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Probable Bioweapon: Influenza Type A Virus – A Short Case Report.

Kshitija Iyer* **and Sumalatha Pola**

M.Sc Integrated Biotechnology, Vellore Institute of Technology, Vellore, Tamil Nadu, India

MTech Biotechnology, Satyabama University, Tamil Nadu, India

***Corresponding author:** Kshitija Iyer, M.Sc Integrated Biotechnology, Vellore Institute of Technology, Vellore, Tamil Nadu 632014, India, Tel: +04423760545; E-mail: kshiiyer@gmail.com

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Abstract

Influenza type A virus (Influenza virus A), an old foe of mankind, is presently the most significant pathogen causing both pandemics and epizootics, worldwide. The proliferative husbandry of poultry and pigs, primarily, constitutes a key factor in ongoing generation of pandemic and pre-pandemic strains, which is fueled by remarkable wild aquatic bird permissiveness of the virus. Those attributes are here thoroughly inquired into, so as to profile and rate threat and usability. Also, various human interventions and misuses, including human experimental infections, undesirable vaccinations, as well as unauthorized and unskillful operations, led to bad corollaries and may rather be reassessed and modified or disallowed. Diversified interfaces between influenza and human manners are thereby brought out and elucidated, along with their lessons.

Keywords: Influenza type A virus; Bioweapon; Pandemics; Epidemics; Pathogenicity

Introduction

Influenza pandemics are generated by type A of the causative virus – a prominent anthropozoonotic single-stranded segmented RNA virus (family Orthomyxoviridae: Influenzavirus A) – which is hosted by numerous animal species, chiefly avian. The avian host range of Influenza A Viruses (AIVs) is practically endless, while migratory waterfowl comprise the principal – usually sub clinically infected – reservoirs, carriers and spreaders. Pandemic influenza strains are thought to have primarily emerged about 6000 years ago. Man is a secondary disseminator of pandemic and seasonal strains, while pigs and horses are the main mammalian animal hosts. Sever – at times catastrophic – epidemics within poultry, pig and horse farms are not rare [1].

The recent, 2009 swine-derived flu pandemic virus, broke out 91 years after a previous swine-derived influenza pathogen had formed and had brought about a horrible pandemic. Common denominators marking the two strains – the porcine origin, the H1N1 antigenic subtype, the triple genomic source (swine-human-avian), and the proximate geographical provenance (USA in 1918 and Mexico in 2009) – in contrast to the other non-porcine, moderate Asiatic pandemic strains H2N2 (in 1957) and H3N2 (in 1968), gave rise to fears about the anticipated profile of the then evolving 2009 pandemic [2]. Presently, however, more than two years after the emergence of the 2009 strain, it is fairly clear that its potency is much less intense than its past, 1918 pandemic analogous strain.

Likewise, in a sense, the 14 years that already passed since the initial appearance of the extremely virulent H5N1 strain in 1997 in Hong-Kong, throughout which no transition from endemicity to pandemicity took place, as often wrongly forecasted, apparently indicate that this pathobiologically invasive strain is yet inherently non-contagious among humans, though remarkably transmissible and lethal among chickens and turkeys, at the same time [3]. But the ostensible limitedness exhibited by the H1N1 and H5N1 flu viruses in those two connections, albeit meaningful, might be severely misleading, broadly speaking. The protean nature of IAV makes it, in general, mostly unpredictable all along its history, in many respects. Its innate potency and variance are basically unrestricted, by almost whatever parameter, namely antigenicity, infectivity, transmissibility, pathogenicity, epidemicity and ecogenetics. When biotechnological manipulations are added to this versatile natural profile, the outstanding modularity of that pathogen is further singled out. Either way, it is an extraordinary virus, with unique potential as a warfare agent, both anti-human and anti-animal.

