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Overview on Prevention and Control Measures for Human Infection with HPAI H5N2 Virus in Taiwan in 2012

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Abstract

Outbreaks of highly pathogenic avian influenza (HPAI) A (H5N2) in poultry that occurred in Taiwan in early 2012 have raised much public concern. Although previous studies and surveillance data from foreign countries and Taiwan showed that the threat caused by avian influenza H5N2 virus to human health is extremely low, Taiwan CDC has convened expert consultation meetings to determine relevant prevention and control measures and has held the First Meeting of the Task Force for HPAI H5N2 Outbreak in Poultry in collaboration with the Bureau of Animal and Plant Health Inspection and Quarantine (BAPHIQ) of Council of Agriculture (COA), Food and Drug Administration (FDA) of the Department of Health (DOH), local health departments, and local animal disease control centers to discuss the control procedures in response to the outbreaks. In addition, Taiwan CDC has published the Guidelines for Prevention and Control of Human Infection with Avian Influenza H5N2 Virus for the general public based on the contents described in the National Influenza Pandemic Preparedness Plan about the issues of outbreak investigation, health information dissemination, and health monitoring of the close contacts. Meanwhile, if necessary, the monitoring of viral infections will be conducted by detecting viral RNA and antibody titer among the close contacts to understand the impact of the outbreaks on their health. No human cases had been clinically diagnosed when the H5N2 outbreaks occurred in poultry in 2012.

This article provides a brief introduction on avian influenza viruses, avian influenza H5N2 outbreaks that have occurred in Taiwan and other countries, threats of H5N2 virus to human health, how to prevent infection with H5N2 virus, and the prevention and control

strategies for human avian influenza case and response measures against an epidemic in Taiwan. Also, we have summarized key issues from the Guidelines for Prevention and Control of Human Infection with Avian Influenza H5N2 Virus. We hope that this article will help citizens have a better understanding on the prevention and control of avian influenza H5N2 virus infection and can be used as a reference in formulating the infectious disease control policy.

Keywords: highly pathogenic H5N2 avian influenza, serological surveillance, Guidelines for Prevention and Control of Human Infection with Avian Influenza H5N2 Virus

Introduction

Low pathogenic avian influenza (LPAI) A (H5N2) outbreaks in poultry farms occurred in Taiwan in late 2003 and 2008, respectively. Although the outbreaks were well controlled after taking actions of culling chickens in the affected poultry farms, other sporadic infections with LPAI H5N2 viruses were also identified between 2010 and 2011. Subsequently, several epidemics caused by HPAI H5N2 viruses among poultry population were continually detected in Taiwan in early 2012. These have raised public concern about whether the H5N2 virus will spread from poultry to human or even cause illness in human. Previous studies in other outbreaks in poultry showed that although H5N2 virus might infect human and produce detectable antibody in human body, however, no cases have been clinically diagnosed in Taiwan and other countries. However, in order to ensure the citizens' health and safety, the Centers for Disease Control of Taiwan (Taiwan CDC) and local health departments have followed the National Influenza Pandemic Preparedness Plan to initiate relevant prevention and control measures for human infection and actively conducted risk communication and health education for the public by issuing news releases, hosting press conferences, and distributing pamphlets with questions and answers on avian influenza immediately after receiving the notification of outbreaks in poultry.

Although H5N2 virus does not cause serious threats to human health currently, influenza viruses are constantly evolving and very likely to develop new variant strains. Consequently, health authorities and agriculture authorities need to continuously cooperate closely with each other and actively conduct preparedness and response activities for every possible incident, to prevent the variant strains of avian influenza viruses that can cross species barrier and infect human from emerging so as to protect citizens' health.

Overview on avian influenza viruses

Avian influenza viruses belong to influenza type A viruses. They can cause diseases and epidemics among birds and poultry population. It is believed that wild birds are the natural host for all known subtypes of avian influenza viruses, and the viruses are carried by migratory birds from one country to another and infect poultry or cause epidemics among

poultry population there. [1] Based on the severity of clinical presentation in poultry, avian influenza viruses can be classified into two groups: HPAI viruses and LPAI viruses. The symptoms caused by LPAI viruses are mostly limited to respiratory and digestive tracts while the HPAI viruses can result in whole-body infection in poultry. [2] The HPAI viruses have high virulence, and its fatality rate can reach as high as 100%. All HPAI viruses currently identified belong to either the H5 or H7 subtypes. [3] Although LPAI viruses have low virulence, they have potential to evolve into new variant strains that are highly pathogenic. [4, 5]

Most avian influenza viruses have not caused disease in human to date. The classification of high pathogenicity or low pathogenicity is made on the basis of the ability of the virus to cause disease in poultry, but there is no absolute correlation between the virulence of the viruses in poultry and in people. Some types of avian influenza viruses have been proved to be capable of infecting human and causing disease, but they have been limited to the viruses of the H5, H7, H9, and H10 subtypes. [3, 6] Avian influenza virus is thought to be one of the pathogens that have the highest potential to cause pandemics among human population. Of the avian influenza viruses, HPAI H5N1 virus has drawn most attention since it has repeatedly caused epidemics among poultry population in parts of Asia and northern Africa. It has been proved to be able to spread from poultry to human, and it may have the ability to cause limited human-to-human transmission. [7] From 2003 through July 5, 2013, a total of 633 laboratory-confirmed human cases with avian influenza A (H5N1) virus have been officially reported from 15 countries. Of those cases, 377 died, with a case-fatality rate of 60%. [8] The data from the World Health Organization (WHO) show that most human H5N1 cases have been traced to direct or close contact with H5N1 virus-infected poultry or contaminated environment.

