European Journal of Epidemiology **10**: 455–458, 1994.

Source for influenza pandemics

Christoph Scholtissek
Institut für Virologie, Justus Liebig Universität, Giessen, Germany

Abstract. There are three ways how influenza A viruses can escape the immune response in the human population: (1) By antigenic drift. This means by mutation and selection of variants under the selection pressure of the immune system. These variants have amino acid replacements mainly in the epitopes of the hemagglutinin. (2) By antigenic shift. This means replacement of at least the hemagglutinin gene of the prevailing human strain by the allelic gene of an avian influenza virus by reassortment. (3) As a rare event, direct or indirect introduction of an avian influenza virus in toto into the human population. A prior introduction of an avian virus into pigs and an adaptation to the new host might be a presupposition for its final passage to humans. In this sense the nowadays situation is reminiscent to that of about 100 years ago, when an avian virus was presumably first introduced into pigs, and from there into humans. Immediately or some time thereafter the disastrous Spanish Flu in 1918/19 had killed at least 20,000,000 people in one winter. Pandemic strains can be created by all three means, however the most common way is by reassortment. In order to recognize a pandemic strain as soon as possible a worldwide surveillance system and collaborating laboratories equipped with corresponding modern technologies are required.

Key words: Antigenic drift, Antigenic shift, Influenza pandemic, Influenza phylogeny

Introduction

The genome of influenza A viruses consists of 8 single-stranded RNA segments (genes) of negative polarity. Because of the extremely high mutation rate of RNA viruses, influenza variants with amino acid replacements in the epitopes of the surface glycoproteins appear easily under the selection pressure of the immune system, leading to the antigenic drift. Drift variants mostly cause relatively defined epidemics, but occasionally they spread worldwide. Viruses with a segmented genome exhibit the phenomenon of reassortment during a double infection of a cell or an organism. In the example shown in Figure 1 the prevailing human influenza strain has received a new gene coding for the major surface antigen, the hemagglutinin, from an animal influenza virus. This new shift variant can cause the next pandemic, because no neutralizing antibodies against the new virus are present in the human population. Such a reassortment between a human and an avian influenza strain, suddenly creating a new pandemic virus, has happened the last time in 1968 [1].

The pig as 'mixing vessel' for the creation of new shift reassortants

There exist two major reservoirs of influenza A viruses, one in humans, and another one in water fowl[2]. However, human influenza viruses do not spread in the avian population, and vice versa, avian influenza viruses do not spread in humans. Therefore, the question arises, where this mixing of virus genes (Figure 1) occurs. It was found that pigs exhibit a relatively low species barrier towards infection with avian or human influenza viruses. This observation is supported by studies on sequences of the nucleoprotein (NP) gene [for reviews see 3–5]. The NP gene was chosen, because it is the major determinant for

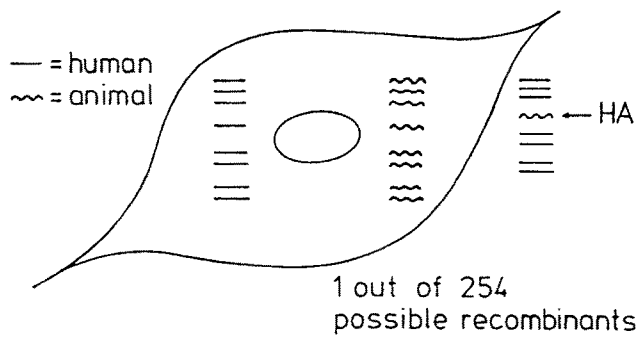

Figure 1. Scheme to explain the creation of a new pandemic influenza A strain by antigenic shift. A cell becomes doubly infected by an animal virus and by the prevailing human strain. One of the 254 possible new reassortants has the gene constellation shown on the right, which could theoretically cause the next pandemic.

species specificity [6]. In the phylogenetic tree constructed by using the NP sequences of 100 different influenza strains (Figure 2) it can be seen, that swine viruses (SW) are scattered among the avian as well as the human branch, while human and avian viruses were never mixed. Thus 'avian-like' and 'human-like' influenza viruses can be isolated from pigs relatively frequently.

Because of a dense cohabitation of humans, pigs and water fowl around fish ponds in villages in China the probability of the creation of new pandemic strains is the greatest in Southeast Asia. This might explain why all the pandemics in historical times have started from this area [7, 8].

