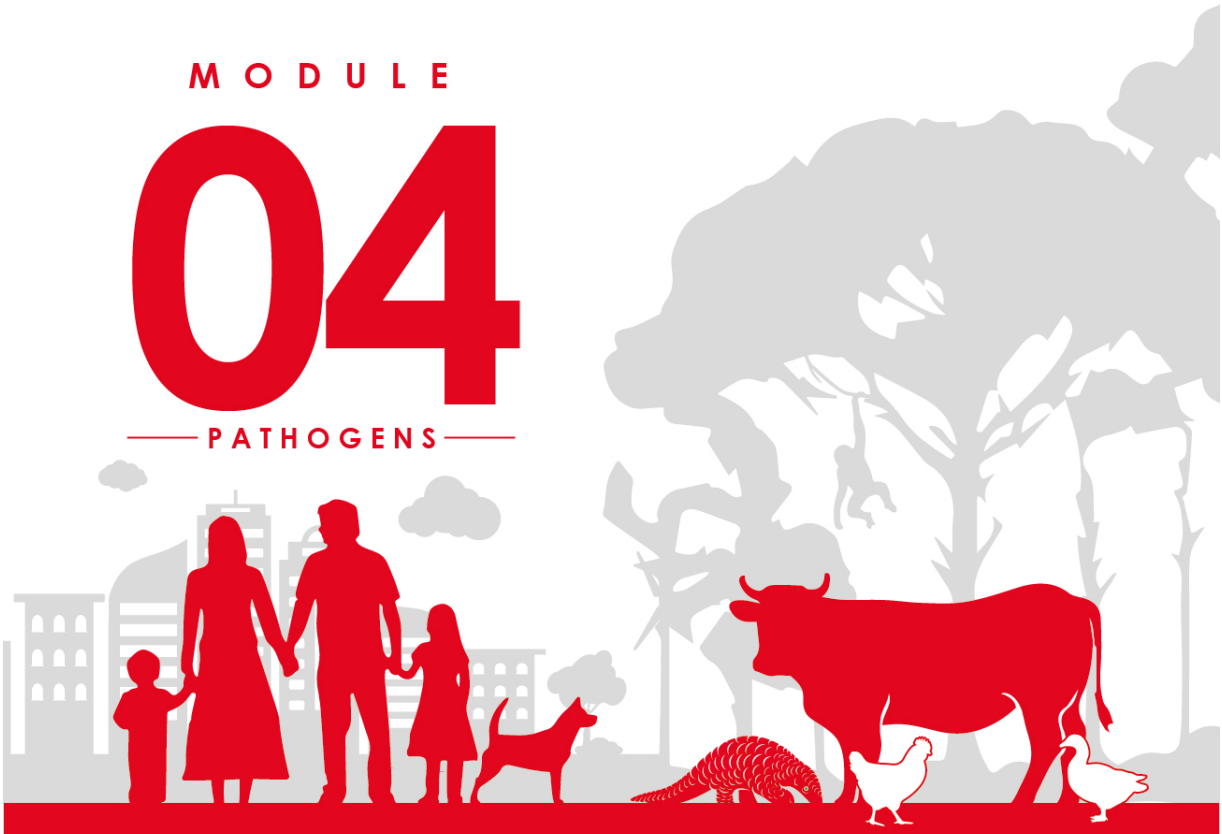
MODULE

04

PATHOGENS



How to Identify and Characterize Priority Pathogens to Guide Efforts to Address Zoonotic Disease Spillover

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MODULE 4: HOW TO IDENTIFY AND CHARACTERIZE PRIORITY PATHOGENS AND ANIMAL HOSTS TO GUIDE EFFORTS TO ADDRESS ZOONOTIC DISEASE SPILLOVER

The goal of this module is to review and develop guidelines and tools to identify and prioritize zoonotic pathogens, especially those with pandemic potential and their animal hosts/reservoirs, in the context of SEA and the populations at highest risk. The prior (SARS) and ongoing human coronavirus epidemics/pandemics (MERS, COVID-19) and similar scenarios for influenza A virus will be used as examples related to these goals and to illustrate zoonoses, spillover and spillback of these pathogens among humans and animals. Case examples of the potential for new coronaviruses (CoVs) to emerge as WHO "Disease X" are presented. Finally biosafety and biosecurity measures and information sources related to work on high impact zoonotic pathogens are described.

Background, Introduction and Historical Context for Emergence and Re-Emergence of Zoonotic Pathogens

Due to an everchanging, globalized world, zoonotic spillovers and the rapid dissemination of pathogens are becoming increasingly inevitable. For centuries emerging infectious diseases (EID) have been spilling over as zoonoses from animals to humans with some spilling back from humans to animals (reverse zoonosis), creating the potential for secondary spillback to humans (see Box 4-1 for definitions of terms). However, the frequency of emerging/re-emerging zoonotic diseases has accelerated over the past 25 years (see Fig 4-1), with many EID causing severe illnesses, deaths and often pandemics. The increasing human population coupled with changes in climate, land use pattern, agricultural industry changes, international travel and commerce and increased human susceptibility to infections were identified as the top macro-level drivers of such rapid and sustained zoonotic spillover (Daszak et al., 2013; Karesh et al., 2012; Tajudeen et al., 2022). Underlying drivers of increased risk of EIDs that exacerbate the spillover/spillback also include microbial evolution; expanding human–animal–environmental interfaces; climate change; and human behavior (food consumption etc.) (Baker et al. 2021; Allen et al. 2017).

BOX 4-1 Glossary of terms referenced in this review

Zoonosis

An infectious disease that is transmitted from animals to humans. e.g., influenza virus, ebolavirus, SARS coronaviruses.

Reverse zoonosis/spillback

An event in which a previously zoonotic pathogen that has undergone spillover into humans infects novel, nonhuman animals, e. g., transmission of SARS-CoV-2 from humans into mink or white-tailed deer.

Spillover

An event in which a species-specific pathogen establishes infection in a novel susceptible host, e. g., transmission of Nipah virus from bats into pigs.

Secondary spillover

An instance of spillover that occurs when a previously zoonotic pathogen that has undergone spillover into humans infects novel, susceptible animals that in turn infect naïve or previously-exposed humans, e. g., transmission of SARS-CoV-2 from humans into mink or white-tailed deer and then back into humans.

Adapted from Sparrer et al., 2023

Keusch and colleagues assessed major RNA virus outbreaks that have occurred since the 1960s. Studying these outbreaks allowed them to prevent opportunities for emergence and examine common features. Many of these include ancestral viral origins in bats, birds, and other mammals, along with intermediate hosts and animal reservoirs. The research team also identified pathways for community spread and zoonotic spillover that are responsible for local, regional, and international disease outbreaks. (Fig 4-1) (Keusch et al., 2022). Notably most of the recent EID are caused by RNA viruses belonging to six major virus families as represented in Fig 4.1. The preponderance of RNA viruses among EIDs is attributed to the rapid evolution of RNA viral genomes via mutation, recombination and/or reassortment, and, for some RNA viruses (influenza A virus, coronavirus), a broad host range and highly efficient respiratory and enteric transmission in humans and animals. Fig 4-1 further illustrates multiple regions (identified by countries or regions listed in parentheses in the figure) for the origin or re-emergence of EID outbreaks based on the presence of the underlying drivers of EID.

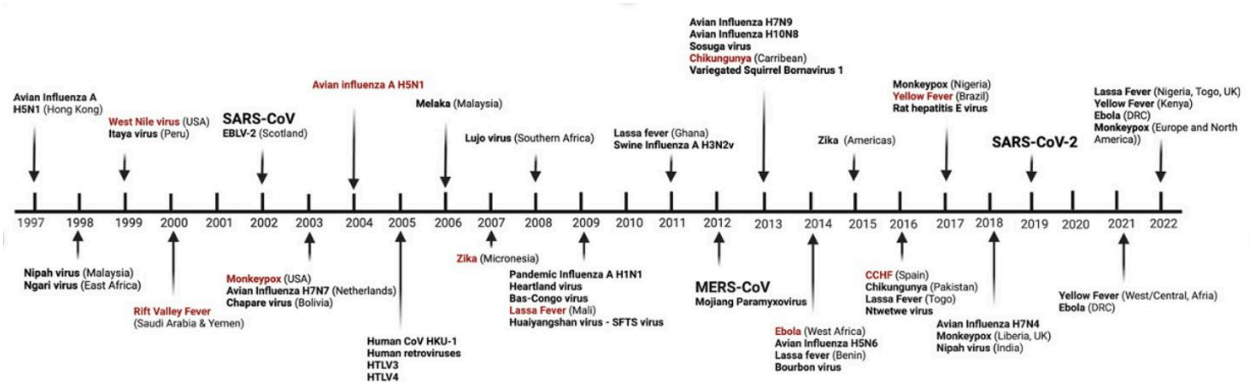

FIGURE 4-1 Historical context: emergence and repeated zoonotic spillovers to humans of select RNA/DNA viruses associated with outbreaks, epidemics, and pandemics, past 25 years. Based on Keusch et al. 2022.

