World Health Organization

QUALITY CRITERIA FOR THE EVALUATION OF CLIMATE-INFORMED EARLY WARNING SYSTEMS FOR INFECTIOUS DISEASES

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ACRONYMS

AN	actual no-outbreak
AO	actual outbreak
CAR	conditional auto-regressive models
EWS	early warning system(s)
FN	false negative
FP	false positive
GI	Getis-Ord Gi statistic
GIS	geographical information system
GLMM	generalized linear mixed models
GWR	geographically weighted regression
IHR	International Health Regulations
IT	information technology
LISA	local indicators of spatial association
M&E	monitoring and evaluation
MoH	Ministry of Health
NPV	negative predictive value
PD	probability of detection
PF	probability of false alert
PPV	positive predictive value
RCT	randomized controlled trial
ROC	receiver operating characteristic
SAR	spatial auto-regression
SMS	short message service
TN	true negative
TP	true positive
WHO	World Health Organization
WMO	World Meteorological Organization

EXECUTIVE SUMMARY

The frequency of infectious disease epidemics is increasing, and the role of the health sector in the management of epidemics is crucial in terms of response *(1)*. In the context of infectious disease epidemics, the use of climate-informed early warning systems – EWS (the organized mechanism to detect as early as possible any out-of-control state of disease phenomena *(2)*) – has the potential to increase the effectiveness of disease control by intervening before or at the beginning of the epidemic curve, instead of during the downward slope. Currently, the initiation of interventions is heavily reliant on routine disease surveillance systems – data that often arrive too late for preventative response. However, forecasting of disease outbreaks using surveillance and weather information shows promising potential *(3,4)* – there also remains further scope to examine seasonal climate forecasts *(5–7)*. By combining these elements in new EWS based on computational models, it will be possible to improve both the timeliness and impact of disease control.

Until recently, EWS have rarely applied statistical methods to detect changes in trends or sentinel events that would require intervention, and generally lacked essential assessment for effective, implementable and scalable tools. In most cases, EWS rely on an in-depth review of incoming data by local epidemiologists, which rarely follow a systematic process. The World Health Organization (WHO) is strengthening existing surveillance systems for infectious diseases to enable the development of more robust and timely EWS, which has resulted in the rapid development and innovation of EWS for disease outbreaks.

The core elements of climate-informed EWS are to: (i) monitor environmental conditions; (ii) forecast high-risk conditions, initiate active surveillance; (iii) send alerts and communication; and (iv) establish a mechanism for early response. However, in view of the advances in mathematical modelling, the availability of big data and their complex analytical designs – as well as issues related to the quality of national surveillance programmes and local response protocols – other technical and operational aspects are essential for monitoring the effectiveness and cost-effectiveness of existing decision-support tools.

In June 2019, an expert meeting on using climate and weather information for predicting and preparing for cholera and vector-borne diseases was convened in Geneva, Switzerland, and supported by the Climate Change and Health Unit (WHO), the World Meteorological Organization (WMO), the Met Office (United Kingdom), UK AID and the Department for International Development. One key outcome from this meeting was the need for the development of quality criteria for validating a prediction model.

1 INTRODUCTION

1.1 Rationale

Epidemic EWS are often defined marginally as tools for detecting and predicting an impending disease outbreak, but this definition usually fails to clarify whether the warning information is effectively used to reduce risks. EWS should be perceived as an information system designed to support decision-making of national and local-level institutions to enable vulnerable groups in society to take action to mitigate the impacts of an impending risk. With this in view, EWS should not only be a time- and space-function for informing of probable disease outbreaks, but should also help improve coordination among relevant stakeholders, such as local epidemiologists, meteorologists, entomologists, the national and local management agencies that assess risk and develop response strategies, and the public communication channels used to disseminate warning information. Therefore, a complete and harmonized evaluation design for the assessment of EWS performance is warranted to effectively manage outcomes and harmonize test results of EWS.

1.2 Scope and purpose of the guide

This guide aims to outline key technical and operational criteria surrounding the performance, application, implementation and effectiveness of EWS and to illustrate how an understanding of these issues can be used for the evaluation of EWS for multiple infectious disease outbreaks. This guidance is aimed at national authorities of infectious disease programmes and health information systems of ministries of health (MoH).

Specifically, this guide provides a set of essential evaluation criteria related to key components, design and application of climate-informed EWS, with a focus on aspects related to the indicators used, statistical performance, operational aspects and communication, as well as the cost-effectiveness of EWS. These guidelines show users how to evaluate the performance of existing EWS and support the decision-making phases for the implementation process. Tools that are under development can also benefit from the design and recommendations proposed in this guide to achieve effective climate-informed EWS.

1.3 How to use the guide?

The guide comprises five interrelated "steps" for the evaluation criteria and each step can also be applied independently. The first step concerns overarching issues important to early warning, such as criteria related to the outbreak and climate (including references to non-climate) predictors employed by the tool. The second step is designed to assess key structural features of the prediction model and their prediction quality, while the third step provides a checklist of key initiatives that should be considered when evaluating the statistical features of the EWS. This (third) step is specifically related to the "retrospective" phase of the early warning process (i.e. the training phase of the prediction model where historical surveillance records of disease outbreaks and possible alert indicators are processed and calibrated to generate a prediction algorithm). The fourth step focuses on evaluating the overall effectiveness and cost-effectiveness of the EWS based on a range of different study designs. The fifth step proposes a set of comprehensive criteria for evaluating the operational features of the EWS. Both the fourth and fifth steps are related to the "prospective" phase of the early warning process (i.e. the application of the derived prediction algorithm using prospective real-time surveillance data).

