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Threat of an Influenza Panzooty: A Review Based on Conservation Medicine

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ABSTRACT

Among reemerging illnesses, influenza constitutes one of the main concerns. The avian influenza has recently demonstrated the strong transmission capacity of the etiological agent - a virus from the Orthomyxoviridae family – associated to high pathogenic manifestations of the illness. The strong mutation capacity of this virus, through different hosts, reveals how important integrated actions aiming at monitoring its presence in different species are. The swine infection represents an additional concern not only in relation to that species but also in relation to the possibility of the virus to mutate and adapt to humans. The elements that determine the pathogenicity of the various viral subtypes must be well understood, for the tools used to control the illness - such as vaccination - may promote viral mutation and thus render the control even more difficult instead of favoring it. The present review aims at characterizing various components involved in the virus maintenance in different species as well as the determinant elements involved in its evolution, from the point of view of Conservation Medicine, which is the branch of science that deals exactly with the interaction among the environment, human beings, and animals, thus creating a holistic vision not only of the problem but also of the coherent and effective actions involved in their solution.

Key words: Swine flu, avian flu, reassortment, conservation medicine, panzooty

INTRODUCTION

Influenza, the illness that devastated the world on the onset of the 20th century, provided the world with a profusion of examples followed by recommendations and rules aiming at minimizing the impacts and dimensions of a possible epidemiological disaster, a situation that emerges again nowadays. In 1918, at the time of the Spanish influenza, the relation between the illness and the 'influence' of celestial body conjunctions had already been overcome, and it was exactly that 'influence' that lent its name to the illness known as 'influenza' (Lamb and Krug, 1996). In that context, some treatment and recovery recommendations - which today may sound funny – have been registered, such as: *"The Spanish influenza is rife in Niterói, and doctors recommend people to take Paraty [alcoholic beverage] with lemon as a preventive measure; and everybody knows that the best white rum is best prepared with lemon, and that it is available only at 51 Barão de Itapetininga Street"*. Or even worse, *"Do not panic: smoke Sudan [cigarette brand?]!"* (Bertucci, 2004). And, we ask ourselves: how will our practices be evaluated a hundred years from now? The bottom line is that we accept the risks and the task of creating rules and recommendations based on our perceptions of what is right and true at a certain moment in time.

Around 1900, the publication of 9,000 scientific articles per year was registered and, more recently,

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in 2005, statistics pointed at the production of 2,465 scientific articles per day *(*Economist, 2005*).* These figures reveal that the intensity of changes in our convictions about the scientific truth, often based on hypotheses is very dynamic and disturbing, for it imposes an almost daily review of scientific concepts.

The influenza virus has coexisted with human beings for 400 years, but at the turn of this century, influenza regained its position as 'the star' of calamities and damages, bringing about a deep concern about people living close to avian species or to its sub products, and its resulting health risks (Earn et al., 2002). The avian influenza, or 'chicken flu', incites both folk imagination and scientific updating, producing many reasonable recommendations in accordance with present days convictions, and many not so much. However, we can and must set up some concepts that may help in understanding the mechanisms related to maintenance and transmission of the virus, besides the forms it presents and its risks concerning the avian industry, as well as its zoonotic aspects. These clarifications may guide the practices associated to the animal industry, and they may justify avian/swine management and also sub product management and even wild species management, whenever influenza is involved as a risk or as a fact. From the latter point of view, the relevance to other animal species may assume in maintaining the virus in nature has been known since the 30's, and what is even more serious, in the transformation or mutation of circulating viruses, making its dissemination among humans easier. The global diversity of species and systems involved in the emergence and maintenance of illnesses has determined the opening of a new chapter in science, in which the relationships among all involved components must be evaluated not only in a risk analysis but also in on-going management. This new discipline is called Conservation Medicine and it aims at interconnecting human and animal health, the environment, and their changes (Daszak and Cunninghan, 2002).

