

# Indicators for human exposures to zoonotic pathogens





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## Abbreviations/Glossary

### Abbreviations

AIV	Avian Influenza
CCHF	Crimean-Congo Haemorrhagic Fever
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
OHHLEP	One Health High Level Expert Panel
Prezode	Preventing Zoonotic Disease Emergence
WNV	West Nile Virus

### Glossary

Human exposure: Contact of human population with a zoonotic pathogen

Pathogen circulation: Level of transmission of a pathogen within a community or a population (i.e., pathogen pressure)

## Executive summary

The COVID-19 pandemic has highlighted the urgent need for effective strategies to prevent and diminish the impact of emerging infectious diseases, particularly those that originate from animals (zoonoses). Despite the potential benefits of investing in zoonotic disease prevention, which are estimated to be just 1% of the cost of the COVID-19 pandemic, —such efforts have not received sufficient worldwide attention.

Recognizing this critical need, the World Health Organization (WHO) and the Preventing Zoonotic Disease Emergence Initiative (PREZODE) initiative have collaborated to develop a set of standardized indicators aimed at qualifying the likelihood of zoonotic disease emergence. The proposed indicators focus on characterizing potential human exposure to zoonotic pathogens by providing assumed proxies of pathogen circulation in animal populations and intensity of human-animal contact. These indicators are designed to measure the impact of prevention strategies over time and across the different stages of pathogen emergence. They provide a concise measure of human exposure to zoonotic pathogens while considering uncertainty.

To measure and validate the indicators, an expert-driven study involving 275 contributors, gathered independent estimates of pathogen circulation and levels of animal/human contact intensity at a country scale. The results of this study showed a clear association between the indicators of potential human exposure and documented zoonotic infection events for Avian Influenza (AIV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Further, the indicators were tested through simulation of prevention strategies targeting specific aspects of zoonotic disease transmission. These simulations showed the actionability of the proposed indicators in guiding effective prevention strategies.

Moving forward, the plan is to enhance the reliability and scalability of the indicators developed here. This will involve expanding expert participation to consider an increasing spatial resolution as well as other pathogens. It will also require integrating critical variables such as livestock-wildlife contact. Moreover, the long-term vision is to transition from expert opinion-based indicators to a quantitative approach based on data interoperability and more advanced analytical techniques.

These WHO-PREZODE efforts represent a significant step towards improving global prevention and preparedness against future pandemics. This initiative provides actionable tools to measure, monitor, and mitigate the emergence of zoonotic diseases. To allow prevention strategies and preparedness to be designed and implemented now, we propose the creation of a global expert group to be engaged every year to provide the most accurate estimation of human zoonotic exposure through new elicitation studies.

## Rationale of the work

The world continues to face ongoing threats from the emergence and re-emergence of infectious zoonotic pathogens with epidemic and pandemic potential. The emergence of SARS-CoV-2, resulting in the continuing COVID-19 pandemic, has inflicted devastating health and socio-economic consequences at an unprecedented scale. This pandemic has demonstrated how an emerging novel pathogen can impact every aspect of our daily lives and impose a dramatic burden on our societies. The scientific and public health communities recognize it will be crucial to improve our preparedness and response to similar future pandemic threats. In particular, prevention will require the development of sustainable strategies against emerging zoonoses, aiming to reduce spillovers and curb pandemic threats at the source.

Although investing substantially in prevention strategies against zoonotic emergence would cost only 1% of the estimated cost for the COVID-19 pandemic (Dobson 2020), primary prevention approaches (OHHLEP, 2023) still do not make it onto the agendas of international academic, public health and operational organizations. One of the reasons for this is the challenge of quantifying disease emergence risk, which is a complex, multidimensional, and multifactorial issue. Furthermore, the ability to evaluate the impact of prevention strategies is hampered by the absence of documented and widely accepted indicators. Therefore, operationalizing the One Health approach to strengthen prevention strategies requires an initial set of basic indicators that can reliably measure how the risk of spillover is being reduced by the interventions applied.

In this context, PREZODE together with WHO convened a working group of 16 members with varied expertise and backgrounds to propose standardized indicators that can qualify the likelihood of zoonotic exposure of human populations. The proposed indicators are intended to be actionable, i.e., to reflect the impact of the implementation of a prevention strategy along the process of zoonotic pathogen emergence and over time.



# 1. Conceptual framework of the indicators

## Spillover theory

The worldwide circulation of a novel pathogen (*i.e.*, a pandemic) is the final stage of the natural spillover process. Before a pathogen circulates locally or regionally in people, the core process generally begins with ecological conditions that result in the spillover of a zoonotic pathogen from animal to human populations (pre-emergence step, Figure 1, Bernstein et al, 2021). For a zoonotic spillover to be successful, a pathogen must overcome a series of barriers to move from circulation in wildlife (e.g., wild birds or bats) and livestock (e.g., poultry or camels) populations to human infections (see Figure 1, Plowright et al., 2017). A list of possible barriers is detailed in the Annex 1.

The prevention of spillover, which is one component of primary prevention, involves strengthening the different barriers in ways that are relevant to the involved mechanisms and populations. This approach may allow an upstream impact, relying on the conditional dependence between each step (see Figure 1).