Each step includes a checklist for evaluating the corresponding criteria and a colour code indicates the level of performance of the given EWS component. The codes and their interpretations are given below:

No	**RED –** If the answers to the criteria questions are "No", this component should be assigned a RED code.	**RED code:** indicates that the EWS has NOT adequately addressed the issues of the corresponding component.
Neutral	**ORANGE –** If the answers to the criteria questions are "Neutral", this component should be assigned an ORANGE code.	**ORANGE code:** indicates that the EWS is neither exceptionally strong nor exceptionally weak.
Yes	**GREEN** – If the answers to the criteria questions are "Yes", this component should be assigned a GREEN code.	**GREEN code:** indicates that the EWS has clearly addressed the issues of the corresponding component.
NA	**WHITE –** If the answers to the criteria questions are "NA", this component should be assigned a WHITE code	**WHITE code:** this does not contribute to the overall criteria assessment of the tool

2 A BRIEF OVERVIEW OF THE MONITORING AND EVALUATION OF CLIMATE-INFORMED EWS

The monitoring and evaluation (M&E) of the EWS, be it internally via the local EWS users (e.g. district health officers/managers), externally through consultants and regional epidemiologists, or both, should be done on a regular basis at early development and post-implementation stages. A full M&E of the EWS should take place within 1–2 years of inception, followed by a routine assessment every 2–5 years. The M&E of EWS should be a comprehensive process capturing technical, statistical and operational aspects, including the assessment of the system capacity for rapidly detecting and supporting the management of disease outbreaks in a timely manner. The M&E assessment should typically address the capacity of the EWS to detect and define information related to the acute health event; provide risk assessment analysis, and; facilitate a platform to ensure prompt investigation and response at the national and local levels.

A structured and complete external M&E of EWS will ensure reassessment of the tool sensitivity, timeliness and usefulness. This will inform district health managers and policy-makers about the means to enhance the surveillance system and ensure compliance with national programmes and acceptability by different stakeholders. The M&E should also assess the level of integration of early warning and response within the existing public health surveillance systems and its cost-effectiveness after trialling over time and space.

3 PLANNING: STEPS FOR ASSESSING KEY EVALUATION CRITERIA FOR CLIMATE-INFORMED EWS

3.1 STEP 1: Defining the outbreak and climate predictors

Under step 1, the assessment will include the following criteria:

i. Evaluating the climate alert information
ii. Using climate information for disease prediction
iii. Using non-climate information for disease prediction
iv. Declaring an outbreak

Evaluating the climate alert information

The goals of an EWS are not only to predict the probability of disease risk given climate anomalies but also to downscale to regional and local impacts and translate into relevant metrics. In other words, the challenge is to translate the "policy-relevant" time horizon into lead-times necessary for response and intervention over a well-defined geographical area and based on the climate information that are proven best predictors of disease outbreaks (e.g. temperature, humidity, rainfall). However, useful and timely climate data are often not available, biased or otherwise inaccessible to those who need them most. This is typically the case for existing EWS development projects and efforts are being made to alleviate the problem of data availability and use. Hence, quality criteria assessments are needed to handle climate data limitations – such as their types, definition, reporting, completeness and quality – during the process of disease outbreak predictions *(8)*.

Criteria for using climate information for disease prediction

Important characteristics of climate variability and longer-term climate change, such as the frequency, severity, spatial distribution and predictability of, for instance, floods or drought, are crucial for the application of EWS. Applying a defined threshold for meteorological conditions is equally important for the adequate functioning of climate-informed EWS. Different methods – including descriptive or advance statistical methods as well as expert judgement – can be used for defining thresholds for meteorological conditions. For instance, percentiles associated with a significant excess in mortality in a specific setting can be used as a local threshold of meteorological conditions *(9)*.

EWS can potentially link science and society, the terms of which require extraordinary care to achieve a balance between over-warning and under-warning tuned to the actions the society takes in response to an early warning, which can be both costly and disruptive. Furthermore, climate variability introduces a great challenge to EWS, raising concerns such as: What lead-time might be available for reliable predictions? How fast or slow would climate variability manifest itself in conditions that affect societies? And what factors can influence the types of response and their sensitivity to predictive information? In this context, proposing a set of evaluation criteria for climate indicators employed by EWS will be crucial for maintaining reliable and useful forecasting of diseases outbreaks (Table 1).

Table 1. Evaluation criteria for climate indicators employed by EWS

	Yes	No	Neutral	NA
1. Is there a routine collection and use of climate indicator information in your setting (e.g. temperature, humidity, etc.)?				
2. Does the climate indicator employed by the EWS rely on existing evidence from the literature/local reports showing the ability to predict disease outbreak?				
3. Does the climate indicator employed by the EWS rely on existing methods to define a threshold for climate conditions?				
4. Is the climate indicator employed by the EWS defined in the same way over time (e.g. in terms of the unit of measurement, which can ensure consistency for measuring trend)?				
5. Are data for the climate indicator used by the EWS collected in the same way over time (i.e. as reported by different sources of climate information or a different mechanism of information retrieval, e.g. from local meteorological stations or other international open-access sources)?				
6. Will data be prospectively available/accessible for climate-based prediction in a timely manner (i.e. routinely on a daily, weekly or monthly basis)?				
7. Is the climate indicator information reported as quantitative variables?				
8. Does the climate alert information follow routine quality and completeness checks prior to use?				
9. Are there any climate data with an established dose-response relationship that can be used to develop a prospective indicator that may potentially provide a reasonable lead-time?				

Note: These criteria can be used separately for each type of alert indicator.

Criteria for using non-climate information for disease prediction

In the context of EWS, climate indicators are generally the most encompassing predictors and these differ across different diseases. However, other types of predictors have been shown to be relevant to the early warning process. Such alert indicators include sociodemographic (e.g. age and other population data, poverty, etc.); entomological (e.g. ovitrap, house index, container index, Breteau index *(10)*); and geotagged satellite and social media data (e.g. Internet search trends, Facebook or Twitter user information, google maps as well as information on local/regional movement patterns) *(11)*. Those indicators can provide useful information for the development and advancement of more accurate and efficient prediction of spatio-temporal spread of diseases (Table 2).

Table 2. Evaluation criteria for non-climate indicators employed by EWS

	Yes	No	Neutral	NA
1. Is there a routine collection and use of non-climate indicator information (e.g. sociodemographics, ovitrap, house index, etc.)?				
2. Does the non-climate indicator employed by the EWS rely on existing knowledge from the literature/local reports for the prediction of disease outbreak?				
3. Is the non-climate indicator employed by the EWS defined in the same way over time (e.g. sociodemographic records are consistently defined over time, and a consistent definition is also given to entomological terms such as ovitrap (being measured as an average or proportion), Breteau index, house index, etc.)?				
4. Are data for the non-climate indicator used by the EWS collected in the same way over time (e.g. different sources of sociodemographics, entomological or geotagged satellite and social media information and different mechanism of information retrieval, e.g. search engine tools)?				
5. Will (some of) non-climate information be prospectively available for prediction (i.e. routinely on a daily, weekly or monthly basis)?				
6. Is the non-climate indicator quantitative?				