The impact of avian influenza, as an illness restricted to fowl, may generate specific damages in its exclusive manifestation in avian species. Thus, the risk of a panzootic among fowl assumes - in countries like Brazil - an economic besides the sanitary connotation, and the impact of that illness maybe a lot greater within this realm for, as Brazil is the largest avian exporter in the world, restrictions and barriers imposed by the perception of an outbreak of fowl influenza would certainly bring about more severe consequences than those resulting from its perception among human beings, at least initially. Nevertheless, the different presentations of the virus associated to its degree of pathogenicity and morbidity, and the different forms of manifestation of the illness in various species, may require more comprehensive control strategies. Aiming at making the alarm detecting the virus presence go off as early as possible and also to guarantee, in a possible manifestation of the illness, the presence of the virus as restricted to its original species, thus preserving human health at a subsequent level (Garcia-Garcia and Ramos, 2006).

The avian influenza can manifest as an acute and lethal disease and require an intense control. But it can also manifest as a benign low mortality disease, as it happens among humans at present, which denotes variability in its manifestation, associated to different viral subtypes. Anyway, due to this virus's capacity of presenting intense or frequent mutations, a watch and ward and a dissemination control prove to be necessary (Gross, 1996). A virus of the *Orthomyxoviridae* family is involved in its etiology, and this virus presents some correlations with the *Paramyxoviridae* family, which has the Newcastle bird disease virus as one of its relevant representatives - the two viruses being control objects of the Brazilian National Program for Avian Health (*Programa Nacional de Sanidade Avícola* - PNSA) of the Ministry of Agriculture, Cattle Raising, and Provision (*Ministério da Agricultura Pecuária e Abastecimento, MAPA, 2001*). The circulation possibility of the influenza virus in other animal species and the transformations and adaptations resulting from these situations generate a far more comprehensive spectrum of monitoring and illness control, for the PNSA actions must be intercurrent with the perception of influenza in various animal species, besides the avian species. Such measures aim at controlling possible foci and minimizing the zoonotic impact of this illness whenever there is a possibility of its being transmitted to humans, a factor that can be favored by the virus adaptation or mutation to other species, mainly the swine species.

Conservation Medicine

Conservation Medicine share the common aim of trying to achieve ecological health. Conservation medicine studies the multiple two-way interactions between the pathogens and disease on the one hand, and between the species and ecosystems on the other. By reaching out to multiple disciplines, conservation medicine provides new skills, new tools, and new vision to the field of both conservation biology and medicine. In essence, with increasing population numbers and the expanding human footprint on the planet, human and animal disease interactions become more frequent and more real. By bringing disciplines together, conservation medicine can contribute to solving environmental problems by improving problem definition (Tabor, 2002).

The Virus

Classification

The genus influenza is representative of the *Orthomyxoviridae* family, which is composed of enveloped viruses with their genetic material based on single stranded RNA, segmented, with negative polarity, and classified into three types or viral species, labeled A, B, and C, of which the segmented RNA is present only in type A. Viruses of the same type share certain hemaglutinant antigens, hemaglutinin (HA), or neuraminidase (NA). In types A and B, hemaglutinin and neuraminidase undergo genetic variations, which constitute the basis for the emergence of new strains of the virus; and type C is antigenically stable. As type A viruses are the most frequent among mammals and the responsible for avian influenza, there is a possibility for this type to circulate in different species, which - for a virus with high mutation intensity (10^{-3} a 10^{-4}) - favors the emergence of new subtypes when the interspecies barrier is broken. Type B virus occurs more intensively among humans, present in yearly influenza epidemic and also detected in various animal species (Capua and Alexander, 2002), such as the sea lion in Punta del Este - Uruguay. There is still another classification proposal which includes a fourth viral type, also labeled *Thogotovirus*, or type D, apparently characteristic of insects that can occasionally infect mammals, and even a fifth type labeled *Isavirus*, responsible for the infectious anemia in salmons (Alexander, 2006).

Subtypes

Among influenza viruses from group A, that infect humans, mammals and avian, 16 different HA proteins and 9 NA proteins are known, which, through possible combinations among them, identify a certain subtype of the virus. The influenza viruses are, therefore, identified by type (A, B, and C) and subtype determined by its HA proteins, numbered from 1 to 16. And, NA proteins, labeled from 1 to 9. All the main combinations between hemaglutinins and neuraminidases have been isolated from avian species, mainly among the wild water-species (Webster and Huise, 2004).