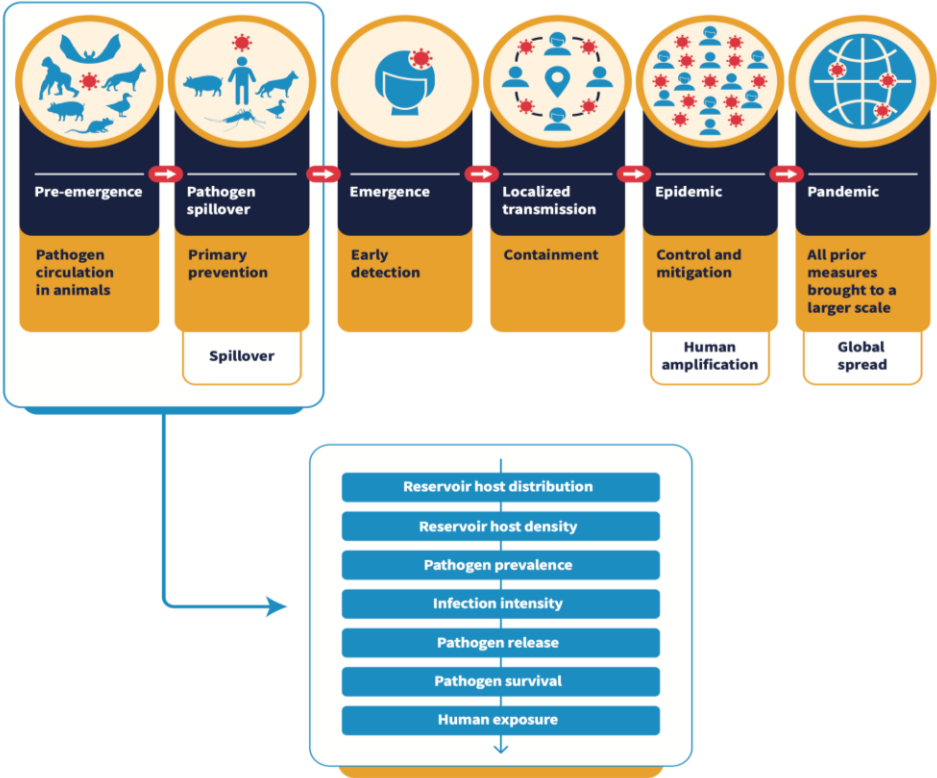


Figure 1: Different steps before pandemic initiation. This working-group is focusing on the first two steps (pre-emergence and pathogen spillover) and will consider all the drivers involved during these two steps (bottom right). Adapted from Bernstein et al (2021) and Plowright et al (2017).

## Design criteria for indicators

The indicators will focus on the circulation of the target pathogens among wildlife and livestock populations, and their contact intensity with humans. According to Plowright et al. 2017 (Figure 1), pathogen circulation in wildlife and livestock depends on host distribution, host density, community composition, pathogen prevalence, infection intensity, pathogen release from the host and pathogen survival and spread. Environmental stressors like deforestation or population density can shift the effects of these drivers, increasing or decreasing the risk linearly or nonlinearly. Ultimately, successful spillover depends on the extent and intensity of wildlife or livestock pathogen interactions with humans, and the ability of the pathogen to infect, replicate and spread amongst them.

## Scope of the indicators

The indicators presented here consider the steps until and including human exposure but do not incorporate measures of structural and immune barriers that must be overcome to enable human-to-human spread. Therefore, the indicators are designed to characterize and measure the steps up to human exposure to zoonotic pathogens. Four pathogens were selected to stress-test the approach: Avian Influenza Viruses (AIV), Middle East Respiratory Syndrome Coronavirus (MERS-Cov), Crimean-Congo Haemorrhagic Fever (CCHF) and West Nile Virus (WNV). These pathogens, part of the WHO R&D blueprint pathogens, were selected to have a wide range of epidemiological characteristics (e.g., different transmission routes, different animal species involved, different history of spillover to humans).

## Composition of the indicators of human exposure to a zoonotic pathogen

Recall human exposure to a zoonotic pathogen is dependent on the level of pathogen circulation in the animal populations and the intensity of human contact with these populations. These different factors are influenced by local (e.g., rainfall, temperature, animal population density, etc) and global factors (e.g., climate change, wildlife trade, etc).

Figure 2 shows the conceptual characterization of these pathways.