Avian influenza H5N2 outbreaks in poultry in foreign countries and Taiwan

A. Outbreaks caused by HPAI H5N2 viruses among poultry population have been detected in several countries/regions, including *Pennsylvania* in the USA (1983), Mexico (1994), Italy (1997), Texas in the USA (2004), Zimbabwe (2005), and South Africa (2004 and 2011). [9, 10] The H5N2 virus that caused the Pennsylvania outbreak have undergone mutations and converted from a low pathogenic strain to a highly pathogenic strain during April-October of 1983. [4] In recent years, outbreaks caused by LPAI H5N2 viruses also have been reported continuously from a variety of countries in the world, such as Japan, Sri Lanka, Germany, Italy, Portugal, Ireland, USA, Canada, and Haiti. [11]

B. In Taiwan, outbreaks caused by LPAI H5N2 viruses have occurred at 21 poultry farms in several counties/cities during December 2003-March 2004, when the poultry at the 21 affected poultry farms were all culled. In October 2008, a LPAI H5N2 outbreak occurred in Kaohsiung County, and the 18,000 chickens at the affected poultry farm were totally

culled. [12] Afterward, scattered outbreaks due to LPAI H5N2 viruses were also detected during 2010-2011. In early 2012, outbreaks caused by HPAI H5N2 viruses in poultry farms in central Taiwan were first reported and then other HPAI H5N2 outbreaks continuously occurred in several poultry farms in central and southern Taiwan.

Threat of avian influenza H5N2 viruses to human health

A. Assessment of the impact of avian influenza H5N2 viruses on human health

To clarify the risk and threat of avian influenza H5N2 infections to human, serological investigations on close contacts to poultry in areas affected by avian influenza H5N2 epidemics have been conducted in Italy, South Africa, Japan, and Taiwan.

a. Between October 1997 and January 1998, eight HPAI H5N2 epidemics had occurred in two provinces of northern Italy. During this period, none of the 32 close contacts have presented respiratory symptoms and no viruses have been isolated from the throat swab specimens collected from them, and the *microneutralization assay* for their serum specimens indicated that they did not have infections with H5N2 viruses (sera with a titer < 1:80 were considered as negative). [13]

b. In 2004, outbreaks caused by HPAI H5N2 viruses occurred at two ostrich farms in Eastern Cape Province of South Africa. The investigation showed that among the serum specimens collected from the 130 people involved in the outbreaks, including slaughtering plant workers, animal disease control personnel and veterinarians, three were positive for H5N2 antibody (a titer of >1:40 was considered as positive) by *microneutralization assay.* The antibody titers for the three people were 1:80, 1:640, and antibody-positive conversion, respectively, but none of them had presented serious symptoms. Although some of the workers at the affected poultry farms had shown mild respiratory symptoms and conjunctivitis, in consideration of the confounding factors of seasonal respiratory diseases, allergens and dust in the environment, and smoking, the investigation could not determine whether these symptoms were caused by infection with H5N2 viruses and found no evidence to support that H5N2 viruses had the ability to spread from human to human. [14]

c. During June-December 2005, 40 outbreaks due to LPAI H5N2 viruses were identified in the Ibaraki Prefecture located in eastern Japan. The investigation conducted by local governments for the 257 workers at the affected poultry farms found that all workers were in good health and did not have influenza-like illnesss, and no viruses have been isolated from the specimens of throat swabs. However, 48 of them obtained a positive results (a titer of >1:40 was considered as positive) in the second antibody test, and, of the 48 workers, 20 had a four-fold increase in antibody titers of paired serum specimens. Nevertheless, the investigation pointed out that the seasonal influenza vaccine administered within 12 months before serum collection might have increased the possibility of gaining a positive antibody test result. [15]

d. For the several avian influenza H5N2 outbreaks that have occurred in Taiwan since 2003, Taiwan CDC has always initiated relevant actions for prevention and control of possible human infections immediately after the occurrence of the outbreaks and, if necessary, a specimen of the close contacts would be collected for monitoring the possibility of human infections. In addition, a study was initiated in 2004 to monitor the seroprevalence of avian influenza H5N2 and H7N7 viruses in people working in poultry farms, conducting disease control, implementing culling of poultry in an infected poultry farm, or performing laboratory testing. [16] Merely three asymptomatic poultry workers found to have seropositive reaction to A/H5N2 antibody during the outbreak in 2012.

B. Avian influenza H5N2 viruses and food safety

Previous studies indicated that avian influenza H5N2 viruses have been isolated from egg yolk, egg white, and eggshell of the eggs laid by infected poultry or birds. [17] The influenza viruses can survive on objects with smooth surface for as long as 24-48 hours and on those without smooth surface for more than 12 hours. In addition, the viruses can live in raw meats for 35 days under low temperature condition of 4℃ and can live for only 6 days under the body-temperature condition of 37℃. Cooking at a temperature of 70℃ or higher will inactivate the viruses. Therefore, cooked poultry meat, eggs, and their relevant products are safe for consumption. However, we need to take special precaution during the process of handling and preparing the food, such as the freezing and defrosting process of foods, and take steps to prevent cross contamination between raw and cooked foods. Up to now, there has been no known case of human infection with avian influenza virus through consumption of cooked poultry meat, eggs, and their products. The Food and Agriculture Organization of the United Nations (FAO) and WHO also pointed out that there are no risks to people of acquiring avian influenza from consuming fully cooked poultry meats and eggs. [18]

C. WHO's viewpoint about the impact of H5N2 virus on human health

Mr. Gregory Hartl, spokesman for the WHO's Global Outbreak Alert and Response Network, has made comments publicly in response to the occurrence of the HPAI H5N2 outbreaks in Taiwan: "H5N2 virus is only a type of avian influenza viruses. Although we cannot predict the future development of the virus, no confirmed human cases of avian influenza H5N2 have been identified by the WHO to date. It is possible that some people might have been infected with avian influenza H5N2 virus but have not been detected, or human cases of avian influenza H5N2 may occur in the future. However, the possibility that H5N2 virus may affect human health to the same extent as the H5N1 virus is low so far."

