Comparison of Active and Passive Surveillance of Dengue in Machala, Ecuador

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Abstract

Dengue is a major emerging infectious disease, endemic throughout the tropics and subtropics, with approximately 2.5 billion people at risk globally. Active (AS) and passive surveillance (PS), when combined, can improve our understanding of dengue's complex disease dynamics to guide effective, targeted public health interventions. The objective of this study was to compare findings from the Ministry of Health (MoH) PS to a prospective AS arbovirus research study in Machala, Ecuador from 2014-2015.

Dengue cases in the PS system were compared to laboratory confirmed acute dengue illness cases that entered the AS study during the study period. Variables of interest included age, class, and sex. Outbreak detection curves by epidemiologic week, overall cumulative incidence and age-specific incidence proportions were calculated. Descriptive statistics were tabulated for all variables of interest. Chi-square tests were performed to compare demographic characteristics between the AS and PS data sets in 2014 and 2015.

177 and 245 cases were identified from January 1, 2014 to December 31, 2015 by PS and AS, respectively; nine cases appeared in both systems. AS identified a greater number of laboratory-confirmed cases in 2014, accounting for more than 60% of dengue illness cases in the study area. In 2015, the opposite trend was observed with PS identifying 60% of the dengue illness cases in the region. Younger patients were more frequently identified by PS, while older patients were identified more frequently by AS. The cumulative incidence proportion for laboratory confirmed dengue illness reported via PS to the MoH was 4.12 cases per 10,000 Machala residents in 2014, and 2.21 cases per 10,000 Machala residents in 2015.

Each surveillance system captured different demographic subgroups within the Machala population, possibly due to differences in healthcare seeking behaviors, access to care, emerging threats of other viruses transmitted by the same mosquito vector and/or differences in clinical presentation due to changes in the predominant dengue serotype in circulation. Integrating AS with pre-existing PS can aid in identifying additional cases in previously under diagnosed subpopulations, improving our understanding of disease dynamics, and facilitating the implementation of public health interventions to reduce the burden of disease.

Background

Dengue is a mosquito-borne infectious disease that is a leading cause of morbidity and mortality on a global scale. It is the most prevalent mosquito-borne viral disease worldwide with approximately 2.5 billion people at risk for the disease and 400 million people infected annually (1). Since the 1980s, dengue has rapidly reemerged in the Americas and other tropical and subtropical regions; the four dengue virus serotypes (DENV1-4) co-circulate in endemic regions (2). Dengue is a complex disease that is influenced by many different elements including social determinants, vector control, land use and vegetation, and climate across timescales (3).

The rapid growth of urban areas throughout dengue endemic regions of the world has increased the number of people at risk of disease (4). The Aedes (Ae.) aegypti mosquitoes are highly adapted to the urban human environment. They prefer to inhabit areas in and near homes, and female mosquitoes oviposit in containers with standing water. The abundance of Ae. aegypti is due, in part, to haphazard urban sprawl resulting in water reservoirs within densely populated areas—the ideal conditions for mosquito proliferation and disease transmission. In Ecuador, the populations that are disproportionately affected tend to also be those with public health and social challenges, such as periurban communities whose members have limited education, income and substandard housing (5–7).

Despite mandatory reporting of dengue in Ecuador, under-reporting of illness is a major concern with many downstream impacts as it hinders accurate calculations of the true disease burden and appropriate allocation of scarce public health resources (8–11). There are several potential reasons why dengue cases go unreported: (1) lack of recognizition of symptoms by patients or physicians, (2) preference for self treatment for dengue-like symptoms, (3) barriers to accessing health care, and /or 4) limited resources of the health system which impact ability to confirm a dengue diagnosis.

The clinical manifestations of dengue are wide-ranging. Some infectious are asymptomatic, while others present with fever and non-specific symptoms, usually resembling flu-like symptoms and muscle aches. Many cases resolve without clinical intervention, but in some cases, the disease can progress to potentially fatal hemorrhage, shock, or death. According to the World Health Organization (WHO) guidelines (12), dengue without warning signs is defined as fever plus any two of following symptoms: nausea/vomiting, rash, aches/pains, positive tourniquet test, and leukopenia. Dengue with warning signs includes the definition above for dengue without warning signs and at least one of following warning signs: abdominal pain/tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement > 2 cm, and increased hematocrit concurrent with rapid decrease in platelets(12). Although it is important to seek medical attention for dengue with warning signs, there are currently no targeted therapeutic treatments available in most parts of the world, and access to a dengue vaccine is limited. In addition, the vaccine is currently recommended only for use in dengue-seropositive individuals due to long term safety issues observed in seronegative individuals in the safety followup (13,14).