The presence of two related factors, such as the circulation in various animal species and the intense mutation rate of some of the subtypes, requires a global strategy in the influenza control that goes beyond the scientific specializations, promoting interdisciplinary studies, since those mutations could favor interspecies barrier breakages. The role of swine in the influenza virus epidemiology is an extremely relevant chapter for the control measures success, since this species could facilitate the transmission of avian influenza to humans or even contribute to the generation of subtypes of the virus characterized by a high degree of pathogenicity, not only to humans but also to birds (Brown and Alexander, 2000).

The first isolation of the influenza virus was done by Shope and collaborators in swine in 1931, and two years later in humans, despite the fact the illness had already been clinically reported for swine, in the middle west of the United States, in the summer of 1918 (Easterday and Hinshaw, 1992). The first isolation of the wild fowl virus happened in South Africa in 1961, and it was not before 1970 that systematic investigations started to catalog the presence of the virus in various species (Alexander, 2006). Since research on swine influenza began, subtypes H1N1, H3N2, and H1N2 have often been identified with swine circulation all over the world, with reports from China and from a large part of Europe, in addition to H9N2 subtype foci co-circulating in swine and avian populations, and H4N6 subtype in Canada (Peiris et al., 2001). The analysis of subtype H9N2 viral receptors specificity shows that the present samples in swine have maintained a high affinity with type α(2.6) receptors, which are common among the humans and low affinity with type α(2.3) receptors, which are common among the avian, a fact that is determined by the position of certain amminoacids in the hemaglutinin (Ito et al., 1998).

The clinical identification of swine influenza can occur by the manifestation of light respiratory signs accompanied to nasal discharge, fever, and lethargy, which - mainly by the Brazilian exploratory model - is perceived by a smaller weight gain by individuals during the process.

On the other hand, the presence of influenza in the avian exploration can simply contribute, as a secondary factor, to the emergence of syndromes in the swine respiratory complex, where bacteria such as *Mycoplasma*, *Bordetella*, and other agents may cause big damages (Murphy et al., 1999). It is in this condition that greater efforts must be made in order to identify and control the illness, for its presence tends to be silent and its maintenance in exploration could, in the medium run, favor the emergence of new viral variants with extraneous exposures of the main focus. Virus maintenance in exploration means, as in other control situations, a selection pressure onto the agent when, in an attempt to control the problem, the individuals resort to adaptive immunity mechanisms; and through the action of antibodies and defense cells, they try and eliminate the infectious agent. In practice, it means that the influenza virus will find different individuals with a different range of antibodies, and this means that, after three or four cycles of replication and infection in these individuals, it can impute a mutation intensity to the virus, which is strong enough to result in the emergence of a new viral strain, often within the same subtype (Suarez and Schultz-Cherry, 2000). Such variations, which can be compared to the mechanisms involved in the maintenance of seasonal influenza epidemic in humans, are favored by drift mutations presented by the influenza virus when small genome changes - not larger than 2-3% of it - determine the emergence of new strains with low crossed immunity among subtypes (Andreasen and Sasaki, 2006).

Historically, the mutation rate of the drift type among swine is a lot smaller as compared to that for humans (Olsen et al., 2000), but there is no doubt it happens and is determined by the same factors. The influenza virus affinity with different animal species - also known as the interspecies barrier – grants to the various subtypes a mutation rate within the infected species - the larger the intensity of the individuals in the population in question is, the bigger the rate - but with low chances of adapting to other species without breaking the interspecies barrier (Webster and Huise, 2004; Ito and Kawaoka, 2000). Restriction of influenza virus in certain species happens mainly because of the affinity of different viral subtypes, through viral hemaglutinin with receptors found in host cells. In eukaryotic cells, a varied range of glycoconjugates are profusely found in the plasma membrane and, among the carbohydrates present in the membrane glycoconjugates, the sialic acids stand out, which constitute a family of 9-carbon complex carbohydrates usually linked to other carbohydrates through α-cetosidic links, which occur in nature in about 50 types.

