Could influenza be a possible biological warfare agent? Part II

Czy grypa jest możliwym czynnikiem broni biologicznej? Część II

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Abstract: The threat of the use of biological weapons in the current terrorist reality becomes more real. Thus, understanding the present state of knowledge in the early detection of biological warfare agents, including the flu virus, and the possibility of conducting effective virological analyses, becomes a necessity for laboratory diagnosticians, physicians and nurses. The plans to prevent the consequences of a potential biological attack can only be based on the interpretation and extrapolation of hypothetical data, experimental data or can be based on events from the past. The preparation for this threat, which may or may not occur, requires sound knowledge of the causative agent. Spraying such a causative agent in an aerosol form is considered to be an especially dangerous action in the bioterror as it carries a risk to large populations of the people affected. Hypothetical objects of the attack can include places of special population density. Critical places to perform an attack using biological aerosols are highly urbanized areas, which have efficient air conditioning systems (public buildings and subway stations). This paper was presented as a oral presentation of the same title at The International Conference – Advances in Pneumology. October 25–26, 2013 Kassel, Germany [1].

Streszczenie: Współcześnie zagrożenie użyciem broni biologicznej staje się coraz bardziej realne. Z tego powodu znajomość obecnego stanu wiedzy w zakresie wczesnego rozpoznawania czynników broni biologicznej, w tym również grypy, a następnie możliwości skutecznego prowadzenia analiz wirusologicznych staje się koniecznością dla diagnostów laboratoryjnych, lekarzy wszystkich specjalności i pielęgniarek oraz przyszłych adeptów tych zawodów. Plany zapobiegania następstwom potencjalnego ataku biologicznego mogą się opierać jedynie na interpretacji i ekstrapolacji danych hipotetycznych, doświadczalnych lub zdarzeń z przeszłości. Przygotowanie się do tego zagrożenia, które może, ale nie musi, nastąpić, wymaga ugruntowanej wiedzy o czynniku sprawczym. Rozpylenie takiego czynnika sprawczego w formie aerozolu uznaje się za szczególnie niebezpieczne działanie w wojnie biologicznej, ponieważ stanowi ono zagrożenie dla dużych populacji ludzi. Obiektami hipotetycznego ataku mogą być miejsca o szczególnym zagęszczeniu mieszkańców. Newralgicznymi miejscami do przeprowadzenia ataku z użyciem aerozoli biologicznych są wysoce zurbanizowane tereny z wydajnymi systemami klimatyzacyjnymi (budynkami użytku publicznego i stacjami metra). Pracę pod tym samym tytułem w formie ustnej prezentacji przedstawiono 25–26 października 2013 r. na międzynarodowej konferencji „Advances in Pneumology" w Kassel (Niemcy) [1].

Key words: influenza, prophylaxis, bioterrorism, biological weapon, threat
Słowa kluczowe: grypa, profilaktyka, bioterroryzm, broń biologiczna, leczenie

Introduction

Terrorist activities have been used for centuries as an effective tool in the fight against a stronger opponent. In the 20th and early 21st century terrorism became one of the most dangerous phenomena affecting safe world order [2, 3]. Although this trend is almost as old as mankind, nowadays, unlike in the past, terrorists have improved and brutalized their methods of operation, and through the internationalization of their acti-

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vities they threaten safety on a regional, national and even global level [2, 4]. One of the forms of terrorism is the use of biological means of warfare. The available literature shows that several countries are constantly developing technologies which can be used to produce biological weapons, and about 20 countries are suspected of having such weapons and the means of transporting them [5, 6]. The paradox is that among these countries there are also those that signed and even ratified the Convention of 1972 on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, and are also signatories to the Geneva Protocol of 1925 [2, 7].

One of the biological weapons threats which could be used on a global scale by terrorists is the human influenza virus. The purpose of this paper is to present the characteristics of the human influenza virus in order to justify concerns pertaining to its potential use by terrorists.

Influenza – general information

Influenza is a viral disease commonly occurring all over the globe. The possibility of its spread has been proven by the pandemic of a dangerous form with complications, which occurred after World War I [8, 9]. These complications include bronchitis and pneumonia, the exacerbation of symptoms of chronic respiratory infections, sinusitis, myocarditis, encephalitis, inflammation of the muscles, obstetric complications, diarrhea and vomiting, and secondary bacterial infections.