Current herd immunity against IAV, due to natural infections and vaccinations, has for long been reckoned to be a blocking factor that depreciates the usability of this virus as a Biological Warfare Agent (BWA). Also, the pandemics that followed the 1918 one were all mild to moderate in terms of virulence and mortality rates, thus lowering the index of this virus as a weapon. It was therefore inadequately attractive, generally speaking, for many decades to most bio-weaponeers.

During the last two decades, the comprehension of molecular biology and molecular epidemiology of IAV underwent a quantum leap – inter alia including the experimentally full viable reconstruction of the formidable 1918 pandemic strain from replicated genetic material, the meticulous monitoring of the deadly H5N1 virus, and the comprehensive tracking of the 2009 porcine-originated H1N1 pandemic – thus posing IAV as a pathogen of paramount challenge to both man and animal husbandry. The present study aims to point at and analyze the implications of the current scientific and strategic positions of IAV, in relation to its competence as a distinctly modular, highly potent BWA. Collaterally, various controversial and misuse events pertaining to influenza viruses, which took place in actuality and might tentatively bear grave repercussions are discussed in the last chapter of this paper. In order to thoroughly meet those objectives, some of the findings that are included in the sources covered here are

entirely cited. As a starting point, a previous review on bioterrorism, including the IAV pathogen, [4] was used.

Characterizing the Threat

The threat of IAV as a weapon can be featured, basically, at three levels:

- Concrete intelligence
- Inferential intelligence
- Feasibility evaluation as bioweapon and sufficiency/insufficiency of countermeasures.

Concrete Intelligence: North Korea

Reliable unclassified data pertains to merely North Korea, in terms of concrete intelligence. The British intelligence agency MI6 has learned that the pariah state of North Korea is trying to weaponize the Highly Pathogenic (HP) H5N1 virus, thereby making it the ideal threat for al-Qaeda, as well [5]. According to this source; North Korea's Biological Warfare Program (BWP) is nearly the largest in the world. Among its numerous scientists, technicians and laboratory assistants are hundreds scientists who worked on the Russian bio-warfare program, mostly Biopreperat. Some of them had been trying to exploit the 1918 Spanish flu virus as a potential weapon. A high-ranking defector from North Korea's Academy of Sciences has told intelligence officers that the research to weaponize the virus is a priority. The project is under the control of the country's top geneticist and head of its BWP, Dr. Yi Yong Su, who is known to have a close relationship with Kim Jong II, the country's supreme leader. She has assigned eight research centers to work on various aspects of successfully weaponizing the H5N1 virus. But the sophisticated research on this virus is being conducted at Institute 398 at Singam-Ri, south of the capital Pyongyang. U.S. satellite images show the area is ring-fenced by three battalions of soldiers. Only visible above ground are a cluster of concrete-block buildings and fuel storage tanks. The defector has said the laboratories, including two dealing with the latest molecular biological technology, are hidden far below ground. Connectedly, the Bush administration has given briefings classified "Top Secret/ Sensitive Compartmented Information", to members of Congress and the Senate on the threat [6].

Inferential Intelligence: Iran as a Test Case

At the level of inferential intelligence (in difference of unclassified concrete intelligence), it would be fairly reasonable to estimate that states like China and Russia include IAVs in their ongoing BWPs. Also, while North Korea evidently possesses the H5N1 virus as a BW, its grand ally, Iran – with whom North Korea maintains strong military strategic bonds, including in the area of Biological Weapons (BW) [7] – constitutes a challenging test case, in that respect. Iran is known to be the most predominant state worldwide, in terms of affinity towards terror organizations, of which some are practically cultivated by her. In June 2011, Iran (and Syria) "remain leading state sponsors of terrorism," top US counterterrorism official John Brennan said, while introducing a new American anti-terrorism strategy [8]. Iran is considered, as well, to be the most advanced state within the Moslem block, in terms of biological weapons, including pathogens intended for bioterrorism and agroterrorism [9,10]. Various wild strains of HP H5N1 have been isolated in Iran, yet an unknown part of them has been reported to the AIE [11].