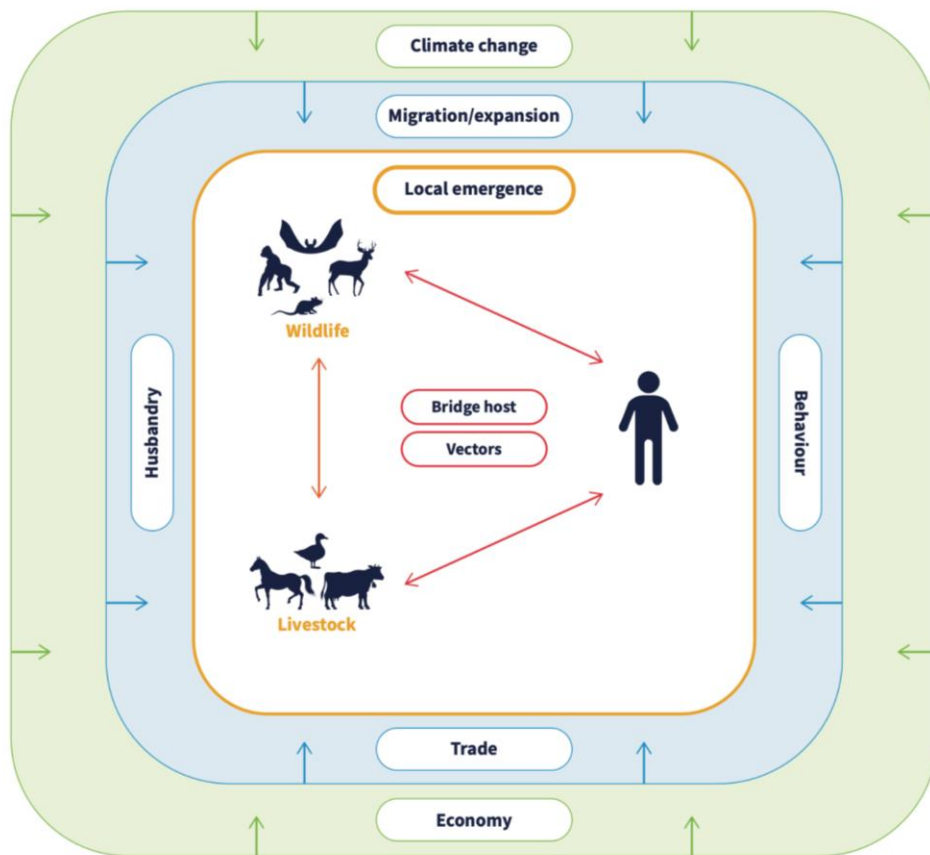


Figure 2: Characterization of the pathways used for zoonotic infection in humans.

Relying on these pathways, the indicators of human exposure to a zoonotic pathogen are constructed as follows. For both wildlife and livestock populations that could transmit the pathogen, the level of pathogen circulation is classified according to three different ranked levels (defined in Annex 2). This will give the following visual representation of human exposure to a zoonotic pathogen (figure 3):

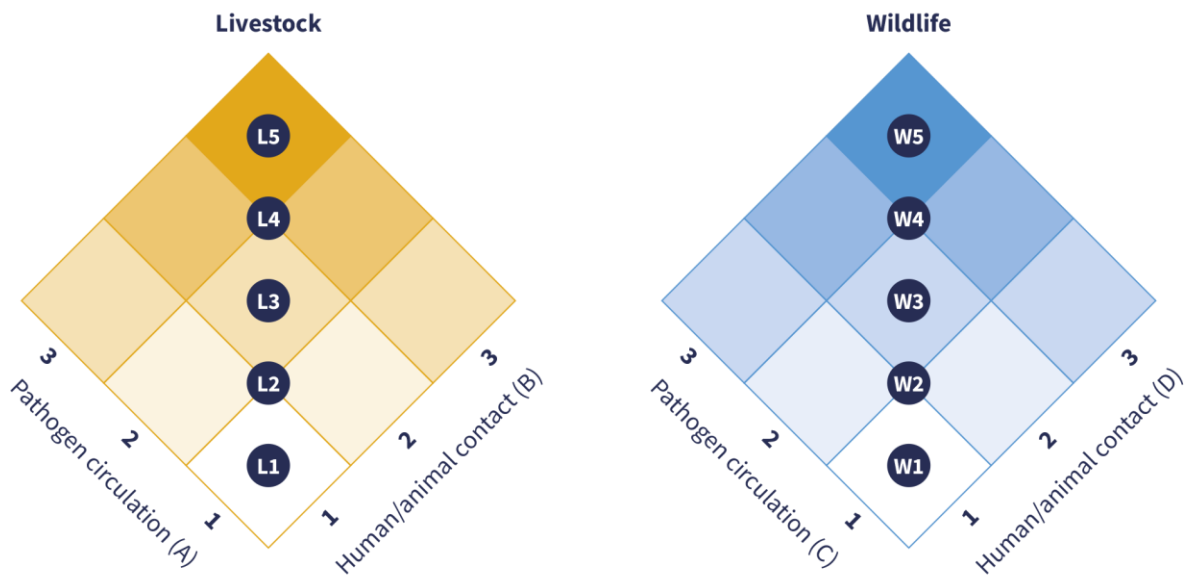


Figure 3: Representation of human exposure according to the pathogen circulation in wildlife and livestock, and the strength of human/animal interface in wildlife and livestock

First, human exposure to a pathogen can be characterized through four axes, which are the levels (maximum three) of pathogen circulation in both wildlife and livestock and of human/animal contact interface:

The level of pathogen circulation in livestock (A)

The level of human/livestock interface (B)

The level of pathogen circulation in wildlife (C)

The level of human/wildlife interface (D)

For instance, human exposure can be summarized as L-2:3/ W-1:2 for a pathogen with moderate circulation in livestock, intense contact between livestock and humans, a low circulation in wildlife and moderate contact between wildlife and humans. These levels are relative and represent low, moderate and maximal values for each of these axes (see definition below).