Epidemiological risks in the case of influenza, and using influenza as a potential biological weapon, is connected with the fact that the health care system is burdened with a large number of patients, and an impaired social system as a result of mass absenteeism due to illness [8, 10, 11].

Therefore, it is very important to implement effective prevention methods by which the risk of the disease spreading and the spread of epidemic influenza can be reduced.

Breakdown of biological threats

Pathogens that may be used in a bioterrorist attack are microorganisms that have the ability to infect the object of their attack, which is a eukaryotic host, and to grow in it. These steps lead to the formation of clinically recognizable diseases that kill the host or cause an inability or an impairment of the ability to perform normal bodily functions [2, 12]. The definition presented in this way is very general in nature because it needs to be adapted to different cases of potential bioterrorist attacks aimed directly against humans, animals or plants with economic implications [2].

Microorganisms which can be used as agents in a biological attack, called mass destruction biological agents, can be used to achieve the objectives listed below:

- military (biological warfare)
- terrorist
- criminal.

The American Center for Disease Control and Prevention (CDC) has divided the biological threats that could be used by terrorists into four groups: A, B, C and D [5, 13].

Group A: the most dangerous pathogens, with high morbidity and mortality, and the ability to spread rapidly. This group includes the smallpox virus (*Variola virus*), anthrax (*Bacillus anthracis*), plague (*Yersinia pestis*), tularemia (*Francisella tularensis*), botulism (*Clostridium botulinum* toxin), viral hemorrhagic fever – filoviruses (e.g., *Ebola*, *Marburg*) and arenaviruses (e.g., *Lassa*) [2, 3].

Group B: factors that cause moderate morbidity and mortality, and with a moderate rate of spread. These include some of the factors that cause diseases in animals (Q-fever *Coxiella burnetii*, brucellosis – *Brucella*, glanders – *Burkholderia pseudomallei*, Psittacosis – *Chlamydia psittaci*), diseases caused by food pathogens (Salmonelloses – *Salmonella*, dysentery – *Shigella dysenteriae*, dysenteries – *E. coli*, cholera – *Vibrio cholerae*, toxin – *Clostridium perfringens*), staphylococcal enterotoxin B – *Staphylococcus aureus*, encephalitis viruses (equine, Venezuelan, Eastern and Western encephalitis) and ricin toxin (*Ricinus communis*) [2, 3].

Group C: pathogens which in the future may be subjected to genetic engineering research for easy production and rapid spread, with a high morbidity and mortality rate, e.g. the hantavirus [2, 7].

Group D: a group which consists of pathogens that will probably never be used as biological weapons. This group includes the influenza virus, which is very easy to identify epidemiologically, and HIV, because of the long latency period. Although the viruses mentioned in this group are not included in the high-risk group, it seems that they may be particularly important and dangerous from the point of view of criminal cases, especially in analyzing influenza. The purpose of a criminal bioterrorist attack is to cause fear and

panic among the population (including rescue teams), and chaos in many areas of society, along with economic losses [2, 7, 10]. In this case, not only will it cause great panic or psychosis in the community, but it might also lead to aggressive behaviour directed against authorities exercising power.

The characteristic features of a bioterrorist attack with the influenza virus and the emergence of infections.

The occurrence of a biological attack with biological weapons, including the influenza virus, may be suspected in the following occurrences:

1. High morbidity and death rates in a short period of time, with symptoms similar to those of influenza.
2. Occurrence in a particular area where such cases are extremely rare or unrecorded.
3. Poor response or lack of response to routine medical treatments for the occurring disease (severe diseases), which may mean that terrorists are using a new, previously unknown mutation of the influenza virus.
4. The occurrence of cases with atypical symptoms or among the vaccinated population (which indicates a genetic modification of the virus).
5. The occurrence of even a single case of the disease in a person who has not recently been in contact with the environment where there is an influenza epidemic.
6. An unexplained increase in incidences of endemic disease.
7. Mass murrain in farm animals (influenza in pigs or birds).
8. The appearance of dust or mist after the flight of a foreign aircraft.
9. Unusual methods of transmitting diseases (e.g. through an aerosol spray) [5].

