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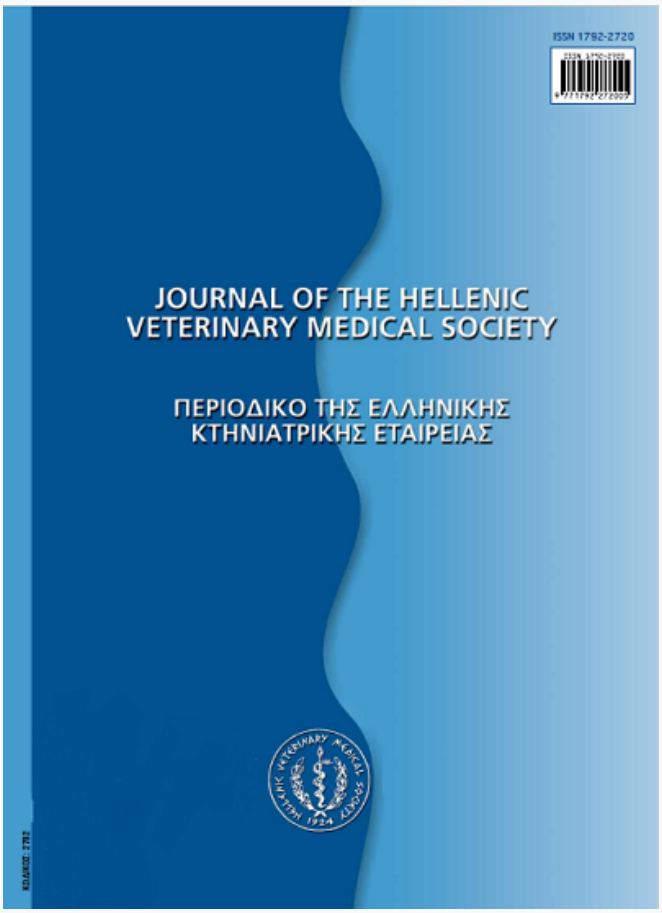

Human influenza pandemics: Myth and reality

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Πανδημία γρίπης του ανθρώπου – Μύθος και πραγματικότητα

Tsiodras S.[1,2]

ΠΕΡΙΛΗΨΗ. Η παρούσα εργασία προσπαθεί να ρίξει φως σε συγκεκριμένα ερωτήματα και λανθασμένες πεποιθήσεις, σχετικές με την εποχική, την πανδημική και τη γρίπη των πτηνών, εστιάζοντας κυρίως σε θέματα που αφορούν στην πανδημική γρίπη. Ανάμεσα στην εποχική γρίπη, την πανδημική και αυτή των πτηνών υπάρχουν σημαντικές ομοιότητες, αλλά και διαφορές. Ιστορικά, στοιχεία από παλαιότερες πανδημίες συνεισέφεραν τόσο στην αξιολόγηση του κοινωνικού, οικονομικού και πολιτικού αντίκτυπου όσο και στην προετοιμασία για μία μελλοντική πανδημία στον άνθρωπο. Τα στελέχη που κυκλοφορούν τώρα, όπως αυτό της γρίπης των πτηνών H5N1, απαρτίζουν κίνδυνο για τη δημόσια υγεία για μία μελλοντική πανδημία. Λαμβάνοντας υπόψη την κλινική εικόνα, φαίνεται ότι σε περίπτωση που το νόσημα προκαλέσει πανδημία, ο βαθμός θνησιμότητας θα είναι υψηλός, ιδιαίτερα σε ευπαθείς πληθυσμούς. Επιπλέον, φαίνεται ότι η ανάγκη για διαγνωστικό έλεγχο επιβεβαίωσης θα ελαττώνεται, καθώς η πανδημία θα βρίσκεται σε εξέλιξη, ενώ ένας αντιϊκός παράγοντας δεν θα είναι αρκετός. Παράλληλα, στην επιστημονική κοινότητα δεν υπάρχει ομοφωνία σχετικά με την επιτυχία ενός H5N1 εμβολίου πριν την πανδημία. Έτοιμα προγράμματα σε περίπτωση πανδημίας, τα οποία θα επιληφθούν λεπτών θεμάτων όπως είναι τα αντιϊκά φάρμακα, οι εμβολιασμοί πριν την εμφάνιση μιας πανδημίας και τα μη φαρμακευτικά μέτρα, είναι απαραίτητο να σχεδιαστούν και να ελεγχθούν στην πράξη, ώστε να διαπιστωθούν τα ενδεχόμενα προβλήματα εφαρμογής τους.

