Influenza at the Human-Animal Interface: PAHO Recommendations to Strengthen Intersectoral Work for Surveillance, Early Detection, and Investigation

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Objective

This document provides a summary of influenza viruses at the human-animal interface. It presents recommendations for surveillance strategies, monitoring, early detection, and steps of general case investigation that should be taken for influenza viruses at the human-animal interface, as well as guidance in their reporting.

This document is intended as a reference for public health authorities in human and animal sectors who deal with surveillance of influenza viruses.

Background

Animal influenza viruses are distinct from human seasonal influenza viruses and have not yet demonstrated the ability to be sustainably transmitted from person-to-person among humans. However, zoonotic influenza viruses (animal influenza viruses that may occasionally infect humans through direct or indirect contact prior to symptom onset) can cause disease in humans ranging from a mild illness to death. If these viruses acquire the capacity to spread easily among humans, either through adaptation or acquisition of certain genes from human viruses, they could trigger an epidemic or a pandemic.[1] When the swine influenza virus infects a human, the term "variant" influenza virus is used and the letter "v" (for "variant") is used after the name of these swine viruses, to distinguish these from human viruses of the same subtype.[2]

From 21 January to 22 June 2020, four new human infections from avian influenza A(H9N2) viruses and one new human infection from influenza A(H1N1)v virus were reported in China,[3] and one new human infection with influenza A(H1N2)v virus was reported in Brazil.[4]

[1] WHO. Influenza virus infections in humans. Available at: https://www.who.int/influenza/human_animal_interface/virology_laboratories_and_vaccines/influenza_virus_infections_humans_Oct_18.pdf

[2] WHO. Standardization of terminology for the influenza virus variants infecting humans. Available at: https://www.who.int/influenza/gisrs_laboratory/terminology_variant/en/

[3] WHO. Influenza monthly risk assessments. Available at: https://www.who.int/influenza/human_animal_interface/HAI_Risk_Assessment/en/

[4] WHO. Disease Outbreak News. Available at: https://www.who.int/csr/don/09-jul-2020-influenza-a-brazil/en/

In June 2020, the Chinese Academy of Sciences' Institute of Microbiology, Center for Influenza Research and Early-Warning, published a report entitled "Prevalent Eurasian avian-like H1N1 swine influenza virus with 2009 pandemic viral genes facilitating human infection." The article describes swine influenza viruses with genes from Eurasian avian-like A(H1N1) lineages and internal human genes, seasonal A(H1N1)pdm09 virus, and swine influenza triple reassortant viruses detected through swine surveillance from 2011 to 2018 in China. The swine influenza viruses were classified based on their genetic markers and termed genotypes G1-G6. Viruses with similar gene combinations, including the G4 genotype, were previously reported among swine in China by the Harbin Veterinary Research Institute, in a 2016 publication. G4 genotype viruses have been the dominant genotype among swine population in China since 2016.[5]

Sporadic zoonotic infections in humans with G4 genotype swine influenza viruses have been reported. The WHO Collaborating Center (CC) at the Chinese Center for Disease Control and Prevention (China CDC) has previously reported human infections by Eurasian avian-like A(H1N1)v viruses, including two recent cases with the G4 genotype; the most recent human case reported in November 2019. A candidate vaccine virus (CVV) from a closely related Eurasian avian-like A(H1N1) virus has been developed by the WHO CC at the China CDC and is available for vaccine development for pandemic preparedness purposes. Antigenic characterization studies to assess the cross-reactivity are being performed.[6]

The recent zoonotic influenza events and interconnectedness of animal infections, human infections, and environmental contamination highlights the urgent need to work together to strengthen influenza surveillance and response. The framework for this collaboration already exists through several mechanisms: a) the Global Influenza Surveillance and Response (GISRS) network; b) the tripartite WHO-Food and Agriculture Organization of the United Nations (FAO)-World Organisation for Animal Health (OIE) collaboration; and c) the One Health Initiative, whose aim is to promote cross-sectoral collaboration to address the risks of zoonoses and threats at the human-animal interface.