The purpose of surveillance is to assess the burden of disease in a population (15). There are two types of surveillance methods, active and passive, and both are utilized in tracking dengue infections worldwide. An active surveillance (AS) system is a resource intensive approach in which public health officials continuously test members of the community, regardless of symptom status (16). Passive surveillance (PS), a less resource-intensive approach, is the accepted standard for dengue surveillance in many countries with mandatory reporting of dengue (17). Passive surveillance only accounts for those who recognize that they are sick and seek treatment in a clinical setting. Anyone who does not seek treatment is not counted in PS, resulting in underreporting (17).

The WHO states that the most effective surveillance strategy for decreasing incidence of dengue transmission is AS(18); however, AS is not widely used because of the expense and logistics required (1,7). Most regions that have implemented this method have done so as part of a research project. Several such studies have demonstrated that AS reveals the presence of significantly more cases of dengue than are reported via PS (8,9,19–22). One study conducted to assess disease burden via both AS and PS in Latin America found that AS identified a 10-fold higher case load as compared to the national PS system (8). An additional study in Nicaragua reported an approximate 21 fold increase per year as compared to the Ministry of Health (MoH) PS system (9). A study in French Guiana showed that AS was able to detect an outbreak 3 to 4 weeks earlier (23). Because of resource limitations, AS is rarely implemented as an operational public health approach; however, if AS studies were streamlined, those methods could complement and extend an existing PS system in key surveillance sites, such as hotspots of disease emergence.

PS is a useful tool in informing disease trends; however, this approach can lead to mischaracterization of disease burden due to systematic underreporting in certain subpopulations, hindering control efforts, and furthering disease transmission (8,19,24). Lack of reporting also results in underestimates or biased estimates of disease burden and dispersion, potentially leading to the misallocation of scarce public health resources to prevent transmission. Overall, a combined surveillance approach (using AS and PS) would likely provide more accurate estimates of disease incidence and strengthen prevention and control efforts for dengue (19,22).

The objective of this study was to compare dengue case data from the MoH PS system to a prospective AS arbovirus study in Machala, Ecuador. Incidence of disease, the demographic profile, and timing of the case reports were of interest, as earlier detection of an increase in dengue cases could trigger early interventions and reduce disease transmission. Overall, the protection of specific subpopulations at greater risk of infection, and the enhancement of public health control efforts, could result in reduced dengue burden.

Methods

Study Site

All data used for this comparative analysis were collected from Machala, Ecuador, a coastal port city in southern Ecuador and the capital of El Oro province; there were approximately 270,000 residents at the time of this study (2014–2015). The incidence of dengue and the density of Ae. aegypti mosquitoes in Machala is amongst the highest in Ecuador, as well as other Latin American countries and Asia(5,25–27). Dengue is transmitted seasonally, with more cases reported during the hot, rainy season from February to

May. Dengue outbreaks have been observed to correlate with extreme climate events, such as El Niño events that strongly impact local rainfall and temperatures in southern coastal Ecuador(3,5,6).

We selected four (of 23) sentinel outpatient clinics located around Machala and operated by the MoH; sites were chosen based on a high burden of dengue in the community catchment areas and their interest and ability to participate in the study (25). The clinics included Brisas del Mar, Rayito de Luz, Mabel Estupiñan, and El Paraiso. In addition, the Teófilo Dávila Hospital, the primary public hospital run by the MoH, was included as it is the province-level reference hospital where the outpatient clinics refer patients with severe dengue illness (25). Public clinics and hospitals are required to report cases of dengue-like illness (with and without warning signs) to the MoH for patients seeking care.