Note: This table can be used separately for each type of alert indicator.

Declaring the outbreak

Defining a threshold for declaring a disease outbreak (such as dengue, chikungunya, cholera outbreaks, etc.) is challenging and can vary depending on the type and magnitude of the disease, capacity of the local health system, and the methodological approach that underlies the prediction model *(12)*. The definition of an outbreak can also be based on the target population – for instance, certain diseases are of importance when they aim at vulnerable groups such as children, elderly and pregnant women. Furthermore, case reporting in surveillance systems varies in terms of time-unit – daily, weekly and monthly – which can have significant operational implications during the disease control process. Hence, the methodological approach employed to define an outbreak threshold should be chosen and evaluated carefully, as this can significantly influence the performance of the model (Table 3).

Table 3. Evaluation criteria for outbreak indicators

	Yes	No	Neutral	NA
1. Do you rely on the existing definition of outbreak for declaring outbreaks in your setting?				
2. Does the definition of outbreak follow a rationale for the use of the term "disease outbreak" (e.g. in *epidemiological* terms, outbreaks occur at many different levels of intensity, duration and velocity in deviations from seasonal means, driven by a range of factors that determine transmission suitability; from a *public health* perspective, however, the term "outbreak" refers to a situation where routine surveillance, treatment and control capacities are exceeded and exceptional interventions are required)?				
3. If the definition of an outbreak is based on identified periods of excess burden, has there been a thorough assessment of baseline health-care surveillance, control and treatment capacities (e.g. measures of the number of beds, insecticide stockpiles, the quality surveillance teams)?				
4. Does the definition of disease outbreak take into account the variability of outbreak characteristics over time and space (i.e. using non-standardized definition but one that can adapt to the disease-specific outbreak characteristics in a given place and time; for instance, five dengue cases in district X1 and five dengue cases in district X2 are not equivalent)?				
5. Does the outbreak threshold vary with the severity of the outbreak (i.e. "low", "moderate", "high" instead of adopting a qualitative or dichotomy – no outbreak/outbreak format)?				
6. Is the outbreak definition based on more reliable information other than reported and suspected cases (e.g. hospitalized or laboratory-confirmed cases)?				
7. Is the outbreak definition incorporated alongside other reported information, such as data on the percentage of positive diagnostic tests, entomological indices and/or environmental signals?				
8. Is the outbreak indicator measured on the basis of additional data on actions that are taken during the outbreak response (additional data on response includes staff surge capacities, resources for additional mass fogging, rapid sentinel surveillance and/or the speed of deployment of each of these; this defines what weekly cases should fall under the remit of routine activities and what number of cases should trigger exceptional measures)?				
9. Is there a clear definition of the outbreak "start" period?				
10. Is there a clear definition of the outbreak "stop" period?				

Note: This table can be used separately for each type of outbreak indicator. In instances where multiple outbreak indicators are present, you may choose to evaluate the outbreak indicator that is mostly used by the validated EWS.

3.2 STEP 2: Evaluating the structural and statistical features of the EWS

Under step 2, the assessment will include the following criteria for the statistical and technical characteristics of the model:

i. Assessing the types of indicators processed by the EWS
ii. Assessing the temporal-based prediction of the EWS
iii. Assessing the spatial-based prediction of the EWS
iv. Assessing the use of big data in the prediction model

Practical aspects such as possible limitations of accessing data will not be dealt with in this section.

Characterizing the EWS: the prediction model

Integral to such EWS is an exposure–response relationship to compute the risk of a disease epidemic on the basis of meteorological and epidemiological conditions. The practical importance of defining and declaring an epidemic is the level of support that may be triggered by the EWS. Declaring an epidemic too late will lead to avoidable and unnecessary morbidity and mortality and to wastage of resources if control options are implemented late in relation to the natural development of the epidemic curve. Declaring an epidemic prematurely may lead to overreaction at the expense of scarce resources and may distort the reality of the situation. Therefore, a clear and timely definition of an outbreak is important for EWS. In addition, characterizing other risk factors of the EWS is essential for valid and practical applications of EWS. For this purpose, a list of specific quality criteria for assessing the components of the statistical model is proposed below.

Assessing the types of indicators processed by the EWS

The effectiveness of prediction can be influenced by the volume, quality and nature of the information used and hence, it is useful to assess what, how and why a certain number and types of climate indicators are processed by the EWS.

Several approaches are often used as evaluation criteria for statistical models, including the signal-extraction approach (also known as the indicators approach) and the regression analysis approach *(13)*. The former is based on monitoring the types and numbers of explanatory variables used in the model (climate information) and evaluating whether the behaviour of those variables differs around the outbreak episode; while the latter uses more classical estimation techniques relying solely on outbreak events. This section focuses on the signal-extraction method, which is more relevant to this guide.

The signal-extraction method requires defining a signalling horizon, a threshold level, and then classifying the signals; the signalling horizon or outbreak window is the period within which the indicator would be expected to have an ability for anticipating outbreaks (Table 4).

This step is typically performed during the retrospective phase of the early warning process.

Table 4. Evaluation criteria used in the signal-extraction approach

	Yes	No	Neutral	NA
1. Is the EWS considered an alert-informed model (i.e. uses information from meteorological variables to predict probabilities of disease outbreaks, not only based on previous trends of outbreak cases – i.e. case-informed model)?				
2. Can the EWS process multiple types of alert predictors per analysis (i.e. at least two different types of meteorological predictors, e.g. temperature, rainfall, humidity, all in one model)?				
3. Does the EWS allow users to calibrate different cut-offs and settings related to the alert predictors (this is ideal to handle situations related to the completeness and quality of information of the climate indicator)?				
4. Does the EWS allow an independent calibration process per alert predictor (i.e. adjusts for alert-specific cut-offs and settings)?				