Genomic data relating to some of the reported strains was published, while other strains are not profiled in open literature. Not by chance, so it seems, Iran chose Indonesia – the most populous Moslem country globally, and the most H5N1-afflicted country worldwide – to cooperate with Iran for a joint project aiming to produce H5N1 vaccine. In November 2007, an agreement was signed in Tehran for that purpose, on the basis of the Iranian ―advanced pharmaceutical industry, which could be used to develop bird flu vaccines by working on the Indonesian virus‖, as stated by Indonesia's Health Minister, Dr. Siti Fadilah Supari [12]. Notably, the Indonesian H5N1 influenza strains are known to be the most virulent ones across the world. Earlier, in 2006, claiming Western governments could be developing viruses for dissemination in developing countries, with the goal of generating business for pharmaceutical companies; Supari refused WHO researchers access to Indonesia's H5N1 bird flu virus samples [13]. She further expressed concerns as to whether the isolated Indonesian field strains are used for developing vaccines or for BW by Western countries [14] Iran thus gained, at any rate, direct access to Indonesian field strains of particular virulence, both to man and poultry, and tentatively created in Iran a large-scale production line for influenza viruses – being it the H5N1, or any other influenza virus – up to containable extremely pathogenic strains. Whether or not in conjunction with al-Qaeda or other terrorist organizations, the Muslim block is regarded as a major threat of bioterrorism worldwide. Considering that the 2001 anthrax attacks were not initiated from within the US, [15] it is most plausible that that outstanding sabotage originated from the Muslim block [16].

Feasibility Evaluations Made in Canada, USA, Britain and Russia

Overt information regarding the feasibility of IAV employment as a bioweapon in general, and, relatedly, sufficiency (or insufficiency) of countermeasures, is not uncommon, naturally, as intelligence is. Such information – including but one declassified intelligence report – is herewith presented in short.

A declassified Canadian intelligence report prepared by the J2 Directorate of Strategic Intelligence – a secretive military's intelligence arm of National Defense charged with producing intelligence for the government – has warned the federal government that avian influenza could be used as a weapon of bioterrorism [17]. Although heavily censored, the report, entitled ―Recent Human Outbreaks of Avian Influenza and Potential Biological Warfare Implications‖, was obtained under the Access to Information Act by The Canadian Press. The report outlines in broad terms the methods that could be used to develop a manmade strain of influenza capable of triggering a human pandemic. It notes virus passaging, while not entirely predictable, could be a "potentially highly effective" way to push a virus to develop virulence. "Such forced antigenic shifts could be attempted in a biological weapons program," the report says. Passaging involves the repeated cycling of strains of a virus through generations of a species of animals or through cell culture. The process can be used to either ratchet up or dial down the virulence of a virus, depending on which of the ensuing offspring - the mild or the severe - are selected in each cycle for the next passage. The report also raises the spectra of a pandemic strain engineered in a laboratory using reverse genetics, and suggests that technically challenging process allows scientists to custom tailor a flu virus, taking genes from a virulent but not highly transmissible strain, for instance, and melding them with genes from a virus that transmits well from person to person.

Irrespective of modifications through genetic engineering, the aspect of aerogenic AIV stabilization was taken care of in the far past, already. Feasibility studies, apparently related to the weaponization of IAV as aerosol, were conducted in the 70s at the Naval Bioscience Laboratory, University of California, and pointed out that the addition of polyhydroxy compounds exerted a protective effect on airborne stability [18]. In that study, the strain WSNH, propagated in human, chick embryo and bovine cell cultures, and aerosolized from the cell culture medium, was found maximally stable at low relative humidity(RH), minimally stable at mid-range RH, and moderately stable at high RH. Most lots of WSNH virus propagated in embryonated eggs and aerosolized from the allantoic fluid were also least stable at mid-range RH, but two preparations after multiple serial passages in eggs showed equal stability at mid-range and higher RH's. Airborne stability varied from preparation to preparations of virus propagated both in cell culture and embryonated eggs. Contemporarily, throughout an equivalent endeavor, similar studies were comprehensively conducted in the then Soviet military, and upgraded thereafter.

