Gulf Rapid Risk Assessment:
Highly Pathogenic Avian Influenza H5N1

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This document has been developed by the Gulf Center for Disease Prevention and Control (Gulf CDC) for the awareness of public health authorities within countries of the Gulf Cooperation Council. The rapid risk assessment provides guidance based on the information available to the Gulf Public Health Emergencies Network as of 15 October 2023.

I. Event Background

(a) Signal detected by Gulf CDC

The Gulf CDC has been detecting an increasing number of signals of Highly Pathogenic Avian Influenza H5N1 (HPAI H5N1) infections globally. Since the establishment of Gulf CDC's Epidemic Intelligence in October 2022, a total of 63 avian influenza H5N1 signals[1] were detected. Of these signals, 6 were human cases (see table 1.). All cases were symptomatic with respiratory manifestations, such as cough and severe pneumonia, as well as fever; some developed further complications involving failure of the liver, kidneys, and jaundice.

Table 1. Examples of human cases of H5N1 detected by the Gulf CDC between October 2022 and October 2023

Date of signal detection	Location	Description of case	Presumed Exposure
21-10-2022	Viet Nam	5-year-old girl, developed cough, fever, jaundice, renal, and liver failure. Survived	Backyard poultry (chickens and ducks)
01-12-2022	China	38-year-old woman, developed pneumonia and passed away.	Backyard poultry

[1] Signals are not inclusive of all global infections. List of global infections can be found on: https://www.fao.org/animal-health/situation-updates/global-aiv-with-zoonotic-potential/en

26-02-2023	Cambodia	11-year-old girl developed sever pneumonia and passed away. 1 contact, **her father, tested positive**[2] but was asymptomatic.	Not reported.
05-03-2023	China	53-year-old woman, developed severe pneumonia and survived.	Backyard poultry
10-10-2023	Cambodia	50-year-old man, symptoms were not reported, and passed away	Backyard poultry
11-10-2023	Cambodia	2-year-old girl, developed symptoms of coughing, high temperature and vomiting, and passed away.	Backyard poultry

In addition to human cases, the detected reports suggest that avian influenza outbreaks in domestic and wild bird populations across multiple regions have increased, indicating a wider geographic spread of the virus since mid-2022. Other mammalian species (such as sea lions, dolphins, foxes, raccoons, minks, cougars,) are being infected as well.

(b) Hazard detected (Possible zoonoses and important animal diseases outbreaks)

1. Global Burden and Epidemiology

Avian influenza viruses are commonly found in wild birds, primarily affecting waterfowl. HPAI A(H5N1) viruses, in particular, have been characterized by their ability to cause severe illness and high mortality rates in infected birds, particularly gallinaceous poultry.

During 2020, the HPAI A(H5N1) **clade 2.3.4.4b** virus emerged from previously circulating A(H5Nx) viruses and has become a panzootic with unexpected characteristics. This virus has caused the largest HPAI epidemic historically observed in Europe, with a total of 2,467 outbreaks in poultry, 47.7 million birds culled in the affected establishments, 187 outbreaks in captive birds, and 3,573 HPAI virus detections in wild birds with an unprecedent geographical extent affecting 37 European countries (1). In late 2021, the clade 2.3.4.4b A(H5N1) virus also crossed the Atlantic Ocean to North America along migration routes, causing outbreaks in poultry and wild birds in several Canadian provinces and the U.S.A. where a record number of birds were affected (in 2022, more than 49 million birds in 46 states have either died or been culled (2). The current global trends suggest that the virus transmission is deviating from its usual seasonal cycle in many regions. Given the extensive spread of clade 2.3.4.4b A(H5N1) viruses among wild birds, predatory and scavenger mammals, which consume these birds, have experienced sporadic infections of the virus.

There have been increasing reports of spill over to **non-avian species** including wild terrestrial and marine mammals, such as minks, ferrets, foxes, raccoons, seals, mountain lions, dolphins,

[2] Note: the virus responsible for these infections is genetically distinct from that causing global outbreaks in birds.

cast and dogs. While the occurrence of these infections was likely, the number of them was unexpected.