Active Surveillance

Figure 1 provides a flowchart of active surveillance and passive surveillance recruitment methods for the study. The AS study design and diagnostic procedure have been described previously (25). Briefly, individuals (index subjects) were recruited into the AS research study after visiting one of the four MoH clinics or the Teofilo Davila Hospital with clinical signs and/or symptoms of dengue (see Fig. 1). Index subjects were referred to our study technician or nurse; informed consent was obtained and demographic and clinical information were recorded. At the time of clinical evaluation, a 20 ml blood specimen (adjusted for age and weight by United States National Institutes of Health criteria) was obtained by venipuncture from each participant. Samples were processed at the diagnostic laboratory within the Teofilo Davila hospital. Acute dengue infections were confirmed via serum with NS1 rapid strip tests. A maximum of four index subjects that tested positive for dengue were randomly selected each week to participate in the community surveillance component of the study. Members of the index subject's household and members of four neighboring households within a 200-meter radius of the index household, the typical flight range of the Ae. aegypti mosquito, were invited to participate in the study. The same demographic and clinical information was gathered from these individuals, as well as a blood sample.

Blood specimens were separated via centrifuge into serum, cells and plasma and stored at -80 °C. Samples were tested for dengue using NS1 and IgM enzyme linked immunosorbent assay (ELISA) at the laboratory in Machala. Samples were then shipped to SUNY Upstate Medical University where Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) was used to confirm dengue infections and virus serotypes (25). Positive cases of dengue in the AS system (herein called dengue illness) were defined as individuals with the presence of one or more of the following symptoms: fever, nausea/vomiting, rash, muscle/joint pain, abdominal tenderness, bleeding, diarrhea, headache, retro-orbital pain, drowsiness/lethargy, who tested positive for dengue virus by RT-PCR, NS1 rapid test, NS1 ELISA or IgM ELISA. There were 33 individuals in 2014 and six in 2015 in the AS system who had positive laboratory tests but no symptoms. These cases were excluded from the analyses reported in this manuscript since they did not fit the definition of dengue illness (symptoms and positive lab confirmation).

Passive Surveillance

Ecuador has a mandatory PS reporting strategy for dengue with and without warning signs as well as for other mandatory reportable health conditions. If the patient is classified as having dengue with warning signs, they are admitted to the local hospital where a physical exam is administered and a blood serum sample collected to confirm dengue infection via RT-PCR at the national reference laboratory of the MoH in the neighboring city of Guayaquil. Patient demographics (age, sex, pregnancy status if applicable), clinical characteristics (start date of symptoms, final clinical diagnosis), and diagnostic laboratory results are recorded. If dengue diagnosis is ruled out, an 'other' diagnosis is recorded. If the patient seeking care is classified as dengue without warning signs, their information is entered into a separate MoH PS dataset based on clinical symptoms and not via RT-PCR confirmation. Patients classified as dengue without warning signs are entered into the database in 'group form' by reporting institution or clinic, but without names or ages.

For this analysis, the MoH provided de-identified data on reported dengue cases from the entire city of Machala to the study team. We created two PS datasets by extracting dengue cases from these MoH reports for the same sentinel clinics/hospital utilized in the AS study from January 1, 2014 through December 31, 2015. In the primary dataset, we identified patients diagnosed with dengue with warning signs and with laboratory confirmation (referred to as dengue illness). In the second data set, we included cases with dengue-like symptoms but without warning signs and without laboratory confirmation (referred to as possible dengue).

Dengue cases in the two PS datasets were compared to dengue illness cases that entered the AS study during the same period of time. Duplicate patients were identified by matching the date, sex, and age. Variables of interest included age class (< 5, 5–19, 20–64, 65+), and sex (male, female), and pregnancy status (pregnant, not pregnant). The pregnancy status variable was not available in the PS data set without warning signs. Due to the small sample size, we were not able to compare pregnancy status across surveillance systems.

Statistical Methods

Microsoft Excel (Version 16, Microsoft Corporation, Redmond, Wash, USA) was used for data quality assessment. The Statistical Package for the Social Sciences (SPSS - IBM Corp. Released 2013, IBM SPSS Statistics for Windows, Versions 25 and 26, Armonk, NY: IBM Corp.) was used to calculate overall cumulative incidence and age specific incidence proportions, to construct outbreak detection curves by epidemiologic week, and to run all analyses. Descriptive statistics were tabulated for all variables of interest. Chi-square tests were performed to compare cohort demographic characteristics between the AS and PS data sets in 2014 and 2015. Duplicates were ommitted from both the PS and AS systems in these chi-square analyses. Results with a p value of ≤ 0.05 were considered statistically significant. Results were not corrected for multiple comparisons.