Among 20 pathogens and toxins evaluated as candidate bioagents by a highly distinguished Russian expert, influenza was ranked the 8th, and the rating of influenza was 17, while that of smallpox was 26 (maximal) and that of HIV was 5 (minimal) [19]. The Russian expert, Anatolii A. Vorobev, was previously a Major General, serving as the Soviet Biopreparat's deputy director, responsible for scientific matters, and later member of the Russian Interdepartmental Scientific Council for Conventional Problems of Chemical and Biological Weapons within the Presidium of the Russian Academy of Sciences and the Russian Munitions Agency. Notably, the ranking of influenza and the additional pathogens mentioned therein took place in 2001 – before the devastating return of the H5N1 strain, in 2003 – and was based on the following criteria and parameters:

- Human sensitivity to the pathogen
- infectious dose for infection via
- aerosol contagiousness
- possible routes of infectiousness
- survival in aerosol and in the environment
- characteristics of the disease (severity, lethality, disease
- period) possibility of mass production of the bioagent
- possibility of rapid diagnosis
- various means of prophylaxis
- various means of treatment.

Contemporarily, in 2001, in the Meeting on Bioterrorism held by the Royal Society and British Association for the Advancement of Science, nine principal biological agents were listed by Professor Harry Smith, Chair of the Royal Society Working Group on Biological Weapons, as being most likely to be employed in any outbreak of asymmetrical warfare [20]. In addition to influenza, mention was made of *B. anthracis*, *S. typhi*, smallpox, botulinum toxin, cholera, plague, VEE, and ricin.

During the recent decade, the importance of IAV as a potential BW significantly increased, as reflected in scientific literature. Considering influenza virus to be the most powerful potential bioterrorism weapon, Madjid et al proposed (in a work supported by the US Army's Disaster Relief and Emergency Medical Services) the following steps to address that threat [21]:

The CDC should classify influenza virus as a 'critical agent for bioterrorism. Immunization should be expanded, possibly by requiring it for all medical personnel. Laboratories that work with influenza virus should strengthen their security. Antiviral drugs should be stockpiled and vaccine-making capacity should be increased. The government should consider a gene-sequencing and vaccine development program. Surveillance efforts should be intensified and include incentives for reporting of clinical cases. The fitting of ventilation systems with virus detection and inactivation is needed. Even in terms of merely an anti-human bioterrorism weapon, this multiform anthropozoonotic virus has been reckoned in that study to be an ultimate pathogen, in some respects even clearly exceeding the formidability of smallpox virus. Taken together with the fact that influenza virus is readily accessible and may be causing more deaths than previously suspected, the possibility for aerosol transmission suggests an enormous potential for bioterrorism, according to that study. In addition to spontaneous mutations and reassortments, since the terrorist attacks of September and October 2001, the possibility of malicious genetic engineering used to create more virulent strains ought to be considered. Also, because of the similarity between early symptoms of influenza and other bioterrorism agents (such as anthrax), clinicians need to understand the differences in symptoms and signs, and be aware of the initial screening tests for anthrax and influenza. Since the two diseases could coexist it is unfortunate that there are, to date, no point-of-care tests to diagnose both and thus minimize confusion and panic, according to that paper. Immunologically, researchers at the Stanford Medical Center studied how to guard against influenza virus if it were to be unleashed as an agent of bioterrorism [22]. The project focused on how the immune system of adults and children reacts to the virus. By understanding how the immune system offers protection against influenza, researchers hoped to improve protective vaccines against the virus if it were to be used — perhaps in a modified form with elevated infectivity — with the intent of causing widespread illness and death. Potential agents of bioterrorism include anthrax, smallpox and the plague, but influenza has characteristics that could make it a weapon, according to Dr Ann Arvin, the Lucile Salter Packard Professor of Pediatrics and professor microbiology and immunology, who was the principal investigator for that study. She added that some of the destructive qualities of influenza include highly efficient person-to-person transmission, its potential for being aerosolized (which can magnify the area of exposure), and its ability to cause life-threatening, or at least incapacitating illness. Krug [23], observed that certain events had highlighted the potential of IAV as a bioterrorist weapon: the development of laboratory methods to generate IAVs by transfection of DNAs without a helper virus; and the high virulence of the H5N1 virus that infected people in Hong Kong in 1997. He postulated that antiviral drugs that are directed at functions shared by all IAVs constitute the best line of defense against a bioterrorist attack; consequently, new antiviral drugs need to be developed, and the few currently available antiviral drugs should be stockpiled.