PAHO recommends that Member States continue to strengthen intersectoral work, specifically in sharing information being generated in both animal and human sectors on a weekly basis, and strengthen influenza surveillance in both sectors to detect unusual respiratory events, reduce the risk of infections, and ensure coordinated risk assessments and outbreak response. Thus, further reinforcing the last Recommendations of the 17th Inter-American Ministerial Meeting on Health and Agriculture (RIMSA-PAHO/WHO, 2016a, 2016b).

PAHO reiterates that all human infections caused by a novel influenza subtype are notifiable under the International Health Regulations (IHR) and that States Parties to the IHR (2005) are required to immediately notify WHO of any laboratory-confirmed case of recent human infection caused by an influenza A virus with the potential to cause a pandemic. The case definitions for purposes of IHR notification are available at: https://www.who.int/ihr/capacity/case_definitions/en/

[5] Publication available at: https://www.pnas.org/content/early/2020/06/23/1921186117

[6] https://www.who.int/docs/default-source/coronaviruse/transcripts/virtual-press-conference---1-july---covid-19.pdf?sfvrsn=9dbbd973_0

Animal avian and swine influenza

Avian influenza is a major transboundary animal disease that can affect local economy, threaten the food chain, and can even compromise food security in the most vulnerable economies (OIE/FAO, 2013). Avian influenza is classified by the OIE according to its presentation in poultry, following molecular and pathogenic criteria, as highly pathogenic avian influenza (HPAI) or low pathogenic avian influenza (LPAI) (OIE, 2019). While HPAI viruses often cause severe disease presentation, usually with high mortality in poultry, LPAI viruses present as milder episodes in poultry, associated to subtypes H5 and H7, which makes their clinical detection difficult (or impossible) (OIE/FAO, 2013)/

Swine influenza is an infectious disease of pigs, which may occur with clinical signs or asymptomatic. While morbidity normally reaches 100% in pigs, mortality is rare. When pigs are sick, they will show typical signs of acute upper respiratory syndrome, and may include fever, fatigue, anorexia, and/or weight loss. As a result, daily weight gain may be affected, a standard production trait (OIE, 2009).

All episodes of HPAI, as well as LPAI in poultry, require mandatory notification to the OIE and, therefore, should be a component of the official veterinary service (OVS) surveillance strategies of countries (OIE, 2019). The presence of swine influenza is not part of the list of diseases requiring notification to the OIE, as the disease in pigs is mild and it is not regarded as a common public health risk (OIE, 2009). As a result, many countries do not include the surveillance of swine influenza as part of the OVS duties.

Recommendations

Surveillance in humans

Surveillance for the emergence of novel influenza viruses with pandemic potential should be ongoing throughout the current COVID-19 pandemic. Due to the constantly evolving nature of influenza viruses, PAHO continues to stress the importance of severe acute respiratory infection (SARI) and influenza-like illness (ILI) surveillance to detect virologic, epidemiologic, and clinical changes associated with circulating influenza viruses that may affect human health.

In addition to active case-finding, contact identification, and activity monitoring conducted during zoonotic events, it is recommended to enhance existing SARI and ILI surveillance systems in locations where cases reside, where animal outbreaks are occurring, or where the source of infection is suspected. The geographical area targeted will need to be assessed on a case-by-case basis and is defined by the suspected exposures of the case under investigation. The duration of the enhanced surveillance will depend on the findings of the investigation and whether there is evidence indicating that sustained transmission may be occurring in the area. A minimum of one month of enhanced surveillance is reasonable to start.

Enhanced surveillance includes the following:

- Implementation of laboratory diagnostic capacity for testing suspected cases in a local health care facility, if feasible, or establishment of mechanisms for rapid transfer of specimens to a reference laboratory with testing capacity.
- Raising awareness of the need for surveillance to identify suspected cases and the use of a suspected case definition for case identification for use by health care workers in the community.
- If SARI or ILI surveillance is in place, expansion to other facilities in the area. If it is not, consider initiating SARI or ILI surveillance at health care facilities in the community where the case was identified.
- Increase the testing number for suspected SARI cases at local health care facilities in the area under investigation. If resources allow, consider increasing testing of milder cases of ILI presenting to surveillance sites.

To complement SARI and ILI surveillance, PAHO recommends strengthening and interlinking early warning systems to achieve situational awareness and coordinated joint risk assessment between human and animal sectors.