Cumulative incidence proportions (overall and age-specific) were calculated for cases identified by the MoH PS system (dengue illness as well as possible dengue) using the city of Machala population estimate for 2016 (n = 276, 691) and the age-specific population figures for Machala, also for that year(28). Note that the hospital serves the entire population of Machala and the four sentinel clinics serve a subset of the city's population. However, incidence calculations are based on the entire population of the city of Machala, to provide a common demoninator. Cumulative incidence proportions displayed are per 10,000 persons per year.

Results

Overall, more cases of dengue illness were identified in 2014 than in 2015. The AS identified 205 cases of dengue illness, accounting for approximately 60% of disease burden that year in the study catchment area included in the analysis, while PS identified 116 cases of dengue illness in 2014, with four duplicate cases observed. In 2015, AS identified 40 dengue illness cases while PS identified 61 cases of dengue illness, with five cases identified in both systems in 2015. The cumulative incidence proportions for dengue illness identified by PS was 4.12 cases per 10,000 people in 2014 versus 2.21 per 10,000 people in 2015.

As noted ealier, the MoH PS also registered cases of possible dengue (clinical symptoms only, but without warning signs and laboratory confirmation). There was no equivalent grouping in the AS system. In 2014, there were 650 clinical cases of possible dengue reported via PS, while there were 812 possible dengue cases in 2015.

Cumulative incidence of dengue across the five clinical sites, combining both dengue illness and possible dengue cases from PS, were similar at 27.6 per 10,000 residents in 2014 and 31.55 per 10,000 residents in 2015. Table 1 summarizes the cumulative incidence overall, and by age categories for the two PS data sets created from the MoH data.

In Tables 2 and 3 we compare the demographics of dengue cases identified through the three datasets: (1) AS with symptoms and lab confirmation (dengue illness), (2) PS with warning sign symptoms and lab confirmation (dengue illness), and (3) PS with symptoms but no warning signs or lab confirmation (possible dengue). In 2014, there were no significant differences in the frequencies of males and females with dengue identified via AS versus the two PS data sets (p=0.63 and 0.72 see Table 2). Age group differences were apparent, however (Table 2 and Figure 2). The dengue illness cases identified by PS (with warning signs and lab confirmation) were more likely to be in the the 10-14 age bracket, while those identified by AS were more likely to be aged 20 plus years (p=0.004 across all age groups). In 2014 the pattern by age category observed in those with possible dengue (no warning and no lab confirmation) via the PS system was similar to that observed in the AS system for individuals with dengue illness (symptoms and lab confirmation); individuals over 20 years of age comprised more than 40% of cases in both of these data sets (shown in Table 2).

In 2015 (see Table 3), no gender differences were observed across the surveillance datasets; however, females made up a higher overall proportion of cases in 2015 as compared to 2014. Again, children and adolescents (see also Figure 3) comprised the most frequently observed groups in 2015 in the PS dengue illness (warning signs and lab confirmation) dataset, while adults 20 years plus were more frequent in both the AS dengue illness and PS possible dengue datasets.

Of interest were differences across the two year study period with respect to cases less than 20 years of age with confirmed dengue illness. We found that 5-9 year olds were the most frequent age group in the PS dengue illness dataset in 2015, while the 10-14 years olds were the largest age group in the dengue illness PS dataset in 2014.

Epidemiological curves of both AS and PS dengue illness cases revealed bimodal transmission peaks in 2014, with the first peak for both AS and PS dengue illness at approximately 21 weeks (mid May). The second transmission peak for PS occurred soon after, at 25 weeks (mid June), while the second transmission peak for AS occurred later, around 27-28 weeks (mid July, see Figure 4a,b). Possible dengue cases reported via PS in 2014 peaked between 22 and 26 weeks (Figure 4c). In 2015, there was only one transmission peak for AS dengue illness at approximately 15-20 weeks (early April to May). PS revealed bimodal transmission peaks of dengue illness at about 22 and 28 weeks (early June and mid July, see Figure 4d,e). Possible dengue cases in 2015 (Figure 4f) demonstrated bimodal peak transmission at 20-24 weeks with a slight resurgence at 26-28 weeks.