As components of glycoconjugates, the sialic acids are found linked to hexoses, such as α(2.3) or α(2.6) or β-Gal and linked to other sialic acids like α(2.8). These sialic acids perform many physiological functions in the organism, as cellular renewal mediators, where its presence in the erytrocites is determinant, in addition to their action in the inflammatory and immune response (De Fátima et al., 2005). Their role as influenza virus specific cell receptors, however, is very important in understanding the factors related to the illness dissemination, and also in its diagnosis and control. The common subtypes of the influenza virus among avian are preferably linked to sialic acid α(2.3) Gal receptors, which are profusely present in the bowel epithelium of fowl, mainly water birds, and also in their respiratory epithelium, but absent in humans, except for its occasional presence in deep and scarce locations in their inferior respiratory system (Gambaryan et al., 2005a). The common viruses among humans, on the other hand, are preferably linked to sialic acid receptors with type α(2.6) Gal links, present mainly in the trachea epithelium and absent in avian (Ito, 2000). Bird viruses have a limited replication capacity in humans, and this makes the direct transmission from birds to humans more difficult (Beare and Webster, 1991). But in swine not only the avian but also the human virus have an optimum replication capacity, for both receptors - α(2.3) and α(2.6) - are found in the trachea epithelium cells of swine.

The reassortment

It is at that very moment, when, at random, two different viruses could infect the same cell and replicate in that cell in the trachea of swine, that a third virus could emerge, recombined with a good replication capacity in humans (Michiels et al., 2006). It is the fact the virus's genome is composed by a segmented RNA that favors this type of mutation called 'reassortment' or 'rearrangement' or even 'antigenic shift'. For the fact the influenza virus is segmented, genetic reassortment can occur when a cell from the host is simultaneously infected with a virus from two different but related strains. If one cell is infected with two strains of type A virus, for example, some of the viruses of their offspring could contain a mixture of eight segments of the genome of each of the two strains (reassortment) (Wright and Webster, 1996).

The increasing concern with the emergence of a new influenza pandemic, is founded exactly on this fact. Despite the different virus strains being species specific, that is, avian viruses infect only avian, and so on, in certain situations, viruses coming from human beings can infect swine and really succeed in replicating, the same way the avian viruses do (Horimoto and Kawaoka, 2001, Zhou et al., 1999). In the cells of those swine, infected with two different strains of the virus, a reassortment could happen among the eight segments of each type forming a new strain, with a totally different antigenic constitution, but with a replication capacity among human beings (Webster et al., 1992).

Thus, not only the relevance of influenza as a respiratory illness in swine, but especially the crucial role of swine in the epidemiology of outbreaks of the influenza virus among humans, and also the role of humans as infection source for swine become evident (Brown, 2000).

Swine are naturally infected with virus types H1N1, H3N2, and although less often H1N2 (Bean et al., 1992). This includes virus H1N1 of the classic swine influenza, virus H1N1 similar to the one found in avian, as well as the H1N2 with an H1 similar to the H1N1 found in humans. Influenza viruses similar to human H3N2 infect swine and can cause clinical signs of the illness (Olsen et al., 2002). There are evidences suggesting that different variants of virus H3N2 have been transmitted to swine since 1968 (Van Reeth et al., 2003). Those variants can remain in swine after they have disappeared from the human population. The swine influenza was initially observed in the United States during the 1918 human pandemic, and in 1933 it allowed the association of the illness with the virus from swine isolates. The clinical signs of the illness in swine are very similar to those found in humans (Brown, 2002a). In 1979, samples of the swine influenza virus were isolated in Europe having genes of avian origin, and later studies have shown that subtypes H3N2 of the virus, which circulated in swine, had come from avian ancestors and had already undergone some type of rearrangement, and this demonstrates the relevance of monitoring the circulation of the influenza virus in swine for detecting potential pandemic strains (Campitelli et al., 1997).

Swine are also susceptible to experimental infection with all subtypes of the avian influenza A virus the subtype H9N2 of influenza was successfully isolated from swine in Hong Kong (Brown, 2002b; Capua and Alexander, 2002). The inter-species transmission of the influenza virus has been repeatedly demonstrated. However, the presence of the previously mentioned barriers restricts such dissemination. The viral hemaglutinin is the main responsible for such restriction among hosts, mainly due to its role in the recognition and adsorption to the host's cell. In order that such adsorption provokes a conformational change in the hemagglutinin, which is a trimer, it must be triggered off by the action of host's proteases in a hemagglutinin site called 'cleavage site' (Tong et al., 1998) or even through bacterial proteases, occasionally present in the host (Mancini et al., 2005). The endosome's pH formed after adsorption and virus penetration is decisive for the fusion of the viral envelope with the cell membrane culminating in the success of the infection, when it is possible to observe the conformational changes of hemagglutinin that allow such fusion (Wharton et al., 1995). The cleavage site stability is decisive in the viral strain's pathogenicity, and the abundance of proteases in certain sites of the body may determine the manifestation of the illness, restricted to the respiratory tract, or as a syndrome affecting various systems (Cross et al., 2001; Webster and Huise, 2004).