The primary focus of early detection is to detect events that may signal human-to-human transmission of an influenza virus with the potential to spread widely in humans. An early warning system for outbreaks should have the following characteristics:

- Sensitive, timely, and universal;
- A defined list of signal events that public health authorities should be notified immediately;
- A mechanism for investigating, evaluating, and responding to signal events; and
- A clear mechanism[7] for reporting signal events nationally and internationally.

The early detection activities that individual Member States carry out will greatly vary according to their available resources, but may include:

- Monitoring and analysis of routinely reported data from existing surveillance networks;
- Monitoring media sources for reports of unusual clusters or patterns of respiratory disease; and
- Monitoring for outbreaks of respiratory disease in animals.

Examples of triggers for the investigation of unusual events include:

- A case resulting from an influenza strain that does not normally circulate among humans (e.g., variant influenza viruses);
- An increase in acute respiratory disease among humans—unrelated to COVID-19—that is higher than expected by demographically or epidemiologically linked group, by geographical location, by severity, or by another factor; and

[7] https://www.who.int/ihr/publications/9789241596664/en/

- A SARI case (an acute respiratory infection with history of fever or measured fever of ≥ 38°C and cough; with onset within the last 10 days and requiring hospitalization), for which COVID-19 was ruled out, with one or more of the following criteria:
    - Does not respond to standard treatment or severe clinical deterioration, and without a conclusive laboratory result;
    - Associated with direct or indirect exposure to animals;
    - With travel history of 14 days prior to the onset of symptoms in countries where emerging viruses are circulating (e.g., influenza A(H7N9));
    - Occurring in a health care worker who has treated a SARI patient who had animal contact or exposure; and,
    - Part of a cluster of SARI or pneumonia cases without conclusive laboratory results.

Complementary surveillance in animals

The OVS also has a role in the early detection of influenza A strains present in the animal population, to improve pandemic preparedness and response. The OVS surveillance should be directed to detect the presence of circulating strains in the animal population or demonstrate their absence. There are international recommendations for developing avian influenza surveillance, seeking, among other objectives, to detect the presence of both clinical and subclinical avian influenza disease and to achieve early detection that enables international alerting, allowing for rapid control and prevention of spread. (OIE, 2019; Vapnek, 2010; WHO, 2017a). Surveillance also supports the early detection of zoonotic strains and provides information that can contribute to the response and preparation for possible pandemics (OIE/FAO, 2013; WHO, 2017b). With this intended purpose, recommendations can be extended to swine influenza.

There are two main strategies to be followed by the OVS to achieve their objectives: general surveillance, commonly known as "passive surveillance," and a more targeted approach, known as "active surveillance." These strategies must be clearly defined in national legislation that outlines the responsibility of the OVS as it pertains to avian and swine influenza (e.g., veterinary acts) and the OVS should be provided with sufficient resources to implement the strategies (Hogwood and Gunn, 1984; Hupe and Hill, 2016; Sabatier, 1986; Vapnek, 2010).

Passive surveillance

- Relies on the national system to detect and report suspected cases of avian influenza (normally associated with HPAI), which should be extended to include swine influenza.
- Avian influenza should be established as a disease requiring mandatory notification (in accordance to OIE recommendations), with defined notification requirements imposed, and roles outlined for all relevant stakeholders (including producers, local veterinarians,

slaughterhouses, etc.) so that they may immediately report suspicions of the disease to the OVS (Vapnek, 2010). Consideration should be given to the inclusion of swine influenza as a national notifiable disease to enhance its detection and reporting.

- Key roles of the OVS in implementing this strategy are to:
  - raise awareness about influenza in animals and the importance of the topic;
  - explain how it can be identified according morbidity/mortality and other clinical signs;
  - outline who should be contacted and how, in case of suspicion; and
  - ensure public-private cooperation.

- Furthermore, the OVS must be able to respond to suspicious cases with a system of detection, registration, investigation, and confirmation or discarding of cases (Martin et al., 2006).

Active surveillance

- Consists of studies designed ad hoc to search for evidence of infection.

- National policies must recognize the need for, and support, the implementation of regular active surveillance based on serological samples reporting previous exposure to the virus, complemented by molecular and/or virological monitoring of positive cases (OIE/FAO, 2013; Vapnek, 2010).

- Veterinary services should have the capacity to develop an adequate study design for sampling, to meet the objective of detecting (or ruling out) circulating LPAI strains in the poultry population and swine influenza strains in pigs.