For both livestock and wildlife, some combinations may represent a level of human exposure that cannot be distinguished. For instance, a pathogen belonging to level 1 for wildlife circulation and

level 2 for wildlife/human interface (W-1:2) may not be different from a pathogen belonging to level 2 for wildlife circulation and level 1 for wildlife/human interface (W-2:1). Nevertheless, we can assume that human exposure should be higher than that of a pathogen with a level 1 for both wildlife circulation and human/wildlife interface (W-1:1).

Then, we can identify “categories” of exposure to zoonotic pathogens (maximum 5) from both wildlife and livestock. Consequently, a more synthetic representation of the previous example with a pathogen L-2:3/W-1:2 can therefore be categorized as L-3/W-2.

Finally, human exposure to zoonotic pathogens can be categorized similarly by combining categories of human exposure from wildlife and livestock, producing nine composite categories of human exposure (figure 4). The previous example of pathogen L-2:3/ W-1:2, categorized as L-3/W-2 would therefore fall into category 4.

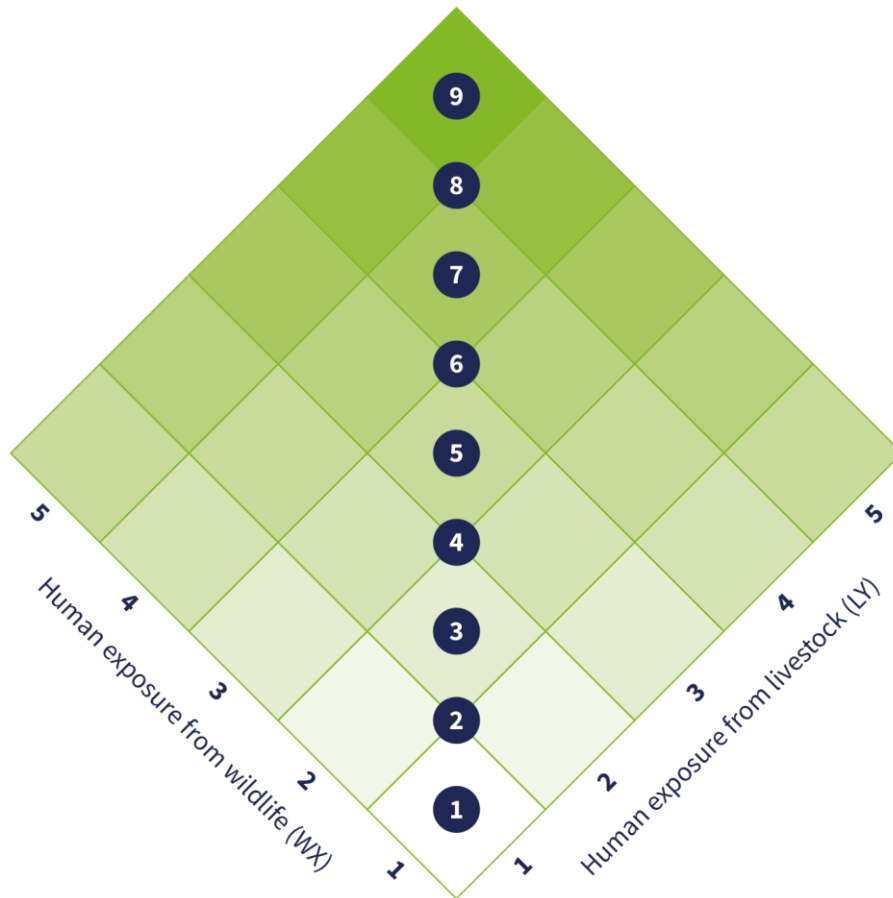


Figure 4: Representation of the human exposure categories to zoonotic pathogens combining human exposure from wildlife and livestock.

## Estimations

We asked 275 experts to estimate indicator values at a country scale. Each member of the working-group provided a list of experts on the different pathogens which were combined with experts working regularly with the WHO and a bibliography search. For a given pathogen and/or country of their choice, experts were tasked with providing estimates for: (i) the level of pathogen circulation in livestock, (ii) the level of contact between livestock and humans, (iii) the level of pathogen circulation in wildlife, (iv) the level of contact between wildlife and humans, and (v) the level of contact between wildlife and livestock (this last criteria is not considered in the indicator so far). Detailed definitions can be found in Annex 3. Each expert had the opportunity to provide estimates for the variable of their choice. Furthermore, we requested these professionals to offer a self-assessment of their confidence in their estimation for each item. Expert identities were anonymized in the final dataset.

## 2. Results

In total, 60 experts provided 196 estimates for the different levels previously explained (Figure 5). Of the four pathogens assessed, Avian Influenza Virus received the highest number of estimates (87), followed by MERS-Cov (52), WNV (38) and CCHF (19). Additionally, some countries received more estimates than others, with much lower numbers of estimates for Africa as a whole.