PRIORITIZATION OF HIGH IMPACT ZOONOTIC PATHOGENS WITH PANDEMIC POTENTIAL

The US-Centers for Disease Control and Prevention defines high consequence pathogens as those causing "highly contagious or lethal viral, bacterial, fungal, prion, and related infections and diseases of unknown origin." The World Health Organization has a similar definition. Many

agencies and institutes have established approaches and tools to prioritize high threat zoonotic pathogens and those with pandemic potential or have assembled lists of such pathogens (see Table 4-1, Primary Sources for Prioritization of Pathogens, at end of module). These resources are highlighted and summarized at the end of this Module. Notably RNA viruses are overrepresented, and several RNA virus families are common to multiple lists of high impact or pandemic potential zoonotic pathogens: *Orthomyxoviridae, Orthoparamyxoviridae, Flaviviridae, Coronaviridae, Arenaviridae, Filoviridae, and Rhabdoviridae.* These virus families include influenza A virus, Nipah virus, flaviviruses, coronaviruses, lassa virus, Ebola virus, Marburg virus, hemorrhagic fever viruses, rabies and others**.** Three additional tables (Tables 4-2, 4-3, 4-4) at the end of the module provide concise lists with valuable citations to round out this discussion of zoonotic and high-impact animal pathogens in the region.

Table 4-2 Zoonotic Pathogens in South-East Asia with Pandemic-Causing Potential

Table 4-3 Important Zoonotic Pathogens in South-East Asia

Table 4-4 High Impact Emerging/re-emerging Animal Pathogens in South-East Asia

COMMON CHARACTERISTICS OF PATHOGENS WITH PANDEMIC POTENTIAL

Reviewing pathogens that have served as the causative agents of past human pandemics reveals several common characteristics (see Box 4-2). Indeed, Casadevall has defined pathogenic potential as "proportional to the fraction of individuals who become symptomatic after infection with a defined inoculum and can include such attributes as mortality, communicability, and the time from infection to disease" (Casadevall, 2017). Adalja et al. extended this kind of analysis to define "pandemic potential" and identified seven characteristics to be considered essential components for pandemic potential (Box 4-2) (Adalja et al., 2019). They concluded that respiratory-borne RNA viruses are the most likely to cause global disease, in agreement with earlier work (Woolhouse et al., 2013). Augmenting these are considerations of direct virus-human host interactions as depicted in Fig 4-2. Experimental studies of animal viruses based on a four-part research framework to proactively identify animal viruses that may infect humans (Fig 4-2) has been proposed as an alternative monitoring strategy to that of merely sequencing viruses in nature to try to predict the next pandemic virus. This would measure viral properties that align with human infection, and pinpoint viruses that serve as the greatest risk for zoonosis and then study them further.

BOX 4-2. Seven characteristics of Human Pandemic or Epidemic situations for Zoonotic Pathogens*

1. Efficient and sustained human-to-human (or animal-to-animal) transmissibility (consider zoonotic animal to human transmission as well)
2. A concerning or high case fatality rate and/or morbidity rate
3. The absence of effective or widely available public health countermeasures

4. An immunologically naïve host population (human or intermediate animal host)
5. Virulence factors enabling immune system evasion
6. Respiratory (or enteric or direct contact) mode of spread.
7. Ability to transmit during incubation periods and/or during mild or asymptomatic illnesses would further augment spread.

Adapted and modified from Adalja et al., 2019

To infect humans, an animal virus requires four biological properties:: it must use the human ortholog of its cellular entry receptor and enter human cells; it must use human intracellular proteins to multiply itself and leave human cells; it must bypass human innate immune responses; and it must evade pre-existing human adaptive immunity (antibodies and T cells) (Warren et al., 2023). Data suggest that the overwhelming majority of animal viruses do not have all of these properties

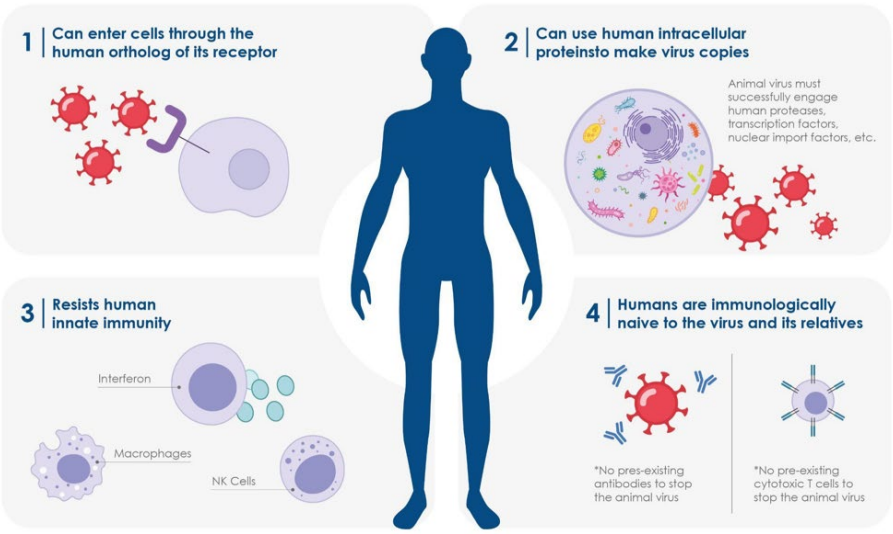

FIGURE 4-2 The four biological properties of an animal virus that can infect humans. Figure adapted from Warren and Sawyer, 2023.

WHO "Disease X" and Pandemic Preparedness

WHO has suggested that the next pandemic could be caused by "Disease X" – which is included in its list of top priority pathogens - and that it is a matter of "not *if* but *when*" a new zoonotic pathogen will spillover to humans to establish sustained human-to human transmission. (N.B. Some readers may encounter an alternative name "Pathogen X"—this guidance uses the WHO convention). It is reasonable to assume there are a large number of undiscovered viruses with unknown zoonotic and pathogenic potential. Scientists know currently of only ~250 viruses that infect people, which means >99.5% of the potential infectious viruses are unknown. (Woolhouse et al., 2012).

The Coalition for Epidemic Preparedness Innovations, or CEPI, was established in 2017 to develop a rapid response program – striving to begin testing new vaccines within a month of the sequencing of a new pathogen. CEPI classified Disease X as a serious risk to global health security, for which the world needed to prepare:

> "If we can produce vaccines against Disease X in a matter of months instead of a year or more, we could revolutionize the world's ability to respond to epidemic and pandemic diseases. Disease X and other emerging infectious diseases pose an existential threat to humanity. But for the first time in history, with the right level of financial commitment and political will, we could credibly aim to eliminate the risk of epidemics and pandemics."
>
> Tom Mooney, Senior Communications & Advocacy Manager, CEPI

Host Reservoirs and Intermediate Hosts for Emerging/Reemerging Human and Porcine Coronaviruses

Keusch and colleagues compared major coronavirus outbreaks in people and swine over the past millennium and the projected reservoir and intermediate hosts (Keusch et al., 2022). As highlighted in Figure 4-4, coronaviruses have emerged in humans as zoonoses and in animals from several common reservoir hosts and intermediate hosts as depicted (see also Figure 4-1). Fig 4-3 illustrates evidence supporting the origin and source of emergence of many of these viruses in wildlife, including bats, other mammals, and avian species, often involving an intermediate animal host. The time of the initial spillover as determined by molecular clock analysis or the discovery of the virus by epidemiologic or virologic methods, presumed reservoir host, and the major intermediate hosts for human and swine CoVs are depicted. In Fig 4-3, black animal silhouettes indicate the likely reservoir (above) or intermediate host (below); PDCoV, porcine delta-coronavirus; SADS-CoV, swine acute diarrhea syndrome coronavirus; HCoV, Human coronavirus; PHEV, Porcine Hemagglutinating Encephalomyelitis virus; HKU-1, HKU-1 human coronavirus; Hu-PDCoV, Human-Porcine Delta coronavirus; Hu-CCoV, Human-Canine coronavirus.

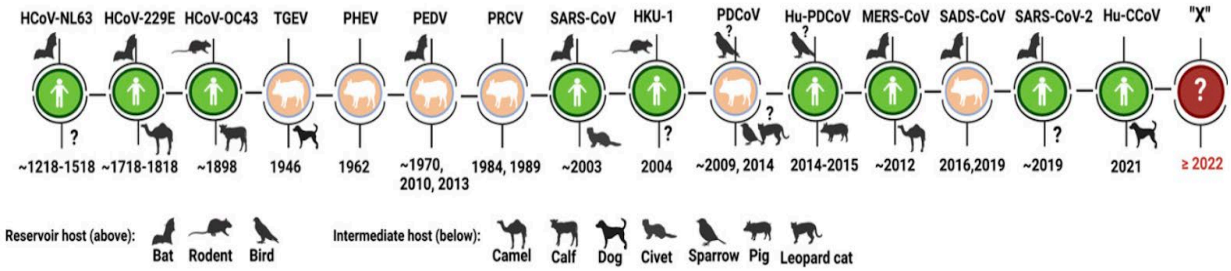

FIGURE 4-3. Timeline of the emergence of CoVs in people or swine over the past millennium. (Keusch et al., 2022). Note: "X" denotes future unknown "Disease X".