- The capacity and preparation of official services to develop a robust survey design, execute, and followup, is key to the implementation of this type of policy (Hupe and Hill, 2016; Schofield, 2004).

Laboratory detection

National influenza centers and national reference laboratories for human influenza

In the Americas, all national influenza centers (NICs) and national reference laboratories for human influenza, inside the WHO GISRS, use molecular diagnostic protocols and reagents developed and validated by the WHO Collaborating Center at the US Centers for Disease Control (CD). These CDC kits for real-time reverse transcription polymerase chain reaction (RT-PCR) detection of influenza viruses are available through the International Reagent Resource (IRR).

The CDC influenza A/B typing and influenza A subtyping panels can indicate unusual influenza A viruses, including potential novel influenza viruses or potential variant influenza viruses. For this reason, all markers on each panel should be used while performing molecular diagnostic assays.

When using the CDC kits for influenza detection in human specimens, the detection of the InfA marker with no amplification of any of the subtypes markers or amplification of only one of the influenza A(H1N1)pdm09 subtype marker is **indicative of a potential novel influenza A virus** (Table 1). The unexpected detection of the pdmIfA marker together with the detection the H3 marker is indicative of a potential Influenza A(H3N2)v virus.

Table 1: Interpretation of real-time RT-PCR results indicative of potential unusual influenza virus.

Marker*						Results
InfA	InfB	pdmInfA	pdmH1	H3	RP	
+	-	-	-	-	+/-	Influenza A - Unsubtyped POTENTIAL NOVEL INFLUENZA VIRUS
+	-	+	-	+	+/-	Influenza A POTENTIAL INFLUENZA A(H3N2)v
-	-	-	-	-	+	Negative
-	-	-	-	-	-	Inconclusive

*Curves of the real-time RT-PCR assay must present the standard typology with a logarithmic phase and a plateau crossing the threshold line within 38 cycles (Ct <38).

<u>Important considerations for NICs and National Reference Laboratories for Human Influenza:</u>

- When an influenza virus with pandemic potential is suspected, including unsubtypeable or potential variant viruses, a sample should be sent within one week to a World Health Organization (WHO) Influenza Collaborating Center (CC) for further characterization.

- The sample should be shipped as soon as an unusual real-time RT-PCR pattern is detected and should not be delayed, even if additional testing in the country is planned.

- Under WHO's Pandemic Influenza Preparedness (PIP) Framework, Member States are expected to share their influenza viruses with pandemic potential on a regular and timely basis with the Global Influenza Surveillance and Response System (GISRS). The viruses are used by the public health laboratories to assess the risk of pandemic influenza and to develop candidate vaccine viruses.

National veterinary laboratories

National veterinary laboratories should be able to detect a wide range of circulating strains of avian influenza, including both serological assays, such as AGID and ELISA, and molecular testing, such as RT-qPCR. The diagnostic capacity for avian influenza should include notifiable subtypes such as H5 and H7, but it is also recommended to included other subtypes such as H9. Laboratories should also be able to detect circulating strains in pigs, particularly those that have greater zoonotic component, including swine influenza virus A(H1N1), A(H1N2), and A(H3N2). When national veterinary capacity is insufficient, it is important to establish adequate arrangements with the regional animal reference laboratories for diagnostic support, including efficient courier services for timely sample shipment.

The regional reference veterinary laboratories should play a key role by assisting the country veterinary laboratories with diagnosis (e.g., in the process of confirmation, contributing the typification of country samples, etc.). Regional reference veterinary laboratories also assist with performance evaluation of the national veterinary laboratories and with training for methods of diagnosis.

Case investigation

In the case of a **confirmed or suspected** human infection caused by a novel influenza virus with pandemic potential, including a variant virus, the following guidelines should be followed:

- A thorough epidemiologic investigation of history of exposure to animals, travel, and ill contacts should be conducted, even while awaiting confirmatory testing.
- The epidemiologic investigation should include early identification of unusual respiratory events that could signal person-to-person transmission of the novel virus.
- Clinical samples collected from the time and place that the case occurred should be tested and sent to a WHO CC for further characterization within the first week of detection.
- Standard infection prevention and control (IPC) procedures and standard precautions should always be applied, and personal protective equipment (PPE) used according to risk, to protect the health of the investigators. Appropriate PPE[8] (according to the most probable modes of transmission) should be used when in contact with symptomatic persons and in situations where human-to-human transmission is suspected.
- The epidemiological investigation should include information from the OVS and (animal production) private sector about the origin of the animals and the records of movements in and out of the premise. This information will contribute to define the scope (location) of investigations on humans exposed to the infected animals.
- Information from OVS could inform about potential episodes of influenza (both notifiable and non-notifiable) occurring in the area and farms related to the event.