How to prevent avian influenza H5N2 virus from infecting human

Since no confirmed human cases of avian influenza H5N2 have **occurred** in the world, the human H5N2 influenza vaccine is not available right now. Although the Taiwan CDC has stockpiled human influenza A/H5N1 vaccine, no clinical studies indicate that H5N1 influenza

vaccine could offer cross protection to H5N2 virus. Part of the reason that we recommended people at high risks of infection receive vaccination against seasonal influenza [19] is to reduce the probability of genetic reassortment of avian and human influenza virus, but the vaccine, in fact, did not offer protection against avian influenza H5N2 virus.

Previous studies indicated that having contact with birds, poultry, or contaminated environment is a strong risk factor for human infection with avian influenza. [20] Therefore, we recommend that the public should avoid contact with poultry, birds, or poultry died from an unknown cause, and should avoid purchasing or rearing birds or poultry smuggled or of unknown origin. While cleaning the droppings of poultry reared at home, you will have to wear a mask and latex gloves, and thoroughly wash your hands after working on the cleaning. In addition, unnecessary or unprotected personnel should avoid visiting live poultry markets and poultry farms. Personnel working with poultry have to wear appropriate personal protective equipment in doing the routine work to protect their own health.

Prevention and control strategies for human infection and response measures against an epidemic of avian influenza in poultry in Taiwan

Since the avian influenza viruses have been considered one of the pathogens most likely to cause an influenza pandemic in human, the Taiwan government has been continuously conducting various preparedness and control activities for human infections based on the four major strategies and five defensive lines described in the Influenza Pandemic Strategic Plan. The four major strategies are Surveillance and Assessment, Interruption of Transmission, Antivirals, and Influenza Vaccine. The five defensive lines include Containment Abroad, Border Control, Community Epidemic Control, Maintenance of Medical System Functions, as well as Individual and Family Protection.

Several HPAI H5N2 outbreaks occurred one after another in Taiwan in early 2012. Although no human cases of avian influenza H5N2 have been clinically diagnosed to date and the investigations conducted by different countries showed that the risk of human infection with H5N2 virus was low, the viruses might still be able to infect close contacts in very rare instances. Therefore, Taiwan CDC has actively carried out various prevention and control measures in response to the HPAI H5N2 outbreaks to ensure citizen’s health, including:

A. To closely monitor epidemics that occur in Taiwan and foreign countries

Information about the avian influenza outbreaks in poultry and human in other countries are continually updated through communication with the WHO, World Organization for Animal Health, Taiwan Embassy, and National IHR Focal Point of Taiwan. The occurrence of avian influenza infection in human in Taiwan is monitored through the operation of the Infectious Disease Announce System and the Contract Virological Laboratories, and the information on avian influenza epidemic in animal is updated through close communication between the Taiwan CDC and the one-stop window at the COA, and through the meetings with the COA.

B. To fully implement the cross-ministry mechanism of vertical and horizontal communication

The Taiwan CDC always has staff participate in meetings periodically convened by the COA, Executive Yuan, including the Executive Yuan Communication Meeting on Avian Influenza Prevention and Control, and the Review Meeting on Management Measures for Slaughter, Production, and Marketing of Poultry. These meetings facilitate information exchange on progress of avian influenza prevention and control, and enable the coordination and communication of prevention and control policies with relevant ministries, as well as the aggregation and integration of capacity among ministries.

In response to the HPAI H5N2 outbreaks in poultry, Taiwan CDC immediately convened the First Meeting of the Task Force for HPAI H5N2 Outbreak in Poultry, in which the BAPHIQ of COA, FDA of DOH, local health departments, local animal disease control centers, and the commander of Taiwan CDC's Medical Networks for Infectious Disease Prevention and Control (hereafter simply referred to as the Medical Networks) were invited to participate. In addition, Cross-Ministry Communication Meetings on HPAI H5N2 Avian Influenza Outbreak in Poultry were co-hosted by COA and DOH on a non-periodic basis to promptly discuss issues pertaining to collaboration in the prevention and control of avian influenza outbreaks in poultry and in human.

C. To strengthen implementation of border control and notification of smuggled poultry/birds

Different quarantine measures, including strengthening of fever screening at entry points and collection of information on detail travel itinerary and exposure history, will be taken in response to the epidemic development for incoming passengers from avian influenza affected areas. Moreover, personal protection measures for quarantine officers will be improved to protect health and safety of the officers engaged in quarantine work. Since bird smuggling has become a possible route other than incoming passengers that may introduce avian influenza virus from overseas to Taiwan, relevant ministries of the Executive Yuan have expanded the scope for monitoring of bird smuggling to both HPAI and LPAI affected areas, and have improved the procedures for notification and management of persons involving the live bird smuggling.