Criteria for assessing the temporal-based prediction of the EWS

The first level of decision-making is associated with the following questions: What action must be taken in the outbreak risk areas, when, and for how long? While research has shown diverse effects of a range of time-lags between independent variables and epidemic disease transmission (prediction window), no systematic review exists that can provide a definitive range of an appropriate time-lag for each covariate *(3).*

The main objective of temporal prediction is to identify the onset time of the disease outbreak and its duration (Table 5).

Table 5. Criteria for assessing the temporal prediction of the EWS

	Yes	No	Neutral	NA
1. Does the EWS generate a temporal prediction of an outbreak (i.e. generates a probability for a disease outbreak to take place at certain time or after the specified window time)?				
2. Are there evidence-based estimates of time-lags associated with the climate indicators used by the EWS (e.g. published reports or expert opinion documenting estimated window of time-lag between the change in the alert indicator and the disease outbreak)?				
3. Does the prediction model address the diverse effects of a range of time-lags between independent variables and epidemic disease transmission, when multiple predictors are being processed by the model?				
4. Does the EWS allow accurate and timely applications for response/intervention (i.e. not too broad window of prediction [e.g. ≥26 weeks ahead] or too short window [≤2 weeks ahead])?				
5. Does the EWS systematically handle the differences in climate indicators that can be expected in different areas and seasons (e.g. does the EWS allow the calibration to include different periods of records for alert indicators, which can potentially handle issues related to missing information or outliers)?				

STEP 2

Criteria for assessing the spatial-based prediction of the EWS

Defining hotspots based on the history of infections is a crucial method for developing programmes to prevent epidemics and ensure more efficient and cost-effective strategies.

Stratification at the city or local level requires the EWS to adopt analytical and theoretical methods to study the spatial patterns of the incidence of a health event. These patterns may appear as "unusual" spatial aggregates or clusters of a disease or areas where a disproportionate number of cases are concentrated (hotspots). It is worth noting that in the context of EWS, spatial prediction alone is less useful. Spatial risk mapping should be combined with the temporal model for an effective public health response.

While mapping of case incidence tends to be an ideal spatial prediction approach, given the issues related to the case reporting and notification in registered or unregistered populations, other advanced approaches are practised in EWS. These statistical methods help determine with broad levels of certainty whether the unusual patterns are indeed the product of disproportionate distribution of cases within specific areas of the locale *(14)* (Table 6).

Table 6. Criteria for assessing the spatial prediction component of the EWS

	Yes	No	Neutral	NA
1. Does the EWS generate spatial prediction (i.e. risk mapping) of the disease outbreak in sub-levels of the administrative area (e.g. if the prediction is at the district level, can the prediction go down to the household, neighbourhood or village levels)?				
2. Can the EWS process disease cases together with their geographical coordinates for the spatial prediction (e.g. the hospital location from where cases are reported)?				
3. Does the EWS provide information on the spatial method applied?				
4. Does the EWS have appropriate visualization of the spatial prediction?				
5. What is the method used by the EWS for the spatial prediction?				
i. Does the EWS use the "mapping of case incidence and distribution" approach for the spatial prediction?				
ii. Does the EWS use the "interpolation approach (e.g. kernel density, kriging)" for the spatial prediction (*i.e. other interpolating methods such as smoothness, e.g. smoothing spline, may yield different values*)?				
iii. Does the EWS use the "hotspot analysis (e.g. LISA, Gi*)" approach for the spatial prediction?				
iv. Does the EWS use the "spatial effects models (e.g. GLMM, CAR, SAR, GWR)" approach for the spatial prediction?				
v. Does the EWS use "simulation models" approach for the spatial prediction?				

LISA: local indicators of spatial association; Gi*: Getis-Ord Gi statistic; GLMM: generalized linear mixed models; CAR: conditional auto-regressive models; SAR: spatial auto-regression; GWR: geographically weighted regression.

Note: For criteria #5, these alternative models follow the ascending order of difficulty, required data and calculation power whereas only one alternative is possible for each model.

Criteria for assessing the use of big data in the prediction model

The emergence and re-emergence of infectious diseases as a result of the interaction between changing climate and human systems are influenced by increased human mobility (both short- and long-distance). This warrants the adoption of new frameworks for assessing the linkage between disease transmission, climate change and public health interventions in order to reach effective EWS. The use of data mining techniques in combination with surveillance data has emerged as an alternative source of real-time, high-resolution geospatial data on a large scale. The application of this unique aspect of publicly available satellite, social media or other dynamic data to study the human dimensions of the introduction and spread of emerging infectious diseases can improve the outbreak preparedness and response planning by pinpointing receptive areas for proactive countermeasures in a timely fashion *(15,16)*. Examples of such data include static spatial predictors such as local infrastructure or those updated less frequently like risks of flooding/drought as well as the types of vegetation and housing (Table 7).

Table 7. Criteria for assessing the use of big data in the EWS

	Yes	No	Neutral	NA
1. Within your surveillance system, are there readily and routinely available big data to use for EWS?				
2. Does the EWS have system capacity to download, utilize and process big data (e.g. internet stability, processing speed, optimized algorithm)?				
3. Does the EWS allow the use of dynamic data (big data) as alert predictors of disease transmission, people mobility patterns and disentangled connectivity between populations (e.g. near-real-time geocoded Twitter, mobile phone data)?				

3.3 STEP 3: Evaluating the performance of the EWS (retrospective phase)

Under step 3, the assessment will include the following criteria:

i. Assessing the temporal and spatial prediction accuracy
ii. Assessing the statistical performance of the EWS
iii. Assessing approaches for overcoming methodological challenges

Assessing the temporal and spatial prediction accuracy

The EWS should assess the spatial and temporal variability that can help detect the presence of hotspots for a given period – that is, areas that disproportionately contribute to transmission and where outbreaks are most likely to begin. Thus, the EWS should be able to ensure performance measurements of the time- and space-prediction of the model.

This section addresses quality criteria related to the retrospective phase of the model (#1, #2 and #3) as well as the prospective routine applications of the tool (#4, #5): (Table 8).