Case Examples for Different Potential Pandemic Threats for Emerging Coronaviruses

The following case examples illustrate newly recognized or ongoing potential pandemic threats for CoVs: "WHO Disease X".

Case Example 4-1: SARS/SARS-CoV-2-related betaCoVs circulating in bats.

One prior pandemic (SARS) and two ongoing epidemic/pandemic events (MERS, COVID-19) caused by zoonotic coronaviruses have occurred in the last 2 decades (Fig 4-1, 4-3). Bat species are the ancestral hosts for all 3 of these human coronaviruses. The likely intermediate animal hosts are known for SARS-CoV (civet cats, raccoon dogs) and for MERS CoV (camels), but unknown for SARS-CoV-2 (suspect pangolins or raccoon dogs) (Huang et al., 2023; Crits-Christoph et al., 2023; Liu et al., 2023) A concern is that some SARS-related and SARS-CoV-2-related bat strains of the virus bind to human ACE2, suggesting a possibility of direct bat-to-human transmission. (Ge et al., 2013; Temmam et al., 2022)

Case Example 4-2: Severe Acute Diarrhea Syndrome (SADS) alphaCoV in bats and pigs.

FIGURE 4-4. Bat farm in Cambodia. Photo credit: Vibol Hul

In 2016 and continuing in 2019, a new alphaCoV disease called Severe Acute Diarrhea Syndrome (SADS) emerged in swine in Southern China and killed approximately 50,000 baby pigs. By genetic analysis, the infection appeared to be directly transmitted from bats to pigs on the farms. (Gong et al., 2017; Pan et al., 2017; Zhou et al., 2018). More concerning, the virus infects primary human lung and intestinal cells *in vitro*, suggesting a risk for human spillover (Edwards et al., 2020).

Case Example 4-3: Porcine deltaCoV in pigs, birds and humans.

Porcine deltaCoV was first detected in pigs in Hong Kong in 2012 (Woo et al., 2012) and genetic analysis showed it was most closely related to deltaCoVs in songbirds. In 2014, this virus caused an epidemic in pigs in the United States (Yang et al., 2014). It is a generalist virus with a broad host range, infecting avian species (Boley et al., 2020), swine (Jung et al., 2014), ruminants, human cell lines (Li et al., 2020) and most recently, humans (Lednicky et al., 2021). There have

been 3 confirmed infections of children who displayed mild febrile illness, in school clinics in Haiti (Lednicky et al., 2021). Two different lineages of porcine deltaCoV were isolated from the infected children.

FIGURE 4-5. Pigs in Chrey Thom, Cambodia. Photo credit: Vibol Hul

Case Example 4-4: A new canine alphaCoV (CaCoV) detected in humans

The new human canine alphaCoVs (designated HuPn-2018 and Z19) (Vlasova et al., 2021; Lednicky et al., 2021; Vlasova et al., 2022) have recombinant spike genes from dogs, cats and swine alphaCoVs and additional mutations within the backbone of a CaCoV IIb strain. The human CaCoV (HuPn-2018) was detected in children with pneumonia in Malaysia (Vlasova et al., 2002) and mild cases (Z19) occurred in mission workers back from Haiti (Lednicky et al., 2021). The temporally related (samples from 2017-2018), but geographically isolated viruses showed very high (99.4%) nucleotide identity between the 2 human CaCoV strains. The prevalence of related strains in humans or in dogs has not been evaluated.

The above CoVs are related to viruses that have already spilled over to humans and caused pandemics (SARS, SARS-CoV-2), or that may have potential for human infections based on in vitro experiments with human cells (SADS, PDCoV) or recent spillovers in humans (PDCoV, human-CaCoV) that could represent an early stage of adaptation to humans, prior to the possibility of sustained human-to-human transmission.

Spillovers, spillbacks, and secondary spillovers of SARS-CoV-2: analytical and *in vitro* predictors

Here we discuss spillover of zoonotic pathogens to humans (zoonosis), spillback from humans to animals (reverse zoonosis) and secondary spillovers from the new animal host to humans (see Box 4-1, Figures 4-7, 4-8) as exemplified by SARS-CoV-2. Prediction of transmission of SARS-CoV-2 from animals to humans was studied by Fischoff and colleague

using combined analytical and laboratory approaches (Fischoff et al., 2021). Review of existing data and literature identified about 50 confirmed spillover/reverse secondary spillover events in about 50 mammals. In the study, three kinds of data were used to develop an algorithm for prediction of zoonotic transmission: 1) comparing amino acid sequences of ACE2 binding sites for viral attachment; 2) estimating binding strength at these sites using three dimensional structures; and 3) laboratory experiments. Machine learning models were trained on existing mammalian data and included geospatial and other species traits. The results expanded predictive capacity across more than 5000 species (of about 6500 total mammalian species worldwide) and identified a number of mammalian species in global hotspots that deserve specific attention (Figure 4-6). Many of the mammals identified as having potential zoonotic capacity were domesticated animals, e.g., pets, farmed or traded animals, validated in lab animal models, and many predictions were consistent with experimental evidence. The top 10% of animals demonstrating predicted SARS-CoV-2 zoonotic capacity were found in the tropics.

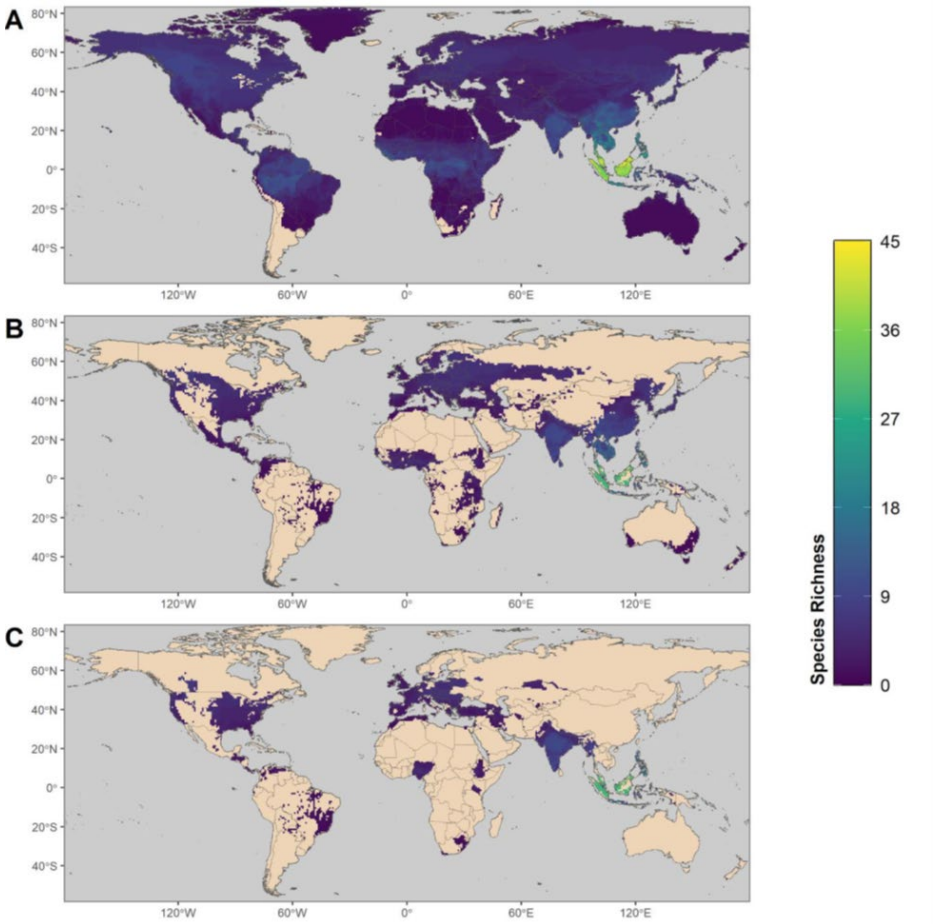

FIGURE 4-6 Three maps showing the global distribution of species with projected ability to transmit SARS-CoV- 2. (A) shows global species richness of the top 10 percent of model-predicted zoonotic capacity. Ranges of this subset of species were filtered to those associated with human-dominated or human-altered habitats (B), depicts the subset of species that overlaps with areas of high human SARS-CoV-2 positive case counts (C) (as of 15 February 2021, there were more than 100,000 cases).
Source: Fishhoff et al., 2021.

