The Early Warning And Response System (EWARS-TDR) For Dengue Outbreaks: Can It Also Be Applied To Chikungunya And Zika Outbreak Warning?

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The Early Warning and Response System (EWARS-TDR) for dengue outbreaks: can it also be applied to chikungunya and Zika outbreak warning?

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Abstract.

Background. In the Americas, endemic countries for *Aedes*-borne diseases such as dengue, chikungunya, and Zika face great challenges particularly since the recent outbreaks of CHIKV and ZIKV, all transmitted by the same insect vector *Aedes aegypti* and *Ae. albopictus*. The Special Program for Research and Training in Tropical Diseases (TDR-WHO) has developed together with partners an early warning and Response System (EWARS) for dengue outbreaks based on a variety of alarm signals with a high sensitivity and positive predictive value (PPV). The question is if this tool can also be used for the prediction of Zika and chikungunya outbreaks.

Methodology. We conducted in nine districts of Mexico and one large city in Colombia a retrospective analysis of epidemiological data (for the outbreak definition) and of climate and entomological data (as potential alarm indicators) produced by the national surveillance systems for dengue, chikungunya and Zika outbreak prediction covering the following outbreak years: for dengue 2012-2016, for Zika 2015-2017, for chikungunya 2014-2016. This period was divided into a "run in period" (to establish the "historical" pattern of the disease) and an "analysis period" (to identify sensitivity and PPV of outbreak prediction).

Results. In *Mexico*, the sensitivity of alarm signals for correctly predicting an outbreak was 92% for dengue, and 97% for Zika (chikungunya data could not be obtained in Mexico); the PPV was 68% for dengue and 100% for Zika. The time period between alarm and start of the outbreak (i.e. the time available for early response activities) was for dengue 6-8 weeks and for Zika 3-5 weeks. In *Colombia* the sensitivity of the outbreak prediction was 92% for dengue, 93% for chikungunya and 100% for Zika; the PPV was 68% for dengue, 92% for chikungunya and 54% for Zika; the prediction distance was for dengue 3-5 weeks, for chikungunya 10-13 weeks and for Zika 6-10 weeks.

Conclusion. The implementation of an early warning and response system (EWARS) could predict outbreaks of three *Aedes* borne diseases with a high sensitivity and positive predictive value and with a lag time long enough for preparing an adequate outbreak response in order to reduce the magnitude or avert the occurrence of outbreaks with

their elevated social and economic tolls.

Keywords: Zika, chikungunya, dengue outbreak, early warning, Colombia, Mexico

Introduction

The arbovirus diseases dengue, Zika and chikungunya are transmitted by the same insect vector *Aedes aegypti* or *Ae. Albopictus*, they present an increasing public health concern in endemic countries. 3,9 billion people living in 128 tropical or sub-tropical countries are at risk of being infected with these viruses (1,2,3,4). Currently there is no specific pharmacological treatment nor an effective vaccine for public health use so that vector management is the only measure of prevention (5). These diseases have a high social and economic impact, particularly when they appear as epidemic outbreaks. An estimate of the economic costs of a chikungunya outbreak in Colombia 2013 showed an approximate cost of 100 million dollars to the government (equivalent to 0.04% of the national gross domestic product of 2013) (6). Estimates of the costs of an outbreak of dengue in 2011 were 12 million US$ in Vietnam, 6.75 million US$ in Indonesia, 4.5 million US$ in Peru and 2.8 million US$ in the Dominican Republic (7). The Zika outbreaks occurring between 2015 and 2017 caused losses of 7 to 18 Billion dollars in Latin America, including both the direct and indirect costs due to microcephaly and Guillain-Barré syndrome (8). Therefore, the need for early outbreak detection (when the outbreak has already started) or better outbreak prediction (when the outbreak has not yet started) to initiate response activities and mitigate or even suppress an outbreak.

But early detection of outbreaks poses a challenge, since no universally accepted or proven sets of early warning indicators exist (9,10). A systematic review showed that countries are generally lacking outbreak prediction tools that can be implemented by fairly unskilled users, and can automatically manage complex data sets (9,11). In reality, in most countries the early outbreak detection -if any- is based on the increase of case numbers above a pre-established threshold (meaning that the outbreak has started already). With this in mind, the Special Program for Research and Training for Tropical Diseases (TDR) at the World Health Organization (WHO) initiated together with research institutions, national dengue control services and academia in ten endemic partner countries, the development of a web-based Early Warning and Response System (EWARS) for dengue, with potential uses for other arbovirus disease outbreaks (9,12). After initial retrospective analyses in 5 countries (Brazil, Mexico, Dominican Republic, Vietnam, Malaysia) (10,13) – typically including calibration and prediction algorithm building using historical records of diseases and alarm indicators – EWARS was tested prospectively. Subsequently, in Brazil, Mexico and Malaysia to evaluate it is qualitative and quantitative performance and user friendliness (13).

However, EWARS has never been tested for other emerging *Aedes*-borne diseases, such as chikungunya and Zika. This study therefore aims to test the performance of EWARS for predicting outbreaks of the three *Aedes* borne arbovirus diseases (dengue, chikungunya and Zika) using available data of the national surveillance systems in our two target countries. The response component of EWARS will not be covered in this paper.