Table 8. Criteria for assessing time and space prediction accuracy

	Yes	No	Neutral	NA
1. Does the EWS produce statistics to measure the proportion of successful prediction within a certain time interval?				
2. Does the EWS produce statistics to measure the proportion of delayed time-to-prediction of outbreaks (delayed, when the EWS forecasting has missed the outbreak, i.e. came late in time)?				
3. Does the EWS produce statistics to measure the proportion of time-to-first false alert?				
4. Does the EWS provide visual analysis of the information (historical data on cases, incidences of entomological data) for spatial pattern?				
5. Does the EWS produce statistics to examine the scale of transmission (hotspot)?				

Assessing the statistical performance of the EWS

To enable response and policy actions for disease outbreaks, the focus should rather be on identifying precise periods with a specified forecast horizon. Nevertheless, policy-makers can be assumed to have relative preferences for conducting two types of errors: issuing false alerts and missing outbreaks *(17)*. Therefore, it is essential to quantify how well an EWS discriminates between periods of outbreaks and no-outbreaks by identifying the optimal cut-off. The higher the probabilities during the observed no-outbreak periods, the larger is the optimal cut-off and the society rendered more vulnerable. This demonstration of the prediction model is equally essential for evaluating the cost-effectiveness of the tool, as discussed in the next step (step 4).

Figure 1. Outbreak (event) prediction results

		Predicted event		
		Alarm signal	No alarm signal	
Actual event	Outbreak	**TP** True positive	**FN** False negative	**AO** = TP+FN
	No outbreak	**FP** False positive	**TN** True negative	**AN** = FP+TN

AO: actual outbreak; **AN**: actual no-outbreak

Figure 1 describes a summary for the probability of detection (PD) and the probability of false alert (PF) a model should produce – PD is a metric for measuring the true alert signals in relation to the total number of actual outbreak events, PF is a metric measuring how many false-positive predictions are wrongly classified as outbreak events. Hence, all EWS should be able to determine a statistical measure of performance, such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the receiver operating characteristic (ROC) (Table 9). Ideally, a model should determine the optimal cut-off as the threshold that minimizes the difference between the weighted sensitivity and the weighted specificity, where the weights are defined by the optimal cut-off *(18)*. These parameters are crucial for evaluating the effectiveness and cost-effectiveness of the EWS (step 4) (Table 9).

This step is typically performed during the retrospective phase of the early warning process.

Table 9. Criteria for assessing the statistical performance of the EWS

	Yes	No	Neutral	NA
1. Does the EWS have the appropriate and timely feedback mechanism to record the outcome of the signal (i.e. discarded as no-outbreak, suspected outbreak with no laboratory confirmation, laboratory-confirmed outbreak signal, etc.).				
2. Does the EWS systematically provide outputs to quantify the TP, FP, TN and FN measures of disease predictions, which are useful for measuring the overall EWS effectiveness (e.g. wasted vector control resources/activities)?				
3. Has the EWS been evaluated using some measurements of effect (e.g. sensitivity, specificity, PPV, NPV, ROC)?				
4. Can users of the EWS calibrate the pre-specified cut-off for optimizing the prediction performance?				
5. Does the EWS allow the pre-specified cut-off relevant to the context in which the prediction is applied (i.e. a cut-off could be based on whether optimizing sensitivity or specificity has greater practical value)?				
6. Does the EWS allow a data-driven cut-off for the prediction model (i.e. relies on the local "historical data" for generating an optimal cut-off for optimizing the measurements of effects)?				
7. Can users of the EWS calibrate the data-driven cut-off for optimizing the prediction performance?				
8. Does the EWS generate measurements other than sensitivity, specificity, PPV, NPV, ROC for quantifying the model performance; for instance, the timeliness indicator (i.e. how accurate the prediction lead-time was) or, the prediction accuracy in terms of the magnitude of the outbreak (i.e. case numbers, geographical spread)?				

TP: true positive; FP: false positive; TN: true negative; FN: false negative; PPV: positive predictive value; NPV: negative predictive value; ROC: receiver operating characteristic.

STEP 3

Assessing approaches for overcoming methodological challenges

This section aggregates the number of outbreak and no-outbreak periods correctly identified by the EWS in an accuracy measure. We can thus be confronted with an undesirable situation in which the optimal cut-off correctly identifies all in-control periods, but only a few or none of the outbreak periods. This criterion is specifically concerned with "when" an outbreak ends and "how" long would the outbreak period last *(19)* (Table 10).

This step is typically performed during the retrospective phase of the early warning process.

Table 10. Criteria for assessing approaches for overcoming methodological challenges

	Yes	No	Neutral	NA
1. Does the EWS allow users to calibrate different cut-offs and settings related to the outbreak predictors?				
2. Does the EWS allow adjustments for districts/localities with variant endemic size (i.e. handling low- vs high-endemic settings)?				
3. Does the EWS adjust for the possible inconsistent trend of disease outbreaks (i.e. adjust for local interventions that might potentially reduce the number of cases over time or the possible change in trends due to other factors like changes in disease serotypes)?				
4. Does the EWS handle the variation of outbreaks expected in different areas and seasons (i.e. does the EWS propose a calibration of window size for outbreak predictors with marginal errors)?				
5. Can the EWS adjust for unusual alert-outbreak relationships (e.g. non-linear relationships in the case of extreme heat or floods)?				
6. Does the EWS account for the size of an outbreak (number of cases per geolocation unit)?				
7. Does the EWS employ a flexible model approach, such as interactions, autoregression, curve fit, or others, which can ensure adequate modelling of outbreak predictors?				

3.4 STEP 4: Evaluating the cost-effectiveness of the EWS (prospective phase)

The overall process of EWS for infectious diseases is a resource- and time-consuming endeavour and tends to include extensive activities to respond to disease outbreaks in a timely manner.

Despite recent advances in EWS, these models are unable to detect all disease outbreaks and can potentially miss an event or fail to detect an outbreak. While the cost of building an EWS is usually small, mainly for EWS with calibration features being automatically performed, there is still a need to deploy models for disease outbreak prediction cautiously. It includes the cost of failures arising from the alert signals that are missed by the prediction models. It is desirable to examine which predictions (alert signals) are more likely to contain true signals so that district health managers can allocate constrained resources in a cost-effective manner. Furthermore, the severity of disease outcomes (numbers of people possibly affected, virulence of the pathogens, etc.) is crucial determinants of the tolerance of false-negative and false-positive signals from the EWS. Therefore, proposing assessment criteria of the cost-effectiveness of EWS is important for the practical application of these models, which are typically performed during the prospective phase of the early warning process (Table 11).