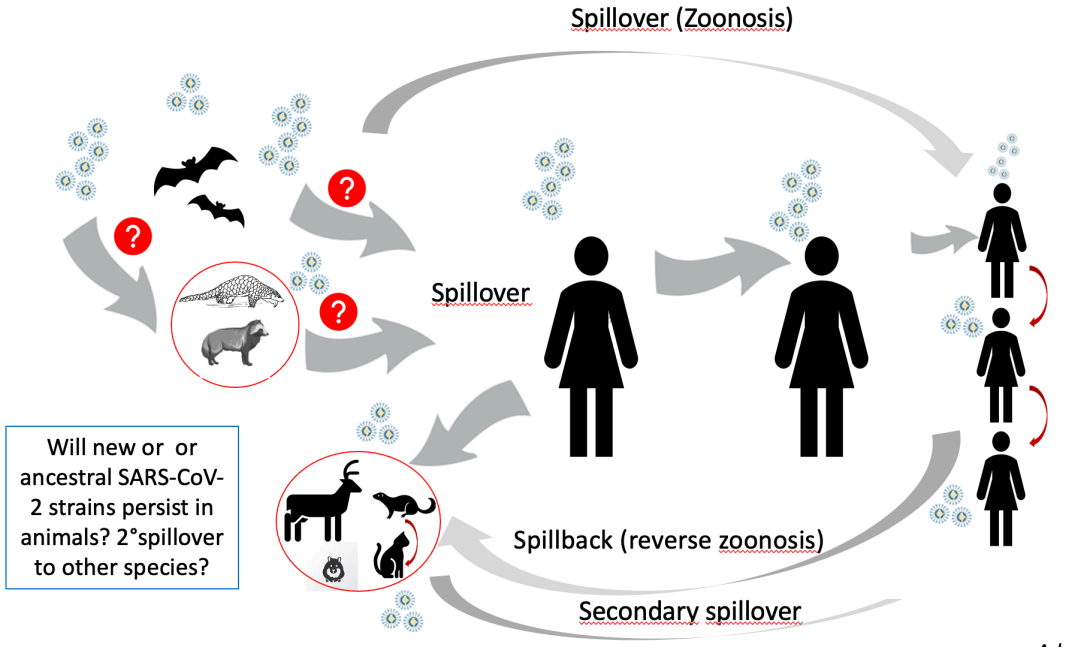

FIGURE 4-7 SARS-CoV-2 in animals: potential new host reservoirs for secondary spillovers to humans? Adapted from: Isabella Anna Eckerle (personal communication).

Although there are exceptions, such as HIV, one hallmark of zoonotic pathogens most likely to spillover and cause widespread disease in humans is a broad host range (Cleaveland et al., 2007). This characteristic is exemplified by various CoVs, as summarized , specifically for SARS-CoV-2 (Fig 4-7, Fig 4-8) where continued spillover of SARS-CoV-2-related viruses from ancestral bat hosts (Temmam et al., 2022) or potentially from intermediate animal hosts is a concern (illustrated graphically in Fig 4-7). Also new animal hosts for SARS-CoV-2 could become established following spillover from humans into the new host (reverse zoonoses), thereby maintaining a virus reservoir and persistence, followed by secondary spillback from the new animal hosts into humans (discussed below) (Figures 4-7, 4-8).

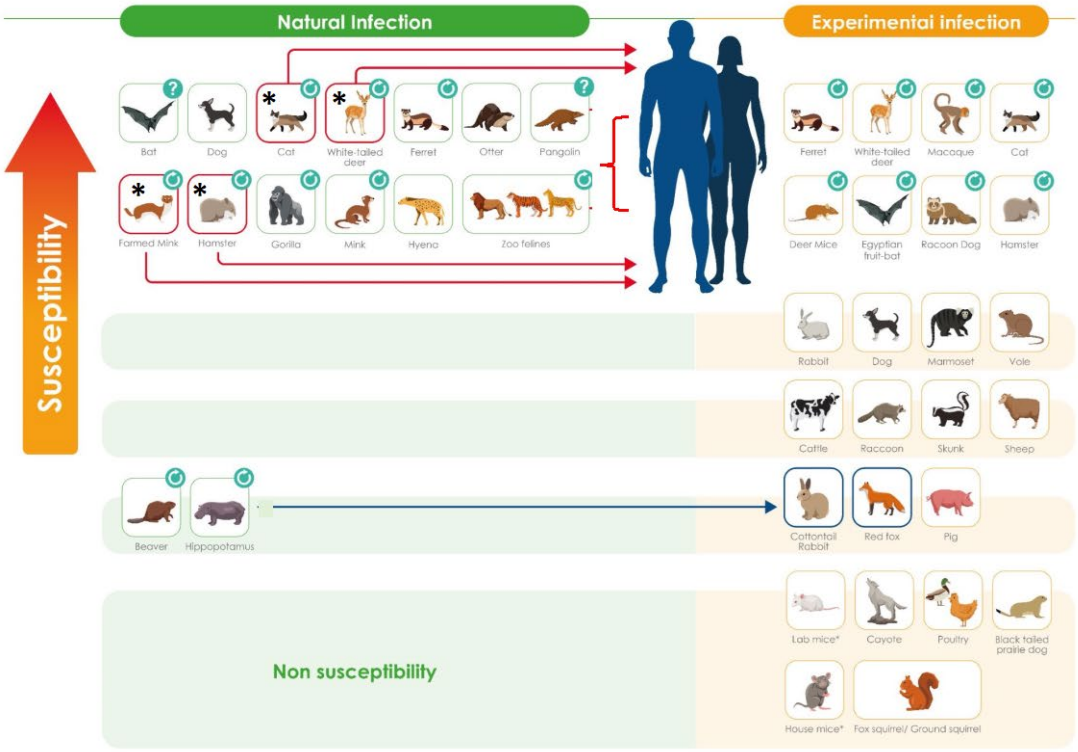

FIGURE 4-8 Infection and transmission of SARS-CoV-2 in animals and documented spillback from humans to animals and secondary spillover from animals to humans (animals denoted by*). Adapted from Keusch et al., 2022.

Case examples of spillback and secondary spillover of SARS-CoV-2

Some viruses spillback from humans into animals (reverse zoonosis) and establish additional animal reservoirs with virus persistence (Sparrer et al., 2023; Cox 2023). Examples of SARS-CoV-2 spillback from humans into animals, followed by zoonotic secondary spillover back into humans, are summarized in Fig 4-7, 4-8 and include:

- Spillback from human caretakers to farmed mink, with secondary spillovers from mink to humans in Europe and North America (Munnink et al., 2021)
- Recent secondary spillovers from a cat to a veterinarian (Sila et al., 2022) in Bangkok, Thailand and from a zoo lion to caretakers in the US (Siegrist et al., 2023).
- Reports of multiple spillbacks from humans to white-tailed deer (Hale et al Nature 2021; Kuchipudi et al., 2022) with at least one report of secondary spillover from deer into a person (Pickering et al,, 2022).
- A hamster outbreak in Hong Kong involving hamsters infected with human strains that then caused secondary spillback into humans (Yen et al., 2022).

Case examples of targeted animal reservoirs and intermediate or bridging host species to monitor for surveillance of zoonotic coronaviruses.

Table 4-5 lists possible target animals to monitor for CoV zoonoses based on historic (determined by molecular clock viral genetic analysis) or recent spillover of zoonotic CoVs to humans (reviewed in Keusch et al., 2022).

TABLE 4-5 Possible target animals to monitor for CoV zoonoses – see end of Module.

We are aware that felids and carnivores are infected by SARS and SARS-CoV-2. We know that ungulates including cattle and camelids were involved in the endemic human alphacoronavirus, 229E and the betacoronavirus OC43 zoonotic spillovers and the continuing spillover in the middle east of the betacoronavirus Middle East Respiratory Syndrome (MERS) (Keusch et al., 2022). SARS-CoV-2 is present in another ungulate species--white-tailed deer and also in other wildlife species (Table 4-5; Figures 4-7, 4-8).

Interspecies transmission, Spillovers and Spillbacks of influenza viruses

Case Example 4-5: Emerging Influenza A viruses

Influenza A pandemics arise when animal viruses, either whole, or in part, contribute animal viral hemagglutinins and/or neuraminidases or other gene segments to an existing human influenza A virus. Three influenza A pandemics occurred in the 20th Century (caused by H1N1, H2N2 and H3N2 virus subtypes) and one (H1N1 subtype) pandemic has occurred to date in the 21st Century. Pandemic-like respiratory disease outbreaks have been recorded throughout human history with 3-4 such pandemics occurring, most of these believed to be caused by influenza, but some of these may have been caused by coronaviruses or other respiratory viruses (Krammer et al., 2018).