Discussion

A major finding of this study was that older individuals with confirmed dengue illness (symptoms/warning signs and lab confirmation) were more likely to be identified by AS in both 2014 and 2015 whereas children and adolescents with confirmed dengue illness were more likely to be reported via PS for both study years. While gender differences by surveillance system and/or dataset were not apparent in either year in any of the data sets, females made up a higher proportion of cases in all data sets in 2015. Also of interest was the observation that the proportions of adults with possible dengue reported to the MoH PS data system based on clinical symptoms only were more similar to the proportion of adults identified via AS and could represent similar clinical presentations and/or less severe disease.

The strengths of this study include the ability to compare a research-based AS system to an existing, mandatory PS system in an area with a high burden of arboviral illness. Since mandatory reporting of dengue fever has been required for some time in Ecuador, laboratory diagnostics were used to confirm dengue illness in a subset of more severe patients in the PS system. Overall, the methods for the collection of AS data were thorough, and included similar data to that collected routinely by the MoH. The cluster study design of the AS is relatively efficient compared to more intensive surveillance methods (e.g., cohorts), increasing the likelihood that this could become an operational AS approach for Ministries of Health with limited resources.

The observed demographic differences can be attributted to a combination of cultural factors, health seeking behaviors, the lack of clinical treatment options and differences in the clinical and immunological profiles of study subjects (8,9,19,29). Active surveillance is effective in detecting infections in individuals who are less likely to utilize standard clinical treatments (8,9,20,21,30).

Alternative medicine and home remedy care is a popular cultural norm in Ecuador, often viewed as an equally effective treatment method for dengue by the general population (11). It is likely that many in the cohort of 20-64 year olds in this analysis did not seek clinical care because they were asymptomatic, had mild disease symptoms or were using alternative medicine to treat their symptoms. In addition, prior studies suggest that older males are generally less likely to seek clinical services than females (31); females, as the primary caregivers, are more likely to take themselves and their children to the doctor (29).

Other potential explanations for the demographic differences detected by surveillance system could include the lack of knowledge of disease dynamics and social inequalities such as limited education, income, and access to care as well as substandard housing and location within the city (5,7,10,16,32). Although many Machala residents do attend MoH health clinics for care, they may not recognize that other household members exposed to the same environment are also at a higher risk for infection, a phenomenon consistent with a lack of knowledge about dengue and its transmission dynamics. Urban/periurban location may contribute to the social inequalities seen in healthcare in areas with low socioeconomic status, substandard housing, and inadequate urban infrastructure (e.g., piped water, sewerage, garbage collection). Individuals living in periurban areas of the city are thought to be at increased risk for disease and may be among the cohort of cases not reported to the passive surveillance system, although a spatial analysis was beyond the scope of this study (5,7). These individuals may not have the ability or resources to take time off from work or to travel to receive clinical care.

Previous literature also has shown that the greatest burden of acute dengue infections occurs in children under 10, while the most severe manifestation of dengue is amongst adolescents aged 14 to 20 years who are likely experiencing a second infection(25,33,34). Results of our AS and PS comparison study support these observations. The highest frequency of confirmed dengue illness in both 2014 and 2015 occurred in those under 20 years of age reported via PS to the MoH. The adult dengue disease burden was more likely to be reported via AS (confirmed dengue illness), or in the the PS with clinical symptoms only (possible dengue) data set in this comparative analysis.

The youth (5-19 years) age range could also be classified as school aged children and adolescents, a cohort at risk of exposure to daytime mosquito bites around the home and school. Students are also in close proximity to one another, which allows for the mosquitos around the school to potentially spread dengue. Since “school” is the common denominator, school could potentially also be a focus for a strategic intervention for disease control. Many studies have concluded that comprehensive school interventions for prevention have been shown to be an effective strategy for dengue vector control (34–37). There is however, mixed evidence of the role of schools in propagating dengue virus transmission (38,39).

Overall in 2014, there was a higher incidence of laboratory confirmed dengue infection observed in Machala, Ecuador than in 2015. AS was successful in identifying a larger proportion of laboratory confirmed dengue cases in 2014 than was identified through PS reporting to the MoH, demonstrating the added benefit of conducting AS in a high disease burden area. Given the time frame of clinical illness, infections malaria, chikungunya and Zika were unlikely. The first cases of chikungunya were identified in Machala 2015 and the first cases of ZIKV in 2016; no autochthonous malaria cases were reported from 2012-2017 (40). It is likely that the outbreak of chikungunya superseded dengue infections in 2015. The emergence of chikungunya virus in Latin America was closely followed by the emergence of zika virus. Although there were no reported cases of zika in Machala at the time of this study, news of the WHO declaring zika a disease of global concern may have increased awareness and may have instilled a sense of fear which led residents to seek clinical care (41). The WHO declaration also led to increased financial resources and surveillance strategies for at risk regions.