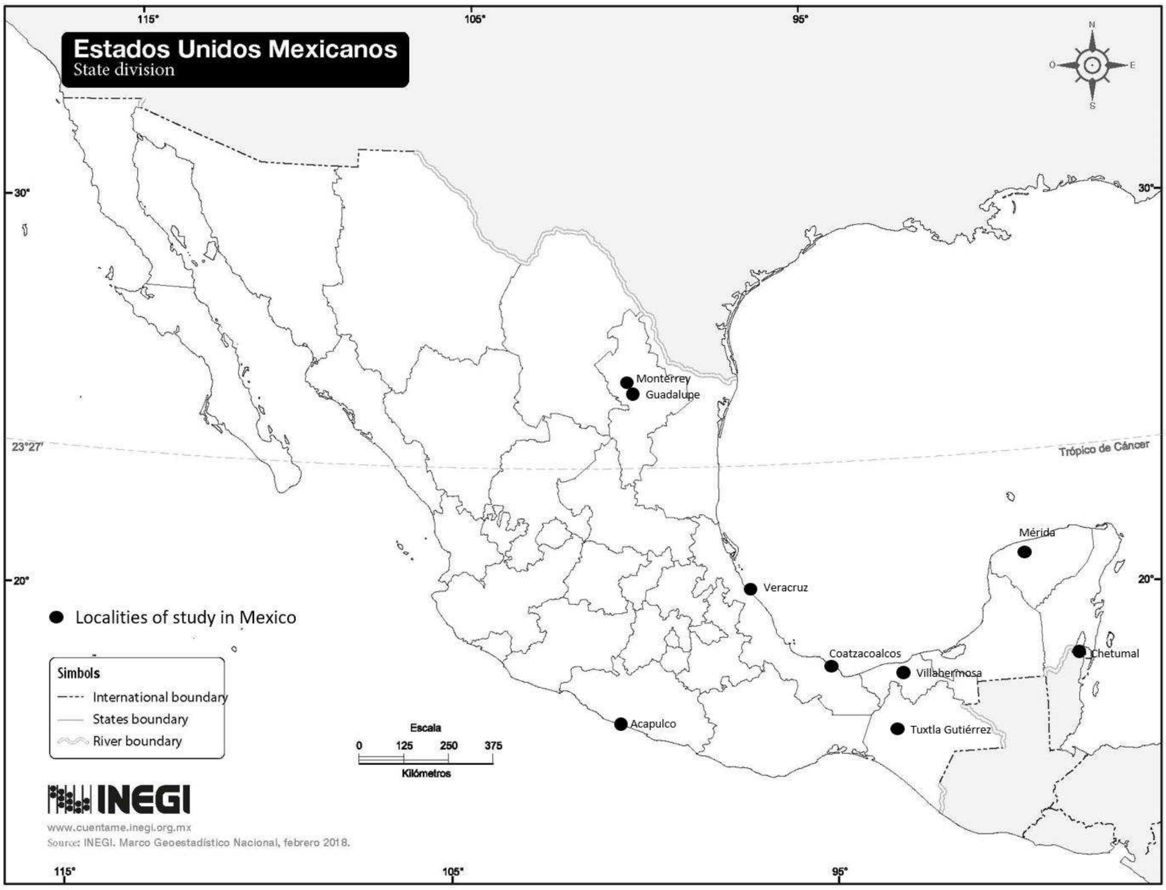
Methods

Description of study sites

In both target countries the selection of study sites was dictated by the availability of information from the National Surveillance System and National Meteorological Institutes (14,15).

In Mexico we received the data set from 9 districts (labelled as “localities”) for Zika and chikungunya as well as weekly meteorological data. In Colombia*,* we received a complete data set including weekly meteorological information and epidemiological data with individual notification for Zika and chikungunya in the urban area of Cúcuta; In Mexico, from the 137 highly endemic urban districts (as the 3 disease occur mainly in urban environments due to the opportunities of vector breeding), only 9 were analyzed because they had complete information records of disease and alarm indicators for the past 5 years, essential for the EWARS process. The localities selected were Tuxtla Gutierrez, Acapulco, Ciudad Guadalupe, Monterrey, Chetumal, Villahermosa, Coatzacoalcos, Veracruz and Mérida (Map 1). The total population of these 9 districts is around 5 million inhabitants (16). All of them possess suitable conditions for dengue vector breeding. The climate is tropical with average annual temperatures around 24°C and rainfall above 1000 mm (except for Ciudad Guadalupe, Monterrey, and Mérida with around 700 mm).

Map 1. Localities of study in Mexico



In Colombia, Cúcuta, the capital of the State ("departamento") of Norte de Santander was included which has around 750.000 inhabitants, 1.176 Km^2 in area size and is located on the border area with Venezuela (Map. 2). The climate is tropical (temperatures ranging between 21 and 36 °C; average annual rainfall 655 mm; annual relative humidity between 70% and 75%) (17). While dengue outbreaks have a long history in Cúcuta, outbreaks of CHIKV and ZIKV were reported only after 2014 and 2015, respectively (17).

Map 2. Locality of study in Colombia

Public Health Surveillance system

In Mexico, the national surveillance system with its permanent notification of clinical cases of dengue, chikungunya and Zika including neurological complications feeds into the online platform SINAVE- National Epidemiological Surveillance System (for “Sistema Nacional de Vigilancia Epidemiologica”) where entomological data (ovitrap indexes) and response activities (entomological platform) are registered. Both platforms receive on a weekly basis the information from all public and private health centers. Since 2018, Mexico has the fully integrated EWARS tool for dengue outbreak prediction in its national surveillance program, providing a national coverage of outbreak prediction and response activities.

In Colombia, the National Public Health Surveillance System (SIVIGILA for "Sistema Nacional de Vigilancia en Salud Pública") provides systematic and timely information on the number of dengue, Zika and chikungunya cases. The information gathered by the centers of health care of the public and private health system, is compiled and transmitted to the SIVIGILA, which updates the results weekly. The data for the present study corresponded to cases reported in the urban area of the city of Cúcuta. Only cases with an individual report in SIVIGILA (form 217) and with complete information required by the EWARS system were included in the analysis (18). Data were obtained from the local surveillance system, with certified authorization. In Colombia, the EWARS for dengue is not yet been established nationally but is being tested in the city of Cúcuta, which is the actual study setting.

Overview of the EWARS

The concept of the EWARS model is based on the Shewhart method (19) a method that adopts systematic control charts, using the historic mean and standard deviation of the outcome variable to define states of 'in-control' and 'out-of-control' throughout the model evaluation process. When applied to dengue, an Endemic Channel chart is produced which represents the number of cases within the expected normal range, or the 'in-control' state, while anything above this Endemic Channel (or, moving average) is considered representative of an unusual number of cases and, an 'out-of-control' state (i.e., an outbreak). The EWARS has advanced into an online tool (dashboard) which facilitate more structured training, applications and experience sharing among a broader range of users, also with the aid of a series of published computer-assisted user's workbooks (10,20,21). These user guides illustrate methodological, technical and operational aspects crucial for the tool processing. This includes details of how both digital and paper-based surveillance records of diseases and indicators can be prepared for applying in the tool. Figure 1 illustrates the elements of inputs and outputs of the EWARS tool, which is divided into retrospective (a phase of sliding window time-series cross-validation and algorithm building) and prospective (phase of inputting weekly alarm information for generating the outbreak signals) components.

Data collection of outbreak and alarm indicators

In Mexico, the data collection started in January 2012 and continued until December 2018. The data set has been provided by SINAVE and by the entomological online platform from the Secretary of Health. In Colombia, Cúcuta, the study covered the period from January 2012 to December 2017. All reported cases of dengue, chikungunya and Zika were included using the standardized case definitions by the Ministry of Health (MoH) and the National Institute of Health/INS corresponding to the WHO definition (1) and PAHO definition for chikungunya and Zika (22, 23).

For the application of EWARS, the temporal unit was defined as the epidemiological 'week' (from Sunday to Saturday) and the spatial unit was based on pre-existing administrative units (districts). At least three years of surveillance data records were retained for the EWARS analysis including a variable indicating the 'population size' of the corresponding districts.

Surveillance data on dengue, Zika and chikungunya recorded the individuals' place of residence, age, sex, date of onset of symptoms, date of case registration at the health center or hospital and the type of case ('probable', 'confirmed' by laboratory or by clinical symptoms and 'hospitalized' cases). However, in the EWARS spread sheet we captured only district of residence, week of reporting and type of case as well as potential alarm indicators such as meteorological and entomological indicators:

-*Epidemiological (disease pattern)*: weekly number of cases (probable cases for chikungunya and Zika, hospitalized cases for dengue) and weekly averages of the age of the patients.

-*Meteorological (potential alarm indicators)*: mean weekly outdoor air temperature (in Celsius), relative humidity (in %), and total weekly rainfall (in mm).

-*Entomological (potential alarm indicators)*: percentage of positive ovitraps (i.e. proportion of positive ovitraps with *Aedes* eggs per week, average egg count per trap (Mexico only). (NB: Larval indices were useless as alarm indicators as they are usually not collected in a systematic way as the ovitrap system in Mexico (9).