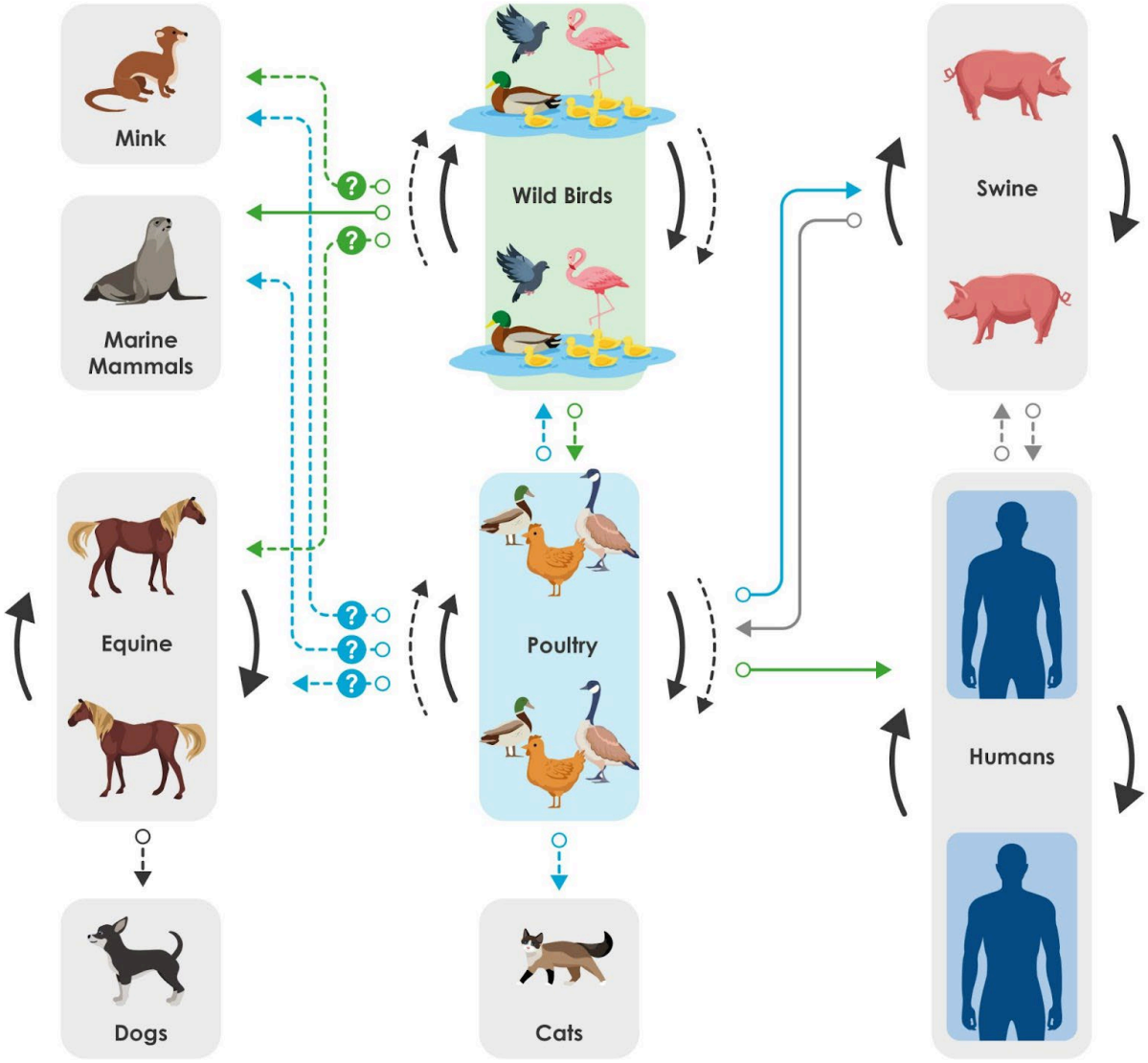

FIGURE 4-9 Influenza A viruses – Interspecies transmission, spillover and spillback. Dashed lines and "?" indicate potential interspecies transmission. Adapted from OSU background page and Keerstetter et al., 2021.

In addition, zoonotic spillovers, sometimes associated with severe disease and death, but without sustained transmission have been reported repeatedly. Such zoonotic spillovers occurred repeatedly for avian H5N1 and H5N6 viruses (arising from the Guangdong 1996 H5 lineage) and also with H7N9, H7N7, H7N3, H9N2, H6N1 and H10N8, and others, in different geographic regions (Uyeki et al., 2019; Short et al., 2015). Viruses established in domestic poultry in Asia (e.g. H5N1, H5N6, H7N9) have been associated with hundreds of zoonotic infections. Zoonotic transmission has also been reported with swine viruses of H1 and H3 subtypes in North America and Asia (Short et al, 2015). One such spillover led to the influenza A H1N1 pandemic in 2009. Since swine are susceptible to many human and some avian influenza viruses, they have been hypothesized to be a "mixing vessel" in the genesis of pandemic influenza.

Host reservoirs for Influenza A virus

Wild aquatic birds are the natural reservoir of influenza A viruses with a wide diversity of viral hemagglutinins (subtypes H1 – H16) and neuraminidases (N1 – 9) (CDC, 2024; Venkatesh et al., 2018). Bats also harbor novel H17 and H18 subtype viruses (Tong et al., 2013), but so far these have not been associated with spillovers to other species. A few of the aquatic avian virus subtypes are established in terrestrial poultry (e.g. chickens). Avian viruses repeatedly spill over into other mammalian species including swine, horses, dogs, and aquatic mammals, sometimes adapting to sustained transmission establishing long-term lineages in these mammalian species (Fig 4-9). H1 and H3 subtypes are also established as long term lineages in swine, while H7 viruses circulate long term in horses, with further spillover into canine species (Fig 4-7) (Wille and Holmes, 2024; Lloren et al., 2017).

Spillover of Influenza A viruses to avian and mammalian species

Interspecies spillover of influenza A viruses from avian species to other avian and non-human mammalian species is not uncommon (see Fig 4-9). Terrestrial poultry such as chickens or quail harbor a more restricted range of influenza A subtypes (e.g. H5N1, H9N2, H7N9, H6N1 etc.) than seen in the natural reservoir, aquatic waterfowl. These spillovers are usually accompanied by reassortment with pre-existing viruses prevalent in chickens such as H9N2 as illustrated by the emergence of H5N1, H7N9, H10N8 and more recently H3N8 (Hemida et al., 2019). The establishment of these viruses in domestic poultry is more likely to lead to zoonotic transmission (e.g. H5N1, H7N9, H10N8, H3N8). Similarly, influenza A virus spillover from either aquatic or terrestrial poultry to other mammalian species including pigs, horses, aquatic mammals, dogs, and other species (see Fig 4-9) (Runstadler and Puryear, 2020). Recently, highly pathogenic avian influenza A (H5N1) has spilled over from wild birds to a range of terrestrial (e.g. mink, badger, bear, fox, pig, raccoon etc.) and aquatic (e.g. dolphin, otter, seal) mammalian species, with convincing evidence of transmission demonstrated between mink and seals (WHO, 2022). These ongoing interspecies spillovers pose threats to both animal health (e.g., current poultry deaths caused by highly pathogenic avian influenza A(H5N1) or humans.

Spillover of avian influenza A viruses to humans

Spillover events of highly pathogenic avian influenza viruses to humans and other species are more likely to be detected because they may cause more overt and severe disease than that in the host. However, it is important to recognize that although past human pandemics were not caused by low pathogenic avian influenza viruses, where spillover may be less overt, it is important to also maintain active one health surveillance for spillover events of low pathogenic influenza to humans and between other species. The need for "one health" surveillance to monitor spillover events between species and to humans is an important aspect of ongoing risk assessment for pandemic threats. An example of such a network is the WHO Global Influenza Program-led Quadripartite surveillance and application of the Tool for Influenza Pandemic Risk Assessment (TIPRA) process (WHO, 2020; Cox et al., 2014).

Spillback of influenza A viruses from humans to other mammalian species

Spillback of influenza A virus (reverse zoonosis) has been reported, most often from humans to swine. At least 12 instances of spillback of human influenza viruses establishing sustained transmission in swine have been reported, but this is likely to be a gross underestimate

(Trovão and Nelson, 2020). Swine influenza viruses derive some or all of their gene segments from humans or from avian species, subsequently leading to further reassortment of these viruses in swine. The 2009 H1N1 pandemic virus which emerged from swine, spilled back to swine as the pandemic virus spread globally (Mena et al., 2016). The 2009 H1N1 pandemic virus gene segments, reassorted with previous enzootic swine and many swine influenza A virus lineages in Asia, North America, and perhaps elsewhere, have one or more 2009 H1N1 pandemic virus genes within them. Also, some influenza viruses common in China have Eurasian Avian origin H1 gene segments (antigenically divergent from H1 viruses endemic in humans at present) with multiple human 2009 pandemic H1N1 gene segments within them (i.e. potentially well adapted to humans), posing significant pandemic threats (Sun et al., 2020).

Other zoonotic influenza viruses may also pose concerns.

Cattle are a leading reservoir for influenza D viruses (Collin et al., 2015; Ruiz et al., 2022). The recent finding of asymptomatic influenza D virus infections in dairy cattle workers suggests that influenza D virus is present in dairy cattle environments and can result in worker exposure (Leibler et al., 2023).

Surveillance

Employing a One Health surveillance effort with an early emphasis on the interface while targeting viruses or key viral families (i.e., influenza viruses, coronaviruses, enteroviruses, flaviviruses, hemorrhagic fever viruses, filoviruses, adenoviruses, paramyxoviruses, etc.) is imperative for early warning, preventing inter-species transmission, determining extent of viral spread and controlling pandemics. Zoonotic viruses must be detected rapidly to prevent their transmission to humans and to other species by monitoring the human-animal-environmental interface, the One Health connection (reviewed in Keusch et al., 2022). Prevention of initial spillover at local and regional levels to mitigate sustained human-to-human transmission and avert new epidemics or pandemics relies on effective surveillance programs that provide early and accurate warning. Surveillance methodology and applications in the fight to control or mitigate zoonotic spillover is examined in Module 5: How to design and conduct risk-based surveillance for zoonotic diseases at the human-animal Interface.