Evaluating the effectiveness and cost-effectiveness of the EWS

The discovery of unwanted health events is primarily based on the "*detection*" of changes (out-of-control) in the health situation within a time-period and in certain geolocations; thus, a frequent false-positive reaction of the system should be avoided. The "*prediction*" of a geographically defined unwanted health situation means to forecast a future scenario based on a set of relevant alert predictors with applied methodologies to answer the question: "what does the successor scenario of the current health event sequence look like?" Another important piece in this overall early warning process is the "*estimation of the consequences of an outbreak*" including the personnel load [human resource/workforce required] and cost of public health services.

Quasi-experimental designs (e.g. difference-in-difference analysis), modelling-based approaches or cross-sectional study designs are innovated and applied in statistics, big data analytics, epidemiological studies and action plans, which collectively constitute the core components of a typical EWS. These designs can serve in assessing the effectiveness and cost-effectiveness of the EWS in mitigating disease outbreaks. Such feasible approaches can also replace randomized controlled trials (RCT) that are not widely practised in the field of EWS for infectious diseases, mainly due to their cost and complexity. The evaluation of the effectiveness of the EWS should be incorporated into the system design so that adequate adjustments can be made to maximize the benefits of the system while minimizing cost. The cost-effectiveness of the system can be explored under different scenarios of sensitivity and specificity *(20)*. In the context of EWS for infectious diseases, the above designs can be more feasible if applied to a large geographical region (to reduce bias due to people mobility or behavioural changes) and include subpopulations based on characteristics such as age and socioeconomic status.

In this step, the use of quasi-experiments, modelling-based or cross-sectional designs will address both the effectiveness (*showing evidence of mitigating disease outbreaks*) and cost-effectiveness (*showing evidence of effective reduction of disease outbreaks in relation to the cost*) evaluation of the EWS.

Table 11. Criteria for assessing: a) the effectiveness and b) the cost-effectiveness of the EWS

	Yes	No	Neutral	NA
a. Assessing the effectiveness of the EWS				
1. Is there a systematic collection of parameters that can facilitate the effectiveness evaluation process of EWS (examples of parameters are listed under step 3, e.g. PPV)?				
2. Have quasi-experiments been used to assess the effectiveness of the EWS?				
3. Have modelling-based designs been used to assess the effectiveness of the EWS?				
4. Have cross-sectional designs been used to assess the effectiveness of the EWS?				
5. Assessing the study outcomes based on the type of method used for evaluating the effectiveness of the EWS:				
i. If case quasi-experiments were used to assess the effectiveness of the EWS, did the EWS show any evidence of superiority to the existing (or neutral situation) approach in reducing the frequency and severity of outbreaks in the studied population?				
ii. If case modelling-based designs were used to assess the effectiveness of the EWS, did the EWS show any evidence of superiority to the existing (or neutral situation) approach in reducing the frequency and severity of outbreaks in the studied population?				
iii. If case cross-sectional designs were used to assess the effectiveness of the EWS, did the EWS show any evidence of superiority to the existing (or neutral situation) approach in reducing the frequency and severity of outbreaks in the studied population?				

STEP 4

	Yes	No	Neutral	NA
b. Assessing the cost-effectiveness of the EWS				
1. Is there a systematic collection of parameters that can facilitate the cost-effectiveness evaluation process of the EWS (e.g. records of the initial investment made to set up the EWS, routinely collected data on the operational costs of running the EWS, or costs of outbreak (and routine control) response)?				
2. Have quasi-experiments been used to assess the cost-effectiveness of the EWS?				
3. Have modelling-based designs been used to assess the cost-effectiveness of the EWS?				
4. Have cross-sectional designs been used to assess the cost-effectiveness of the EWS?				
5. Assessing the study outcomes based on the type of methods used for evaluating the cost-effectiveness of the EWS:				
i. If case quasi-experiments were used to assess the cost-effectiveness of the EWS, did the EWS show any evidence of superiority to the existing (or neutral situation) approach in reducing the frequency and severity of outbreaks in relation to the cost of responding to the predicted outbreaks, for a defined geolocation and during a specific time?				
ii. If case modelling-based designs were used to assess the cost-effectiveness of the EWS, did the EWS show any evidence of superiority to the existing (or neutral situation) approach in reducing the frequency and severity of outbreaks in relation to the cost of responding to the predicted outbreaks, for a defined geolocation and during a specific time?				
iii. If case cross-sectional designs were used to assess the cost-effectives of the EWS, did the EWS show any evidence of superiority to the existing (or neutral situation) approach in reducing the frequency and severity of outbreaks in relation to the cost of responding to the predicted outbreaks, for a defined geolocation and during a specific time?				

STEP 4

3.5 STEP 5: Evaluating the operational features of the EWS

This step focuses on the evaluation of EWS tailored to the needs of policy-making and the properties of the underlying surveillance data. Hence, it is crucial that district managers and health policy-makers who apply EWS acknowledge that disease outbreaks are often outlier events, particularly if: (i) dynamics during the periods of outbreaks differ significantly from the periods of no-outbreaks; (ii) outbreaks are commonly more costly (in terms of response/control and health system utilization); and (iii) outbreaks occur rarely (typically in some districts/geolocations and during some seasons) *(18)*. Therefore, the prediction tool should essentially facilitate practical and operational aspects to support local district health managers with a timely response and action plan, i.e. the EWS.

Under step 5, the assessment will include the following criteria:

i. Assessing the implementation of the EWS
ii. Assessing the integration, flexibility and adaptability of the EWS
iii. Assessing the alert delivery and dissemination
iv. Assessing the resources and coordination of the EWS
v. Evaluating the overall feasibility of the early warning process.

Assessing the implementation of the EWS

To ensure an effectively, including implemented EWS, the tool must be people- and system-centred and should integrate elements underpinned by effective governance and institutional arrangements and the involvement of all stakeholders, including local communities and consideration of the public interest (Table 12). Failure to address these aspects can result in failure of the whole early warning and response process.