As a rare event, an avian influenza virus can be introduced to toto into a mammalian population forming a stable lineage

A surprising feature of the avian NPs in Figure 3 is, that there is no depth in this branch. This means, that the bird NPs are under no selection pressure to change. They are optimized. In contrast, the NPs of the human or classical swine viruses are under a strong selection pressure. From these data it is concluded that the avian viruses stayed in the bird population since centuries almost unchanged, while the mammalian influenza strains were derived from an avian ancestor virus. If the number of nucleotide substitutions, starting from the common root, is plotted against the time of isolation, the regression lines as shown in Figure 2 were obtained. From the extrapolation of these lines towards the time axis it can be concluded that an avian ancestor virus was stably introduced, presumably first into the pig population about 100 years ago, and shortly thereafter into the human population. It is not clear from these data, but it might be assumed that an avian virus first entered the pig population and, after some adaptation to the new host, passed to humans forming a stable new lineage [9–11]. The human influenza B and C viruses presumably also have an avian influenza A ancestor introduced into the human population much earlier [9]. Possibly additional lineages might have died out in the meanwhile. Shortly after the latest establishment of a human influenza virus lineage we had the disastrous Spanish Flu in 1918/1919 killing at least 20,000,000 people worldwide in one winter.

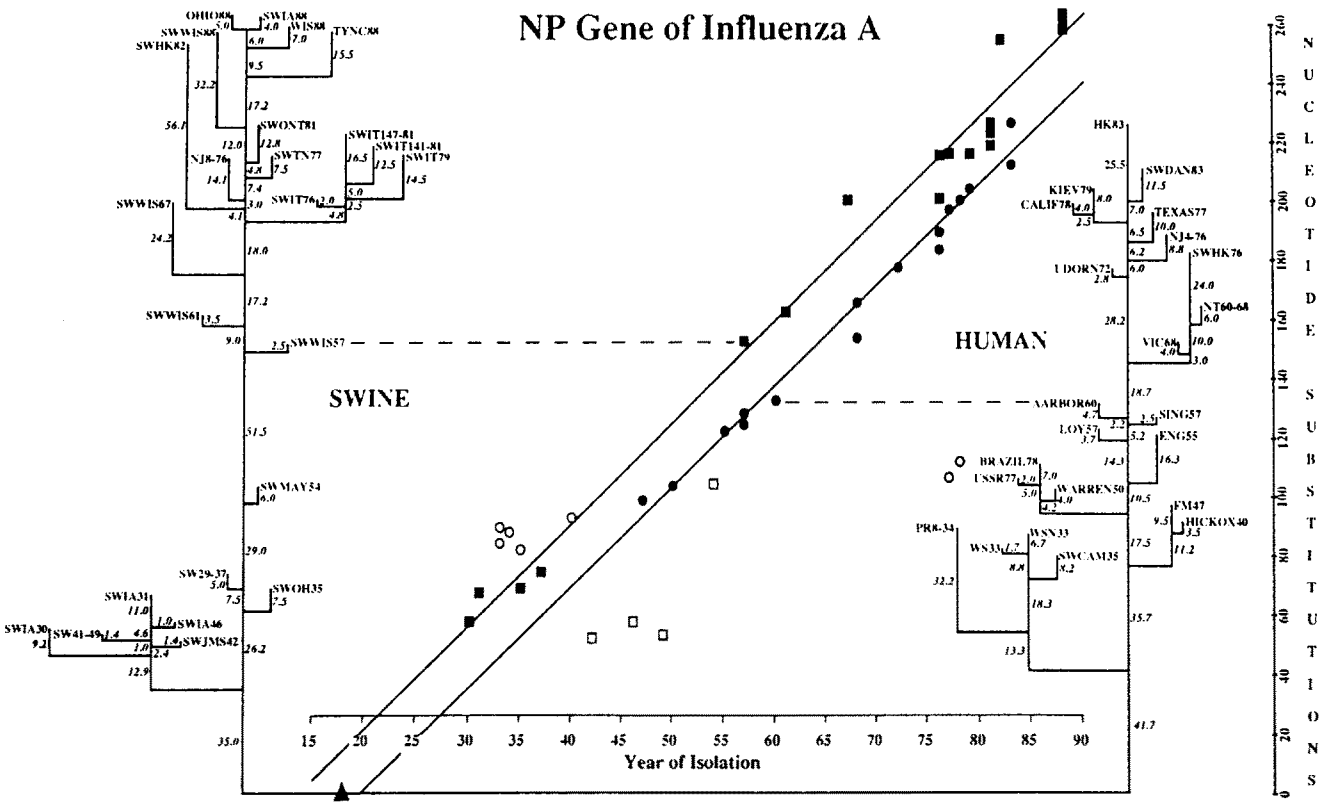

Figure 2. Evolutionary rate determinations for the NP genes for human (circles) and classical swine (squares) virus isolates. The evolutionary rates are estimated by regression of the years of isolation (horizontal scale) against the branch distance from the common ancestor node of the nucleotide phylogenetic tree (total nucleotide substitutions vertical scale [4]. For abbreviations see Figure 2. Only the closed symbols were used for the calculations of the best fitting lines. The closed triangle is the assumed human-pig divergence point plotted at 1918. At the left and right phylogenetic trees of total nucleotide substitutions are shown in a different way. Side branches are indicated originating from a hypothetical main stream.