Data analysis

Analysis by the EWARS tool:

During the retrospective phase of EWARS, the weekly average number of cases of each of the three arbovirus diseases was calculated for four or five years and compared with the expected “normal” or seasonal range of cases illustrated in the endemic channel (9,10) which is the area between +/- z* SD of the moving average, the z-value being the multiplier of the standard deviation of the moving average of weekly case numbers; see Fig. 1). The Endemic Channel (moving average + (Z*SD)) was generated (“moving average” for each week of observation means that the average of number of cases in the 3 weeks before and after plus the week of observation were included; 10,20,21). Weekly cases exceeding this Endemic Channel for two or more weeks (“outbreak window”, see below) are indicating an outbreak.

During this retrospective phase, the algorithm and all parametric coefficients needed for calculating the alarm threshold (“outbreak probability”) are computed: these coefficients depend primarily on the sensitivity (i.e. the proportion of correctly predicted outbreaks out of all outbreaks) and positive predictive value, PPV (i.e. the proportion of correct alarms out of all alarms) as direct measures for deciding on the best calibrated settings, i.e. those with highest sensitivity and PPV. (For more details on the calibration of EWARS see the user guide by WHO-TDR) (20,21). The calibration in a national control program is done by an epidemiologist usually at the MoH. Less skilled district staff uses the prospective phase of EWARS, observing by means of the EWARS software the weekly number of cases against the upper line of the endemic channel and the pattern of alarm indicators against the pre-defined alarm threshold (see Fig. 1). An alarm is triggered when the alarm indicator (‘outbreak probability’) crosses the proposed ‘alarm threshold’ (9, 13) once prospective weekly information on the relevant alarm indicator(s) are fed into the system. Accordingly, instant numerical and graphical demonstration and interpretation of a possible outbreak and its corresponding response plan is illustrated to the user at a given prediction week (time between the prediction and an outbreak to occur).

Figure 1a. Snapshot of the retrospective dashboard, including graphical and numerical visualization of the calibration process and parameters

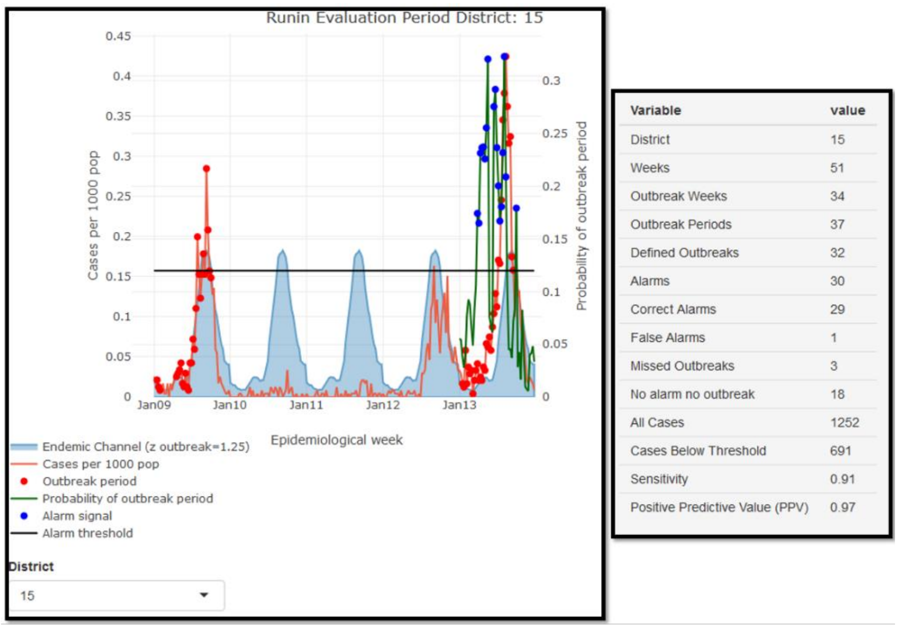
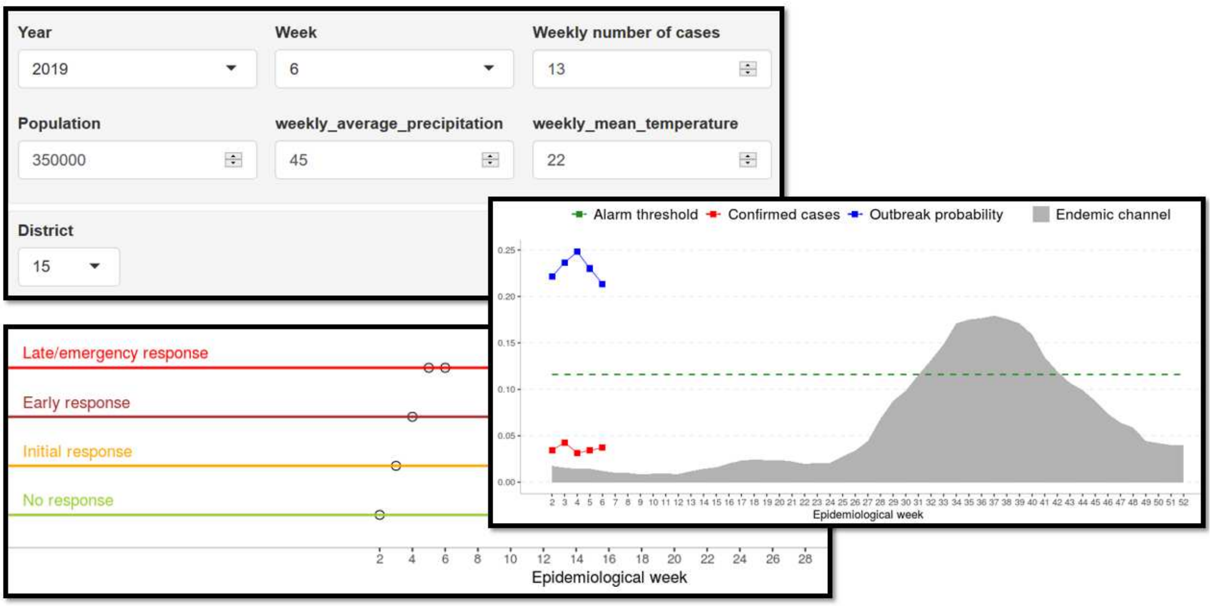


Figure 1b. A snapshot of the prospective dashboard, including an interface for prospective (weekly) data input prediction (alarm signal against rate of outbreaks) and structured response plan using a generic staged-response format (adoptable based on the national vector response protocol).



Based on recommendation from previous reports (13), ‘hospitalized’ cases showed to be the best outbreak indicator for the prediction of a forthcoming dengue outbreak using EWARS. However, when the proportion of “mild” cases is high and patients are rarely hospitalized (such as in chikungunya and Zika), ‘probable’ or ‘confirmed’ cases were used as outbreak indicators. In this study, z-values (i.e. the multiplier of SD to get the upper limit of the endemic channel) and alarm thresholds were determined for chikungunya and dengue via both manual and atomized procedures (which can assess the calibration settings via a 1000 iteration process per district (21). Technically, both manual and automated processing follow the same analytical process: define “ window sizes” of alarm and outbreak indicators (i.e. how many weeks with an alarm indicator being above the alarm threshold to declare it an “alarm signal” and for how many weeks of case numbers being above the upper limit of the endemic channel to declare it an “outbreak”), define above which level (alarm threshold) the alarm indicator turns into an alarm signal (i.e. gives an alarm) and define the prediction distances (i.e. the time period between alarm and start of the outbreak in weeks). These variables are tested and only values that give the highest sensitivity and PPV are retained in the EWARS model. While a single alarm assessment is more straightforward, the model does take into account and adjusts for the different prediction distances associated with each alarm indicator when running multiple regressions. In this sense, the automated model is more efficient in running multiple trials and thresholds for producing the highest sensitivity and PPV for outbreak prediction.