Table 1. *The type of clinical material, depending on the direction of research.*

Type of test	Type of clinical material
Determination of anti-hemagglutinin antibodies towards selected strains of the influenza virus (type/subtype)	Serum[1]
Detection of the influenza virus (types A and B) and other respiratory viruses by using the RT-PCR method	Throat swab[2] Nasal swab[2] Nasopharyngeal swab Aspirate or nasopharyngeal lavage Nasal lavage Bronchial system lavage[3] CSF[4] Middle ear effusion[5]

[1] For the correct interpretation of the results, the test should be made for a pair of sera, i.e. for serum from an acute period of the disease and serum collected during convalescence.
[2] It is recommended to provide a combination of the test sample, i.e. a swab from the throat with nasal swabs.
[3] In the case of a lower respiratory tract infection.
[4] In the event that there are complications associated with the nervous system.
[5] In the case of otitis media.

Tabela 1. *Rodzaj materiału klinicznego w zależności od kierunku badań.*

Rodzaj badania	Rodzaj materiału kilnicznego
Oznaczenie poziomu przeciwciał antyhemaglutyninowych w kierunku wybranych szczepów wirusa grypy (typ/podtyp)	Surowica krwi[1]
Wykrywanie wirusa grypy (typ A i B) oraz innych wirusów oddechowych metodą molekularną RT-PCR	Wymaz z gardła[2] Wymaz z nosa[2] Wymaz z nosogardzieli Aspirat lub popłuczyny z nosogardzieli Popłuczyny z nosa Popłuczyny z drzewa oskrzelowego[3] Płyn mózgowo-rdzeniowy[4] Wysięk z ucha środkowego[5]

[1] Aby właściwie interpretować wyniki, badanie powinno zostać wykonane dla pary surowic, tj. surowicy z ostrego okresu choroby, a następnie surowicy pobranej w okresie rekonwalescencji.
[2] Wskazane jest dostarczenie łączonej próbki do badań, tj. wymazu z gardła wraz z wymazami z nosa.
[3] W przypadku zajęcia dolnych dróg oddechowych.
[4] W przypadku powikłań ze strony układu nerwowego.
[5] W przypadku zapalenia ucha środkowego.

One of the possible scenarios for implementing protective measures in the case of a bioterrorist threat involving influenza

In Poland, as in other countries, and not only in Europe, it is necessary to take into account the issue of biological hazards in the emergency response system. It is important to organize the system for the detection and identification of biological warfare threat agents, including influenza, in such a way as to involve various health services, medical services and laboratory diagnosticians, as well as the fire brigade, the police and the army. The system should include:

1. Epidemiological surveillance, allowing for the quick analysis of data concerning the threat, and the rapid spread of information about influenza cases, showing the increased incidence in certain parts of the country and the world.
2. Teams of specialists, e.g. biological reconnaissance groups, whose tasks would include taking appropriate samples of a potential infectious material. Table 1 shows the type of clinical material depending on the direction of the research.

An important element of the procedure is proper preservation when sending the collected samples to the appropriate laboratory.

1. In the case of Poland it would be a territorially appropriate branch of the Provincial Sanitary-Epidemiological Station.
2. The Influenza Virus Research Institute, the National Center for Influenza at the National Institute of Public Health and the National Institute of Hygiene, which in this case acts as the diagnostic coordinator.
3. A network of laboratories adequately equipped and capable of performing quick identification of the pathogen by using the most modern diagnostic techniques. It would be best if the laboratories had Biosafety Level 3 (BSL-3).
4. A team of highly qualified specialists (virologists), who are laboratory diagnosticians and would be able to take care of the training center established in the case of a biological threat. It would be the best if such an organization was integrated into the reference laboratory. In the diagnosis of influenza such a function is performed by the WHO Collaborating Center at the Influenza National Institute for Medical Research in London. The tasks of this group would include carrying out training, testing equipment and developing and standardizing procedures, as well as developing information and training materials through the activities of the National Centers for Influenza.

The presented system of services for the recognition and identification of pathogens should cooperate with emergency response centers at the level of the provinces and similar structures formed at government level. In an efficient system of defence against biological weapons the authorities and technical measures should also be taken into account to eliminate the consequences of the use of these weapons. This applies to individual deactivation, collective deactivation and environmental remediation. In the case of influenza it would also concern the organization of first aid, segregation and transportation of patients, maintaining readiness and opportunities to develop appropriate hospital facilities, the training of medical and non-medical personnel, including fire service, police and civil defence, and securing an adequately large supply of medicines and vaccines against influenza.