Fortunately to date, there is limited evidence for mammal-to-mammal spread and minimal evidence of acquisition of adaptive genetic mutations outside of those in polymerase basic protein 2 (PB2) gene.

From December 2021 to 14 July 2023, 12 **human** cases of A(H5N1) belonging to the 2.3.4.4b clade, out of the 15 human A(H5N1) detections, were documented (3). Only 8 of the 2.3.4.4b have been officially reported to WHO thus far (4).

2. Transmission

While the primary transmission route of HPAI A(H5N1) is bird-to-bird, there have been sporadic cases of bird to mammal as described above. With the notable exception of infections in sea mammals, mammal cases are usually linked to close contact with infected birds or contaminated environments. There is no evidence of human-to-human transmission of the clade 2.3.4.4b virus.

II. Health Condition Background (in humans)

While the spectrum of clinical symptoms of H5N1 in humans may vary, infections can lead to an unusually aggressive course, characterized by rapid deterioration and fatality. Initial symptoms of H5N1 infection include a high fever, usually exceeding 38°C, and influenza-like illness (ILI) symptoms; one common ILI feature observed is the early development of manifestations in the lower respiratory tract. Some patients may also experience diarrhoea, vomiting, abdominal pain, chest pain, and bleeding from the nose and gums as early symptoms (5).

The incubation period for H5N1 avian influenza appears to be longer than that of normal seasonal influenza, which typically lasts around two to three days. Current data suggests an incubation period ranging from two to eight days for H5N1 infection, with some cases possibly extending up to 17 days (5).

It should be noted that these data relate to clades other than 2.3.4.4b; it is expected, but not certain that infections caused by clade 2.3.4.4b viruses will behave similarly. In general, our understanding of H5N1 influenza infection clinical manifestations in humans remains limited, as it is an emerging disease. The current understanding may also evolve due to the virus's rapid and unpredictable mutation tendencies (5).

III. Situation Update (in GCC)

There have been no reports of HPAI H5N1 infections in any species across the GCC countries in 2022-2023 to the knowledge of the Gulf CDC as of 27 August 2023.

The H5N1 avian influenza virus was first detected in Egypt in December 2005 during migratory bird sampling. It was closely related to a virus found in Qinghai Lake, China, suggesting transcontinental spread through wild bird migration. Despite control measures, the virus became endemic, with poultry outbreaks exhibiting a seasonal pattern, peaking from November to March. The highest number of outbreaks occurred in major poultry-producing governorates. Active surveillance programs detected H5N1 virus primarily in the commercial sector, followed by an increase in prevalence and detection in all poultry sectors, including co-infections with H9N2 influenza virus. While H9N2 influenza virus became more common, A(H5) viruses remained present (6).

IV. Risk assessment

(a) RRA Purpose/Decision

The purpose of conducting the Rapid Risk Assessment (RRA) on HPAI A (H5N1) is in accordance with the Gulf CDC SOP/001 following the detection of a new emerging or re-emerging disease. The decision to conduct the RRA was made by the Gulf CDC Public Health Emergency Network (PHEN) on 3 August 2023.

(b) RRA Risk Question(s)

What is the likelihood of HPAI H5N1 human-to-human transmission occurring in the GCC countries and what is the impact of such transmission?

(c) Risk Characterization: Estimation of Likelihood and Impact

1. Likelihood of HPAI H5N1 human-to-human transmission in GCC countries

i. Introduction of virus in the community through local spillover from non-human species

Avian influenza viruses (AIVs) face significant barriers before they can successfully adapt to transmit among humans. Among the mutations that are known to aid AIV overcoming these transmission barriers are (noting that rare infection can still occur without the changes below):