D. To establish standard operation procedures

To precisely meet the demand for epidemic prevention and control practice, Taiwan CDC has revised the Guidelines for Prevention and Control of Avian Influenza among Personnel Involved in Handling of Avian Influenza-Affected Place. The contents in the Guidelines include health management, risk communication, and protection measures, and are provided as a reference to the front line workers from relevant ministries responsible for dealing with the avian influenza outbreak affected poultry farms and the bird smuggling incidents. The Guidelines is available for the general public in the influenza prevention and control section of the Taiwan CDC website.

E. To organize and stockpile various resources for control of infectious disease

By establishing three-tier hierarchical stockpiling systems (central government, local governments, and hospitals), Taiwan CDC has stockpiled necessary resources in advance, including flat masks, surgical masks, N95 masks, isolation gowns, and protective apparel, to supply to professionals working in disease control and medical service in ordinary times or during pandemic influenza or other infectious disease epidemic. In addition, Taiwan CDC has signed a contract with a professional company to restore the stockpile items to maintain them in a usable state through various delivery systems.

F. Preparedness of influenza vaccine and strategies for using influenza vaccine

The administering of prepandemic vaccine before the occurrence of a pandemic can produce initial priming effect and can rapidly enhance immunity by giving a booster shot when the pandemic caused by the virus strain contained in the vaccine occurs. Moreover, the chances are that the pandemic period may be shortened, and the transmission rate and mortality rate will be reduced if the vaccine contains the same virus strain as those causing the pandemic or can provide cross-protection. Therefore, Taiwan CDC, based on the WHO recommendations, has stockpiled a type of prepandemic influenza vaccine, the human influenza A/H5N1 vaccine, and conducted the dissemination of the “Voluntary Vaccination Program of human influenza A/H5N1 vaccine” for people at high risk of contact with avian influenza virus and personnel engaging in medical service and disease control when pandemic influenza occurs.

G. To sustain the capacity of the Medical Networks

In order to improve operation mechanism and regional cooperation system among selected hospitals, and to sustain and enhance the hospitals’ capacity in the diagnosis and treatment of infectious diseases in response to a pandemic, the Taiwan CDC has established the Medical Networks in each of the six regions of the country, including Taipei, Northern, Central, Southern, Kao-ping, and Eastern regions. Member hospitals of the Medical Networks are responsible for offering specialized healthcare services for suspected patients of infectious diseases in their region. It is expected that, through the Medical Networks, the patients will be provided with specialized healthcare services at the very early stage of a pandemic, and the surging number of patients can be rapidly separated to different member hospitals to prevent the spread of disease.

H. To conduct prevention and control of avian influenza cases in people working for a bird flu-affected poultry farm

For poultry farms affected by an outbreak of avian influenza, the Taiwan CDC will immediately supervise and assist local health departments to have staff conduct an outbreak investigation, make a name list with basic information of the contacts, and do follow-up on the health of the contacts. If necessary, a specimen from the contacts will be collected for monitoring whether they have been infected. In addition, they will be provided with health education and be required to conduct a ten-day health

self-management. The contacts presenting with any suspected symptoms will be arranged for hospital treatment and notified to the Taiwan CDC, and specimens from them will be collected, by local health departments.

I. Health information dissemination and health risk communication

As part of the response to avian influenza outbreaks, the Taiwan CDC will actively publish news releases and send a letter to medical colleagues to conduct risk communication, and improve health education for the general public through various educational materials and multiple education channels. Moreover, a brochure on avian influenza prevention measures that poultry and animal workers must know and a flyer for educating citizens traveling to other countries about avian influenza prevention are updated annually and provided to relevant poultry workers and those entering or exiting through international ports. When the avian influenza H5N2 outbreak occurred in early 2012, the Taiwan CDC immediately compiled and published the Guidelines for Prevention and Control of Human Infection with Avian Influenza H5N2 Virus and a flyer with Questions and Answers on Avian Influenza. We hope that, through these materials, the public will have a correct and consistent awareness of avian influenza H5N2 prevention and, simultaneously, the social panic arising from incorrect messages can be avoided.

J. To conduct program of Serological Survey for Avian Influenza Viruses among Poultry Workers in Taiwan

The studies conducted by different countries on human infection with avian influenza found that the majority of human avian influenza cases have a direct or indirect contact with sick poultry or have had exposure to environments contaminated with avian influenza virus. This indicated that poultry-related workers are a population at high risk of infection with avian influenza. In order to evaluate the risk of infection with avian influenza among poultry workers in Taiwan, a name list of the poultry-related workers was provided by the COA and the Ministry of Economic Affairs, a stratified sampling method was performed based on the ratio of the number of workers in one county to the total number, and blood specimens were collected from the subjects to monitor the prevalence of antibody against avian influenza and to understand the activity, geographical distribution, and types of the avian influenza virus in Taiwan. The results of the evaluation could be used as a reference for future policy formulation, to ensure citizens' health.

Summary of the Guidelines for Prevention and Control of Human Infection with Avian Influenza H5N2 Virus

Although no evidence shows that H5N2 viruses can cause illness in human to date, in a precautionary manner, Taiwan CDC has stayed updated about the epidemic situation through contact with the one-stop window at the BAPHIQ of COA. Taiwan CDC has also convened expert meetings to formulate the control strategies, strengthened the vertical and horizontal communication mechanism, continually enforced health management of close contacts, and

actively conducted health information dissemination and health risk communication to the public. The followings are summary of the Guidelines for Prevention and Control of Human Infection with Avian Influenza H5N2 Virus [21] to provide reference to the general public.