The proteases that cleave the non-pathogenic strains are found in a limited number of cells or tissues resulting in localized infections, made possible by the hemagglutinin extra-cellular cleavage through trypsin-like enzymes. The strain hemagglutinins having high pathogenicity are cleaved in an intracellular, pH dependent medium (Steinhauer, 1999).

Pathogenicity

Among the influenza virus subtypes, there is a major concern with the avian origin strains which are said to have a high degree of pathogenicity, of which strain H5N1 is the one that was the most prevalent mainly in Asia during the 1990's, and from 2000 on with its emergence in Europe in wild fowl. Among the highly pathogenic subtypes, only those presenting hemagglutinins - besides H5, the H7's and H9's – have been classified so far (Li et al., 2004). These are the subtypes that have manifested with a high degree of pathogenicity in recent foci, whereas some foci can present viruses with the same hemagglutinins, but with low pathogenicity. After its manifestation in the individual, the strain characterization is carried out in laboratory after its isolation through not only intra-cerebral but also intravenous inoculation in one-day-old chicks; and, after monitoring the effect, mortality is verified and pathogenicity is attributed. The low pathogenicity viruses, which include not only those endemic to human population, but also those present in swine detected so far in Brazil, the H5N1 present in North America, and those prevalent in Mexico, are characterized by the presentation of a stable cleavage site in the hemagglutinin, which is only cleaved by proteases present mainly in the trachea, limiting both the intensity of the infection and its dissemination in the organism. After mutation in the amminoacids which form the cleavage site, some strains turn that site unstable allowing proteases to break it, thus favoring infection. This is the main pathogenicity acquisition mechanism of the influenza virus, which can be followed by mutations in other sites which could favor adsorption and viral penetration, in addition to increasing its pathogenicity (Cross et al., 2001).

The nucleotide sequencing of all influenza genome virus has revealed that the 1957's Asian pandemic (the introduction of an A/H2N2 influenza virus), and the Hong Kong pandemics in 1968 (the introduction of an A/H3N2 influenza virus) were caused by an influenza virus resulting from an antigenic rearrangement (Scholtissek et al, 1978; Li et al., 2004). However, the 1918's influenza pandemics (the Spanish flue) apparently affected the human population without the antigenic rearrangement. Claas (2000) characterized samples of the virus isolated from humans, coming from avian, without the viral rearrangement event. However, this fact probably requires the virus to adapt initially to a mammal host. Maybe this was the case of the 1918's pandemic virus (A/H1N1). This virus certainly presented properties that confer extreme virulence to it. One believes that despite the above hypothesis being feasible, the probability of those strains to settle in the human population is low, thus limiting the possibility of antigenic rearrangements in the future (Beare and Webster, 1991; Ito and Kawaoka, 2000).

The analysis of viruses isolated from influenza H3N2 outbreaks, more recently identified in swine in the United States - where subtype H1N1 had previously been prevalent - revealed that these new H3N2 viruses have a profile similar to recent strains of the human H3 virus (Zhou et al., 2000), this virus having possibly originated either from a recombination of human and swine viruses or from recombinations of human, swine, and avian viruses (Karasin et al., 2000).

In 1958, Souza Filho detected antibody reaction against the influenza virus of human origin in 25% of the swine studied in the State of Parana-Brazil. This reference demonstrates an old concern over the manifestation and presence of the virus in swine, showing that, at least in the last 50 years, the virus remains in the swine population of that State and needs more detailed analyses besides the control strategies aiming at a healthy swine industry and mainly at minimizing the risks of its recombination and transmission to humans.