Data analysis:

Descriptive statistics, of both graphics and numeric formats were sought in this paper. In the case of Mexico, while the prediction algorithm was run independently for each of the 9 districts, output values obtained from the prediction process from each district were averaged and presented in the result table (see below). In Colombia, disease incidences were determined for Cúcuta (n cases / 100,000 population).

Ethical aspects:

This study analyzed only secondary data obtained from Colombian and Mexican institutions with the authorization of the Surveillance System (2017). Ethical endorsement was obtained from the Ethics Committee of the University of Freiburg (N°-145/18) which was approved by local health authorities.

Results

Epidemiological features of outbreaks

Before presenting the EWARS analysis of the outbreak prediction of our three target diseases, we show as contextual information for the need of early outbreak warning, the outbreak pattern of the three diseases in Colombia and Mexico during the period of analysis (Figure 2 and 3).

Dengue

For Colombia, 15.811 cases of dengue were included in the analysis, 2013 was an epidemic year with 820 cases per 100,000 population in Cúcuta city, followed by the 2014 outbreak with 785 cases per 100,000 inhabitants. Another increase in dengue was observed before the onset of the 2015 Zika outbreak, it is likely that in the weeks leading up to the confirmation of the first Zika case in the city, many suspected dengue cases would have actually been Zika. In Mexico, 2012 and 2013 were epidemic years for dengue with 1.060/100.000 inhabitants and 1.300/100.000 inhabitants confirmed cases respectively. After those epidemic years Mexico has seen a continuous reduction of dengue cases until 2018 with 12.706 confirmed cases.

Chikungunya

During the chikungunya outbreak in 2014-2015, cases were recorded from week 35 of 2014. An epidemiological peak was observed for week 48 and a downward curve with stabilization of transmission from week 10 of 2015. For the present study, 863 chikungunya cases with individual record and data required by EWARS were included. From the data considered for this study, the incidence rates of 115 cases/100,000 population in 2014 and 20 cases/100,000 population in 2015 were estimated. 128 cases were recorded in 2016. In Mexico, although the first cases appeared during 2014 (222 in the whole country) the chikungunya outbreak occurred during 2015 with 12,588 confirmed cases. After 2015 there has been a steady reduction with 759 confirmed cases in 2016 to only 39 confirmed cases in 2018. The peak of the 2015 chikungunya outbreak occurred around week 29. Unfortunately, in Mexico the weekly numbers of chikungunya cases were not available so that the analysis with the EWARS tool could not be conducted (Fig. 2, 3).

Zika

The Zika outbreak in Cúcuta started in week 51 of 2015 and lasted until week 10 in 2016 (12 weeks). The peak of cases occurred in week one of 2016 (753 cases), and a total of 4605 cases were reported during the years 2015 and 2016. The highest incidence rate was 691.14 cases per 100,000 population. In Mexico the Zika outbreak, after some sporadic cases in 2015, occurred during 2016 with 7560 confirmed cases in the whole country. 2017 also presented a Zika outbreak which was considerably smaller (3,260 confirmed cases). During 2018 the negative trend continued and there were only 860 confirmed cases (14) (Fig. 2, 3).

In the 2013 dengue outbreak, the highest incidence rates in Cúcuta were 819.94 cases per 100,000 population but when chikungunya entered, dengue rates decreased to 215.19 cases per 100,000 population. Similarly, chikungunya rates were lowest, when the Zika outbreak occurred with 691.14 cases per 100,000 population. This phenomenon is worth to be investigated further.

Findings from the EWARS application

The datasets of all three arbovirus disease outbreaks were processed using the EWARS tool. The summary of the model calibrations, parameters including the sensitivity, PPV and lag weeks (i.e. period from alarm to start of outbreak) for each disease per country are presented in tables 1-3. The number of ‘outbreaks’ and of ‘alarms’ –which are the basis for calculating the sensitivity and PPV values- are displayed in the tables as well as the alarm thresholds to show their variation for the three diseases.

Dengue

A value of z=1.0 was found to be the most suitable (i.e. producing the highest sensitivities and PPV values) multiplier of the SD to define the upper limit of the endemic channel with "hospitalized dengue cases" as outbreak indicator. The sensitivity to correctly predict a dengue outbreak varied between 74-92% whereas the PPV ranged between 50-68%, including both single and multiple alarm prediction analysis. The table shows that multiple alarm predictors enhanced the prediction model. The lag time in Colombia ranged from 3 to 5 weeks ahead of an outbreak. Table 1 provides detailed results. The calculations for dengue in Mexico (taken from a previous analysis) were done in exactly the same way as the calculations in Colombia. Unfortunately, we did not get a new data set from Mexico to be able to repeat the dengue analysis.

Chikungunya

Due to insufficient numbers of hospitalized cases found in the Colombian surveillance dataset (as most cases were mild), 'probable cases' were used as the outbreak indicator instead, which revealed a sensitivity range of 77-93% and a PPV range of 48-92%. The lag time between positive alarm and start of the outbreak was 10 to 13 weeks, much longer than that observed with dengue (Table 2).

Zika

Estimates of both sensitivity and PPV for different alarm indicators ranged in Colombia from 50% to 100% (mean temperature and multiple indicators with the highest sensitivities) and from 11%-54% respectively (rainfall with the highest PPV). In Mexico, the range was from 78% - 97% (rainfall with the highest sensitivity) and 77%-100% (mean temperature with the highest PPV) respectively (Table 3). In general, the alarm coefficients were stronger in Mexico compared to those in Colombia. The historically higher number of outbreaks and alarm thresholds in Mexico compared to Colombia were reflected in improved sensitivity and PPV values for predicting Zika outbreaks. The difference may also be caused by differences in data quality which was higher in Mexico. The lag times were longer in Colombia –ranging from 6 to 10 weeks – compared to Mexico – ranging from 4 to 5 weeks.

Table 1. Sensitivity and PPV for dengue outbreak prediction in Colombia and Mexico using hospitalized cases as outbreak indicator

Country	Alarm Indicators	Sensitivity (%)	PPV (%)	No. of outbreaks	No. of Alarms	Alarm threshold	Lag week
Colombia	Mean temp	86	61	76	106	0.69	3
	Rainfall	74	51	76	110	0.70	3
	Humidity	80	60	76	102	0.65	3
	Probable cases	91	50	77	141	0.75	5
	Multiple indicators*	92	68	50	68	0.70	3
Mexico**	Mean temp	81	72	-	-	-	-
	Rainfall	87	65	-	-	-	-
	Humidity	94	50	-	-	-	-
	Probable cases	100	83	-	-	-	-
	Multiple indicators*	84	77	-	-	-	-

*Multiple indicators; temperature, precipitation & humidity, PPV; Positive Predictive Value

** Values from Mexico taken from a previous period (see Hussain Alkhateeb et al. 2018)

Table 2. Sensitivity and PPV for chikungunya outbreak prediction in Colombia using probable cases as outbreak indicator.