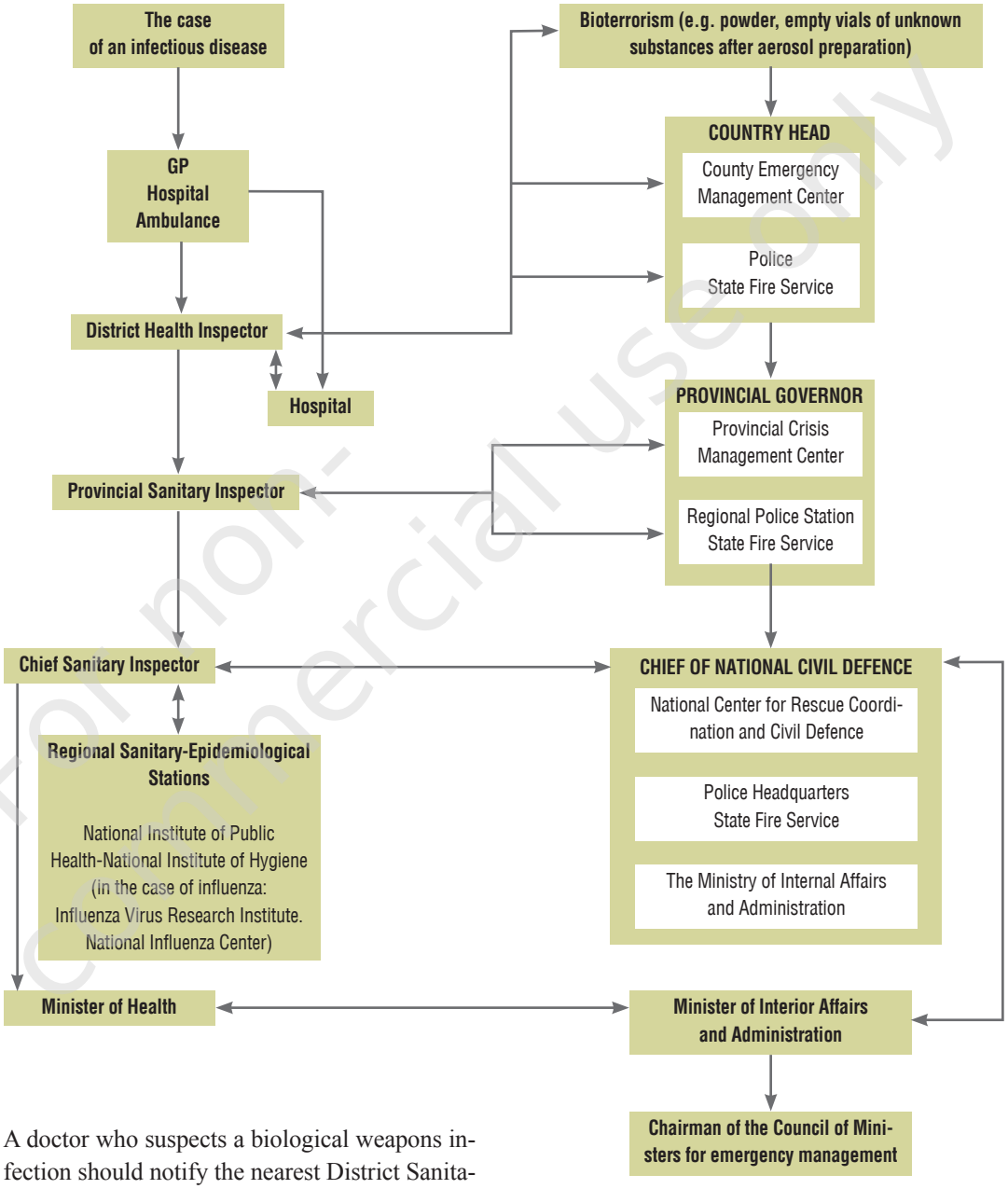
Among scientific experts there has long been the conviction that a global influenza pandemic is inevitable and that the world is not well prepared for it [5, 2, 8]. In the event of a threat, not only related to terrorist use of the influenza virus but also of a pandemic that emerges in a natural way, it is important to have a professional programme developed to give notification of the emerging threat. In the case of incidences and suspected cases of influenza, the integrated epidemiological surveillance system SENTINEL would be helpful. It has been used in Poland since 2004 [14], and is coordinated, as far as virological surveillance is concerned, by the National Center for Influenza, operating in the Influenza Virus Research Institute, the National Institute of Public Health – National Institute of Hygiene in Warsaw. In this case the data provided in the MZ-55 forms, which are analyzed in the Department of Epidemiology, NIPH-NIH, would also be helpful.