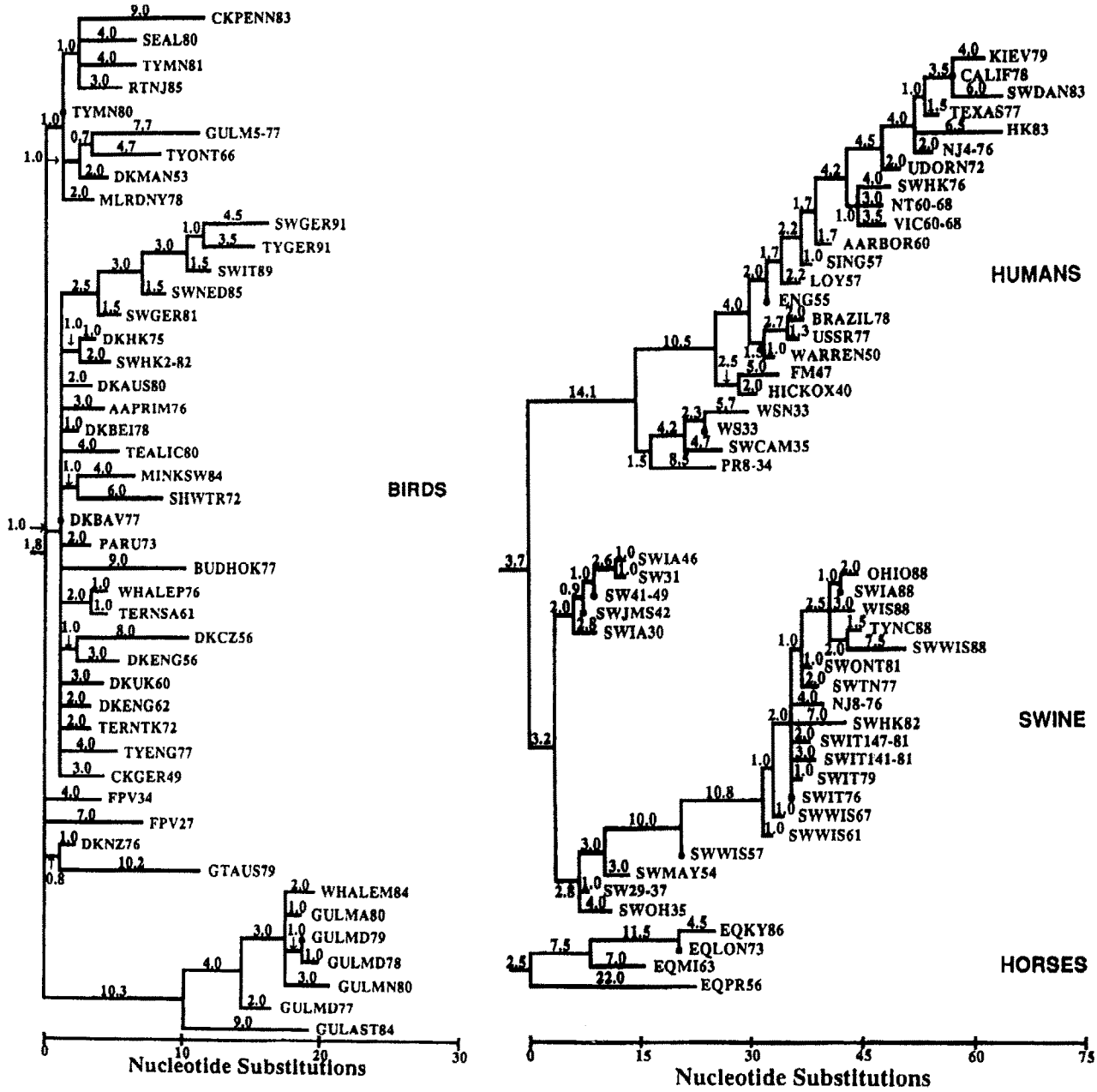

Figure 3. Most parsimonious tree for the amino acid sequences of 100 influenza A virus nucleoproteins [4]. Only non-silent nucleotide substitutions were used for calculation. The two major branches 'birds' and 'mammals' have a common root. Numbers on the tree are the numbers of substitutions required by the strict parsimony procedure. The major abbreviations for the animal strains are: SW swine; EQ equine; DK duck; CK chicken; TY turkey; GUL gull. The human strains do not carry such an abbreviation. The letters thereafter determine the site of isolation: WIS Wisconsin; NJ New Jersey; ENG England; GER Germany; AUS Australia; etc. The two numbers at the end determine the year of isolation. E.g. CKPENN83 A/chicken/Pennsylvania/83.