- Polymerase basic protein 2 (PB2) is a protein that plays a critical role in viral replication. Mutations within the AIV PB2 gene can lead to more severe infections in humans. Notable mutations associated with AIV PB2 adaptation to mammals include PB2-E627K, PB2-D701N, and PB2-T271A. Other mutations such as PB2-S590G and PB2-R591Q have also demonstrated similar effects (7). Many of the clade 2.3.4.4b viruses isolated from mammals have acquired these mutations; the mutations remain rare in viruses from birds.
- Hemagglutinin (HA) is responsible for binding to sialic acid (SA) receptors on the host cell surface and initiating viral entry. AIVs predominantly bind to α2-3-linked SA receptors, which are abundant in avian species. To support airborne transmission between humans, AIVs must undergo mutations to acquire the ability to bind to α2-6-linked SA receptors, which are predominant in the human upper respiratory tract (URT). Mutations within the HA gene, as well as the neuraminidase (NA) gene, which is involved in viral entry and release, might contribute to increased binding affinity for the human α2-6-linked SA receptors. Notable mutations associated with α2-6 binding adaptation include HA-Q222L, HA-E190D/HA-G225D, and NA-S430G (8). Mutations that increase α2-6-linked SA receptors are rare in the clade 2.3.4.4b A(H5N1) viruses.
- Stabilizing HA mutations often accompany the receptor binding changes necessary for human adaptation of AIV. These mutations might increase the virus' pH and heat stability, enabling it to persist and transmit more effectively among humans. A notable mutation associated with increased stability is HA-H103Y although other substitutions , many of which are poorly defined, can have similar effects (9). There is no evidence for stabilizing HA mutations in the clade 2.3.4.4b A(h5N1) viruses, although the samples tested has been in a small number.
- The human innate immune system possesses mechanisms that exert antiviral effects against AIVs, such as the RIG-I and MxA proteins. Mutations have been identified that enhance the ability of influenza viruses to avoid these responses. It remains unclear if previous infections with seasonal influenza A viruses confer adaptive immunity to zoonotic and potentially pandemic viruses and how this influences population-based immunity (10). There is, however, an expected levels of NA cross reactive antibodies to the A(H5N1) N1 in humans due to exposure to A(H1N1)pdm09 viruses.

While recent clade 2.3.4.4b A(H5N1) viruses have not been detected in the Gulf countries, their connectivity to other countries through agricultural trade and bird migration (particularly during the upcoming hunting season Sept 2023 - Mar 2024), shows that the importation of the virus is

plausible as is spillover to humans[3]. The likelihood (See the Gulf CDC Risk Assessment Matrix, SOP001) of this spillover to humans is currently likely. Spillover likelihood may be marginally higher for poultry workers and poultry market visitors. Due to the association of human A(H5N1) cases in other countries and exposure to birds.

ii. Introduction of virus into community through importations from countries reporting recent spillover events

Table 2. Potential of exporting HPAI H5N1 human cases from the highest reporting countries. Exportation refers to the probability of an infected patient leaving an origin in the next 30 days considering global connectivity, and not direct connection to the GCC countries.

Country	Human cases (2021-2023)	Deaths reported	Likelihood of case exportation/ month	Estimated case exportation/ month
United Kingdom	4 cases	-	Moderate	Less than 11 cases
Chile	1 case	-	Moderate	Less than 11 cases
Cambodia	2 cases	1 death	Low	Less than 11 cases
Brazil	1 case	-	Low	Less than 11 cases
Vietnam	1 case	-	Low	Less than 11 cases
China	2 cases	1 death	Unlikely	Less than 11 cases
Spain	2 cases	-	Not calculated	Not Calculated

While the countries listed in Table 2 have highest potential of exporting human cases, the 2 countries with closest links to the GCC and relatively higher importation likelihood from are China and Vietnam. It is important to note that these importations can happen over a long period of time, as such, these estimations should be carefully interpreted.

iii. Likelihood of the assessed risk

Given the factors assessed in (i) and (ii), the overall probability of introduction of the virus is low, but not negligible. There is no current global evidence of human-to-human transmission of the clade 2.3.4.4b viruses. Nevertheless, the worst-case-scenario of the virus mutating and developing the potential for human-to-human transmission should be considered.