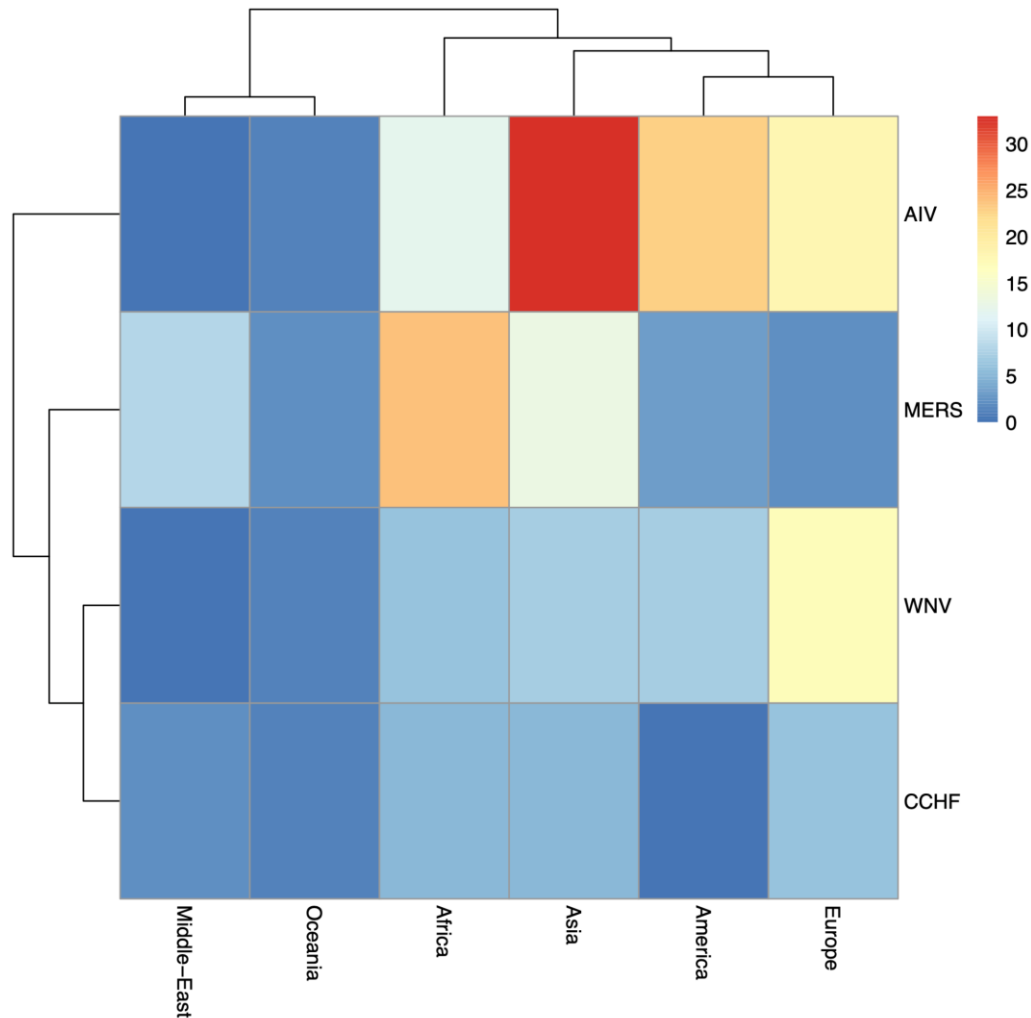


Figure 5: Distribution of the number of answers by continents and pathogens. Connecting lines represent the similarities in terms of answers profiles.

To complete this first database, absence data from MERS-CoV and CCHF were added to the analysis from published literature (Ramshaw et al, 2019, Messina et al, 2015).

## Maps of human exposure categories

Figure 6 shows the resulting indicators for the four pathogens, with the composite category for human exposure, and the respective categories from wildlife and livestock. With the exception of Africa and the Middle East, there are numerous estimates available for Avian Influenza Virus (AIV). As expected, based on existing literature, South-East Asia, Russian Federation, and North America show a high overall level of human exposure. This is determined by considering wildlife and livestock circulation, as well as human-animal contact specific to each country. Crimean-Congo Haemorrhagic Fever (CCHF) has the fewest number of estimates available. The highest category of zoonotic exposure is found in the Congo Basin, which is the pathogen's area of origin. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) demonstrates the highest level of zoonotic exposure in the documented region, particularly in the vicinity of the Arabian Peninsula. Both wildlife and livestock exposure show comparable distributions of high categories. West Nile Virus (WNV) shows the highest overall level of human exposure in Western Europe and North America, regions where WNV was introduced in the past 30 years. This is based on similar categories for both wildlife and livestock. Africa exhibits the highest category of human exposure from wildlife, which is the original location of the virus.