Λέξεις ευρετηρίασης: πανδημία, γρίπη, μύθος, πραγματικότητα

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Human influenza pandemics – Myth and reality

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ABSTRACT. This paper attempts to shed light in certain questions and false beliefs about seasonal, avian and pandemic influenza, mainly focusing on issues surrounding pandemic influenza. Important similarities and differences exist between seasonal, avian and pandemic influenza. Historical lessons from old pandemics help in recognizing their significant social, economical and political impact and guide the current preparedness for a future human pandemic. Currently circulating strains, such as the avian influenza H5N1 strain constitute a danger to public health and have significant pandemic potential. Regarding clinical characteristics it appears that disease associated with a pandemic will have a high case fatality rate especially in vulnerable populations. Furthermore, the need for confirmatory diagnostic testing will likely diminish as a pandemic progresses. With regards to management stockpiling one antiviral agent will probably not be enough. No uniform scientific conclusion about the success of a prepandemic H5N1 vaccine has been reached yet. Complete pandemic plans that address subtle issues surrounding stockpiling antivirals and prepandemic vaccines as well as non-pharmaceutical measures need to be ready and to be tested in practice in order to identify problems with implementation and gaps in preparedness.

Key words: pandemic, influenza, myth, reality

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INTRODUCTION

Important differences exist between seasonal, avian and pandemic influenza.

A lot of lay people, but also health professionals still do not recognize the differences between the three influenzas and why they are discussed together. The term seasonal influenza refers to the annual seasonal increases in influenza rates (during the cold months of the winter for the Northern hemisphere season). The term "avian influenza" is used as an ecological classification term and is non-specific. The current H5N1 avian strain, causing the large multiple outbreaks predominantly in Southeast Asia, is a type A influenza strain that affects domestic or wild birds and other avian species. Any similar influenza A type falls under the same term. Pandemic influenza is rarely seen and for molecular and genetic reasons can only be caused by type A influenza viruses that are also responsible for avian influenza. The current fear is that the circulating avian influenza A/H5N1 strain will evolve into a form that is easily transmitted from person to person and will give rise to the next human influenza pandemic. In this paper we attempt to clear certain false beliefs about seasonal, avian and pandemic influenza as those pertain to the pathophysiology, clinical picture, diagnosis, treatment and prevention issues. Due to its importance the focus of this effort will especially be pandemic influenza.

METHODS

ST independently performed the literature search. The following terms were used in searches of the PubMed database: "influenza", "avian influenza", "influenza A", "H5N1", "seasonal influenza", "pandemic influenza" and "pandemic". Using a web search engine (Google) we screened the same terms in conjunction with the terms "myth" and "realities". All articles identified were reviewed with an emphasis on major reports that included the search terms and review articles concerning the three influenzas from major journals (e.g. New England Journal of Medicine, Science, Nature, Nature Medicine, Lancet, JAMA, PNAS). In addition, broadcasts and reports from major scientific and humanitarian organizations (e.g. WHO, United States CDC, European CDC, European Commission, FAO) and major media organizations (e.g. CNN, BBC, Reuters, Skynews, NY times) were screened for 1 year prior to this report to identify the major areas of interest about the three influenzas that were publicized and identify areas with knowledge gaps in the general public. We screened articles related to the initially identified publications to expand our data sources.

RESULTS

Several knowledge gaps were identified helping in establishing a list of ten myths and realities pertaining to seasonal, avian and pandemic influenza (Table 1).