Brentano et al. (2002) analyzed 2,675 samples of swine serum in the south region of Brazil, and found 50.9% of the fowl runs evaluated positive for H3N2 and, among the, 16.7% of the animals were positive. The degrees of prevalence found are related to the best period for antibody detection in high titers, which occurs between two and three weeks after the infection.

It is important to point out that technician and producers in the swine industry should pay attention to the importance of influenza not only as a swine illness, but also to its relation to public health (Olsen et al., 2002; Jung et al., 2005). In outbreaks of respiratory illnesses in swine, influenza must be included in the differential diagnosis, for which the material must be sent to a laboratory. The material to be collected and forwarded may consist of lung fragments and nasal swabs, for viral isolation. The isolation of the virus(es) that may be circulating in the breeding stock is basic to evaluate, with a higher degree of sensitivity, the role of the influenza virus in Brazilian production systems of swine. For it is through viral isolation that one can produce antigens specific to serological assays and better characterize its origin and pathogenicity (Pospí-Il et al., 2001; Gambaryan et al., 2005).

Since 1997, in North America, the emergence of new strains and their circulation in swine has been detected, when, after a period of 60 years, new subtypes such as H3N2, among others, started to become prevalent in the swine population. The origin of these new subtypes deserves special attention as it denotes the possibility of introducing human variants, previously restricted to the human population and now adapted to other species. Besides this possibility, there is that taking the reverse way, allowing the transmission of swine virus to men, which determines the need for frequent monitoring of the genetic variability of those viruses, providing reliable data in what concerns the distribution and adaptation of them (Olsen, 2002). The implementation of effective control strategies depends on such evaluations, which can justify – as it happened in North America – the introduction of swine specific vaccines aiming at not only controlling the clinical manifestations of this species, but also preventing a possible pandemic. Based on those analyses, the major multinational vaccine producing companies have evaluated the possibility of introducing these products against swine influenza in Brazil, although this may be considered an early decision nowadays, not because of the incidence of the illness, but because of the lack of comprehensive data, as it happens in other countries. Besides grounding the use of vaccines for swine, many works have demonstrated the effects of the crossed immunity with heterologous subtypes of the influenza virus, which would make it possible to choose the best strains and to establish effective calendars for the control of clinical manifestations of the illness since the immune memory coming from vaccination could, in a more intense form that that in humans, promote the desirable protection (Kitikoon et al., 2006).

Concurrent to its application in already existing protocols - such as the formulation of vaccines for humans -, the implementation of new strategies, improving the comprehension of ecology and virus occurrence will allow vaccination of other species and vaccine presentations that permit its safe use in preventing influenza (Ferguson et al., 2003; Ninomiya et al., 2002). The immunization of species involved in the emergence of new subtypes is a point to be considered in pandemic and epizooty prevention, as well as the implementation of mucosal vaccines (Barackman et al., 1999), which could mimic response to the wild agent, but that even today do not comply with the needs for efficacy and safety (Gluck et al., 1999; Kilbourne and Arden, 1999).

Monitoring viral variability is basic for supporting efficient strategies and, like in human experience, the perception of the virus evolution in swine and avian species is important (WHO, 2002). From 1996 to 2000, small variations were reported on human virus subtypes, basically H1N1, in which the molecular analysis allows to conclude that the variants present in Brazil are related to ancestral samples coming from other continents, presenting expected variation coefficients for new vaccine formulations and control strategies (Paiva et al., 2004).

The way a virus manifestation is going to be followed is determined by the perception of different subtypes in various susceptible animal species, and many researchers have demonstrated that the adaptation and mutation capacity of the virus depends on the host in which it replicates and even on different degrees of sensitivity in the viral growth when either cellular cultivation systems or embryonated eggs are used. The adaptation of some subtypes that evolutionarily manifest in swine and turkeys denotes the infection capacity of the virus in nature, when the laboratory results are extrapolated to show effects related to changes in receptors that favor an independent adsorption of the host (Morishita et al., 1996, Gambaryan et al., 2006).