Figure 1 below shows a sample structure of notification and cooperation in an emergency related to a dangerous infectious disease and/or bioterrorism.

In accordance with the presented elaboration the following should be performed:

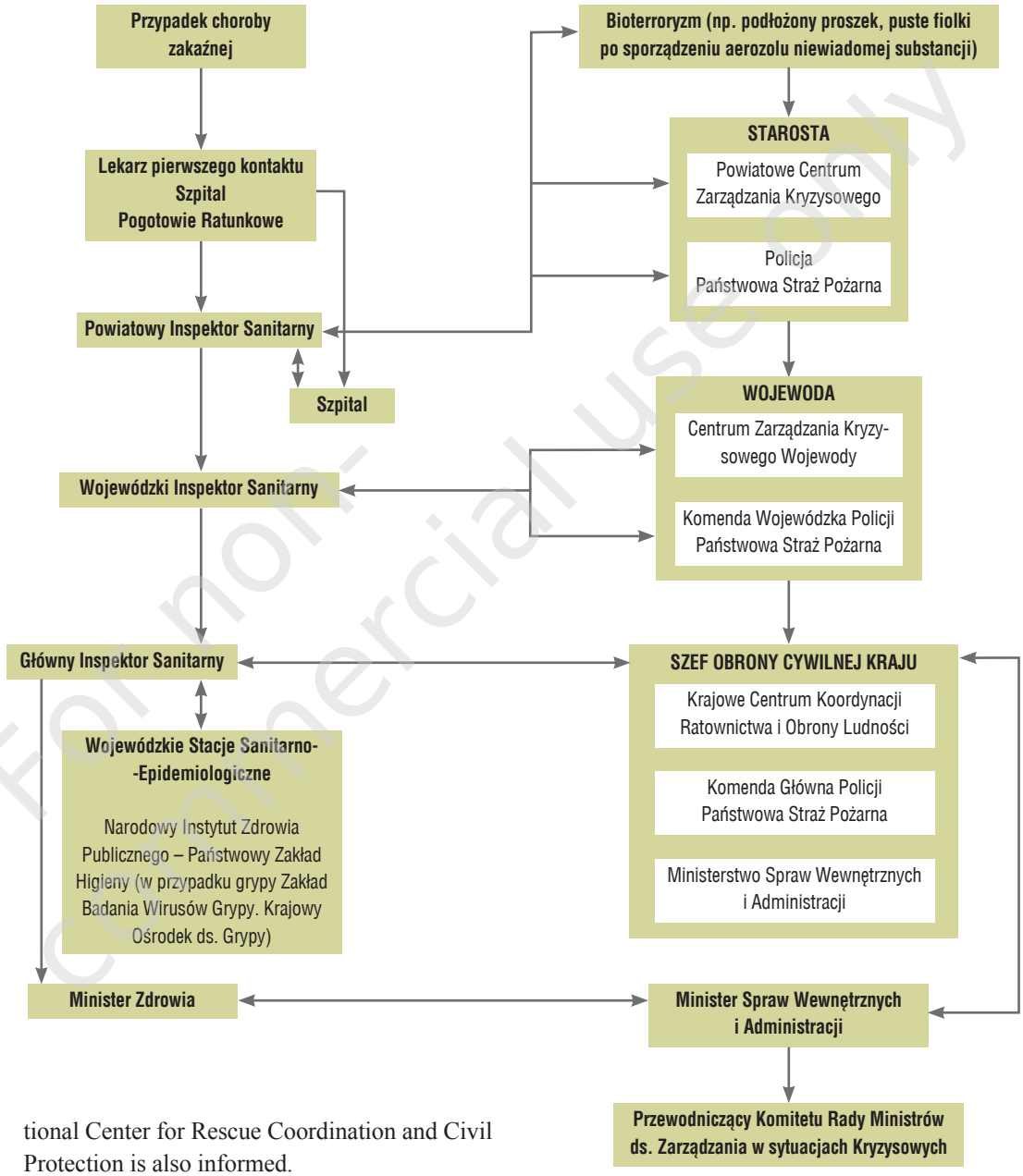
1. An incidence or suspected incidence should be reported to the following:
   – a GP
   – a doctor from the medical emergency services if the patient requires immediate medical attention
   – a hospital doctor.