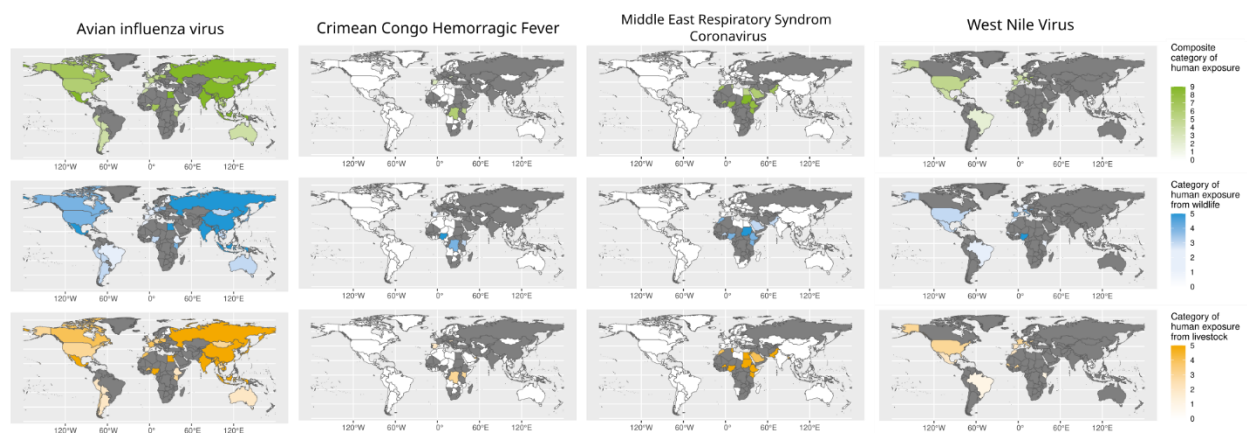


Figure 6. Maps of the composite (top), wildlife (middle) and livestock (down) categories for Avian influenza virus (first column), Crimean-Congo Haemorrhagic fever (second column), Middle East Respiratory Syndrome Coronavirus (third column) and West Nile Virus (fourth column). Human exposure is defined here as a contact between the pathogen circulating in the animal populations and the human population. Data come from estimates provided by the experts during the elicitation study performed during this working-group. All the indicators have been calculated through the methodology previously described and applied on these data. Dark grey areas represent countries where no estimates have been provided during this elicitation study.

## Validation of composite category of human zoonotic exposure

To evaluate the relevance of our indicators, we conducted an analysis to assess the association between the composite category of human exposure and documented zoonotic infection events (Figure 7). We collected data on the number of zoonotic infections caused by AIV (Kim et al., 2016) and MERS-CoV (Ramshaw et al., 2019) in humans since 2010. We compared the density distribution of the composite category between countries with and without documented occurrences. National case counts for CCHF and WNV were unavailable, so they were excluded from this validation exercise.

For AIV, the average composite category in countries without zoonotic infections was 5.39, while in countries with zoonotic infections, it was 7.30 ( $t = -3.13$ ,  $p\text{-value} = 0.0035$ ). The number of occurrences and the composite category value were significantly correlated ( $r = 0.32$ ,  $p\text{-value} = 0.036$ ). Additionally, a Poisson generalized linear model also revealed a significant association (Odds Ratio = 1.31).

The average composite index for MERS-CoV, in countries without zoonotic infections, was 0., whereas in countries with zoonotic infections, the value was 4.875 ( $t = -5.97$ ,  $p\text{-value} = 2.543 \cdot 10^{-5}$ ). The number of cases and the composite category showed a significant correlation ( $r = 0.34$ ,  $p\text{-value} = 6.591 \cdot 10^{-6}$ ). The Poisson generalized linear model indicated a significant association (Odds Ratio = 1.68).

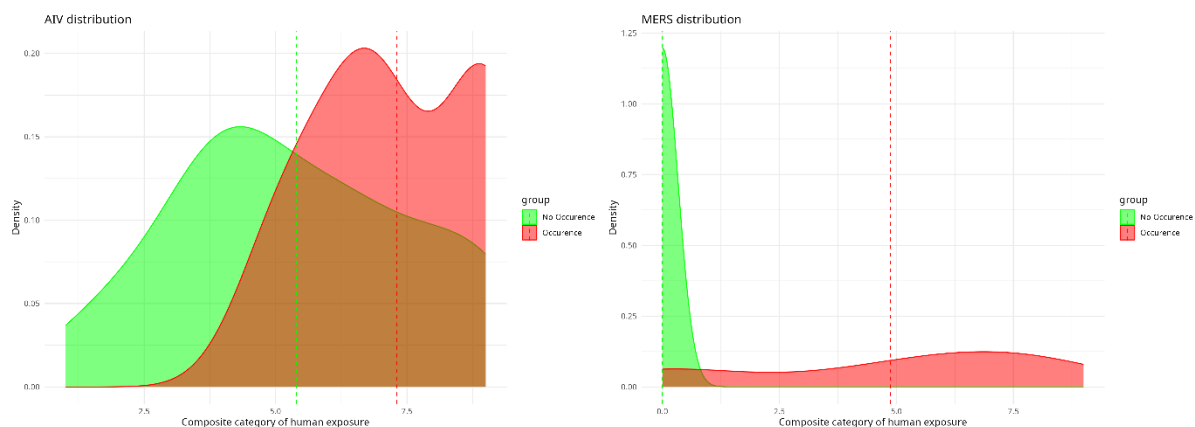


Figure 7: Composite index distribution in countries with and without spillover for a) AIV and b) MERS-CoV. Dashed lines represent the average value of the composite indicator.

## Impact of interventions

To demonstrate the actionable nature of these indicators in quantifying the likelihood of zoonotic human exposure, we simulated prevention strategies for AIV and MERS-CoV. For each scenario, we mapped a new composite category (Figure 8) and calculated the proportion of zoonotic infections that could be averted.

For AIV, the strategy involved a combination of biodiversity conservation programs to decrease pathogen circulation within wildlife (through applying a dilution effect) and a vaccination campaign in livestock. In this scenario, the estimated levels of AIV circulation in both wildlife and livestock were decreased by one to simulate the implementation of this strategy. The impact of this combined intervention was less linear and varied depending on the involvement of livestock and wildlife in the composite category of zoonotic human exposure for each country. Nonetheless, it resulted in an estimated 31% reduction in zoonotic infections.