Especially since 2003, thus, much attention has been paid to the avian HP H5N1 virus in particular, thereby allowing for a comparison of the above listed Russian parameters to Western ones, as reflected in a 2008 George Mason University's PhD dissertation by David Pattie, under the direction, yet, of Sergei Popov, [24] formerly a top bioweaponeer in the Soviet BWP, who had defected to the West in 1992. The parameters used in that dissertation (entitled ―Avian influenza as a biological weapon: Threat assessment and public health alert‖, and referring to the HP H5N1 virus), include:

- Target population susceptibility Morbidity and mortality rates
- Transmission
- Infectiousness
- Environmental stability factors Ability to cause social panic
- Formulation, manufacturing process, and deployment methods Availability and feasibility for production
- Difficulty of distinguishing between natural and deliberate outbreaks Potential manipulation and abuse through biotechnology
- Potential capabilities in biotechnology for terror groups Potential for an Engineered bioweapon
- Agroterrorism Vaccine development Antiviral drugs
- Antibiotics (secondary bacterial infections).

In that dissertation, Pattie observed that HP H5N1 represents an attractive agent for terrorist organizations and other non-state adversaries to harm the United States and its interests. Within that context, mortality disease modeling using the Centers for Disease Control and Prevention's FluAid software demonstrated that HP H5N1 avian influenza, when compared to anthrax, caused similar mortality (approximated between 5 and 9 deaths) when modeled with comparable conditions, attack rates (0.25%), and environmental settings as the 2001 anthrax letter attacks. A second scenario estimated overall mortality for a deliberate introduction of H5N1 influenza virus with high attack rates (ranging from 15 to 35%) and high mortality rates (0.1%, 2.5%, and 32%) at pandemic levels (ranging from 107,575 to 136,741,654). It has thereby been suggested that the United States, through the Centers for Disease Control and Prevention (CDC), should lead the world in properly categorizing H5N1 influenza and other novel influenza A viruses as Category A agents for bioterrorism. Classifying H5N1 influenza and other novel influenza A viruses as Category A agents is justified because of their potential for high mortality (63% for H5N1), availability for weaponization, ease of production, and the overall lack of widely available vaccine protection. The proper classification of H5N1 and other novel influenza A viruses as Category A agents by the CDC could potentially impact future R&D biodefense efforts, thereby providing more effective medical countermeasures for the specific and dangerous threat of influenza.

Assuming that mortality rate is expected to decrease significantly if the HP H5N1 becomes pandemic – a fairly sensible, though not an obvious assumption – US Homeland Security Council estimated [25] that in case a bird flu pandemic breaks out in the USA, the impact could be featured as follows:

- Characteristic: moderate (1957/68-like) to severe (1918-like) Outpatient medical care: 45 million (50% of those ill) Hospitalization: 9,900,000
- ICU care: 1,485,000 Mechanical ventilation: 745,000 Deaths: 1,903,000

The outstanding zoonotic nature of the HP H5N1 virus illustrated the complexity of coping with intentional introduction of this virus during a multiagency exercise [26], which tested multilevel responses to an escalating bioterrorism scenario of an H5N1 outbreak, affecting commercial poultry flocks in the setting of a severe annual influenza season and influenza-like illness among poultry industry workers. The exercise took place in Georgia, USA.