1) Reality: Huge genetic diversity exists for all influenza viruses

The influenza virus genome consists of ten genes encoding for eight structural and two non-structural proteins. Among the eight structural proteins the most well known are the two surface glycoproteins namely hemagglutinin (HA) and neuraminidase (NA). These proteins serve as an envelope for the virus and are evenly distributed over the virion surface, forming characteristic spikes. Variations in these proteins define an influenza A virus subtype, e.g. influenza A/H5N1. So far 16 different hemaglutinin (HA) antigens (H1 to H16) and nine different neuraminidase (NA) antigens (N1 to N9) have been characterized for influenza A. The new HA type is type H16 that was isolated from black-headed gulls in Sweden and the Netherlands in 1999 (Fouchier et al. 2005). Genetic reassortment of two different influenza viruses infecting the same cell may occur resulting in strains that could be markedly different from the original virus (Voyles 2002). Major genetic reassortment events are a prerequisite for a pandemic and are called a genetic shift. A genetic shift can actually occur between human and animal strains as was the case with the 1957 and 1968 pandemic influenza strains. Once a novel influenza strain emerges it should have certain characteristics in order to cause a

Table 1. Ten myths and realities about pandemic influenza as they relate to preparedness

Realities	
1.	Huge genetic diversity exists for all influenza viruses
2.	Wild birds are the natural host for Influenza A viruses
3.	At least 10 pandemics have been recorded in humans in the past 300 years
4.	Only H1, H2 and H3 are known to have caused epidemics and pandemics in humans
5.	The influenza A/H5N1 strain that is currently circulating is considered to have the greatest potential for a human pandemic
Myths	
6.	Dogs are not affected by influenza
7.	Clinical symptoms differ between seasonal, avian and pandemic influenza
8.	Confirmatory laboratory testing is necessary during a pandemic
9.	The pandemic strain will be susceptible to oseltamivir, thus stockpiling one antiviral will suffice
10.	H5N1 vaccines should be stockpiled according to WHO

pandemic. It has to be: a) highly pathogenic for humans; b) easily transmitted from person to person; and c) genetically unique so that it faces a lack of immunity at the population level. On the other hand, small genetic changes of the HA and NA proteins occur in circulating influenza viruses continuously every year, are called a genetic drift and form the basis for the seasonal influenza outbreaks. These changes direct the annual development of new influenza vaccines.

2) Reality: wild birds are the natural host for Influenza A viruses

Inlfuenza A viruses can infect humans, pigs, horses, seals, whales and other animals, but wild birds are the most important natural host. Most pandemics have started in countries where situations favor an intimate association of people with animals (Beveridge 1993).

3) Myth: Dogs are not affected by influenza

Importantly influenza A viruses recently have been shown to be able to infect animals not traditionally known to be affected by influenza, such as felids e.g. cats, leopards and tigers (Keawcharoen et al. 2004; Webster and Govorkova 2006) as is the case with the currently circulating H5N1 strains and dogs as is the case with H3N8 influenza A, a virus strain that is usually associated with infection in horses (Crawford et al. 2005).

4) Reality: At least 10 pandemics have been recorded in humans in the past 300 years

Although it seems that influenza has been around for thousands of years and some of the earliest reports date back to Hippocrates, little is known about true influenza pandemics in the last 300 years. However, starting from the 16th century and going forward, three to four pandemics occur every century over the last 300 years reaching a total figure of at least ten pandemics. During this time, an interval from 10 to 49 years was observed with an average of 24 years between each pandemic and the one following. One of the first well described influenza pandemics that was associated with high death rates is reported in the year 1580, starting in Asia and rapidly spreading to Africa, Europe and the Americas. This pandemic reportedly killed 10% of the population of Rome and left large cities depopulated (Beveridge 1978). During the 18th and 19th century at least seven pandemics occurred. The last pandemic of the 19th century occurred during 1889-90 and was known as the Russian Flu. It is estimated that it killed about 1 million people, a figure similar to the 1957 and 1968 20th century pandemics.

5) Reality: Only H1, H2 and H3 are known to have caused epidemics and pandemics in humans

The Spanish pandemic of 1918 was due to an H1N1 strain. The Asian pandemic in 1957 was due to an H2N2 strain, while the Hong-Kong 1968 strain was a H3N2.