Laboratory Biosafety Infrastructure and Capacity

Laboratory biosafety in SEA encompasses the practices, guidelines, and regulations that ensure the safe handling, containment, and disposal of biological agents and materials within laboratories. While biosafety practices can vary between countries in SEA, there are overarching principles and initiatives aimed at promoting biosafety and biosecurity.

A number of web-based tracking studies have gathered information about existing and new biological containment laboratories. These studies also evaluate the biosafety and biosecurity oversight efforts to coordinate the function of these laboratories. In addition, attempts to assess public health or pandemic preparedness in individual countries also include data about labs and biosafety/biosecurity programs.

- WHO Health Emergency Dashboard
- WHO IHR State Party Self-Assessment Annual Reporting

- WHO JEE Biosafety and Biosecurity
- International Federation of Biosafety Organizations
- Global Biolabs, tracks maximum containment laboratories and their associated programs around the world.
- Global Health Security Index (2021) measures the capacities of 195 countries to prepare for epidemics and pandemics.

It is important to note that biosafety practices can vary across countries in SEA due to differences in resources, infrastructure, and regulatory frameworks. Each country's biosafety system is tailored to address its specific needs while aligning with international standards and best practices outlined by organizations such as the World Health Organization (WHO) and the World Organisation for Animal Health (WOAH). A number of key features are common to biosafety practices around the world. Below are some examples of specific national programs addressing these practices.

National Biosafety Guidelines and Regulations

Many countries in Asia have developed their own national biosafety guidelines and regulations that outline the requirements for laboratories working with biological agents. These guidelines typically cover areas such as facility design, personnel training, risk assessment, containment measures, waste management, and emergency response. Further discussion of laboratory capacity and training can be found in Module 7 "Strategies to overcome barriers, fill gaps and address systemic issues." Examples include:

Biosafety Training and Capacity Building

Several organizations and institutions in Asia provide biosafety training programs to laboratory personnel, researchers, and administrators. These programs focus on educating individuals about best practices, risk assessment, personal protective equipment (PPE) use, and proper handling and disposal of biological agents. Capacity-building efforts aim to enhance biosafety practices across laboratories in the region.

Laboratory Accreditation and Oversight

Some countries have established accreditation systems or regulatory bodies responsible for inspecting and overseeing laboratories to ensure compliance with biosafety guidelines. These bodies conduct assessments, provide recommendations, and issue certifications to laboratories that meet the required biosafety standards.

International Collaboration and Initiatives

Asia actively participates in international collaborations and initiatives aimed at promoting biosafety. For example, the Asia Pacific Biosafety Association (A-PBA) and the Association of Southeast Asian Nations (ASEAN) promote knowledge sharing, training programs, and harmonization of biosafety standards across the region.

Pathogen Security and Biosecurity

Biosafety efforts in Asia also encompass biosecurity measures to prevent the unauthorized access, theft, or intentional misuse of biological agents. Countries work on developing policies, procedures, and training to ensure the secure handling, transport, and storage of pathogens and maintain laboratory security.

Recommendations

- Use various agencies (ASEAN, CDC, WHO, etc) described criteria, tools and approaches to prioritize the high impact zoonotic pathogens specific to each country in SE Asia and to promote biosafety and biosecurity.
- Identify the target animal species to monitor for zoonotic pathogen spillover at the human-animal-environmental interface based on their susceptibility to the priority pathogens and the associated risk assessments. (see Module 5, How to design and conduct risk-based surveillance for zoonotic diseases at the human-animal Interface).
- Prepare for pandemics of unknown emerging zoonotic diseases (WHO disease X) by use of agnostic detection methods (NGS, etc) and development or sourcing of broadly reactive pan-virus family vaccines and antiviral therapeutics.

Conclusions

The frequency of emerging/re-emerging zoonotic diseases has been accelerating in the past 26 years. A majority of these are RNA viruses that have emerged from wildlife reservoirs via direct spillover or through intermediate animal hosts. Prioritization of high impact zoonotic pathogens, especially those with pandemic potential, but also high impact animal pathogens in SEA, is critical to focus resources and the workforce. Sources for approaches and tools and several criteria used to prioritize high threat zoonotic pathogens and the potential animal hosts are provided. Moreover, the WHO scenario of "not *if* but *when"* a new zoonotic pathogen, "Disease X" will infect humans and cause the next pandemic requires novel agnostic approaches to zoonotic disease detection and monitoring and development of broadly reactive pan-virus family vaccines and antivirals.

We further use coronaviruses, including SARS-CoV-2, and influenza A viruses as case examples to illustrate the range of susceptible reservoir and intermediate animal hosts and to highlight targeted animal species to monitor for zoonotic transmission of these viruses to humans. Importantly in the context of One Health, we also emphasize the often-overlooked spillback of these viruses from humans into new animal hosts, which could maintain the virus in a new host reservoir community in which the virus could persist, evolve and spillback into humans, necessitating prevention and control, not only in humans, but also in the susceptible animal hosts.

TABLE 4-1. Primary sources for prioritization of high impact zoonotic and animal pathogens

Source	Title	Description
ASEAN	ASEAN Strategy for Exotic, Emerging, Re-emerging Diseases and Animal Health Emergencies	*This strategic framework reflects all hazards related to biological threats approach adopted by the region and incorporates the lessons learnt from actual events, focusing on nine essential animal health functional areas necessary for AHEP, risk mitigation and response operations.*
CDC	Zoonotic Disease Prioritization Tool (ZDPT)	*Guidance with different lists for each country that goes through the process*
FAO	The Emergency Prevention System for Animal Health (EMPRES-AH); Enhancing the prevention and control of high-impact animal and zoonotic diseases through biosecurity and One Health	*This document describes the EMPRESAH Strategic Plan for 2023–2026, which provides a renewed approach for integrating biosecurity and One Health to support members in managing threats to animal health through enhanced early warning and progressive biosecurity management pathways. The Plan also supports the FAO Strategic Framework (2022–2031) and sustainable livestock transformation for progress towards the SDGs.*
WHO	WHO R&D Blueprint for Epidemics: Updating the WHO list of pathogens with epidemic and PHEIC potential (expected 2023)	*This document focuses on identifying prototype virus family members applicable to other potential threat viruses in the same family. The goal for prioritization is to review transmission, virulence (fatality, sequela rates) and availability of countermeasures for entire classes of viruses as well as the future Disease X threat.*

TABLE 4-2 Zoonotic Pathogens in South-East Asia with Pandemic-Causing Potential

Pathogen	**Source Reservoir**	**Intermediate host**	**Risk factors**	**Spillover causes**	**Location**	**Current Standing**	**Best practices for prevention:**
Henipavirus Nipah Virus (NiV)	Flying foxes or fruit Bats (Eaton et al., 2006)	Domestic animals (e.g., pigs, horses, dogs, cats, etc.) (Islam et al., 2023)	Food-borne (raw date palm sap, foraged fruits, bat bushmeat (Pteropus bats) close contact infected pigs,fruit bats, humans (Openshaw et al., 2017; Simons et al., 2014; Montgomery et al., 2008)	Habitat loss; climate change; food shortages in bats; water contamination; rapid urbanization; ecotourism (McKee et al., 2021)	Emerged as a large outbreak among pig farmers in Malaysia in 1998 (Chua, 2000 Nipah virus: a recently emergent deadly paramyxovirus) Singapore; Paton et al., 1999 Cambodia (Capelle et al., 2020) Philippines (Alam, 2022 Nipah virus`, an emerging zoonotic disease causing fatal encephalitis)	Malaysian government banned open farming of the pig industry; pig farms need to be in an enclosed environment.	Raising awareness among clinicians of signs, symptoms, and risk factors for NiV; contact tracing and quarantining of infected individuals; adhere to personal protective equipment (PPE)
Hendra Virus	Flying foxes or fruit Bats (Calisher et al., 2006). Flying-fox species density--a spatial	Domestic animals, mainly horses	Husbandry, management practices with flying-fox -horse interactions.	Infected commensal rodents (brown or Oriental House rats), cold, dry weather (Matin et al., 2018)	Cambodia, China, Indonesia, Malaysia, Singapore, and Thailand (Quarleri, 2022 Henipaviruses: an expanding	Endemic, with yearly outbreaks, especially in major cities. Treatments have become	Property attributes, husbandry and management practices that reduce flying-fox-horse interaction