Alarm Indicator	Sensitivity (%)	PPV (%)	No. of outbreaks	No. of Alarms	Alarm threshold	Lag week
Mean temp	77	71	13	14	0.80	10
Rainfall	93	48	14	27	0.45	12
Humidity	92	85	15	13	0.75	12

Multiple indicators*	92	92	12	12	0.74	13

*Multiple indicators; temperature, precipitation & humidity, PPV; Positive Predictive Value

Table 3. Sensitivity and PPV for Zika outbreak prediction in Colombia and Mexico. using *defined and probable cases* as outbreak indicators

Country	**Alarm Indicator**	**Sensitivity (%)**	**PPV (%)**	**No. of outbreaks**	**No. of Alarms**	**Alarm threshold**	**Lag week**
Colombia	Mean temp	100	11	2	19	0.05	10
	Rainfall	50	54	2	7	0.05	6
	Humidity	50	11	2	9	0.06	10
	Multiple indicators*	100	14	2	14	0.05	10
Mexico	Mean temp	92	100	36	33	0.50	4
	Rainfall	97	94	28	28	0.40	4
	Humidity (daylight)	88	86	53	52	0.50	5
	Humidity (night)	97	98	29	29	0.50	5
	Positive ovitrap	92	97	25	25	0.40	5
	Average Egg counts	78	77	22	22	0.40	4

*Multiple indicators; temperature, precipitation & humidity, PPV; Positive Predictive Value

Discussion

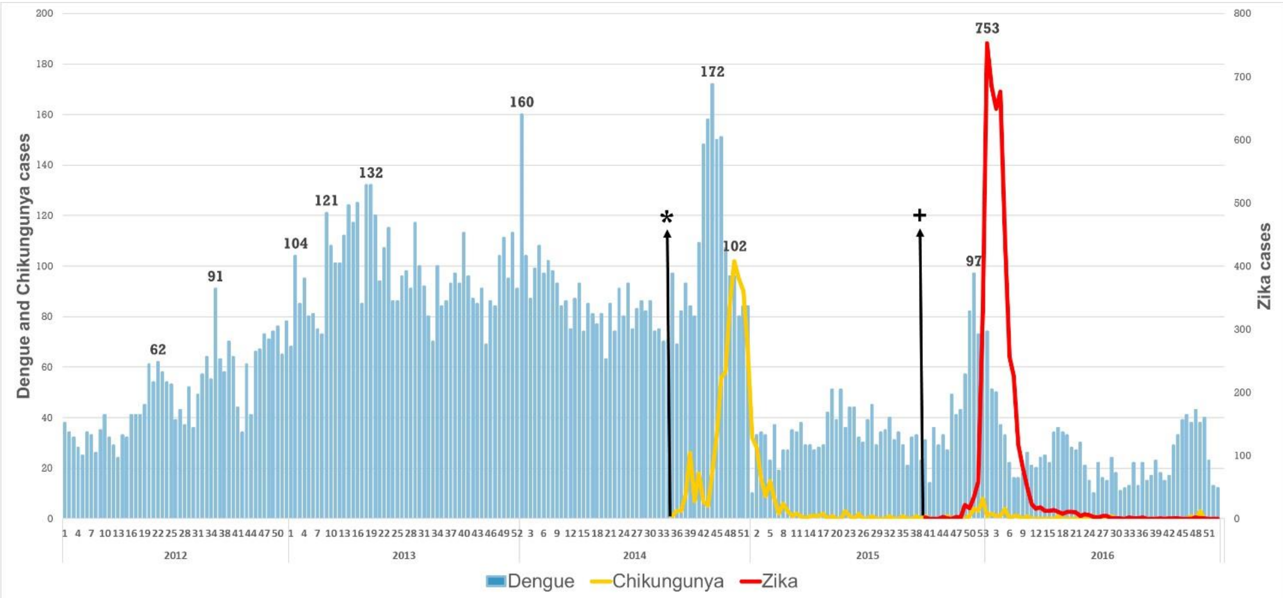
Outbreak pattern

The observation of the outbreak pattern of dengue, chikungunya and Zika in Colombia and Mexico suggests that they are not independent from each other, although they present differences in transmission peaks (see Fig. 2,3). It is assumed that during the first weeks of the chikungunya outbreak in Colombia, the unusual increase of dengue cases (172 cases in week 44 of 2014) was possibly due to chikungunya infections that remained unconfirmed by the laboratory. The later chikungunya cases were correctly diagnosed and the epidemic curve rapidly increased.

The same happened when the Zika outbreak occurred. Two weeks before the peak of Zika cases, there was an increase in “dengue cases”. Many of these were probably Zika infections. Only after the laboratory confirmation of the Zika virus in the national laboratory, the correct diagnoses were notified and the number of reported Zika cases increased. A similar but less pronounced phenomenon was observed in Mexico in 2014/15: At the beginning of the chikungunya outbreak, there was an increased dengue activity probably because the medical doctors did not consider chikungunya to be a diagnostic option. The same happened with the Zika outbreak in 2016 when first dengue case numbers increased and subsequently Zika was detected. The delay in the confirmation of cases can lead to the silent spread of the new disease, which makes control difficult. This situation highlights the need for an improved surveillance system with a focus on early outbreak warning.

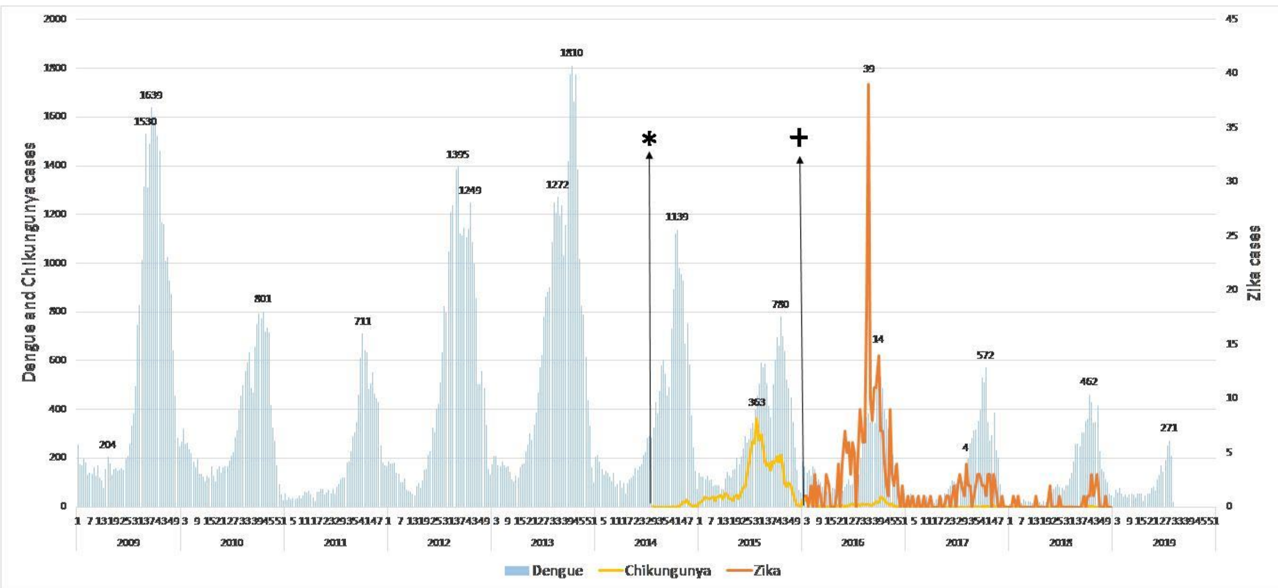
The observation that *Aedes* borne arbovirus outbreaks seem to mutually suppress each other warrants further confirmation.