Specifically for MERS-CoV we focused on reinforcing biosecurity measures in camel livestock facilities to reduce human contact with livestock. In this scenario, we simulated a decrease of one level in the estimated levels of human/livestock contact to reflect the implementation of this strategy. The impact of this intervention, based solely on livestock, resulted in an estimated 15% reduction in zoonotic infections.

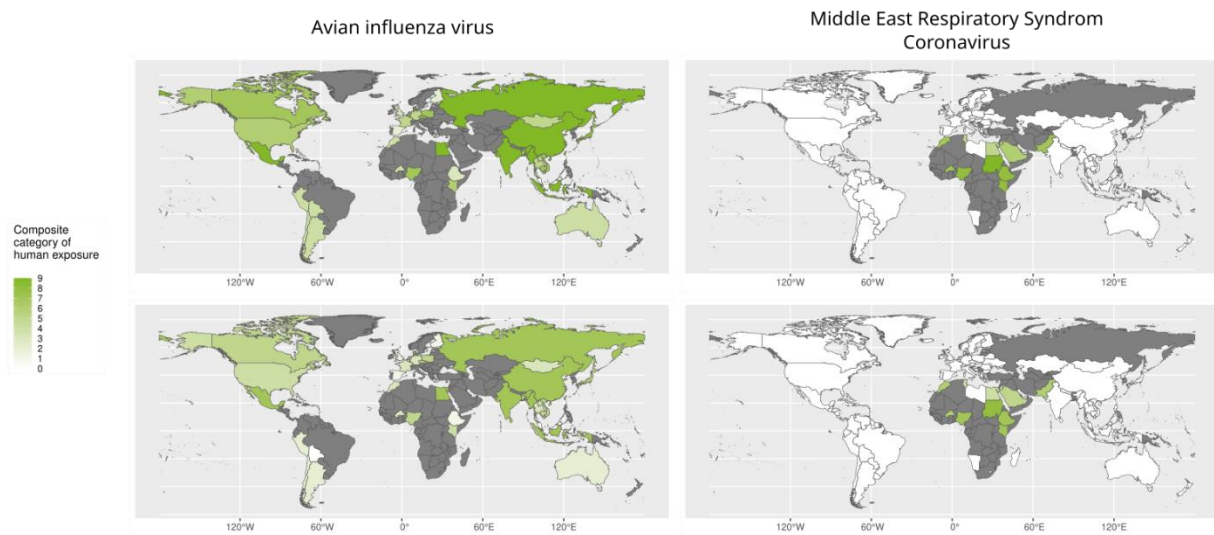


Figure 8: (Top line) Composite indicator without prevention strategy. (Bottom line) Composite indicator with prevention strategy.

### 3. Conclusion

The proposed indicators begin to characterize human exposure by separating pathogen circulation in both livestock (level A) and wildlife (B) with human/animal contact (levels C and D). These axes are aggregated to form categories of zoonotic human exposure. Consequently, the impact of a prevention strategy on any of these axes is reflected in the composite category. Application of this framework to data from an expert elicitation study demonstrated associations between the composite category (derived from expert estimates) and the number of zoonotic cases for AIVs and MERS-CoV. Basic simulations of prevention strategies illustrated how interventions affecting pathogen circulation and/or human-animal contact can reduce the composite human exposure indicator.

These indicators have met their initial goals, demonstrating their actionability in guiding prevention strategies and their validity in replicating zoonotic infections in the tested contexts. However, addressing current limitations and enhancing the indicators' actionability requires a mix of short- to long-term improvements.

In the short term, initiating a new phase of the elicitation study is essential to better characterize the limitations of these indicators. This phase should involve greater engagement of experts with in-depth knowledge of pathogen occurrences in Africa and possibly explore subnational scales to better represent the heterogeneity of zoonotic exposure. Developing rosters of additional experts and leveraging AI and digital scraping of scientific articles can facilitate this process. Additionally, integrating the variable of contact between livestock and wildlife, despite its challenges, is crucial for a comprehensive understanding of zoonotic exposure.

In the medium term, transitioning to a quantitative approach is recommended. This involves utilizing available empirical data, such as pathogen circulation and contact between animals and humans, to estimate indicators without relying solely on expert estimates. Advanced inference methods, coupled with enhanced routine surveillance in animals, can facilitate this shift.

However, addressing heterogeneity in existing datasets and developing interoperability tools are crucial for effective integration of diverse data sources. To this end, the working group is formulating two strong recommendations. The first recommendation is to significantly enhance routine surveillance of animals to obtain reliable indicators for assessing the likelihood of human exposure. Secondly, there is a clear need to develop tools for interoperability of missing data, which would facilitate cross-interrogation among multiple databases and/or provide recommendations for routine surveillance to reduce sampling heterogeneity. Although identifying links between biotic and abiotic factors and the documented level of pathogen circulation and human/animal contact on a

large scale is not trivial, improved interoperability combined with the current explosion of data-mining techniques can make this objective achievable in the mid-term.

In the long term, a pathogen-agnostic approach should be developed. With a broader array of pathogens characterized, it becomes feasible to develop indicators that transcend specific pathogens. By categorizing pathogens based on shared characteristics and monitoring variables that drive pathogen circulation and human/animal contacts in real-time, a more adaptable and comprehensive approach to zoonotic exposure assessment can be achieved.