Pathogen	**Source Reservoir**	**Intermediate host**	**Risk factors**	**Spillover causes**	**Location**	**Current Standing**	**Best practices for prevention:**
	risk factor for Hendra virus infection in horses in eastern Australia			Bat food shortages	global public health concern)	standardized across health institutions, so fatalities are low.	s; Vaccine treatments for horses available for use under permit by veterinarians
Influenza Avian Influenza (H5N1) "G4" swine influenza Eurasian (EA) avian-like H1N1	Wild birds and poultry (Nabil et al., 2020) pigs	Mammals including swine, cats, dogs, tigers, and leopards (Amonsin et al., 2008) (Keawcharoen et al., 2007) (WHO, 2023) (Wang and Palese, 2009)	Poultry trading, live poultry markets, cock fights, general poultry contamination (Hulse-Post et al., 2005; Leung et al., 2007)	Wild birds, multiple poultry species in live markets (Nabil et al., 2020)	Cambodia, China, Indonesia, Japan, Lao PDR, Thailand, and Vietnam (Riedel, 2006) China (Sun et al., 2020)	(see text)	Vaccine-preventable in poultry with controversial control strategies including vaccination of domestic dogs and / or wildlife. Vaccines and anti-virals for humans; TIPRA

Pathogen	**Source Reservoir**	**Intermediate host**	**Risk factors**	**Spillover causes**	**Location**	**Current Standing**	**Best practices for prevention:**
Coronavirus Sarbecoviruses SARS CoV SARS-CoV-2	Rhinolophus bats (Alkhovsky et al., 2022)	Civet cats, racoon dogs (Freuling et al., 2020) Unknown (Pangolins? Zhao et al., 2020) Racoon dogs? Mallapaty, 2023)	Live wildlife markets (Naguib et al., 2021) Live wildlife markets (Alonso-Aguierre et al., 2020).	Wildlife trade and consumption Unknown-wildlife trade and consumption? (Jiang and Wang, 2022)	Emerged in China, 2002-spead throughout SEA—29 countries (Huang, 2004; Lam et al., 2003) Emerged in China 2019 (Maxmen, 2022) Global Pandemic	Disappeared in 2004 but SARSr CoVs still in bats Ongoing	Quarantine, contact tracing, adhere to wearing personal protective equipment (PPE) Early: Quarantine, contact tracing, adhere to wearing personal protective equipment (PPE) New vaccines, antivirals and monoclonal antibody treatments
Reston Ebola	Pigs, Macaque (Demetria et al., 2018)		Hunting of "bush meat", or direct contact with fruit bats (Baudel et al., 2019)	Infrastructure problems, low public awareness	Singapore Philippines (laboratory 2015) (Demetira et al., 2018)		
Flaviviruses (e.g. West Nile, Dengue, Yellow Fever)	Bats, arthropods (Boys et al., 2020)					Ongoing outbreaks	Early detection; control vectors; vaccines and anti-virals

Pathogen	**Source Reservoir**	**Intermediate host**	**Risk factors**	**Spillover causes**	**Location**	**Current Standing**	**Best practices for prevention:**
Filoviruses (e.g. Ebola, Marburg)	bats, rodents, arthropods (potential) (Olival and Hayman, 2014)	hominids	Direct contact with infected host (Smiley-Evans et al., 2018)		Central Africa; projection models into SEA (Peterson et al., 2004 Ecologic and geographic distribution of filovirus disease)	Ongoing outbreaks	Early detection; quarantine; PPE
Poxviruses (Mpox)					Multiple continents (Zhai et al., 2022)		
Paramyxovirus (measles virus, mumps virus, parainfluenza virus, respiratory syncytial virus (RSV)	Bats, rodents for emerging species (Thibault et al., 2017)						

TABLE 4-3 Important Zoonotic Pathogens in South-East Asia

Pathogen	Source/reservoirs	Intermediate host	Risk factors	Spillover causes	Location	Current Standing	Best practices for prevention:
Bacteria							
Anthrax *Bacillus anthracis*	Animal (ungulates) Soil (stable environmental reservoir) (Carlson et al., 2019)	unknown	inhalation of spores (CDC, 2024)	farming consumption of infected meat (Ndolo et al., 2022 ;Wang et al., 2024)	Myanmar Cambodia Lao PDRs Indonesia Philippines Vietnam (WHO, 2008)	Sporadic	Understanding the enzootic reservoir of B anthracis on farmlands
Melioidosis *Burkholderia pseudomallei*	soil (Pongmala et al., 2022) contaminated water (CDC, 2024) various mammals, reptiles (Kelser, 2016)	N/A	Diabetes (Chowdhury et al., 2022)	inhalation, consumption or of inhalation of contaminated dust or water droplets, ingestion of contaminated water, and direct contact with contaminated water or soil, particularly through cuts or abrasions (Virginia Department of Health, n.d)	Thailand (Hinjoy et al., 2018); (Bulterys et al., 2018) Malaysia (Butlerys et al., 2018); (Kingsley et al., 2016)		understanding the geodistribution of Bulkholderia

Pathogen	Source/reservoirs	Intermediate host	Risk factors	Spillover causes	Location	Current Standing	Best practices for prevention:
Group B Streptococcus *Streptococcus algalactiae*	Fish (Chau et al., 2017)			consumption of under cooked contaminated fish (Singapore Food Agency, 2024)	Singapore (Shar et al., 2023) (Rajendram et al., 2016)		consume well cooked fish
Group D Streptococcus *Streptococcus suis*	Pig (Kerdsin et al., 2023)			consumption of undercooked pork (Praphasiri et al., 2015)	Vietnam, Thailand (Kerdsin et al., 2022)		consume well cooked pork
Leptospira	Rodents Association of rodent-borne Leptospira spp. with urban environments in Malaysian Borneo (Blasdell et al., 2019)	cats, dogs, horses (Azócar-Aedo, 2023)		consuming infected urine contaminated food, water (CDC, 2015)	Throughout SEA (Douchet et al., 2022)		improve hygiene, manage the population of rodents.
Coxiella burnetii	Water buffalo, cattle, goat and sheep Chicken (Celina and Cerny, 2022; Sethi et al., 1978)			Inhalation of infectious aerosol or airborne dust, ingestion of milk or milk product from infected animals (CDC, 2019)	Philippines (Galay et al., 2020) Thailand (Doung-ngern et al., 2017)		Pasteurize milk and dairy products

Pathogen	**Source/reservoirs**	**Intermediate host**	**Risk factors**	**Spillover causes**	**Location**	**Current Standing**	**Best practices for prevention:**
Parasites							
Schistosomiasis	Animals (Mammals) (Gordon et al., 2019)	Snails (Sokolow et al., 2016)	Anemia, stunted growth, cognitive impairment, fatigue, infertility, liver fibrosis and bladder cancer (Sokolow et al., 2016)	Contact with intermediate host snails shed (Sokolow et al., 2015)	China, Philippines, Indonesia, Cambodia, Lao PDRs (Ross et al., 2013)		avoid wading in fresh water or drinking unboiled water in area where schistosomiasis is endemic.
Leishmaniasis Leishmania parasite	Humans, animals (mammals) (Reithinger et al., 2016)	Sand fly, (Cecílio et al., 2022)	Fever, anemia and leukopenia (Ready, 2014)	transmitted by the bite of an infected sand fly vector (WHO, 2024)	India, Thailand (Krayter et al., 2015)		vector control. Avoid sandfly bites in areas where Leishmania is endemic

Pathogen	Source/reservoirs	Intermediate host	Risk factors	Spillover causes	Location	Current Standing	Best practices for prevention:
Plasmodium knowlesi	Long-tailed macaques (Jeyaprakasam, 2020)			transmitted by the bite of vector mosquitoes (Fornace et al., 2023)	Malaysia Indonesia Singapore Thailand Vietnam (Shearer et al 2016) Thailand Lao PDRs (Jongwutiwes et al., 2004; Iwagami et al., 2018)		Vector control
Viruses							
Hantavirus	Rodents (Hamdan et al., 2017) Bats (Zana et al., 2019)		Haemorrhagic fever with renal syndrome (Hamdan et al., 2017)	inhalation of aerosolised infectious particles (ECDC, 2024)	Malaysia Indonesia (Lukman et al., 2019)	lack of surveillance data. Seropositivity was reported in 2001.	Rodent control

Pathogen	Source/reservoirs	Intermediate host	Risk factors	Spillover causes	Location	Current Standing	Best practices for prevention:
Japanese encephalitis	Pigs waterbirds such as egrets (SHIC, 2021)	Culex mosquitoes (CDC, 2022)		mosquito bites (Mulvey et al., 2021)	Japan, Thailand, Philippines, Indonesia (Kuwata et al., 2020)		vector control
Herpes B virus	Macaques (CDC, 2019; Hilliard, 2007)			Bite and scratches from macaques, contaminated needle, contamination of wounds with macaque saliva (CDC, 2019; Weigler, 1992)	China (Zhang et al., 2022)		Avoid physical contact with macaques.