Table 12. Criteria for assessing EWS implementation

	Yes	No	Neutral	NA
1. Is there a concrete plan in place with adequate resources and a timeline for the implementation of the EWS?				
2. Does the EWS demonstrate any evidence of prospective predictive ability?				
3. Does the EWS employ an open-source software application?				
4. Does the EWS allow technical and practical adaptations of local public health response and action plans (i.e. the possibility of harmonizing/integrating the local response guidelines into the tool)?				
5. Is the EWS able to access, share and effectively use available data for generating risk management messages?				

Assessing the integration, flexibility and adaptability of the EWS

Integrating the EWS into the existing national surveillance programmes increases the effectiveness and efficiency of the early warning and response process, and this can only succeed if the EWS maintains certain criteria. This evaluation section is concerned with criteria related to the EWS features and their applications and materials to permit the integration of the tool into the existing surveillance systems (Table 13).

Table 13. Criteria for assessing EWS integration, flexibility and adaptability

	Yes	No	Neutral	NA
1. Does the EWS provide standardized technical and operational user guides?				
2. Does the EWS provide a programming package (script) to allow integration into the existing local surveillance systems?				
3. Can the EWS be independent of any external hubs of data sharing (i.e. 100% owned by the local users to ensure data protection)?				
4. Can the EWS function on low-cost IT maintenance be independent of external influence?				
5. Is the EWS in harmony with the resources available for routine maintenance and updates?				
6. Does the EWS provide systematic feedback to users on how to respond or behave for troubleshooting (e.g. missing data, calibration)?				
7. Can the EWS be integrated into relevant education programmes (e.g. trainings in risk awareness, hazard recognition and emergency response actions that are integrated into various educational programmes and linked to regularly conducted assessments to ensure operational readiness)?				
8. Is the EWS adapted for unskilled, inexperienced users (i.e. does not demand skilled users in terms of IT, statistical processing, interpretation and maintenance)?				
9. Does the EWS provide a workable programming script for further modification/innovation?				
10. Is the EWS adapted to allow feedback and improvement mechanisms (to ensure systematic evaluation and system improvement over time)?				

Assessing the alert delivery and dissemination

Having identified a set of potential actions to mitigate the outbreak, and a means of generating the information required for their activation, a system needs to be put in place to communicate the information to decision-makers, including the public. Furthermore, if the EWS coordination unit and the programme partners are not hosted at the same unit or institution, an active, regular and systematic communication should be established between the central EWS coordination unit and the partners. This section is concerned with evaluating the dissemination process of feedback derived from the EWS (Table 14).

STEP 5

Table 14. Criteria for assessing EWS alert delivery and dissemination

	Yes	No	Neutral	NA
1. Does the EWS facilitate a communication channel to link users at the central and district levels during the early warning and response process (e.g. using digital platforms that can organize the planning and response systems)?				
2. Can the EWS integrate risk information (e.g. the magnitude, frequency and severity of the disease outbreak)?				
3. Does the EWS link severity and frequency of alert signals to appropriate response or intervention (e.g. level- or staged-response based on national/local guidelines)?				
4. Does the EWS provide instant prediction and allow immediate alert interpretation (e.g. users' dashboard or graphical visualization with a guided response plan)?				
5. Does the EWS facilitate a communication channel with the public (i.e. mobile application for risk assessment updates or dashboard for read-only visualization)?				
6. Does the warning dissemination mechanism of early warning reach the authorities, other stakeholders and the public at risk in a timely and reliable fashion?				
7. Does the EWS facilitate a real-time dashboard and/or communication platform to engage partners and stakeholders in different sectors, which ensures cross-sector or multisector response (e.g. including meteorological organizations, food safety and animal sectors, to facilitate cross-sector or multisector response)?				

Assessing the resources and coordination of the EWS

By virtue of the broad variety of existing EWS in terms of statistical, technical and operational applications, these tools demand different levels of resources and coordination to ensure successful implementation. The organization of the resources required for the applied EWS needs to be appropriately adapted to the country's context.

Human, technical and financial resources are key aspects for ensuring an effective and sustainable EWS. Hence, the coordination of EWS is important for maintaining efficient and resilient EWS function and a unit responsible for the EWS coordination should be identified at the national and local levels. This will secure a single-entry point for reporting, analysing and prioritizing information as well as verifying signals, assessing risks, and monitoring and responding to acute public health events (Table 15).

During the implementation phase of the EWS, staff development and training needs to be maintained and operators of the EWS should be strengthened by specific courses with special emphasis on the EWS coordination unit. Furthermore, an electronic data management system for the EWS using reliable IT tools is essential to accelerate the transmission of information within the EWS and to spread it among the public. The electronic data management system should cover data reporting, entry and analysis, and include capabilities of the geographical information system (GIS).

It is worth noting that while there is no universally agreed or recommended method for the implementation of an "ideal EWS", this section should be regarded as a functional description rather than organizational recommendations *(21)*.

Table 15. Criteria for assessing resources and coordination of the EWS

	Yes	No	Neutral	NA
1. Is the EWS appropriately linked to a defined technical unit for operating and coordinating the tool?				
2. Is the coordination unit of the EWS adapted to the national or local level in terms of composition (e.g. number of staff, required level of expertise, integration with the International Health Regulations)?				
3. Is the EWS being utilized by skilled epidemiologists or public health experts at the national level?				
4. Has the operator of the EWS received an initial integrated all-hazards approach to training, including field epidemiology and action-oriented surveillance?				
5. Can the EWS be linked to the field epidemiology of the country for securing regular trainings (e.g. including simulation exercise of the tool)?				
6. Is the EWS supported by an electronic data management system with reliable IT tools, which will ensure the transmission of information provided by the EWS?				
7. Does the EWS facilitate real-time dashboard and/or communication platform to engage partners and stakeholders in different sectors, which ensures cross-sector or multisector response (e.g. including meteorological organizations, food safety and animal sectors, to facilitate cross-sector or multisector response)?				
8. Is the warning supported by minimum reference documents and public health emergencies equipment (see Box 1)?				
9. Is the warning supported by laboratory services for rapid confirmation of causative agents during the early phase of outbreaks (see Box 2)?				