A. Prevention and control of avian influenza infection in people working at affected poultry farm

Upon receiving the notification of epidemic information or the time of culling in affected poultry farm from agricultural authorities, local health departments will immediately dispatch staff to conduct an epidemiological investigation. For people exposed to a poultry farm affected by avian influenza, local health departments will first investigate their health status, then, provide them with health education, and require them to perform a seven-day health self-management. For personnel performing culling, local health departments will assist them to conduct relevant control measures and to ensure that a correct personal protection measure has been taken. If any one of them gets influenza-like illness, local health departments will help them to obtain hospital treatment, report them to the Taiwan CDC, collect specimens from them, and evaluate the necessity of prescribing antivirals for them.

B. Surveillance and treatment of suspected human avian influenza infection

Besides monitoring health status of people exposed to poultry farms affected by avian influenza, as described in the previous paragraph, other channels for surveillance and treatment of suspected human avian influenza cases are also applied. For example, physicians are required to immediately notify the local health departments of suspected human avian influenza cases, and the patient will be transferred to one of the responding hospitals assigned by the commander of the Medical Networks for specialized medical treatment. In addition, the contract virological laboratories periodically collect specimens from patients with respiratory tract symptoms to perform viral testing so that we can update information on genetic type, geographical distribution, and seasonal change in the circulating virus.

C. Laboratory testing and criteria for a positive test result

The real-time PCR assay is used to detect viral RNA in the throat swab specimens. The haemagglutination inhibition test is applied to determine the antibody titer in serum specimens. A convalescent serum specimen is collected at an interval of 14-28 days after the acute phase. In single serum specimen, HI titer$\geqq$160 is considered positive. In paired serum samples, a fourfold or greater increase in HI titer and HI titer$\geqq$80 is considered positive.

D. Use of antivirals for treatment and prophylaxis purpose

A suspected human case can be treated with influenza antivirals after they are notified and their specimen are taken, and can be prescribed higher dosage of antivirals or given a longer treatment time with antivirals depending on the treatment progress. The contacts of the suspected cases can be given influenza antivirals for prophylactic treatment based on the decision jointly made by the Branch Office of the Taiwan CDC and the commander of

the Medical Networks. People involved in culling affected by avian influenza also can be given antivirals for prophylaxis according to the evaluation of the risk of exposure to the disease conducted by the commander of the Medical Networks.

E. Procedures for operation of the Medical Networks

When identifying suspected human avian influenza cases, a physician shall report them to local health departments, which shall in turn forward the reports to the Taiwan CDC and the commander of the Medical Networks to start the operation of the Medical Networks. The patients will then be moved, in compliance with infection control practices, to the ward in a member hospital of the Medical Networks. If the hospital where the patient is diagnosed is not a responding hospital of the Medical Networks, the patient will first be isolated at the hospital and then be transferred to a responding hospital by local government together with the hospital.

F. Guidelines on nosocomial infection control in medical facility

When providing healthcare service, healthcare providers should adopt appropriate protection measures in accordance with the principles of the standard and droplet precaution. In principle, the patients should be arranged in a single patient bedroom and be centered in an area for clinical care, and the door to the patient's room should be kept closed at all times to reduce the frequency of entering or exiting through the door. When sucking out secretion from airway of a patient with endotracheal intubation, you should use a closed suction system that has been equipped with a high efficiency particulate air (HEPA) filter. It is essential for healthcare providers to advise patients to properly and frequently wash their hands and to adhere to the respiratory hygiene and cough etiquette.

G. Preparedness and strategy for use of vaccine

Although no human vaccine against avian influenza H5N2 virus is available around the world, the Taiwan government has stockpiled human influenza A/H5N1 vaccine based on the recommendations made by the WHO. Currently, there is no sufficient scientific evidence showing that human influenza A/H5N1 vaccine can provide protection for human from infection with avian influenza H5N2 virus. However, in order to reduce the probability of genetic reassortment of influenza virus and to prevent people from infection with H5N1 virus, the Taiwan government has offered poultry workers with seasonal influenza vaccine free of charge since 2003 and with human influenza A/H5N1 vaccine since 2010.

Conclusion

Investigation conducted by various countries showed that the risk for human to be infected with avian influenza H5N2 virus is very low right now, and there are no clinically diagnosed human cases infected with avian influenza H5N2 virus to date around the world. However, close contacts of sick poultry may become infected and may produce a positive result in serological antibody detection test in an extremely rare situation. Therefore, what

we should do right now is to promptly control outbreaks of avian influenza in animals and continually monitor variation of influenza virus and the health of close contacts so that the risk of cross-species transmission resulting from genetic variation in virus could be prevented or minimized.

