Committee 3
The Threat of Epidemics

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The Spanish Flu - a Pandemic with Extension to an Arctic Norwegian Community

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Clinical Symptoms

Influenza is a disease caused by specific viruses which spreads through the respiratory tract.. Clinically, the symptoms appearing after an incubation period of 1 - 2 days follows exposure to the virus start abruptly with fever (38-41 °C within 12 hours of disease onset), chilliness or frank shaking chills, headaches, aching muscles, fatigue, malaise, and anorexia. In addition to these systemic symptoms, other evidence are from the respiratory tract and eyes. The former are particularly troublesome dry cough, nasal discharge, developing to nasal obstruction, hoarseness, sore throat, the latter are such as burning eyes, photophobia, tears, and pain upon eye movements. In previously healthy, particularly young patients, the fever is lowed by 0.5-1 °C after 1-2 days. The fever lasts 3-5 days. In elderly and patients with predisposing ailments, bacterial pneumonia may develop and accordingly cough with mucous, sputum and cyanotic lips, and rales upon breathing plus feeling of lack of breath (dyspnoea). Bacteria causing pneumonia in influenza patients may occasionally be present in the normal microflora of the respiratory tract. such as Haemophilus influenzae, pneumococci, and staphylococci (Staphylococcus aureus). The last bacterial species may produce an enzyme (protease) enhancing the infectivity of influenza virus.

A few other viruses can cause symptoms similar to those in influenza. The precise diagnosis requires laboratory confirmation, either by cultivation of the virus (from in samples of the respiratory tract), detection of virus by direct methods (antigen based) or from determination of a significant rise in anti-influenza antibody in blood specimens

taken 1-7 weeks apart.

Virus Structure

The virus is sphaerical with a diameter of 100-200 nm, or filamentous with a length up to 1000 nm, and spikes protruding into the surroundings. The genetic material is RNA (ribonucleic acid - as opposed to DNA (deoxyribonucleic acid) in many other viruses and all living organisms (animals, plants, protozoae, fungi)). Protecting the RNA is an inner protein shell and outside a lipoprotein membrane from which the spikes emerge. The spikes are of two types and carry either haemagglutinin (HA) (80 % of the spikes) or neuraminidase (NA). Both are antigens and play central role for the infectious process.

The HA is responsible for attaching the virus particles to the epithelial cells of the respiratory tract lining, these are the primary viral target. The HA is involved in viral invasion into the host cells. It determines virulence of the strain of virus involved in a particular epidemic. In order to initiate the chain of events leading to viral reproduction, the viral HA is cleaved by a protease produced by the infected cell.

The NA destroys a component of the host cell membrane, neuraminic acid (= sialic acid). This component constitutes part of the influenza virus receptor; NA may play a role in attachment. But the major function of NA is to assist in the release of the new lot of viruses produced within the host cell.

Each virus contains RNA polymerase, an enzyme responsible for translating the genetic information on the RNA into the enzymes and components necessary for the production of new viruses.

Three distinct groups of influenza viruses are recognized, types (or species) A, B and C. Types A and B, are the most important for infections in humans. These are distinguished serologically (based on antigenic differences - the composition - of viral constituents, i.e. the matrix (M antigen) and nucleoprotein (NP antigen). The different HA and NA antigens of type A influenza virus have been given sequential numbers (since 1980), H 1 - 13 and N 1 - 9.

Only H1, H2 AND H3 and N1 and N2 are known to infect humans. Several other species of animals may be infected by influenza viruses, e.g. swine and birds. Avian influenza virus attack chicken, geese, and ducks.

Antigenic Variation

To non-microbiologists, it might appear that the above details about the virus are somewhat superfluous. However, this knowledge is required to understand why influenza type A occurs as epidemics with different ability to spread within the population and to kill patients, and at times become so rampant that a global epidemic (= pandemic) develops.

In the Northern hemisphere seasonal influenza usually occurs between December and February; this is the case in Norway, for example. The seasonal different incidence of influenza is often associated with small changes in the HA and NA antigens. As a consequence, the immunity against previously infected patients is low against a new seasonal strain of the virus. Relatively small antigenic changes are called antigenic drift and are caused by mutations leading to minor modifications of the HA and NA antigens involved in attachment of the viruses to respiratory tract epithelial cells.

Mutations of viral RNA occur some 10,000 times more often than mutations of DNA in animals or viruses.

Occasionally, substantial changes occur. These are called shift. A shift is possible because the RNA of type A virus is distributed between 8 separate portions, strands. These may be exchanged if one and the same individual is infected simultaneously by several virus strains. Such reassortment, if occurring in animals which, in certain parts of the world, live in close association with man may have particular consequences for humans. If a double infection occurs with a viral strain of human and another of animal origin the resulting virus may be strikingly different from the strains previously in general circulation. Reassortment occurs at unpredictable intervals. If the result involves either HA or NA, or both, the resulting virus has advantage over viruses to which the general population has already developed immunity. Accordingly, a major antigenic change of HA alone or together with NA represents a shift which is the basis of why, suddenly, the population has become non-immune to a strain of influenza virus and, consequently, may fall victim to widespread and dangerous epidemics of influenza A. Mutations responsible for antigenic drift involves change of only 1-3 amino acids in the viral proteins and, accordingly, have relatively smaller consequences, less antigenic differences between the viruses and, in turn, a lesser impact on immunity within the population; the consequences are mainly relatively localized epidemics (see Table 1).