Figure 1. *A diagram showing the system of notification and collaboration in the case of an emergency arising from the outbreak of an infectious disease and/or the bioterrorist attack associated with it [3].*



2. A doctor who suspects a biological weapons infection should notify the nearest District Sanitary Inspector about this fact.
3. In the case of contact with suspected biological material (powder, empty vials of an unidentified liquid or substance) the police or fire department must be notified.
4. The District Sanitary Inspector is obliged to inform the Provincial Sanitary Inspector, the District Crisis Management Center, Police, State Fire Service and the management of the nearest hospital. Each service is obliged to inform the relevant authorities according to the schedule.
5. In the case of a threat of a dangerous infectious disease and/or bioterrorism, the Provincial Sanitary Inspector is responsible for notifying the Chief Sanitary Inspector, the Provincial Crisis Management Center, Regional Police and the State Fire Service.
6. The Provincial Crisis Management Center must notify the National Center for Rescue Coordination and Civil Protection.
7. The Chief Sanitary Inspector must notify the Minister of Health and the National Institute of Public Health – National Institute of Hygiene. In the case of a threat of influenza this information is sent to the Influenza Virus Research Department. National Influenza Center. The Na-

Rycina 1. *Schemat powiadamiania i współpracy w przypadku zagrożenia wynikającego z pojawienia się choroby zakaźnej i/lub ataków bioterrorystycznych z nią związanych [3].*



tional Center for Rescue Coordination and Civil Protection is also informed.

8. The Minister of Health and the Chief of National Civil Defence must inform the Minister of the Interior.
9. The Minister of the Interior must notify the Committee Chairman of the Council of Ministers for Crisis Management.

The probable impact of an influenza pandemic on world business

A great influenza pandemic is not presently perceived to be so important or real a threat as to justify additional investment in protective measures against influenza, and this may later have disastrous consequences. According to general information provided by the World Health Organization (WHO) in 2007, the result of an influenza pandemic would mean 25% of people in the world would fall ill, and employe's absenteeism would reach levels of at least 35%. In this case the actions of the medical services at the beginning of a pandemic, also possibly during several months after the first cases of illness, will be inadequate, while hospitals and other health facilities will not be able to cope with the millions of patients in need of treatment.

Such a picture, associated with the spread of the pandemic throughout the world, does not include

the cost borne by individual economic sectors. For example, airlines and companies related to them are likely to experience a decrease in the number of travelers, which could be caused by travel bans ordered by public health services. Although manufacturers of protective equipment will obtain larger orders, they will be able to increase their sales of products only if they are able to distribute the products through a network of distributors and transport channels, which may be closed due to the spread of the disease. The stock levels at manufacturers, in pharmacies, hospitals, grocery stores, wholesalers, and retailers that receive deliveries in a *just-in-time* system, may be insufficient to meet the demand even if it is very limited as the effects of the pandemic take hold. Costs will accrue rapidly within the global value chain.

It is estimated that the most severe pandemic (mortality rate at 2.21%), resulting in the death of over 140 million people, could lead to a decline in global GDP by $ 4.4 billion [13–15].

Phenomena such as globalization, *outsourcing, offshoring*, quality concern, and the pursuit of more and more effective solutions, have resulted in networks of complex interdependences being created in the economy which are very sensitive to interference. The rate of dependence on key suppliers and the necessary products and services have increased over the last few decades at an exponential rate. The supply chain (formerly a concern mainly of manufacturing industries) now also plays an important role in the service sector, regardless of the type of industry. Disruptions to the supply chain may have a detrimental effect on the stability of stock exchanges and the yield of shares. Considering the scale of the disruptions, as well as their duration, the impact of an influenza pandemic on the supply chain should be considered. The cause of these disruptions is not really important and neither is which sector a given company represents or when the disruptions take place. Any disruption in the supply chain could have harmful consequences for a company.