Box 1. Minimum reference documents

- Guidelines for the management of acute public health issues
- Surveillance for and response to the burden of disease
- Control practices and tools
- Monitoring, protection and treatment of field workers

Box 2. Laboratory support for EWS

- Provides rapid confirmation of clinical diagnosis
- Identifies the etiology of unusual diseases
- Detects and identifies emerging pathogens and agents
- Helps identify asymptomatic carriers

Evaluating the overall feasibility of the early warning process

From the user's point of view, a climate-informed EWS has a number of applications that need to be viewed in detail for better utilization of the "lead-time" and the usefulness of the associated information. There can be significant implications in the overall disease control process depending on: (i) whether the EWS is used at a regional, central, district or smaller spatial level; and (ii) how the EWS is operationalized between the policy-making and end-user levels *(22).* Those dimensions are essential for ensuring an effective EWS, particularly when integrated within the existing surveillance programmes, and the criteria of evaluation to address the above operational dimensions are crucial (Table 16).

Table 16. Criteria for assessing overall feasibility of the EWS

	Yes	No	Neutral	NA
1. Is the EWS directly linked (e.g. via digitalized systems) to the local/national laboratory systems, real-time surveillance (reporting) and workforce development, which can effectively support the detection component of the tool?				
2. Is the EWS directly linked (e.g. via instant online access) to the local/national meteorological stations or adapted to indirectly retrieve meteorological information?				
3. Does the EWS warn of an epidemic with reference to the severity degree of the detected outbreak (the severity degree of an outbreak is characterized by the incidence, population density of a location, quality of a prevention/intervention and the workforce requirement in this process)?				
4. Does the EWS provide an automated process of alert-outbreak prediction (which can potentially improve the efficiency of the model)?				
5. Is the prediction output relevant to the national response guidelines and can be instantly interpreted by the users, health policy-makers or the public?				
6. Is the EWS adapted to be used, programmed or tested for novel diseases?				
7. Is the EWS independent of political (or other) influences?				

ANNEX: PRACTICAL APPLICATIONS TO CONSIDER FOR EVALUATING THE EWS

Comparing the "null" and "forecasting" models for evaluating the EWS

Ideally, the EWS should generate alert signals to recommend changes from the activities that would otherwise have taken place anyway, which are typically based on the "normal" disease season. In this case, alert signals generated from the EWS that are higher than expected (compared to the seasonal average for any given disease) are critical, as they could promote accelerated interventions and, by association, the cost of the response to disease outbreaks comparing the forecasting model and the "null model" (using the normal disease season number of cases for the null model). Comparing the generated type I (false alerts) and type II (missed outbreaks) between the forecasting and the null models and their differences can be a useful method for deciding on the effectiveness of the EWS in the studied area *(23)*.

Using the prediction statistical results for evaluating the EWS

The prediction model has four typical statistical results referring to the outbreak prediction scenarios: true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN). Ideally, the EWS should be able to correctly detect all outbreaks, which can then facilitate more effective utilization of limited resources. For evaluating the effectiveness of the EWS, the "***recall***" and "***precision***" approach can be adopted as a pragmatic approach *(24)*. The recall measure is defined as the number of TP in relation to the total number of actual outbreak events (AO=TP+FP), whereas the precision measure is defined as the number of TP in relation to the total number of predicted alert signals (TP+FP) (see Figure 1 under step 3). In general, the higher the recall and precision values, the more effective is the EWS. However, to measure the cost-effectiveness of the EWS, a complementary measure of FN/(FN+TN) can be applied in relation to the cost of responding to the predicted outbreaks, for a defined geolocation and during a specific time-period. While the lower value of FN/(FN+TN) indicates higher EWS effectiveness, measuring the FN/(FN+TN) metric in relation to C_i (the average cost of responding to all outbreak alert signals) and C_{fn} (the average cost of missing an outbreak) provides a useful and pragmatic cost-effectiveness assessment of the EWS. Considering this approach, a more cost-effective EWS is the one that satisfies the assumptions proposed in the following formula:

$$FN/(FN+TN) < C_i/C_{fn}$$

Seeking mathematical simulations for evaluating the EWS

Simulation exercises have been shown to be a practical, efficient and cost-effective way for users to evaluate response processes and to prepare for emergency response. Simulation exercises evaluate the ability of the EWS to carry out one or more portions of its generic prediction towards a response plan. They provide experience and practice to those who may be involved in a response and allow users to obtain a routine and timely assessment of the cost-effectiveness of the EWS. Within the exercise, staff and managers may identify knowledge gaps and correct functional inconsistencies that exist in the EWS and adapt them to the local surveillance programme. This can lead to targeted training or improvements in the planning process after the exercise. Hence, conducting a regular simulation exercise will enable testing the resilience of the implemented early warning and response structure in a more efficient manner.

A summary of an appropriate simulation approach using the context of a malaria disease outbreak as an example is described elsewhere *(25)*. The proposed simulation model employs monthly or weekly averages of maximum temperature and the cumulative sum of rainfall to calculate values for key parameters. These parameters are then combined to give the number of new infections, superinfections and people recovering, which are then compiled to estimate the number of disease cases each week or month, depending on the temporal unit used – recommendations are to use epidemiological weeks as temporal units. In summary, the model implies the following submodels:

Submodel 1: it describes the number of (female) mosquitoes as a function of climate indicators (e.g. rainfall and temperature) – this process describes the relationship between temperature and the length of the gonotrophic or feeding cycle (the length of the gonotrophic cycle is the period of time between successive egg laying).

Submodel 2: it describes the relationship between temperature and the sporogonic cycle (the sporogonic cycle is the time taken for the parasite to undergo necessary development in the vector, enabling it to transmit the disease).

Submodel 3: it estimates the vector survival probability per gonotrophic cycle and per day. Combined with submodel 2, this allows the calculation of the probability of the vector surviving long enough for sporogonic development.

Submodel 4: it determines the sporozoite rate (the sporozoite rate is the proportion of vectors with infectious pathogens in their salivary glands).

Submodel 5: it develops the human infection model to estimate the number of new infections, superinfections and recoveries.

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