Currently circulating human influenza A viruses are of H1N1, H1N2 and H3N2 subtype and are strains included in the seasonal influenza vaccine.

6) Reality: The influenza A/H5N1 strain that is currently circulating is considered to have the greatest potential for a human pandemic

An influenza strain, in order to be considered a good candidate to cause a pandemic besides causing human disease, it should be easily transmitted in a population that has never been exposed to a similar strain, thus lacking specific immunity. The H5N1 strain fulfills all these criteria except for the efficient transmission and thus is considered the best candidate for a human pandemic in the immediate future. Moreover, H5N1 is associated with high case fatality rates and is continuously evolving. Thus it could become easily transmissible between humans either through genetic reassortment or via gradual adaptation. Influenza A/H5N1 defines the current pandemic alert level as phase 3 according to the WHO Global Influenza Preparedness Plan. Besides influenza strains of the H5 subtype, H7 subtypes are also considered of great concern since the vast majority of the population, as never been exposed to them.

7) Myth: Clinical symptoms differ between seasonal, avian and pandemic influenza

Influenza like illness is characterized by cough and fever together with symptoms from the upper respiratory tract and other systemic symptoms, e.g. sore throat, headache and myalgias. All influenza strains affecting humans present with the same clinical picture. It is only the degree of severity that changes with the highly pathogenic pandemic strains. These strains are associated with high case fatality rates due to respiratory distress. A highly aggressive bronchopneumonia as well as rapidly evolving acute respiratory distress were characteristics of the 1918 clinical picture (Morens and Fauci 2007). Of note a pandemic may have a greater impact on vulnerable populations, such as children (H5N1 being the best example of a current strain) and pregnant women as was the case with 1918 pandemic. A meta-analysis showed case fatality rates as high as 70% in affected pregnant women during the 1918 pandemic (Barry).

8) Myth: Confirmatory laboratory testing is necessary during a pandemic

Significant advances in the laboratory diagnosis of influenza include the evolution of rapid antigen testing and molecular techniques in addition to the gold standard of culture. Serologic tests are only used to

retrospectively diagnose infection and for epidemiological purposes. During a pandemic it will be difficult to offer specific recommendations about laboratory testing. These will depend on the level of the influenza activity in the community and the severity of the clinical picture. In situation with high attack rates and severe disease the clinical picture alone will suffice to diagnose the infection. It is expected that as a pandemic advances to severe patterns of disease characterized by acute respiratory distress, the need for confirmatory diagnostic testing will diminish and the treatment will be empirically instituted. Nevertheless, other important factors include the availability of resources for testing, the co-circulation of various other influenza strains in the community, the positive and negative predictive values of the laboratory techniques (Weinberg 2005) and surge capacity issues with antivirals.

9) Myth: The pandemic strain will be susceptible to oseltamivir, thus stockpiling one antiviral will suffice

From significant modeling work it has been estimated that an antiviral stockpile covering 20% to 25% of the population can be used until the preparedness of an effective vaccine and would lead to a 50% to 77% reduction in hospitalizations (Gani et al. 2005). Neuraminidase inhibitors and especially oseltamivir are currently being considered as the best monotherapeutic option in the event of a possible influenza pandemic. This is due to misconceptions regarding their safety and resistance profile when compared to ion channel inhibitors like amantadine. However, neurmaninidase inhibitors are associated with important side effects and resistance is emerging even in the recent H5N1 strains (Tsiodras et al. 2007). The truth is that no single anti-influenza drug can be seen as a panacea and antivirals should be seen as a part of a wider package of measures and options to control the potential spread of pandemic influenza, including of course the most important measure that is effective vaccination. In particular and as suggested by recent research (Tsiodras et al. 2007), there may be a potential role for combination therapy, may be an appropriate solution for a pandemic in order to minimize the development of resistance to antivirals. Nevertheless, there is a need for an improved evidence base regarding the exact role for ion channel inhibitors, since no one knows what the susceptibility pattern of a pandemic influenza strain will be.