As such, the likelihood of human-to-human transmission is estimated to be **unlikely** at this time.

[3] The Gulf CDC does not assess the level of importation likelihood of the virus through non-human species, as this estimation is beyond its human public health mandate and beyond this RRA's question.

2. *Impact of Human HPAI H5N1 Infections in GCC countries*

Recent status of the capacities in the GCC countries in 2022-2023 are listed in Table 3.

Table 3. Recent reported status of GCC countries capacities to prepare, detect and response to avian influenza, as reported to the Gulf CDC during the PHEN roundtable meetings.

GCC country	Capacity Update
United Arab Emirates	Infectious disease programs or services have been set up for zoonosis. The zoonosis program was established, and it has a national action plan, policies, strategies, and a monitoring and evaluation framework. However, national programs have not been set up for specific zoonotic diseases.
Bahrain	Several infectious disease programs or services have been established, including those for zoonotic diseases. Currently, there are no national strategies for zoonosis but program strategies are under development.
Saudi Arabia	An infectious disease program specifically addressing zoonosis has been established alongside various other programs. The zoonosis program has a national prioritization framework, an integrated surveillance system among different sectors, routine multisectoral risk assessment and monitoring activities. There is joint emergency teams work together for responding to any zoonotic threats..
Oman	A specific program has been set up for zoonosis. The zoonosis program has a national policy in place and is currently active. However, it does not have a national strategy, action plan, or a monitoring and evaluation framework like the other infectious disease programs.
Qatar	Programs or services for infectious diseases have been set up, including those for zoonosis. The zoonosis program was established between 1979 and 2019. It does not have national action plan, strategies, nor policies with a national monitoring and evaluation framework.
Kuwait	Infectious disease programs or services are available for zoonosis. The zoonosis program was established between 1969 and 2020, and the program is active and has a national action plan, policies, strategies, and a monitoring and evaluation framework.

As some GCC countries still lack strategic plans or programs needed to control and prevent the spread of avian influenza, there may be significant delays in detection of the first few cases. For example, there are limited systems in place developed for ensuring regular collaboration and coordination (including routine sharing of information, joint investigations, etc.) between the Health and Agricultural sectors. This detection delay may lead to the infected individual seeking healthcare at a later stage of the infection, risking further complications and severe symptoms. At worst, these individuals could shed the virus and start a chain of human-to-human transmission.

Nevertheless, despite the global unavailability of specific antiviral drugs for HPAI H5N1, case management capacities of the GCC countries for influenza infections are generally high (e.g. access to neuraminidase inhibitors, such as, oseltamivir (commercially known as Tamiflu or

Oselta[4]), peramivir and zanamivir, and baloxavir. Thus, symptomatic management of human infections (if local spillover or internationally importations are detected early enough) is expected to be high, reducing the potential impact on individual health complications.

Thus, the potential impact of HPAI A (H5N1) infections if transmission occurs in the GCC region is assessed to be **low**.

(d) Risk Characterization: Overall Risk Definition

Risk assessed					
Negligible	Very Low	Low	Moderate	High	Critical

(e) Level of Confidence

This risk assessment is associated with a low level of confidence due to limitations in engaging the agricultural stakeholders in the GCC countries for relevant data (e.g. history of avian influenza detections in poultry, distribution and population of waterfowl species, maps of migratory bird pathways).

(f) Risk Statement

Based on the available data at this point of time, within the next 3 months, the overall risk of a human-to-human transmission occurring in the Gulf is assessed as **Low**. This risk level may be higher for certain population groups (e.g. poultry workers, animal market visitors) or in case of any development in the global and regional epidemic situation.