The threat connected with the influenza virus

In this section the authors present information that is available on the following websites: http://wakenews.net/html/jane_burgermeister.html [17] and the website of an Austrian journalist: http://birdflu666.wordpress.com/2009/04 [18] as well as data contained in the publication by Russell C.A. et al.: The Potential for Respiratory Droplet-Transmissible A/H5N1 Influenza Virus to Evolve in a Mammalian Host. Published in 2012 in *Science* magazine [16].

The following text is only a presentation of the information available from the internet and from the scientific literature. The authors of the paper have not added their own opinions or interpretations in this part.

Recently, increased media coverage can be observed on the variants of avian and swine flu. Among such information is material from an Austrian journalist who has written articles for *The British Medical Journal*, *The Scientist*, *Reuter's Health*, and *The Guardian*. She was a correspondent for Renewable Energy World, a position from which she was fired after she launched a lawsuit against the World Health Organization (WHO) and a number of pharmaceutical companies in 2009 in Vienna, alleging they had conducted organized activities to deprive the life and health of many people by using vaccines containing dangerous additives. According to the journalist, there is evidence that one of the pharmaceutical companies may be part of a secret program connected with the production of biological weapons in the form of a vaccine against avian influenza, and that there are plans to use the avian influenza virus as a biological weapon against people. As evidence of a pharmaceutical company involved in the alleged international secret biological weapons program, the journalist mentions reports on data allegedly confirming that the bird flu virus was created in 1996 by scientists conducting research on biological weapons, and on the virus that caused the influenza pandemic in 1918–1919. According to the accuser, after secret genetic research on the influenza virus a highly dangerous mutation was developed that may be a bioterrorist threat.

Since the mid 1990s the H5N1 virus has been causing fear around the world, which in the context of the presented allegations might be called a form of psychological terror among people. Researchers from the University Medical Center in Rotterdam are said to be on an even more deadly strain causing bird flu. The intention to publish this research has raised concerns among U.S. authorities, who claimed that the report by European researchers could be used by terrorists, for example, and the virus could be used as a biological weapon. The problem is that two teams of scientists have produced dangerous mutants of the avian influenza virus A/H5N1 that may theoretically be spread from human to human and cause a deadly global epidemic, which would have millions of victims. Initially, researchers wanted to publish the results of the work in the scientific press, but the U.S. government asked for a deferment of the publication. In a letter to the prestigious scientific magazine *Science* the Commission for Biosafety suggested that "the description of the methods for

the production of deadly viruses may be used by terrorists". The Commission added that the research done by the scientists is indeed very valuable and can help in the fight against the disease, but that revealing some of the information would do more harm than good. At the beginning of 2012, after a subsequent review, the NSABB finally gave permission for the publication of the research, assessing that the information contained in the scientific publication did not provide information that could be used in bad faith and endanger public health and national security. As the data show, the issue associated with influenza being used as a biological warfare agent, although placed in the Group D standings – factors that will probably never be used as biological weapons, they nevertheless constitute a growing threat that is perceived by both scientists in the international community and journalists, who have a big impact on public opinion, which certainly does not escape the attention of terrorist groups.

Conclusion

Bioterrorism is a multifaceted and dynamic phenomenon, occurring in various forms, from biological contamination to psychological terror. It is difficult now to give a single definition of terrorism as it is changing under the influence of civilization, and especially due to rapid scientific progress. Terrorists adeptly utilize the latest scientific knowledge in their attacks on civilians and military facilities, and certainly know the risks associated with infection by the influenza virus.

The possibility of a disruption in the economic structure of the world supply chain by a pandemic should be taken into account by all companies, especially those that are looking for justifications for making preparations for incidences that in their belief would be associated with the threat of influenza. Analyzing the country projects in which the international business community invests the most in outsourcing activities, it is shown that 70% of them have reported cases of avian influenza, and there was one confirmed case of influenza of avian origin in humans. Assuming that the next pandemic will be caused, at least partially, by the avian influenza virus, especially if the disease spreads through undetected outbreaks of avian influenza in people who work or reside in close proximity with infected poultry, or eat undercooked poultry meat, the great severity of the transmission of the virus from human to human should be expected, as well as the formation of conditions that to a great extent may be conducive to pandemic influenza. In the event that the scale of the disease does not reach a pandemic scale, while the incidences are endemic the population and the economy of the area would still be in a state of constant threat, which in turn could have serious implications for companies operating globally.

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