Acknowledged experts referred to the feasibility of the HP H5N1 strain employability as a bioweapon, [27] as follows.

- Dr. Ken Allibek, presently an American expert and formerly director of the Soviet Union's biowarfare program, Biopreperat, noted that "The threat of a weaponized bird flu virus cannot be over emphasized. It would be the most terrible weapon in the hands of a terrorist. The advantage for al-Qaeda is that an aerosolized weapon would be impossible to detect from one spread naturally by birds. But a lab-produced virus would be far more lethal."
- Dr. Brian Ward, a virologist at McGill University in Montreal contended that if the ultimate goal is panic, social disruption and economic losses, influenza would be a good choice. "To me it's one of the most logical viruses to use. It doesn't have to be a really bad one to throw a huge wrench," Ward said. "I mean, if you want to hurt the world's economy, that's an awfully good way."
- Professor Peter Openshaw, a leading virologist at Imperial College, London, called it: "more terrifying than engineered smallpox. That would be relatively easy to contain because there is a vaccine. But with improvements in laboratory technology, it's becoming much easier to engineer these viruses. It's becoming a terrible concern."
- Professor Hugh Pennington, a leading microbiologist at Aberdeen University, Scotland, noted that "A clever molecular biologist could also try to mix the virus with other viruses so that it could spread person to person, which would be the greatest threat."
- Alongside the presently challenging H5N1 virus, the 1918 pandemic strain was reviewed too, 28 in order to advance discussions among health professionals and policymakers about an effective medical and public health response to bioterrorism, including: building capacity to care for mass casualties, providing emergency burials that respect social mores, properly characterizing the outbreak, earning public confidence in epidemic containment measures, protecting against social discrimination, and fairly allocating health resources. Collectively, the above presented data single out, foremost, the distinctiveness of two specific influenza A viruses, namely the 1918 H1N1 virus and the 1997 H5N1 virus (along with variants of those two viruses). Those are indeed two prominent pathogens. However, the wide array of IAV variants offers more options, which are marked by appreciable modularity.

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Journal of #Bioterrorism and #Biodefense: Past, Present and Future https://www.omicsonline.org/journal-of-bioterrorism-and-biodefense-Past-present-and-future-2157-2526.1000e110.pdf â€¦ 0 replies 0 retweets 1 like. Reply.Â Submissions Open #Journal of Bioterrorism & Biodefense Interested researchers can submit manuscripts via E-mail at: bioterr@journalsres.org Submission Deadline: 15th Dec, 2018. 0 replies 0 retweets 1 like. Reply. Journal of B. Biodefense. ioterrorism &. Journal of Bioterrorism & Biodefense. ISSN: 2157-2526. Khurshid, J Bioterror Biodef 2018, 10:1 DOI: 10.4172/2157-2526.1000168.Â Bioterrorism is the intentional release or threat of release of biological agents, viruses, bacteria, fungi or toxins in order to cause harm to human population, livestock and agriculture. Now a day sometime it is very difficult to differentiate between intentional and unintentional release, so actually you have to prepare yourself against both. The history of bioterrorism is very old; it started in the sixth century B.C. Some examples have also been mentioned by other speakers which took place whether intentionally or unintentionally, but they had harmed life on this planet. Global Biodefense news on bioterrorism preparedness, detection and prevention technologies, and medical countermeasures.Â In October 2019, a House Homeland Security Committee subcommittee held a hearing entitled â€œDefending the Homeland from Bioterrorism: Are We Cutting Edge Chemical and Biological Defense Science: Hot Topics at CBD S&T 2019. by Saskia Popescu, PhD.