In order to prevent the avian influenza virus from evolving into a novel strain that has the ability to infect other animal species or even human, agricultural authorities should continually monitors the infection possibly occurring in animals and implement infection control measures with reference to those that have been conducted in other developed countries. Furthermore, agricultural authorities should immediately inform health authorities of the occurrence of avian influenza virus infections in animals to enable health authorities to conduct prevention and control activities for possible human infections. The Taiwan CDC, in accordance with the of the National Influenza Pandemic Preparedness Plan - Phase II, will continually conduct various preparedness, response, and control activities for pandemic influenza; design various response mechanisms and actions to be taken; and stockpile vaccine, antivirals, and personal protective equipment, to facilitate the effective implementation of epidemic control. Moreover, Taiwan CDC will continually improve health education for the general public and poultry workers as well as strengthen the communication and cooperation mechanism with agricultural authorities and other bureaus or departments so that the relevant epidemic control activities could be rapidly conducted. In addition, routine surveillance of whether avian influenza viruses have the potential to circulate in community is conducted through the contract laboratories, and the program of Serological Survey for Avian Influenza Viruses among Poultry Workers in Taiwan is implemented. Through these monitoring and investigation, we hope that we are able to promptly identify possible human infection with avian influenza virus, prevent the threat of avian influenza epidemic from occurring in Taiwan, and evaluate the impact of avian influenza virus on the health of high-risk populations, and in doing so to protect citizens' health.

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Personal Protective Measures Against Arthropod-borne Infectious Diseases

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Abstract

In Taiwan, the insect-borne infectious disease that residents are most familiar with is probably dengue fever, which causes thousands of infections each year. Scrub typhus and Japanese encephalitis are the other two common insect-borne infectious diseases in Taiwan. It is not easy to eliminate or contain these arthropod-associated diseases and avoiding arthropod bites is still the most effective way to reduce the risk of infection. Although there are many insect repellent products on the market, it is important to choose the most suitable and effective product in order to obtain the best personal protection. This essay reviews relevant literature and aims to offer healthcare workers the most accurate information about personal protection against arthropod-associated diseases.

Keywords: Insect repellent, arthropod-associated diseases, diethyltoluamide

Introduction

Arthropods can be divided into three groups: arachnida, crustacea, and insecta. The most representative vectors of the arachnida group are mites, which transmit Scrub Typhus and ticks, which transmit Lyme disease. The group crustacea includes crabs and small lobsters, which transmit paragonimiasis, as its representative vectors. The most common vectors of the insecta group are fleas, which transmit plague; sand flies, which transmit leishmaniasis; *Anopheles* mosquitoes, which transmit malaria; various insects that transmit filariasis; and *Aedes aegypti*, which transmit yellow fever and dengue fever.

Arthropod-associated diseases still comprise a large proportion of the infectious diseases that represent a major public health threat. Besides the more common diseases such as yellow fever and dengue fever, West Nile fever in the USA and the new bunyavirus in China, having both been frequently reported by the media in recent times, are also transmitted through arthropod bites.

The expansion of urban areas has provided more habitats for mosquitoes. Climate change could also increase the risk of infectious disease. Unfortunately, only a few arthropod-associated diseases can be prevented with vaccines, chemoprophylaxis, or have effective treatment. Most of the diseases can only be offered supportive care to relieve clinical symptoms.

As it is impossible to control all of the disease-carrying arthropods, and currently only yellow fever and malaria have vaccines or prophylactic medicines, personal protection has gradually become the main strategy to prevent arthropod-associated diseases when taking into account environmental and economic concerns. Even when vaccines and medicines become available, they do not necessarily represent the most complete and effective preventative method. Avoiding arthropod bites is still the most important, and sometimes the only, way to prevent arthropod-associated diseases.

Arthropod biting behavior can be influenced by many factors such as seasons, peak activity periods, or a preference for biting either indoors or outdoors [1]. Understanding arthropod biting habits can help to reduce the chances of being bitten. Selecting a personal protective measure appropriate to the environment or combining various protective methods can effectively prevent arthropod bites [2]. Arthropod bites can be avoided by using a combination of the following methods: 1) voiding contact with arthropods. 2) using physical barrier.3) using chemical barriers.

Avoiding contact with arthropods include stay away from areas where vectors are active, especially during their peak biting hours and physical barriers help prevent bites. Chemical barriers always can deter bugs. Arthropod bites or discharges can cause local or systemic reaction and can spread disease. Common chemical barriers used to reduce the risk of insect-borne infectious diseases can be divided into two types: repellents and insecticides. Repellents do not kill arthropods, but as they are not liked by arthropods they can keep arthropods away. Insecticides, on the other hand, kill arthropods upon contact.Repellents and insecticides do not work against each other. Some chemical ingredients can be used for both. Travellers visiting endemic areas are advised to carry insecticide-treated mosquito nets and clothing [1, 3], although this may be inconvenient. Personal protection measures such as applying repellents on the skin, and using insecticides to soak nettings and clothing, can reduce the risk of scrub typhus, malaria, and filarial infections [4]. Although space barriers such as burning insecticide coils are also frequently used, their effectiveness in preventing arthropod-associated diseases has yet to be proven [4].

Physical barriers help prevent bites, while chemical barriers can deter bugs. Arthropod bites or discharges can cause local or systemic reaction and can spread disease. Using repellents, especially in endemic areas, not only prevents diseases, but also avoids the discomfort caused by arthropod bites. For example, some areas in Taiwan have midges whose bites can cause a lot of discomfort. Strengthening personal protection not only stops female adult midges from feeding on blood and depositing eggs, but also avoids allergic reactions [5]. Application of repellent to the skin, combined with long sleeved clothing, can increase protection. Although repellent used outdoors has a limited protection time, it is still an important measure to avoid arthropod bites.

Currently the markets in Taiwan are flooded with various types of insect repellents, such as repellent bracelets, repellent patches, and plant essence repellent lotions etc. Manufacturers' marketing and promotion could mislead consumers about choosing the right repellents or correct use of the products. During the 2011 dengue fever outbreaks in Northern Taiwan, three health workers were infected [7]. This demonstrated the importance of applying correct self-protection to avoid being bitten by virus-carrying vectors. This report discusses various methods in preventing arthropod bites and evaluates their effects. It is hoped that this information can be useful for healthcare workers in self-protection against vector-borne diseases.