Establishment of a new swine virus lineage in 1979 in Northern Europe

Northern Europe was free of swine influenza up to 1979. However, in the winter 1979/80 influenza outbreaks in pig farms were registered in many places in this area. The viruses isolated from diseased pigs turned out to be of avian origin [12, 13]. As can be seen in Figure 3 on top of the Eurasian bird branch, these swine viruses from Europe have established now a new stable lineage with an extremely fast evolutionary rate. They are still related enough to avian viruses to be able to enter the bird population, e.g. causing great economical losses in turkey breeding farms in Germany and Holland [14]. This situation is reminiscent to that of about 100 years ago, and we should watch out where these new 'avian-like' swine viruses go next. If they show up in the human population we might have a situation comparable to that immediately before the Spanish Flu. However, this time we might be prepared by having a corresponding spilt vaccine available.

References

1. Scholtissek C, Rhode W, von Hoyningen V, Rott R. On the origin of the human influenza virus subtypes H2N2 and H3N2. Virology 1978; 87: 13–20.
2. Hinshaw VS, Webster RG. The natural history of influenza A viruses. In: Beare AS, ed. Basic and applied influenza research. Boca Raton, Fl: CRC Press, 1982: 79–104.
3. Scholtissek C. Pigs as 'mixing vessels' for the creation of new pandemic influenza A viruses. Med Principles Pract 1990; 2: 65–71.
4. Scholtissek C, Ludwig S, Fitch WM. Analysis of influenza A virus nucleoproteins for the assessment of molecular genetic mechanisms leading to new phylogenetic virus lineage. Arch Virol 1993; 131: 237–250.
5. Webster RG, Bean WJ, Gorman OT, Chambers TM, Kawaoka Y. Evolution and ecology of influenza A viruses. Microbiol Rev 1992; 56: 152–179.
6. Scholtissek C, Bürger H, Kistner O, Shortridge KF. The nucleoprotein as a possible major factor in determining host specificity of influenza H3N2 viruses. Virology 1985; 147: 287–294.
7. Shortridge KF, Stuart-Harris CH. An influenza epicentre? Lancet 1982 (ii): 812–813.
8. Scholtissek C, Naylor E. Fish farming and influenza pandemics. Nature 1988; 331: 215.
9. Gammelin M, Altmüller A, Reinhardt U, Mandler J, Harley VR, Hudson PJ, Fitch WM, Scholtissek C. Phylogenetic analysis of nucleoproteins suggests that human influenza A viruses emerged from a 19th century avian ancestor. Mol Biol Evol 1990; 7: 194–200.
10. Gorman OT, Bean WJ, Kawaoka Y, Webster RG. Evolution of the nucleoprotein gene of influenza A virus. J Virol 1990; 64: 1487–1497.
11. Gorman OT, Bean WJ, Kawaoka Y, Donatelli I, Guo Y, Webster RG. Evolution of influenza A virus nucleoprotein genes: Implications for the origin of H1N1 human and classical swine viruses. J Virol 1991; 65: 3704–3714.
12. Scholtissek C, Bürger H, Bachmann PA, Hannoun C. Genetic relatedness of hemagglutinins of the H1 subtype of influenza A viruses isolated from swine and birds. Virology 1983; 129: 521–523.
13. Schultz U, Fitch WM, Ludwig S, Mandler J, Scholtissek C. Evolution of pig influenza viruses. Virology 1991; 182: 61–73.
14. Ludwig S, Haustein A, Kaleta EF, Scholtissek C. Recent influenza infections in turkeys and pigs in Northern Europe. In: Hinshaw VS, Easterday BC, eds. Proceeding of the Third International Symposium on Avian Influenza: Madison, Wi: Extension Duplicating Services, University of Wisconsin, 1993: 131–135.

Address for correspondence: Prof. Dr. Ch. Scholtissek, Institut für Virologie, Justus Liebig Universität, Frankfurter Strasse 107, D-35392 Giessen, Germany
Phone: +49 641 702 4990; Fax: +49 641 239 60