[8] WHO. Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care. Available at: https://apps.who.int/iris/bitstream/handle/10665/112656/9789241507134_eng.pdf?sequence=1

Further information, including a description of potential studies that can address public health questions during an investigation and a clinical management algorithm for potential cases in an event of non-seasonal influenza, is available from the WHO on protocol[9] to investigate non-seasonal influenza and other emerging acute respiratory diseases.

Risk assessment

Swine influenza viruses circulate in swine populations in many regions of the world. Depending on geographic location, the genetic characteristics of these viruses differ. Most human cases are exposed to swine influenza viruses through contact with infected swine or contaminated environments. Human infection tends to result in mild clinical illness. Since these viruses continue to be detected in swine populations, further human cases can be expected. However, the likelihood of sustained human-to-human transmission of these viruses remains low, as these viruses have not acquired the ability for sustained transmission among humans.

Notification of cases in humans

1. Human infection caused by a **confirmed** novel influenza virus with pandemic potential, including a variant virus, should be reported immediately via two channels—the WHO International Health Regulations (IHR) Regional Contact Point (via the IHR National Focal Point: ihr@paho.org) and the GISRS managed by PAHO and WHO; the report should include all available results from the epidemiologic case investigation and the virologic characteristics of the virus.

2. Any human infection with a **suspected** novel influenza virus with pandemic potential, including a variant virus, should be reported immediately to the GISRS and information about the suspected case should be shared with the IHR National Focal Point, given it is an unusual event. The report should include all available results from the epidemiologic case investigation and the virologic characteristics of the virus.

[9] Available at: https://www.who.int/influenza/resources/publications/outbreak_investigation_protocol/en/

References

1. WHO Human-Animal Interface. Available online at: http://www.who.int/influenza/human_animal_interface/en/

2. WHO Avian Influenza Food Safety Issues. Available online at: http://www.who.int/foodsafety/areas_work/zoonose/avian/en/

3. World Organisation of Animal Health (OIE). Available online at: https://www.oie.int/

4. Food and Agriculture Organization of the UN (FAO). Available online at: http://www.fao.org/home/en/

5. OFFLU. Available online at: http://www.offlu.net/index.html

6. World Health Organization (WHO). International Health Regulations. Available online at: https://www.who.int/ihr/about/en/

7. WHO. FAO/OIE/WHO Collaboration. Available online at: https://www.who.int/zoonoses/concept-note/en/

8. WHO. Global Epidemiological Surveillance Standards for Influenza. Available online at: https://www.who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf?ua=1

9. WHO. Preparing GISRS for the upcoming influenza seasons during the COVID-19 pandemic. Practical considerations. Available online at: https://apps.who.int/iris/bitstream/handle/10665/332198/WHO-2019-nCoV-Preparing_GISRS-2020.1-eng.pdf

10. Centers for Disease Control and Prevention (CDC). Data Interpretation Update to the CDC Flu rRT-PCR Dx Panel. 6 August 2012. Available online at: https://www.cdc.gov/flu/pdf/swineflu/data-interpretation-update.pdf

11. Centers for Disease Control and Prevention (CDC). Information on Swine/Variant Influenza. Available online at: https://www.cdc.gov/flu/swineflu/index.htm

12. Centers for Disease Control and Prevention (CDC). CDC Takes Action to Prepare Against “G4” Swine Flu Viruses in China with Pandemic Potential. Available online at: https://www.cdc.gov/flu/spotlights/2019-2020/cdc-prepare-swine-flu.html

13. Centers for Disease Control and Prevention (CDC). Information on Avian Influenza. Available online at: https://www.cdc.gov/flu/avianflu/