Physical Barriers

For those who are living in or travelling to areas that are at risk of arthropod-borne diseases, the following methods can be used to create physical barriers:

1. Wearing long sleeves and long trousers. Tucking trousers inside socks or shoes can help avoid insect bites;
2. Wearing light-colored clothing. Light-colored clothing not only avoids the attention of some arthropods, it also makes it easier to spot and remove arthropods attached to the clothing. For example, Lyme disease, which is caused by tick bites, can be avoided by checking whether any tick has bitten, or has been attached to, the human body before heading home. As bacterium is only released from the saliva between 24 and 48 hours after the bite, if a tick is found to be attached to the skin, fine-tipped tweezers can be used to grasp the mouth-part of the tick and carefully remove the tick. It is important that the mouth-parts do not break off and remain in the skin. After removing the tick, washing the bite area immediately with soap can reduce the chances of Lyme disease infection.
3. Minimize the chance of coming into contact with arthropods at work and at home. Installing screens and closing doors and windows so there are no holes for arthropods to enter the buildings. Mosquito net must be well maintained and should not have any large gaps or holes. Tuck the net in underneath the mattress. Be aware that mosquitoes can still feed through the mesh if the net is too close to the skin. Some arthropods can enter the net if the holes of the mesh are too big. It is recommended to choose nets with mesh size 17 to 21 to keep mosquitoes away. To protect against midges (*Forcipomyia taiwana* Shiraki), as they are smaller than mosquitoes, only mesh sizes of 55 or smaller can be effective.

Chemical Barriers

Physical barriers help prevent bites, while chemical barriers can deter bugs. Common chemical barriers used to reduce the risk of insect-borne infectious diseases can be divided into two types: repellents and insecticides.

An ideal repellent is one whose ingredients and form meet the following requirements [6]:

A. Chemicals: repellents

1. long lasting, and is effective against most arthropods;
2. does not cause skin-irritation;
3. has no bad odder;
4. does not stain clothes or cloth fibers;
5. does not leave an oily residue and resists removal by wiping, washing, or sweating;
6. does not erode frequently used plastic material;
7. is stable,
8. economical
9. non-toxic,
10. has sufficient protection time.

DEET (N,N-diethyl-*m*-toluamide; N,N-diethyl-3-methylbenzamide; or diethyltoluamide) is the most widely used repellent. It has been used by the United States Army since 1946, and remains the most effective repellent for over 50 years [8]. In addition to being effective against carriers of dengue fever, such as *Aedes aegypti*, *Aedes albopictus*, it is also effective against *Culex*, *Anopheles*, sand flies, black flies, chigger, hard tick, soft tick, bed bugs, fleas etc. [3]. It is estimated that each year DEET is used by 15 million people in the UK, 78 million people in the USA, and around two billion people globally [3]. Overseas repellent products contain a concentration of DEET from 5% to 100% and come in forms of aerosol, pump spray, liquid, and lotion. Repellents sold domestically are either approved by the Environmental Protection Administration (EPA) as an environmental agent, or approved by the Department of Health (DOH) as an over the counter product. Each category has very different use.

The Chinese name for DEET on the certificate issued by DOH is “待乙妥”, while the name used by EPA is “敵避”. DOH’s website, under the “medicine, medical instruments, skincare products search” section [9], shows that those products which have registered with DOH contain a DEET concentration of between 10% and 50%, and are listed as “over the counter products”. They come in liquid, gel, and cream forms. They are mainly used to repel flies, mosquitoes, fleas, lice, leeches, black flies, midges, bed bugs, and ants. According to the EPA’s “Certificates and Labelling Search Engine of Environmental Agents”, DEET concentrations in these environmental products range between 5% and 15% and come in spray and liquid forms. They are used to repel mosquitoes and midges. Protection times vary according to the DEET concentration (Table 1) [1], consumers need to reapply accordingly to ensure the best protection.

Table 1. Protection time estimates for various concentrations of DEET

% DEET	Protection Time					
	Mean		Lower limit of residual amount		Upper limit of residual amount	
	Minutes	Hours	Minutes	Hours	Minutes	Hours
5	110	2	76	1.5	144	2.5
10	214	3.5	158	2.5	270	4.5
15	276	5	208	3.5	344	5.5
20	319	5.5	243	4	395	6.5
25	352	6	269	4.5	469	8
30	380	6.5	281	5	469	8

Source: Health Canada, Pest Management Regulatory Agency RRD 2002-01(41)

Because products approved by EPA belong to “general hygiene and environmental agents”, they can only be sprayed into the environment or on screens, and should not be applied on the skin. Offer the information between products approved by DOH and those by EPA（Table 2）.