Epidemiology

The genetic variation of influenza viruses makes the emergence of influenza unpredictable and constitute formidable danger to world public health. Shifts have been responsible for influenza pandemics, occurring in 1890, 1918, 1957, 1968, and

1977.The pandemics have been called the Spanish Flu (1918), Asian Flu (1957), Hong Kong Flu (1968), and Russia Flu (1977). The incident in Hong Kong in December 1997/January 1998, which involved slaughter of 1.2 million poultry was due to a strain of H5N1 which resulted from reassortment between an avian and a human strain of influenza virus; the result was only 18 human cases because the new virus had insignificant infectivity in man. In 1976, an epidemic in the US was caused by a strain of the dreaded swine type H1N1; this had the same antigens as the Spanish Flu virus, and therefore caused considerable scare. The result was a massive vaccination campaign involving 40 mill. Americans. This event, perhaps, had political overtones in the US in that the massive campaign showed that the incumbent candidate who took initiative to have the congress fund mass vaccination showed great concern for the population and an implied advantage in the concurrent presidential campaign.

Since 1977, type A strains of H1N1 and H3N2 have occurred in parallel; type B has a lesser incidence and tends to attack young children. Influenza type C infects during childhood but mostly without causing significant illness.

The all time most devastating influenza epidemic has been the Spanish Flu pandemic in 1918. World wide it caused disease in proportions of the population unparalleled since the Black Death . The Spanish Flu killed an estimated 20-40 mill. people, far more than those who lost their lives in both World Wars I and II. In Europe, 2.6 million deaths has been proposed. It is possible that the pandemic started in Asia, as typical of the pandemics (including the one labelled Russian Flu in 1977) , but by consensus the first recorded case occurred in March 1918 at a military camp (Camp Funston) in Kentucky, USA. Within weeks and months, it spread all over the US. Ultimately, he troop transports brought the virus across the Atlantic to the European battle fields - as

well as to the civilian populations.

Three "waves" in the Spanish Flu have been described. The first started with the case at Camp Funston in the US. The "second wave" followed spread with US troops to Europe. The spread was explosive. The "third wave" took placed towards the end of 1918 after the disease had abated, and the early part of 1919.

Viral Spread

Spread of influenza virus between individuals occurs through the air (coughing, sneezing) and between geographical are as in a function of travel. A well documented example is how the virus spread to Africa. This occurred when a British navy ship brought the virus to Freetown, Sierra Leone, where the first African epidemic took place.

Why Called the Spanish Flu?

The warring nations the US, Britain, France, Germany, Austria suffered considerable losses among its troops but put a cap on information of military consequence. Accordingly, for the international audience, the first well documented occurrence of this as a medical disaster of unparalleled proportions, both in terms of incidence and mortality, was reported from Spain. Hence the pandemic has become known as the Spanish Flu. The disease spread to Spain after it emerged in the US or the UK, so the term is actually a misnomer, or to put it in modern terms consistent with the context and implication, the term Spanish Flu represents a blatant example of political (or military) disinformation.

Spanish Flu in Norway

In Norway, the Spanish Flu caused some 13-15,000 deaths among a population of 2.6 million. The registered number of deaths officially reported by doctors at the time as deaths ascribed to influenza was 7308. However, this figure has been reassessed by statistical procedures applying modern data upon precise laboratory determination of the cause. The number of deaths in 1918 was 5.2 times the numbers registered in "normal" years before and afterwards. The reported total number of diseased, regardless of outcome, was 375,000. If this is doubled as well, we deal with an incidence of 30 % for the influenza epidemic of 1918 ! This is some 10-15 times the usual incidence of a seasonal, epidemic flu.

To put the 1918 epidemic in context, the Black Death in 1349-1350 notably wiped out an estimated 1/3 - 2/3 of the Norwegian population. The Spanish Flu had a death rate of somewhere between 0.46 and 0.57 %, the latter being more likely the correct one.

The first known cases of the flu in Norway occurred in capital city on June 15, 1918. By the end of June and beginning of July, the disease had reached epidemic proportions. This happened at a time of the year when influenza is highly unusual, since this its prime incidence ordinarily occurs in December - February in our country. Oslo (then Christiania) got the epidemic before other major Scandinavian cities like Copenhagen, Gothenburg or Stockholm; consequently it has been presumed that the infective agent came by ship from across the North Sea from the British Isles. The commercial and cultural ties at the time were very close between the other important sea fearing nation on the British Isles, perhaps more than between Norway and the European Continent. The disease occurred first and foremost among the population in areas with major movement of people, along the coast and along railroad tracks. Spread by ship was

also responsible for the disease in Svalbard.