V. Recommendations

GCC countries should consider the following recommended actions for better preparedness, readiness, and response against avian influenza:

1. Reviewing national implementation status of activities agreed within the joint GCC meeting on AIV in 2005;

[4] Other brands of oseltamivir in the GCC: Tabuflu, Oselow, Fluvir, Seltafu, Taminil, Flucap

2. Revise and update national policies and procedures for detecting AIV and responding including: culling, establishing free-zones, and waste management for affected farms and sites.
3. Conduct simulation exercises to test current levels of readiness for a local spill-over event and human-to-human transmission;
4. Prioritize the surveillance efforts for timely detection of virological, epidemiological, and clinical changes associated with circulating influenza viruses, which may affect human (or animal) health, and timely information sharing for risk assessment.
5. Review and ensure availability of diagnostic tests of the virus, increase current vaccine, antiviral drugs and personal protective equipment (PPE) stockpiles, in collaboration with other GCC countries;
6. Increase awareness and risk communication for populations at risk (e.g. poultry workers, animal market visitors, bird hunters) for the appropriate use of PPE when in contact with birds;
7. Ensure public communication plans and pre-prepared announcements are in place;
8. Consider restriction on the import of fowl, poultry meat, hatching eggs and fodder from countries infected by bird flu and those suspected of being infected; as well as restriction on imports of waterfowl, terrestrial and ornamental birds from across the world;
9. Activating or establishing a national multi-sectoral one-health preparedness committee of relevant stakeholders. Stakeholders may include:
    - Ministry of Agriculture; or other responsible entity for wildlife or animal health
    - Ministry of Information/Culture; for coordinating and managing effective communication strategies to raise awareness, educate the public, and counter misinformation.
    - Ministry of Foreign Affairs; for cross-border implications
    - Other relevant authorities, such as those involved in border-customs, forecasting, water, food, and marine.

    This committee shall capitalize on the existing Gulf entities such as GCC, GHC, and GCDC and shall plan for regular meetings to monitor and plan for outbreak management and response, as well as the guide joint implementation of activities and effective communications in the event of an outbreak.

10. Enhance cooperative laboratory capacities between GCC countries and among different sectors (health and agriculture) to rapidly respond to zoonotic threats.

11. Establish GCC agreement on information sharing, resource mobilization and experts network.

VI. References

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VII. Annexes

Annex 1: Gulf CDC Signals of Avian Influenza H5N1 detected from 22 October to 02 August 2023.

Date	Country	Hazard
20-10-22	Vietnam	Avian Influenza H5N1*
01-12-22	China	Avian Influenza H5N1*
23-01-23	Spain	Avian Influenza H5N1
08-02-23	Taiwan	Avian Influenza H5N1
08-02-23	United Kingdom	Avian Influenza H5N1
26-02-23	Cambodia	Avian Influenza H5N1* (2 cases)
05-03-23	China	Avian Influenza H5N1*
06-03-23	Peru	Avian Influenza
09-03-23	France	HPAI H5N1
19-03-23	UK	Avian Influenza H5H1
27-03-23	Chile	Avian Influenza H5N1
05-04-23	Belgium	Avian Influenza H5N1
05-04-23	US	Avian Influenza H5N1
09-04-23	Chile	Avian Influenza
09-04-23	US	HPAI H5N1
09-04-23	US	Avian Influenza H5N1
09-04-23	Chile	Avian Influenza H5N1
16-04-23	Israel	HPAI H5N1
20-04-23	USA	Avian Influenza H5N1
21-04-23	Japan	HPAI H5N1
07-05-23	Italy	Avian Influenza H5N1
30-05-23	Brazil	HPAI H5N1
04-06-23	England	Avian Influenza