10) Myth: H5N1 vaccines should be stockpiled according to WHO

An effective pandemic vaccine is considered as the most significant measure for controlling an influenza pandemic. It has been estimated that it will take at least 4 to 6 months to develop a vaccine. Approximately 200-300 mil doses of the seasonal trivalent vaccine are produced annually in nine specific developed countries with vaccine production capacity (Fedson 2003). Thus the use of these traditional resources and procedures will not be enough to respond to the crisis of an influenza pandemic when the global vaccine demand will rise to significantly higher levels. Several steps are introduced to address this problem. These include, but are not limited to the use of newer molecular techniques to prepare seed strains (Luke and Subbarao 2006; Palese 2006), the development of prepandemic vaccines, such as those targeting the H5N1 clades and subclades (Treanor et al. 2006), as well as procedures for global vaccine registration and the negotiation of political agreements that will ensure the adequate production and equitable distribution of pandemic vaccine throughout the world (Fedson 2005). Recent research suggests that an H5N1 prepandemic vaccine may prime the human immune system, thus making one instead of two doses of a pandemic vaccine efficacious during a pandemic (Monto 2006). Very recently WHO issued a statement about the progress with the development of pandemic influenza vaccines indicating that at least 10 countries are developing influenza vaccines targeting H5N1 strains and some of them against other potential pandemic avian strains, such as H9N2(WHO 2007). Despite the fact that some countries, such as the US, have already agreed to stockpile prepandemic H5N1 vaccines, the WHO has recently stated that it still not prudent to make global recommendations in favor of stockpiling H5N1 vaccines due to many scientific uncertainties (WHO 2006). Certainly, such a position may change in the near future.

DISCUSSION

This work identified several points that need clarification with regards to seasonal, avian and pandemic influenza. These included historical lessons showing that influenza pandemics are not new and there is a lot one can learn from studying old pandemics, especially the most recent ones. From these lessons it appears that a pandemic is expected to have significant social, economical and political impact. Thus complete preparedness plans should be available and get tested for issues with implementation in all countries around the world.

In addition, this report identified evidence that currently circulating strains, such as the avian influenza H5N1 strain, constitute a danger to public health and have significant pandemic potential. This is due to specific characteristics, such as the lack of general population immunity and the ability to cause human disease with high case-fatality rates. However, it is important to understand that potentially any strain

could evolve to become a pandemic strain, such as strains harboring hemaglutinins of the H7 or H9 subtype, either through genetic reassortment or gradual adaptation to the human host.

Further, as the global community actively prepares for the next pandemic and as evidenced from the various pandemic plans reviewed, decision makers in various countries have not conclusively decided yet on how to approach sensitive issues in pandemic preparedness in a harmonized fashion. Thus stockpiling antivirals and prepandemic vaccines is not uniformly managed and depends upon the country examined and the available local and national resources. In addition to vaccines and antiviral agents, data assessing the effectiveness of non-pharmaceutical interventions need to be further examined. Strategies, such as the wide implementation of handwashing and respiratory hygiene/cough etiquette, as well as more in more extreme cases isolation at home and quarantine together with social distancing measures have been considered (WHO), but are not specifically addressed in most pandemic plans with few exceptions (CDC 2007).

Several complex issues will arise during a pandemic and need to be addressed during the current preparedness phase. These include issues around individual management of the affected human cases, other interventions that will slow the progress of a pandemic during its early phases and the exact role of animal and avian vectors in the epidemiology of strains with pandemic potential. Lastly, but very importantly, no one can predict the wide public reactions to sensitive issues, such as the equitable hierarchical distribution of scant recourses (vaccines, antivirals and other pharmaceutical supplies) in the event of a huge societal crises, such as an influenza pandemic.

In conclusion, influenza appears to be a continuously emerging infectious disease. Several misconceptions, as the ones identified during the current search, have to be clarified in the minds of political decision makers, the scientific world that does not specifically work with influenza as well as the lay public. Interactions between all the involved parties (not just people involved in health and agriculture), continuous education and training will assist in further identifying gaps in preparedness as we face the challenge of a major disruption produced by a future pandemic.

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