Spanish Flu in Arctic Norway

Svalbard is situated in the Arctic, at 80 degrees Northern latitude. The predominant reason why people lived there at the time was coal mining and hunting. The population at the biggest settlement Longyear City comprised 263, including 37 women and children.

In July 1918, a ship brought the virus to a Swedish mining community at a place called Svea and all inhabitant got sick. At Longyear City, the epidemic virus was also brought by sea; it started on July 8 and was finished by August 5. On July 29, only 20 of the miners reported for work. Incidents at other small hunting stations occurred throughout August. A total of 5 coffins were shipped back to Tromsø, Norway during early September.

Then, on September 21, a ship left Tromsø for Longyear City with 69 healthy young people who were planning to spend the winter in order to earn good money as miners at this remote place. The crew on the ship "Forsete" had all been sick earlier during the summer, and did not succumb to the disease during this crossing, but all the 69 miners got sick during the two days of passage to Longyear City. Some were so sick that they were brought straight to the hospital (with a licensed physician!), but most of the passengers were simply boarded in the miners' barracks. The quarters were rather cramped. There were three bunks above each other and 0.6 - 1 meter between the beds. Consequently, some 80 % of those in the mining community got sick, those who had not been sick earlier that summer. On September 29, the ship returned to Norway and on board were 29 reconvalescents who returned, either on their own accord or

upon the doctor's assessment. Subsequently, the sea soon froze and further communication by sea became impossible for the remainder of that season, until May the following year. During the following days, during October 1 - 7, seven patients died. The physical condition among those remaining was such that they did not bury the corpses until October 27, when a three week period had elapsed since the last death and they considered that the chance of further cases, and perhaps of spreading the infecting agent, was minor.

Information "Buried" at Svalbard

Because influenza virus has only been isolated and cultivated since 1933, information about the very virus itself which has caused the most devastating influenza pandemic is scant. Because the miners buried at Svalbard were presumed to have been lying in the permafrost for the last 80 years, it was thought that the epidemic in Longyear City offered a unique opportunity for obtaining crucial information about the virus. Consequently, it was decided to exhume the bodies. International organiser has been Dr. Kirsty Duncan, who first conceived the idea of the project.

After detailed planning, we received formal permission from the Norwegian heritage and health authorities to exhume 6 bodies and contracted an English company, called Necropolis, to do the ground work under the leadership of Mr. Alan Heginbottom (Canada). The core Norwegian team also includes Professor Bjørn Peter Berdal. The team involved in the exhumation was truly international, Professor Charles Smith, who as forensic pathologist was in charge of taking specimens, and, for virology and financial support Professor John Oxford (UK), Dr. John Skehel (UK), and Professor Robert Webster (USA). Dr. Rod Daniels agreed to carry out the actual laboratory work on the specimens in his laboratory (WHO Reference Center for Influenza, London, UK),

which carries certification at the highest grade of security (biohazard laboratory grade 4) and as such is suitable for even the most dangerous infectious agents. This degree of a containment laboratory was deemed necessary for the possibility that any live virus of this devastating kind were still viable; this safety margin was incorporated in spite of the fact that the likelihood that this could be the case was actually considered extremely low, since storage had been under clearly suboptimal conditions for as long as 8 decades.

Before the exhumation was carried out during August -September, 1998, Mr. Les Davis (Canada) carried out a ground penetrating radar scan across the graves - in order for us to determine whether there were still coffins in the ground, where they were positioned, and at what depth. On the basis of these studies, we thought the coffins would be positioned at a depth of 2- 2.5 m under the ground surface.

Official permission from Norwegian heritage and health authorities to carry out the exhumation followed detailed description of procedures and safety measures. This included ascertaining that the local hospital had an appropriate modern containment unit with suitable atmospheric sluice suitable for isolation of epidemic patients. The surgical and medical hospital facilities were suitable for any untoward event that could occur as a consequence of the exhumation. In consideration of the scant arctic fauna and its susceptibility to ground work of our proportions we had to make certain that there would be no trace of the exhumation after we finished our work. The circumstance that a grave yard was involved entailed particular ethical considerations; the ecclesiastical and heritage officials had their legitimate concerns which we needed to deal with appropriately. The descendant of those buried had to give permission.

Table 1. Influenza virus. Changes in antigenic constitution, year of occurrence and genetic mechanism

Antigen	Year	Genetic change
		Drift
H1N1	1890	Shift
		Drift
H1N1	1918	Shift (Spanish)
		Drift
H2N2	1957	Shift (Asian)
		Drift
H3N2	1968	Shift (Hong Kong)
		Drift
H1N1	1977	Shift (Russian)
		Drift
H5N1	1997	Shift (18 cases, HKG)
		Drift
?	?	Shift