Prevention

According to the OIE (World Organization for Animal Health) recommendations, in general, the use of vaccines for controlling the avian flu would present advantages and disadvantages. The arguments against the use of vaccines are the following:

- the use of vaccines would probably not help in the biosafety measures implementation, as the producer might mistakenly feel that other measures are less important whenever vaccines are being used;
- vaccination may avoid the emergence of clinical signs individually, but would not necessarily provide the virus elimination from the environment;
- the presence of vaccinated animals and the circulation of wild virus could favor the emergence of new viral variants through selection

pressure, as explained by the antigenic drift;
- vaccination could favor the emergence of asymptomatic bearers, thus increasing viral dissemination.

On the other hand, the arguments for the use of vaccines are the following;
- preventing the illness, vaccination can preserve the industry of a country, especially in the occurrence of foci;
- avian vaccination could minimize the possibility of transmission to humans and the emergence of a pandemic strain;
- vaccine flaws could be verified by adopting the sentinel animals, not vaccinated, to trigger off the alarm on potential transmissions;
- vaccination is a necessary step towards a possible eradication of the virus in a given area, where all the individuals should become negative;
- this protocol would not interfere in the control of the illness among the humans, and would even be necessary in some cases.

Analyzing the present-day situation, one can conclude that biosafety measures must be the main focus in controlling influenza, and that the impact of vaccination has specific characteristics in each country. The decision about using or not using vaccination must be based on various aspects, as mentioned above in 'advantages and disadvantages', and the emergence of new technologies in vaccine production will be a determiner for such decisions (Palese and Sastre, 2002). The use of products conformed to the so-called **DIVA** (Differentiating Infected from Vaccinated Animals) is an ever more promising reality in the control of various illnesses, including influenza. In this sense, these technologies, as well as the so-called 'mucosal vaccines', might minimize the disadvantages in using vaccines and favor the control of influenza in the future (Won-Lee et al., 2004; Capua and Marangon, 2006).

As the avian influenza has as its complicating factor a source for generating a pandemic subtype of the virus, the control and prevention of it must be included in an earlier warning protocol, which could minimize the damages of its manifestation as an epizooty mainly in Brazil, because of the relevance of the commercial exploration of avians.

As pandemic anticipation, the prevention and control actions in the swine species may have a more urgent impact considering the capacity of the virus to undergo mutations in that animal species. In practice, different vaccination strategies must be evaluated aiming at prospecting the impact of their use, as compared to present day control methods. All possible interactions must be raised, for the network of interrelations that a possible influenza pandemic or even an influenza panzooty requires coherent analyses and comprehensive plans for its control (Hartvigsen et al., 2007).

Thus, numerous strategies can contemplate an earlier warning, safeguarding not only the future of the swine and avian industries but also that of the human health, for the influenza virus, not only human but also avian, is able to infect and replicate in swine.

Vaccination of swine industry workers as well as swine themselves can contribute to the control of influenza as a pandemic (Jong, 2001). Despites the protocol being early and, in Brazil, far away particularly from the avian influenza, the adoption of it could be decisive. A global prevention plan would require cohesive and objective interdisciplinary actions aiming at long-term benefits, not only to human but also to animal health, where the application of conservation medicine could contemplate such objectives.

RESUMO

A influenza representa um dos principais temores dentre as doenças re-emergentes. A gripe aviária tem demonstrado atualmente a grande capacidade de transmissão do agente etiológico, um vírus da família *Orthomyxoviridae*, associada a manifestações da enfermidade com alta patogenicidade. A grande capacidade de mutação deste vírus utilizando diferentes hospedeiros, denota a importância de ações integradas que visam monitorar sua presença em diferentes espécies. A infecção dos suínos determina uma preocupação adicional não apenas para a espécie mas, com possibilidades de mutação e adaptação do vírus aos seres humanos. Os fatores que determinam a patogenicidade dos diferentes subtipos virais devem ser bem compreendidos, pois as ferramentas utilizadas no controle da enfermidade, como vacinação, podem fomentar a mutação viral e com isto dificultar o controle ao invés de favorecê-lo. Esta revisão tem por objetivo caracterizar vários componentes envolvidos na manutenção do vírus em diferentes espécies, bem como os fatores envolvidos em sua evolução, sob a ótica da medicina da conservação, que é um capítulo da ciência que trata justamente das interações entre o ambiente, o ser humano e os

animais, criando assim uma visão holística tanto do problema, como das ações coerentes e efetivas envolvidas na resolução do mesmo.

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