Additional Resources

1. World Health Organization. (2018). WHO Protocol to investigate non-seasonal influenza and other emerging acute respiratory diseases (WHO/WHE/IHM/GIP/2018.2). Geneva: World Health Organization. Retrieved from: https://www.who.int/influenza/resources/publications/outbreak_investigation_protocol/en/

2. PAHO. (2009). Health establishments preparation for unusual or unexpected cases or clusters of severe acute respiratory infection SARI, 2009. Available at: http://www1.paho.org/hq/dmdocuments/2009/SARI%20English_Module_Final.pdf

3. WHO. Resources for assessing and minimizing public health risks. Available at: https://www.who.int/influenza/human_animal_interface/assessing_risks/en/

4. WHO. (2011). IMAI District Clinician Manual: Hospital care for adolescents and adults guidelines for the management of common illnesses with limited resources. Available at: https://www.who.int/influenza/patient_care/IMAI_DCM/en/

5. WHO. (2018). Quick check and emergency treatments for adolescents and adults. Wall chart available at: https://www.who.int/influenza/patient_care/clinical/IMAI_Wall_chart.pdf?ua=1

6. WHO. (2009). Infection prevention and control during health care for confirmed, probable, or suspected cases of pandemic (H1N1) 2009 virus infection and influenza-like illnesses. Available at: https://www.who.int/csr/resources/publications/cp150_2009_1612_ipc_interim_guidance_h1n1.pdf?ua=1

7. WHO. Influenza public health preparedness guidelines. Available at: https://www.who.int/influenza/preparedness/en/

8. WHO. (2014). Early detection, assessment, and response to acute public health events: Implementation of Early Warning and Response with a focus on event-based-surveillance. http://www.who.int/ihr/publications/WHO_HSE_GCR_LYO_2014.4/en/

9. WHO. (2013). Technical consultation on event-based surveillance: meeting report. Available at: http://www.episouthnetwork.org/sites/default/files/meeting_report_ebs_march_2013_final.pdf

10. WHO. (2007). Interim protocol: rapid operations to contain the initial emergence of pandemic influenza. Available at: https://www.who.int/influenza/resources/documents/RapidContProtOct15.pdf

11. Hill, M., Hupe, P. (2014). The top-down/bottom-up Debate, in: Implementing Public Policy. London: SAGE; 44–58.

12. Hogwood, B., Gunn, L. (1984). Implementation. In: Policy Analysis for the Real World. Oxford: Oxford University Press; 196–218.

13. Hupe, P.L., Hill, M.J. (2016). 'And the rest is implementation.' Comparing approaches to what happens in policy processes beyond great expectations. Public Policy Adm. 31, 103–121. https://doi.org/10.1177/0952076715598828

14. Martin, V., Forman, A., Lubroth, J. (2006). Preparándose para la Influenza Aviar Altamente Patógena Un Manual para países en riesgo Tabla de Contenidos.

15. OIE/FAO. (2013). OFFLU strategy document for surveillance and monitoring of influenzas in animals 2009, 1–36.

16. OIE. (2019). Infection with avian influenza viruses. In: Terrestrial Animal Health Code, pp. 1–18.

17. OIE. (2009). Technical Disease Card. Swine Influenza.

18. RIMSA-PAHO/WHO. (2016a). Panel 1: The intersectoral collaboration on Health and Agriculture for the Sustainable Development Goals: Governance of Zoonotic Diseases.

19. RIMSA-PAHO/WHO. (2016b). Inter American Ministerial Meeting on Health and Agriculture "One Health and the Sustainable Development Goals."

20. Sabatier, P.A. (1986). Top-down and bottom-up approaches to implementation research: a critical analysis and suggested synthesis. J. Public Policy 6, 21–48. https://doi.org/10.1017/S0143814X00003846

21. Schofield, J. (2004). A model of learned implementation. Public Adm. 82, 283–308.

22. Vapnek, J. (2010). Regulatory measures against outbreaks of highly pathogenic avian influenza. FAO Leg. Pap. Online. https://doi.org/10.2139/ssrn.3354970

23. WHO. (2017a). Pandemic influenza risk management: A WHO guide to inform and harmonize national and international pandemic preparedness and response. Geneva: World Health Organization. Licence: CC.

24. World Health Organization. (2017b). Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III): advancing implementation of the International Health Regulations (2005). Manila, Philippines.

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