic. J. Infect. Dis. 2005, 192, 233–249. [CrossRef] [PubMed]
60. Waring, J. A History of Medicine in South Carolina; South Carolina Medical Association: Columbia, SC, USA, 1971.
61. Webby, R.; Webster, R. Are we ready for pandemic influenza. Science 2003, 302, 1519–1522. [CrossRef] [PubMed]
62. Zambon, M. The pathogenesis of influenza in humans. Rev. Med. Virol. 2001, 11, 227–241. [CrossRef] [PubMed]
63. Zimmer, S.; Burke, D.S. Historical perspective-Emergence of influenza a (H1N1) viruses. N. Engl. J. Med. 2009, 361, 279–285. [CrossRef] [PubMed]

How to Cite This Article:
S.S. Kulkarni (2019) Anecdotes of Influenza virus (Swine flu) from chronic age till present. Indian J. Biotech. Pharm. Res. 7(2):1–10.