Until the data availability, interoperability and analysis techniques have reached a sufficient level, it is important to update the likelihood of human exposure to start designing and implementing prevention strategies. This working-group therefore suggest that the network of experts identified for the elicitation study, deeply multi-disciplinary and covering a large geography, can persist and expand through time to provide regular and more complete estimates on the national and sub-national scales for a larger variety of pathogens.

After the short-term perspectives described previously have been implemented (by the end of 2024), the WHO/Prezode secretariat of this working-group will launch every year a new elicitation study with an expert network to update the mapping of zoonotic human exposure. These new elicitation studies can include new pathogens and experts to provide the most accurate estimation of human zoonotic exposure.

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## Annexes

All the data from the expert elicitation study and the code used are available here:

<https://github.com/rocheben/WhoPrezodeIndicator>

### Annex 1 - Barriers for pathogen spillover

Pathogen Circulation in Wildlife and Livestock	
Reservoir Host Distribution	The geographic distribution of reservoir hosts of the target pathogen.
Reservoir Host Density	The density of reservoir hosts of the target pathogen.
Pathogen Prevalence	The prevalence of the target pathogen within wildlife and livestock populations.
Infection Intensity	The intensity of infection within wildlife and livestock populations.
Pathogen Release from Reservoir Host	The frequency and quantity of pathogen release from reservoir hosts.
Pathogen Survival and Spread	The survivability and spread of the target pathogen in the environment.
Environmental Stressors	
Deforestation	The extent of deforestation in the area and its impact on pathogen transmission dynamics.
Population Density	The density of human and animal populations and its effect on pathogen transmission.
Interaction with Humans	
Extent of Interaction	The frequency and closeness of interactions between humans and wildlife/livestock populations.
Intensity of Interaction	The degree of physical contact and the duration of interaction between humans and wildlife/livestock populations.
Pathogen Infectivity to Humans	The ability of the pathogen to infect and spread in humans.

## Annex 2 - Definitions of levels used (Figure 3)

### Pathogen circulation

Level 0: Absence of circulation

Level 1: No cases detected currently (may have been detected in the past) or low level of seroprevalence

Level 2: Sporadic detection suggesting a low maintenance of the pathogen with an intermediate level of seroprevalence

Level 3: Frequent detection illustrating a strong pathogen circulation with a high level of seroprevalence

### Contact intensity between humans and animals

Level 0: Absence of contact

Level 1: Low frequency of contact with animal populations that are not located near human populations OR transmission modes are very indirect (i.e., require a bridge host)

Level 2: Moderate frequency of contact with animal populations that can be easily accessible OR transmission modes are direct, but not high (e.g., sustained contact)

Level 3: High frequency of contact with animal populations that are located close to human populations OR highly efficient transmission modes (e.g., aerosols)

### Contact between wildlife and livestock

Level 0: Absence of contacts

Level 1: No spatial overlap between wildlife and livestock populations, but potential some sporadic contacts

Level 2: Small spatial overlap between wildlife and livestock populations, suggesting occasional contact between wildlife and livestock

Level 3: Livestock facilities are located in areas with high wildlife diversity, suggesting frequent contact between wildlife and livestock

## Annex 3 - Detailed information that was considered by the experts

To ensure consistency across experts, we ask the experts to consider the following specificities to provide your estimates for each pathogen in each geographical unit:

Avian influenza

*Wildlife:* Species of interest: Waterbirds (especially mallards)

Drivers to consider: Temperature, land use, density of waterbodies, migratory routes, prevalence in other places along the migratory routes

Contact with humans: proximity of water bodies

*Livestock:* Species of interest: Poultry

Drivers to consider: Poultry density, poultry trade routes, proximity with waterbodies, type of husbandry

Contact with humans: Number of workers inside pig/poultry livestock facility

Tick-borne diseases (CCHF)

*Wildlife:* Species of interest: Potentially hares

Drivers to consider: Mostly host diversity

Contact with humans: Factors driving tick abundance (mostly temperature, relative humidity, saturation deficit). Human behavior regarding outdoor activities

*Livestock:* Species of interest: Cattle, goat sheep

Drivers to consider: Livestock density

Contact with humans: Factors driving tick abundance (mostly temperature, relative humidity, saturation deficit). Human behavior regarding outdoor activities

Arboviruses (West Nile virus)

*Wildlife:* Species of interest: Wild birds

Drivers to consider: Bird density, migratory routes

Contact with humans: Environmental factors driving mosquito abundance (temperature, rainfall, ...)

*Livestock*: Species of interest: Horses

Drivers to consider: Horse density

Contact with humans: Environmental factors driving mosquito abundance (temperature, rainfall, ...)

MERS-coronavirus

Wildlife

Species of interest: Vespertilionid (insectivorous) bats

Drivers to consider: bat fly length and environmental variables affecting food abundance

Contact with humans: bat/human interaction through deforestation

Livestock

Species of interest: Dromedary camels, Bactrian camels, llamas, alpacas

Drivers to consider: Species densities, husbandry systems, interaction between camelid populations

Contact with humans: Existence of camel markets, camel gatherings, nomadic communities reliant on and living with camels, competitions involving camels (races, beauty pageants)



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