Table 2. The informatuon between repellents approved by the DOH and EPA

Authority	Department of Health (DOH)	Environmental Protection Administration (EPA)
Category	Over the counter product	Environmental and Hygiene agents
Classification (in Chinese)	DOH Medicine Manufacturing	EPA Hygiene Manufacturing, Hygiene Import
Ingredient’s Chinese name	待乙妥	敵避
Use	Spray on skin or clothing from about 10-15 cms away; can also be sprayed on cuffs and hems of sleeves and trousers for increased effect	spray on insect screens when indoors; or on the tents when outdoors such as camping
Warnings	Do not use on materials such as acetate, art silk, or synthetic fiber, furniture, plastic, surface of crystal, leather, oil painting or paint	

Whenever the risk of arthropod-associated diseases is present, it is essential to use appropriate repellents, especially those containing DEET [10] unless there is a concern of an adverse reaction such as an allergy. Some reports have mentioned that using DEET on children could cause encephalopathy, raising concerns over its safety [11]. However, DEET has been used for over 50 years with relatively few reports of ill-effects, most of them caused by incorrect use. There are reasons why many people are very worried about the safety of DEET [12], but nothing has proven that DEET used by pregnant or breastfeeding women could harm their babies [13]. The US Environmental Protection Agency indicates that DEET can be used without posing unreasonable risk to human health or the environment. It recommends that DEET products must be labeled as follows [14]：

1. Read and follow all directions and precautions on this product label.
2. Do not apply over cuts, wounds, or irritated skin.
3. Do not apply near eyes and mouth. Use with caution near the ears.
4. Do not use on children’s hands.
5. Keep products away from children.
6. Do not allow young children to apply this product. Spray the product on an adult’s hands first then transfer it to a child’s skin.
7. Use in moderation, just enough repellent to cover exposed skin and/or clothing.
8. Do not use under clothing.
9. Avoid over-application of this product.
10. After returning indoors, wash treated skin with soap and water.
11. Wash treated clothing before wearing it again.
12. Use of this product may cause skin reactions in rare cases.
13. In the event of an adverse reaction to this product, discontinue use of the product, wash treated skin, and call your doctor for help. Inform your doctor that you have used a product containing DEET.

B.Combining DEET with sunscreen

Exposure to UV rays and arthropod bites are both dangerous environmental risks. UV rays can cause skin cancer and accelerate ageing of the skin. It is recommended to use at least one sunscreen with SPF values of 15 or higher during outdoor activities [15]. The use of repellent and sunscreen combination products is not recommended [16] because when both ingredients are combined it reduces the sunscreen's performance.

If both DEET and sunscreen must be used at the same time, it is recommended that sunscreen be applied first and allowed to penetrate the skin for at least 20 minutes before applying repellent [1]. Montemarano et al. points out that DEET applied after sunscreen could significantly reduce the SPF values [17] by an average of33.5% [16]. However, research by Murphy et al. suggests that sunscreen does not affect the efficacy of DEET repellents [17]. There is no clear conclusion on whether using sunscreen and DEET at the same time, or using sunscreen and DEET combination products, is detrimental to health. However, as it does increase the absorption of DEET and oxybenzoner in the sunscreen, its long term safety requires further evaluation [18] Because sunscreen applied after DEET has been applied could significantly reduce the repellent's protection [18], Montemarano et al. recommend that additional sun protection precautions, such as wearing long sleeved clothing and a hat [16].

C. Essential Oil Repellents

More and more people like to use DEET-free, plant-based essential oil repellents which are often marketed as having natural and beauty benefits. However, being natural does not mean that they are not toxic or without side-effects. For example, a 21-month-old child died after mistakenly taken lemon grass oil, one of the most common "natural" repellent products. Lemon Eucalyptus oil has the same lethal dose as DEET, and serious cases of toxicity when accidentally ingested [12] have been reported. In Taiwan, many popular repellents, especially so-called "natural essential oil" based products, do not have EPA or DOH registrations. After careful consideration, the Department of Health decided to temporarily exclude essential oil based repellent liquids, which are to be applied on skin, from regulatory control (medicines for humans). DOH considers that essential oil products evaporate quickly and have only a short-term effect so they are unlikely to harm the health of the general public [19]. By definition, essential oil based repellent liquids are considered as a general product with limited repellent effect. Research by Fradin et al. points out that repellent containing citronella oil has less than 20 minutes of protection time [10] and thus, is not recommended [1]. The essential oil recommended by US Centers for Disease Control and Prevention is lemon Eucalyptus oil [20], which is a good alternative for people who are allergic to or cannot use DEET [1]. As the efficacy of protection can be affected by many environmental factors and the huge diversity between different types of arthropods, it is recommended to choose repellents whose performance has been laboratory or field tested.

Suggestion for children

Protection for children can be achieved by:1.always choosing insecticide-treated mosquito nets, especially for infants under 6-months; 2.using portable mosquito nets that can be available whenever required to keep arthropods away from children; and 3.using DEET products, which are suitable for children of all ages, as well as other appropriate protective methods.

Conclusion

Arthropod bites can be avoided by using a combination of the following methods:1.Avoiding contact with arthropods – stay away from areas where vectors are active, especially during their peak biting hours.2.Using physical barriers, such as long sleeved clothing or mosquito nettings.3.Using chemical barriers. Common chemical barriers used to reduce the risk of insect-borne infectious diseases can be divided into two types: repellents and insecticides. Repellents do not kill arthropods, but as they are not liked by arthropods they can keep arthropods away. Insecticides, on the other hand, kill arthropods upon contact.

The combined use of insecticide-treated nets and repellents has proven successful in malaria control. It shows that a combinati+on of multiple personal protection measurements is more effective than using single method. Repellents used on skin are the most common choice of self-protective measure, although its efficacy can still be influenced by many environmental factors and entomological differences. Better protection can be achieved by wearing long sleeved clothing in conjunction with the application of insect repellents. Although protection time can be limited during outdoor activities, this is still the most effective self-protective measure against arthropod bites.

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