Figure 2. Time series of analysed cases of dengue, chikungunya and Zika in the urban area of Cúcuta, Colombia during the period 2012-2016˚.



Dengue is in blue; chikungunya is in yellow and Zika is in red. The cases of Zika are quantified on the right. (*) Week of the first case of chikungunya; (+) Week of the first case of Zika).

Figure 3. Time series of cases reported weekly in Mexico, of cases of dengue, chikungunya and Zika during the period 2009-2019.



Dengue is in blue; chikungunya in yellow and Zika in red. The cases of Zika are quantified on the right. (*) Week of the first case of chikungunya; (+) Week of the first case of Zika

Early Warning and Response System (EWARS)

With the purpose of contributing to mitigate the effects of arbovirus outbreaks the EWARS applied in our study appeared to be an adequate tool to predict in Colombia dengue outbreaks 3 to 5 weeks, chikungunya outbreaks 10 to 13 weeks and Zika outbreaks 6 to 10 weeks ahead of the outbreak. In Mexico the lag time was for Zika with 4 to 5 weeks relatively short (not tested for dengue and chikungunya). The variation of lag times for the three diseases may be due to different extrinsic incubation periods (i.e. the time the virus replication and passage from the mosquito gut to the salivary gland requires) but also to the different delays when health services diagnose the diseases (9). A lag time of 6 to 10 weeks will allow the public health services to respond with enhanced vector control measures, shorter time periods for preparing response activities will require the definition of high transmission “hot spots” where interventions can be targeted. The better the control programmes are prepared to identify such high transmission areas and step up the response quickly, the better the chance to mitigate or even avert an outbreak. This has been shown for Mexico (Tejeda, personal communication, to be published shortly) and has triggered the incorporation of risk maps into the EWARS tool (to be made available shortly).

In the case of dengue, the sensitivity of alarm indicators to correctly predict an outbreak varied in both countries between 74 to 92%, being the combination of meteorological indicators the alarm signal with the highest sensitivity. The importance of meteorological alarm indicators underlines the characteristic climate sensitivity of vector borne diseases. This pattern is similar to that of other countries that are using EWARS for dengue outbreak prediction (83-99% sensitivity in Brazil, 50-99% in Malaysia and 79-100% in Mexico) (13). Likewise, the PPV of up to 68% in Colombia and up to 83% in Mexico was similar to those reported in the other countries (40-88% in Brazil, 71-80% in Malaysia and 50-83% in Mexico) (13). Therefore, the EWARS would predict about 9 out of 10 dengue outbreaks in Colombia and Mexico and 7 to 8 out of 10 alarms will be correct alarms. A high proportion of true positive alarms give control officers the confidence that when responding to an early alarm their available resources of insecticides, staff time and others are well spent. However, even in the case of false alarms resources on vector control are not spent in vain as they contribute in any case to keeping vector densities down.

In the case of chikungunya, the sensitivity to correctly predict an outbreak varied among alarm indicators from 77% to 93%, being rainfall and the combination of meteorological indicators the alarm signals with the highest sensitivity. Likewise, the PPV of up to 85% was similar to those reported with dengue in other countries (13). Therefore, the EWARS would predict outbreaks 10 to 13 weeks in advance, providing adequate time to activate response actions (see above).

In the case of Zika, the sensitivity (50-100%) and PPV (11-100%) was similar to the prediction of dengue and chikungunya when using alarm indicators with the highest values for sensitivity and PPV.

It is the first time that EWARS has been evaluated with chikungunya and Zika datasets, and the results were optimal to recommend the implementation. Although only data for three years were analyzed, these results show that EWARS is applicable to *Aedes* borne arbovirus diseases. As the user-friendliness of the application has already been established (13), the next step is to bring it to practical use in endemic countries and monitor its ability to predict outbreaks and trigger effective response.

Limitations of the study

This study was based on the cases registered by the public health surveillance system in Colombia, which classifies the cases as probable, confirmed and hospitalized (1,18). All confirmed cases should present a positive laboratory test, but in the current Colombian database the confirmed cases were sometimes based on clinical criteria. For chikungunya in Colombia, 106,592 cases were reported by SIVIGILA in 2014, 98% of which were confirmed cases according to clinical criteria (18). This reduces the reliability of the case definition. For dengue, the use of hospitalized cases as outbreak indicator was feasible, but in chikungunya and Zika this was hardly the case due to the low proportion of “hospitalized cases”. This limitation was overcome by taking into account probable and confirmed cases as outbreak indicators a suggested by other authors (13,19,20). Furthermore, there is a possibility of overestimation caused by the out-of-sample prediction, which may explains the case of 100% sensitivity observed. This can be reduced by employing a longer-data history of disease and alarm information.

In Cúcuta, more than 23,000 cases of chikungunya occurred, but the majority were diagnosed collectively (“collective reporting” i.e. all patients with fever and other symptoms in the waiting area of a health service are diagnosed as having chikungunya), and only a small proportion of cases had complete information from individualized examination (18) which is the routine approach in Mexico. Collective reporting demonstrates the impact of the chikungunya outbreak on the overstretched health system in Colombia. However, the data analyzed in this study was collected throughout the epidemic underlining the ability of the surveillance system to function under difficult circumstances (22).

The time period for retrospectively testing the validity of the EWARS tool was relatively short (3 years in the case of Zika); longer retrospective observation periods would have reflected better the usual pattern of the disease which is not possible in case of a newly emerging disease.

List of abbreviations

CHIKV: Chikungunya virus

EWARS: Early Warning and Response System.

INS: National Institute of Health (for Instituto Nacional de Salud)

MoH: Ministry of Health

SD: Standard deviation

SINAVE: National Epidemiological Surveillance System (for “Sistema Nacional de Vigilancia Epidemiológica”)

SIVIGILA: National Public Health Surveillance System (for “Sistema Nacional de Vigilancia en Salud Pública”)

PPV: positive predictive value.

TDR-WHO: The Special Program for Research and Training in Tropical Diseases.

WHO: World Health Organization.

ZIKV: Zika virus

Declarations

Ethics approval and consent to participate: The study has been reviewed and approved by the Ethics Committee of the Albert-Ludwigs-University Freiburg, according to Ethics committee minute N°-145/18, signed on 24 April 2018. The manuscript contains secondary data analysis, with collective non-personal information, and permissions obtained from health institutions are available.

Availability of data and materials: The epidemiological data that support the findings of this study are available from the Arbovirosis Surveillance Systems in Colombia and Mexico, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data analysed during the current study are available from the corresponding author (RC) on reasonable request and with permission of CENAPRECE, Mexico and IDS-Norte de Santander, Colombia.

Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interests. The authors alone are responsible for the views expressed in this publication and it does not necessarily represent the decisions, policy, or views of their respective organizations

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Authors' contributions:

RC. Design of the study, data collection and analysis, drafting manuscript

LH-A. Design of study, data analysis, drafting and correcting manuscript

DBV. Data collection and analysis, contribution to the text

GST. Data collection and analysis, contribution to the text

AK. Study design, data analysis, drafting and correcting the manuscript

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Figures

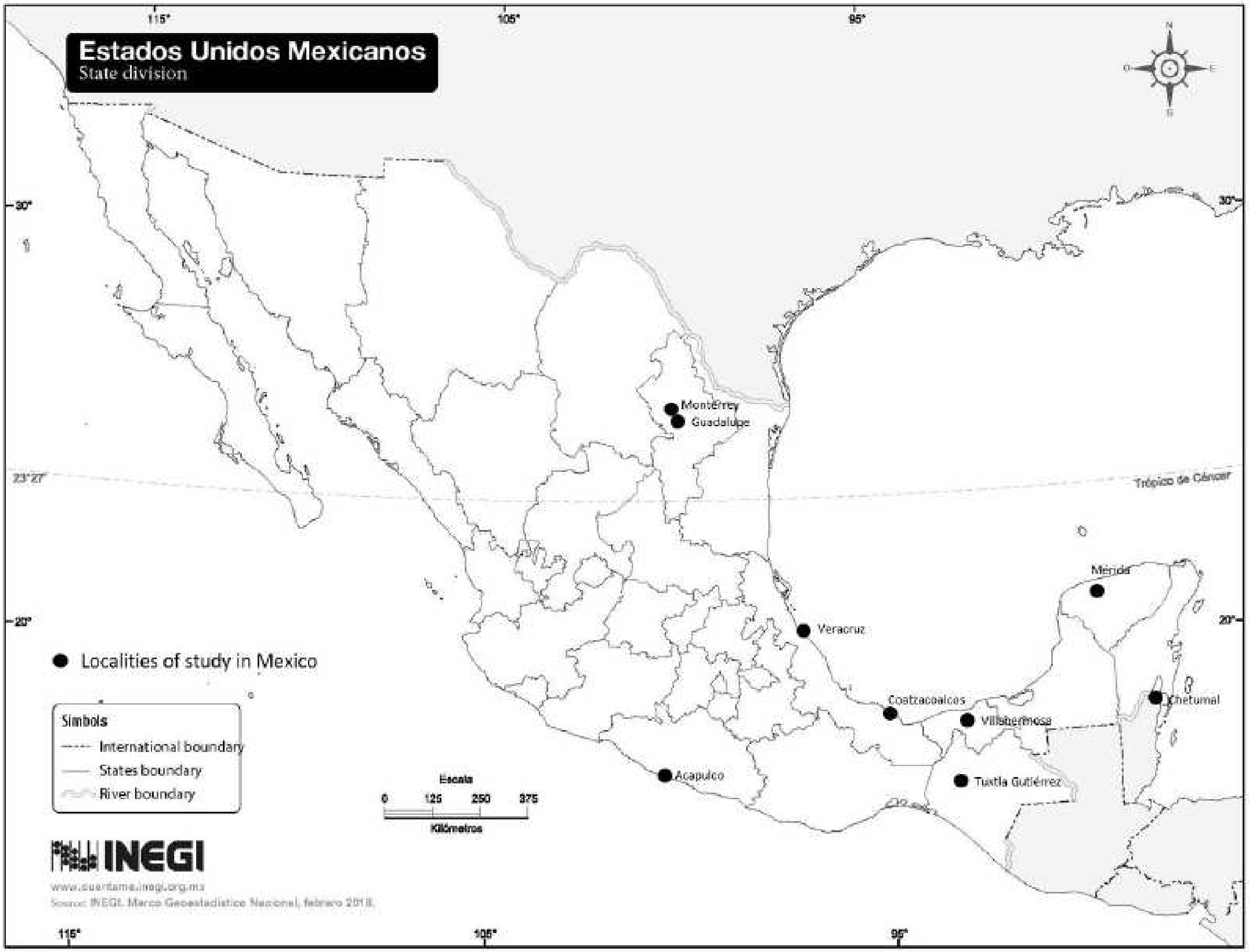

Figure 1

Localities of study in Mexico Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

Figure 2

Locality of study in Colombia Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

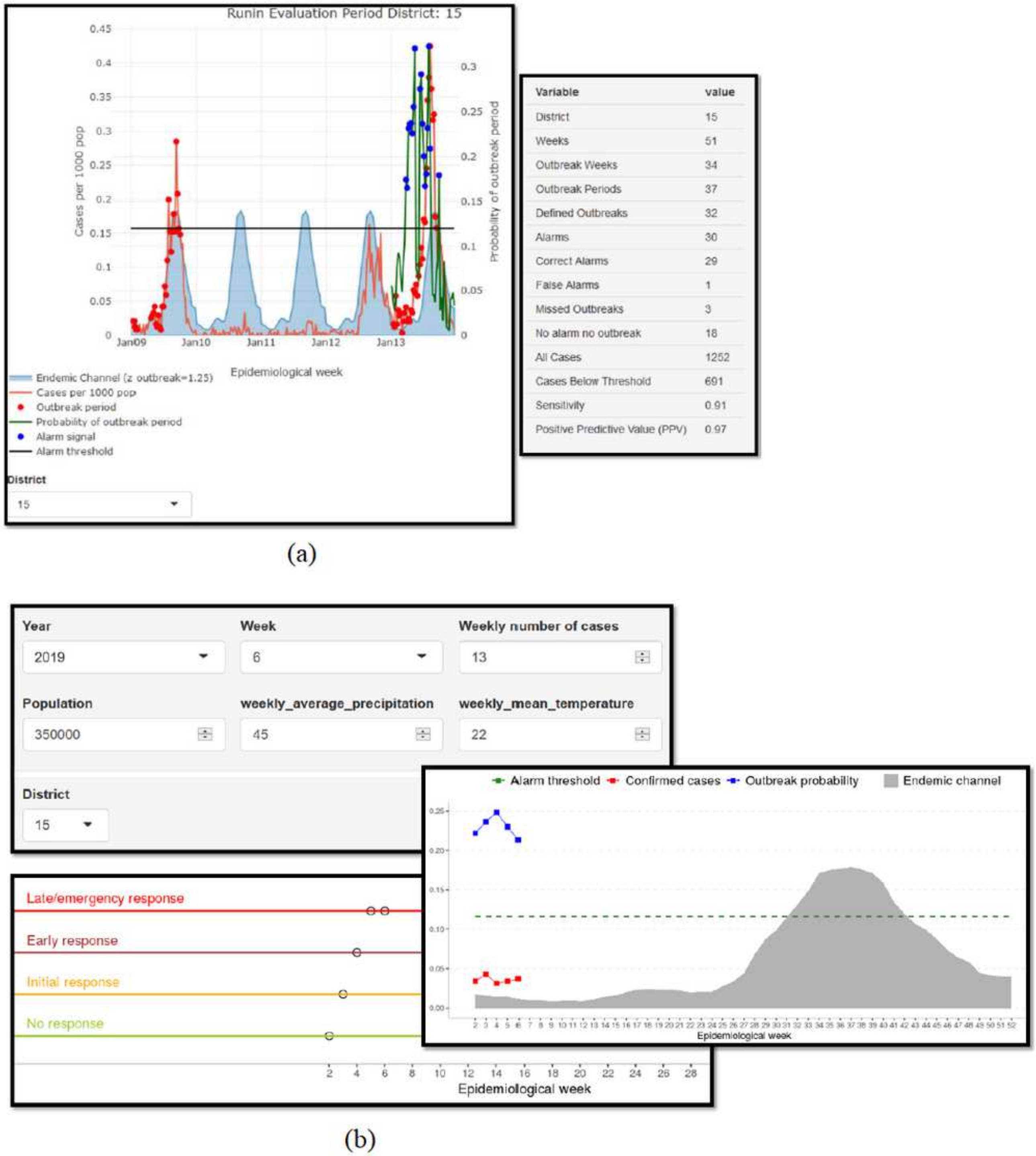

Figure 3

a. Snapshot of the retrospective dashboard, including graphical and numerical visualization of the calibration process and parameters b. A snapshot of the prospective dashboard, including an interface for prospective (weekly) data input prediction (alarm signal against rate of outbreaks) and structured response plan using a generic staged-response format (adoptable based on the national vector response protocol).