25-06-23	Poland	Avian Influenza H5N1
28-06-23	Poland	Avian influenza H5N1
29-06-23	Brazil	Avian Influenza H5N1
29-06-23	Poland	Avian influenza H5N1
09-07-23	Italy	HPAI H5N1
09-07-23	Latvia	HPAI H5N1
09-07-23	Hungary	HPAI H5N1
09-07-23	Ireland	HPAI H5N1
09-07-23	Germany	HPAI H5N1
09-07-23	Togo	HPAI H5N1
09-07-23	Sweden	HPAI H5N1
09-07-23	Norway	HPAI H5N1
11-07-23	Scotland	HPAI H5N1
12-07-23	Russia	HPAI H5N1
12-07-23	Finland	HPAI H5N1
12-07-23	Poland	HPAI H5N1
13-07-23	Germany	HPAI H5N1
13-07-23	Belgium	HPAI H5N1
13-07-23	Belgium	HPAI H5N1
13-07-23	Belgium	HPAI H5N1
13-07-23	Belgium	HPAI H5N1
13-07-23	Germany	HPAI H5N1
17-07-23	Brazil	HPAI H5N1
17-07-23	Finland	HPAI H5N1
19-07-23	Ireland	HPAI H5N1
19-07-23	Ireland	HPAI H5N1
19-07-23	Switzerland	HPAI H5N1

19-07-23	Indonesia	HPAI H5N1
19-07-23	Brazil	HPAI H5N1
19-07-23	Brazil	HPAI H5N1
19-07-23	Estonia	HPAI H5N1
19-07-23	Argentina	HPAI H5N1
19-07-23	Belgium	HPAI H5N1
23-07-23	Colombia	HPAI H5N1
27-07-23	South Korea	HPAI H5N1
27-07-23	United States	HPAI H5N1
30-07-23	Czech Republic	HPAI H5N1
02-08-23	Northern Ireland	HPAI H5N1
10-10-2023	Cambodia	Avian Influenza H5N1*
11-10-2023	Cambodia	Avian Influenza H5N1*
**: indicates human cases*		

Annex 2: Recommendations made by the joint GCC meeting on AIV in 2005

Historically, in response to the call from H.E. the Saudi Minister of Agriculture to address the global outbreak of avian influenza, specifically H5N1, and protect the GCC countries from its prevalence, a meeting was held in Riyadh on November 16th, 2005. During the meeting, discussions encompassed the worldwide epidemiological developments of avian influenza and the national plans and strategies aimed at combating the pandemic (11). Following comprehensive deliberations, the Ministers proposed the increasing capacities of the GCC countries to prepare for, detect and respond to avian influenza. These recommendations reflect the collective joint efforts and commitment of the GCC countries to combat avian influenza and mitigate its impact on public health and agricultural sectors.

Recommendations:

1. Pooling the technical and human resources of each member country to support all GCC countries.
2. Continuously monitoring the global epidemiological developments of avian influenza.

3. Implementing national plans and working towards establishing a unified GCC strategy to combat avian influenza.
4. Sharing information and experiences among the ministries of health and agriculture in the GCC and appointing a liaison officer in each ministry to facilitate direct communication between member countries.
5. Prohibiting the import of birds, poultry products (meat, eggs, poultry feed, etc.) from countries confirmed or suspected to be affected by the pandemic. Strengthening quarantine procedures and promptly sharing relevant information on the import ban within the GCC member states. Additionally, banning the import of ornamental, waterfowl, and wild birds from worldwide sources.
6. Immediately reporting any suspected cases of H5N1 within any GCC country to the other member states through the designated liaison officers.
7. Directing the Standing Committee of Animal Resources to hold continuous meetings and develop a unified future plan for the GCC countries to combat such pandemics and outbreaks, including the establishment of an early warning program.
8. Coordinating efforts among the ministries of health, agriculture, and other relevant governmental authorities in the GCC for the exchange of information on avian influenza.
9. Activating comprehensive early warning and epidemiological surveillance systems to effectively address the avian influenza pandemic.
10. Ensuring the availability of necessary resources for prevention, diagnosis, and treatment of avian influenza in GCC countries.
11. Conducting awareness programs to educate the public about the risks, modes of transmission, and necessary precautions to reduce the likelihood of infection.
12. Keeping abreast of global developments in the production of a specific vaccine for avian influenza and initiating negotiations with manufacturers to ensure timely availability.
13. Collaborating among GCC member states to collectively combat the disease in both bird and human populations once detected.

VIII. Acknowledgements

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