Pathogen	**Source/reservoirs**	**Intermediate host**	**Risk factors**	**Spillover causes**	**Location**	**Current Standing**	**Best practices for prevention:**
Hepatitis E	Pigs, rabbits, bats (Wang et al., 2023) Rodents (Reuter et al., 2020)		Severe liver disease (Zhang et al., 2017)	Consuming contaminated drinking water, uncooked or raw animal meat (CDC, 2020)	Cambodia, Lao PDRs, Indonesia, Singapore, Thailand, Vietnam, Malaysia (Raji et al., 2017) China (Ren et al., 2017)		
Rabies Rhabdovirus	Wildlife Dogs (Ahmed et al., 2015) Cats and bats (Gautret et al., 2015)			Bite and scratch from infected animals (CDC, 2019)	Lao PDRs (Ahmed et al., 2015) Thailand (Thanapongtharm, 2021)	Ongoing	vaccination of dogs and cats, dog /cat population control

Pathogen	**Source/reservoirs**	**Intermediate host**	**Risk factors**	**Spillover causes**	**Location**	**Current Standing**	**Best practices for prevention:**
Pteropine orthoreovirus	Frugivorous bats (Egawa et al., 2017)	Cynomolgus macaques (Tan et al., 2019)		close contact with bats and excrete/inhalation of aerosol (Tan et al., 2019)	Phillipines China Indonesia Malaysia (Egawa et al., 2017; Tee et al., 2023)		Unknown Avoid contact with bats and excreta
Bovine Spongiform Encephalopathy (BSE)	Pigs, sheep (Hedman et al., 2016; Marin et al., 2021)			Consuming contaminated meat or meat product (Concepcion and Padlan, 2023)	Multiple countries (Kumagai et al., 2019)		Test ungulates for prion diseases and slaughter positives

TABLE 4-4. High Impact Emerging/re-emerging Animal Pathogens in South-East Asia

Pathogen	**Source / Reservoir Host**	**Intermediate Host**	**Risk factors**	**Causes of Spillover:**	**Location**	**Current Standing**	**Best practices for prevention:**
African Swine Fever asfivirus	Bushpigs and warthogs (Oura et al., 1998)	All suidae are susceptible (Oberin et al., 2023)	Contaminated swine carcasses, swine products & wastes (Taylor et al., 2020)	Poor biosecurity and hygiene, Swine/pork trade (Nantima et al., 2015; Matsumoto et al., 2021)	Multiple countries (Gallardo et al., 2015)	Stable	Cases have decreased due to good sanitation practices in humans working with swine (i.e. masks and hand washing) but continued outbreaks and re-emergences occur Biosecurity, quarantine and culling, control transport pigs/swine products
Foot and mouth disease (FMD) Aphthovirus	Ruminants such as cattle, sheep, and goats (WOAH, 2023)	Pigs (Iowa State University College of Veterinary Medicine, n.d.)	Recovered or vaccinated animals subsequently exposed to FMDV may become carriers and subclinically infected animals are contagious. (Gortázar et al., 2022)	wildlife reservoir (Rahman et al., 2020)	Multiple countries (USDA, 2021)		Quarantines, culling of positive animals/herds, vaccines
Canine Distemper morbillivirus	canidae (dogs are the main reservoir) (Kapil and Yeary, 2011)	mustelidae, Procyonidae, Hyaenidae, Ursidae, Viveridae (Kapil and Yeary, 2011)	wildlife spillover/spillback (Beineke et al., 2015)	increase in dog population worldwide and widespread urbanisation (Kapil and Yeary, 2011)	Multiple countries (Duque-Valencia et al., 2019)		Vaccination

Pathogen	**Source / Reservoir Host**	**Intermediate Host**	**Risk factors**	**Causes of Spillover:**	**Location**	**Current Standing**	**Best practices for prevention:**
New Castle Disease Virus NDV disease Paramyxovirus	avian species Hypervirulent strains are maintained in chickens; avirulent strains have been found in urban and migratory birds such as pigeons and fowls. (Snoeck et al 2013)	Poultry is susceptible (Dimitrov, 2023)	Possible spillover from migratory birds to poultry (Brown and Bevins, 2017)	Increase in poultry farming (Puro and Sen, 2022)	Multiple countries (WOAH, 2023)		Vaccination
Lumpy skin disease Capri poxvirus	Ruminants especially cattle (Boss spp.) and buffaloes (Bubalus spp.) (Ratyotha et al., 2022)	giraffe, impala eland wildebeest bulls, and springboks (Ratyotha et al., 2022)	blood sucking athropods such as stable flies (Stomoxys calcitrans), mosquitoes (Aedes aegypti), and hard ticks (Rhipicephalus and Amblyomma species), house fly (Musca domestica) (Sprygin et al., 2019)		Myanmar, Vietnam and Thailand (Ratyotha et al., 2022)		vaccination and enhanced biosecurity; vector control (Dubey et al., 2023)
Peste des Petits Ruminants Virus (PPRV) morbillivirus	small ruminants such as sheep and goats. Wild ruminants such as ibex and gazelle.	Cattle, Large ruminants such as water buffalo, pigs	close contact with infected animals via inhalation of infectious nuclei; biting midges (Culicoides imicola)		Africa, China (Mantip et al., 2019;		

Pathogen	**Source / Reservoir Host**	**Intermediate Host**	**Risk factors**	**Causes of Spillover:**	**Location**	**Current Standing**	**Best practices for prevention:**
	(Kumari et al., 2021; Asil et al., 2019)	(Rahman et al., 2020)	(Rahman et al., 2020)		Wang et al., 2009)		

TABLE 4-5 Possible target animals to monitor for CoV zoonoses

Animal	**Hosts/viruses**	**References**
Bats	SARS-r CoVs; SARS-CoV-2; MERS CoV, endemic human CoVs	(Delaune et al., 2021)
Felids	SARS, SARS-CoV-2	(Ferasin et al., 2021; Giraldo-Ramirez et al., 2021; Siegrist et al., 2023)
Pangolins	SARS-CoV-2 targeted surveillance and specimen testing of pangolins trafficked through and confiscated in Vietnam	(Nga et al., 2022; Peng et al., 2021; Huang, et al., 2023)
Carnivores	SARS spillover from civet cats and raccoon dogs in wet markets to humans; detection of a new canine alphaCoV in humans, HuPn-2018 and Z19	(Vlasova et al 2021; Lednicky et al., 2021)
Ungulates-	cattle (endemic human CoV OC43), camelids (endemic human CoV 229E, MERS CoV--ongoing), cervids (SARS-CoV-2-spillover from humans into white-tailed deer and spillback from deer into humans	(Pickering et al., 2022; Palmer et al., 2021; Chandler et al., 2021; Hale et al., 2021; Caserta et al., 2022; Lewis et al., 2023)
Rodents	endemic human CoV HKU1, OC43; SARS-CoV-2, hamsters	(Wang et al., 2023)
Swine (PDCoV, SADS)		PDCoV (Zhang et al., 2016; Jung and Saif, 2017; Li et al., 2020; Lednicky et al., 2021; Saif et al., 2019)
Birds (DCoV)		(Vlasova et al 2021)

TABLE 4-6 SEA region biosafety organizations and resources

Country	Title	Link
Burma (Myanmar)	National Health Laboratory, Myanmar	10.1371/journal.pone.0273380
Cambodia	National Institute of Public Health; Institut Pasteur du Camboge	http://hismohcambodia.org/public/fileupload/EMP%20of%20NIPH%20Lab%20FINAL.pdf; https://pasteur-network.org/en/members/asian-region/institut-pasteur-du-cambodge/
China	National Security Commission; Wuhan National Biosafety Laboratory; Biosafety Lvel 4 training; Biosafety Law of the People's Republic of China, October 17, 2020	https://lssf.cas.cn/en/facilities-view.jsp?id=ff8080814ff56599014ff59e677e003d; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6478205/; http://www.npc.gov.cn/npc/c30834/202010/bb3bee5122854893a69acf4005a66059.shtml
Indonesia	Indonesia Biosafety Clearing House; Indonesian Biorisk Association	https://indonesiabch.menlhk.go.id/; https://internationalbiosafety.org/ifba_members/indonesian-biorisk-association/
Lao PDR	Institut Pasteur du Laos	https://www.pasteur.la/project-carried-on-in-the-lab/project-03/ biosafety-lab/
Malaysia	Malaysian Biosafety and Biosecurity Association	https://mbba.my/ https://internationalbiosafety.org/ifba_members/malaysian-biosafety-biosecurity-association/
The Philippines	Biorisk Association of the Philippines; National Training Center for Biosafety and Biosecurity	https://internationalbiosafety.org/ifba_members/biorisk-association-of-philippines/ https://nih.upm.edu.ph/institute/national-training-center-biosafety-and-biosecurity

Country	**Title**	**Link**
Singapore	Biorisk Association of Singapore; Ministry of Health Biosaftey	https://internationalbiosafety.org/ifba_members/biorisk-association-of singapore/https://www.moh.gov.sg/biosafety/useful-info/useful-info-and-guidelines
Thailand	Biosafety Association of Thailand; BIOTEC Biosafety Program	http://biosafetythailand.org https://www.biotec.or.th/home/en/biosafety-program-en/
Viet Nam	Viet Nam Field Epidemiology Training Program	https://www.tephinet.org/training-programs/vietnam-field -epidemiology-training-program BSL3/4 labs in Viet Nam links?