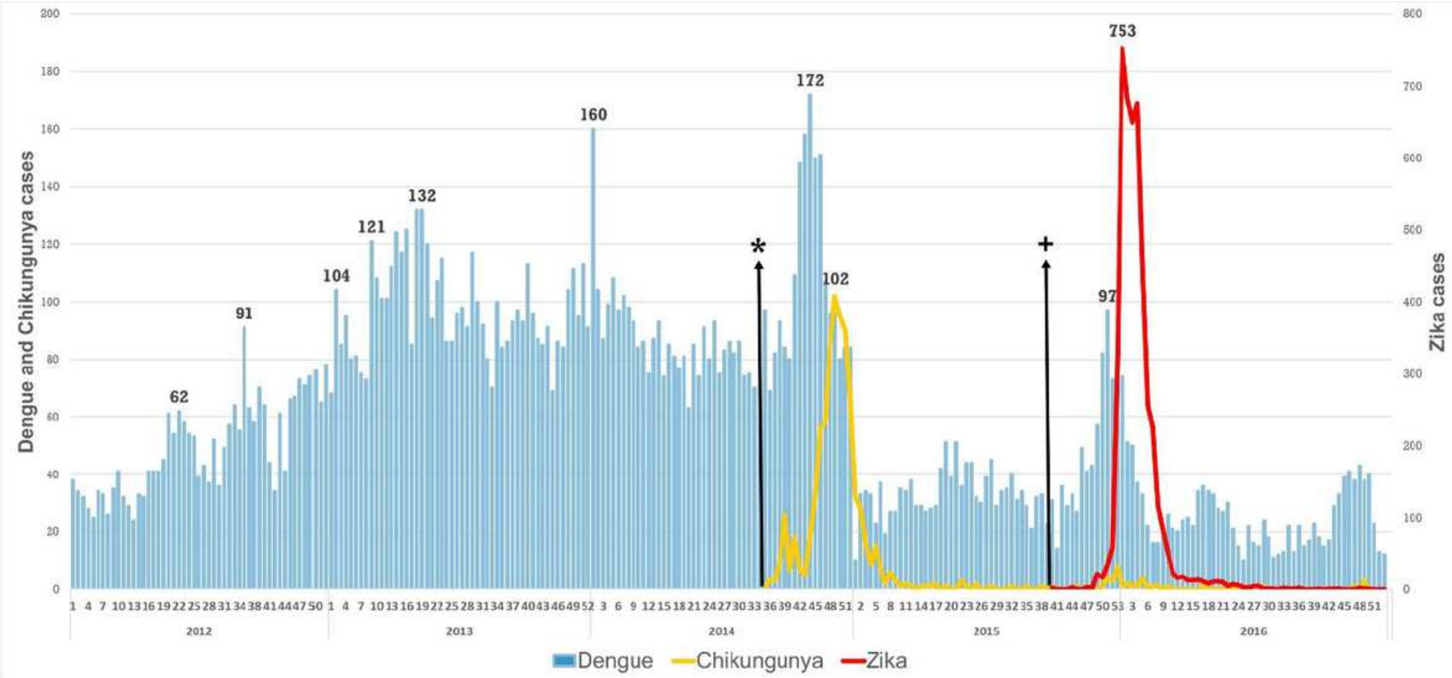

Figure 4

Time series of analysed cases of dengue, chikungunya and Zika in the urban area of Cúcuta, Colombia during the period 2012-2016°.

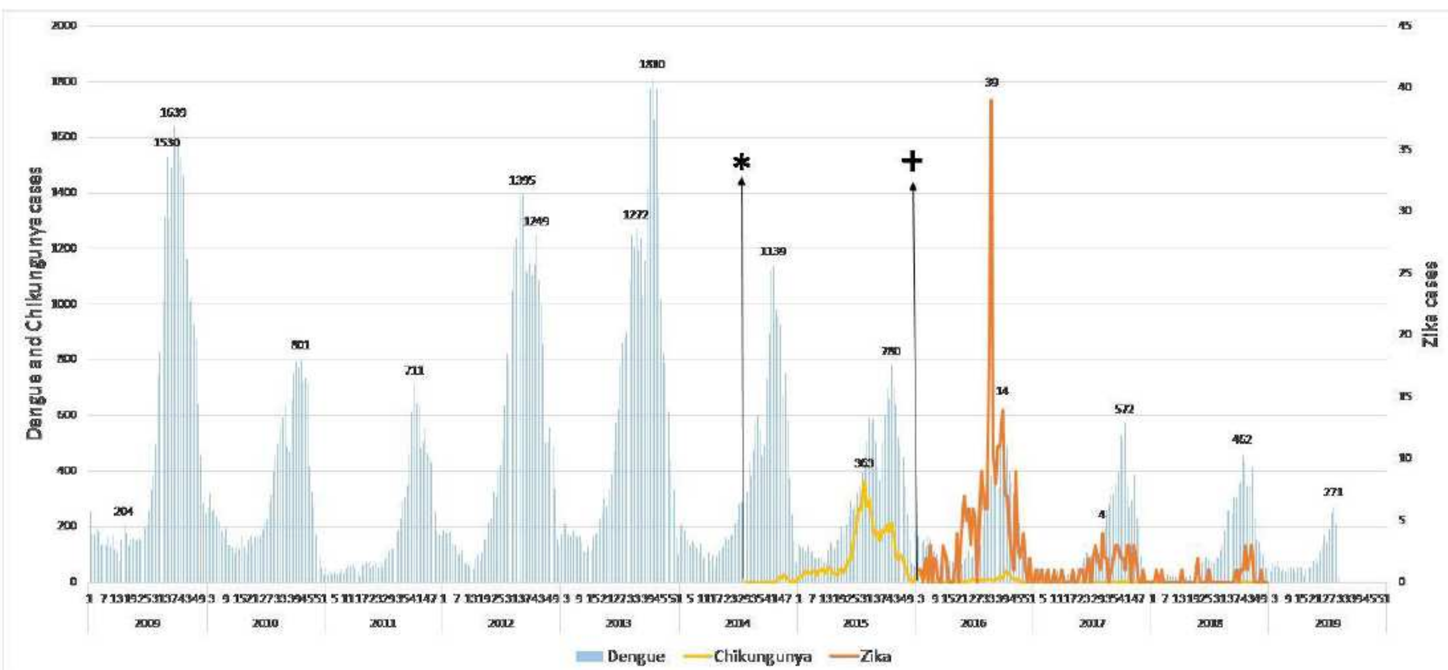

Figure 5

Time series of cases reported weekly in Mexico, of cases of dengue, chikungunya and Zika during the period 2009-2019.