It is possible that some of the "possible" dengue cases from the PS system were attributed to tick borne disease, as our recent study detected antibodies to spotted fever group rickettsial in 25% of individuals clinically diagnosed with dengue from Machala in 2014-2015 (42). However, it is likely that dengue was the primary vector-borne infection circulating in Machala in 2014.

During 2015, PS identified more laboratory confirmed cases of dengue illness than AS even though a majority of cases initially recorded in the PS dengue illness (with warning signs) data set were diagnosed with diseases other than dengue following lab confirmation. In 2015, a chikungunya epidemic emerged; an increased use of health clinics when symptoms appeared likely aided passive reporting overall that year. This behavior may reflect the severity of symptoms associated with chikungunya and a increased awareness of general mosquito-borne diseases in circulation in the region. Nonetheless, awareness of disease symptoms and outcomes by the public is key to influencing health seeking behaviors. Continuing education is a strategy that could help better inform and influence these behaviors resulting in more accurate PS case counts. For individuals who do not receive information or have restricted access to health care facilities, AS is an important safety net to capture additional cases and disrupt transmission.

Local climate likely also influenced observed dengue seasonality and peaks in transmission. Epidemiological curves provide information about peak transmission time and allow for the comparison of transmission dynamics and trends over several years. Our observed epidemiological curves during 2014 and 2015 were consistent with previous literature showing peaks in dengue transmission in this region at the end of the hot, rainy season (25). This timing is likely associated with the presence of open containers and reservoirs of standing water that accumulate during the rainy season, which are an ideal habitat for juvenile *Ae. aegypti*. The transmission of dengue begins when the mosquitos mature from egg to adult, and adult mosquitoes become infectious (able to transmit virus). In 2014, the dengue illness AS and PS peaks occurred around the same week while in 2015, the AS transmission peak occurred earlier than both PS transmission peaks. This suggests that, in some years, AS has the potential to identify cases earlier than the PS, thus informing public health officials of the need for proactive interventions. Other studies have found that complementary active surveillance methods such as syndromic surveillance or sentinel surveillance can lead to earlier detection of outbreaks (19,23).

Limitations

There are some limitations in our study, due in part to the observational nature of the design. Although clinical cases without laboratory confirmation were reported as part of PS (possible dengue cases), there was no equivalent category in the AS system. Nonetheless, we were able to compare the demographics of the possible dengue patient group to both the AS and PS dengue illness data sets, highlighting the similarities and differences. Even though index cases (symptomatic individuals who tested positive for dengue) in the AS study were initially indentified at one of the MoH sentinel clinics or the hospital, we were unable to identify with certainty those cases that also were reported to the MoH PS system. Consequently, we did not include the AS dengue illness cases in incidence calculations of the total burden of disease in the Machala study area. The reported incidence figures are therefore, underestimates of the true burden of laboratory confirmed dengue illness in the Machala area. However, AS study participants were provided results of NS1 rapid tests at time of enrollment. Finally, the incidence proportions reported were calculated based on the population of the Machala area, not the catchment area specific to the clinics or the country level population total. These incidence figures cannot be compared directly to incidence figures calculated either for the catchment area or the country because of the differing denominators employed.

Conclusions

There are known limitations and coverage gaps associated with using only a PS system for tracking and reporting dengue cases and epidemics. Results from this comparative analysis reveal that implementing a national AS policy has the potential to fill this gap, not only by identifying more dengue cases in a timely fashion but in capturing cohorts with dengue who would not routinely be reported to the MoH as part of PS. AS should not replace the existing PS system, but simply run in parallel. This combined approach has the potential to produce more accurate estimates of disease burden, provide a more equitable healthcare system and diminish the burden of dengue in Machala, Ecuador. Future studies may examine clinical, social, and economic factors of the populations captured in each system as to more accurately estimate the cost-benefit of disease surveillance systems.

Abbreviations

AS: Active arbovirus research surveillance study

PS: Passive surveillance

MoH: Ministry of Health

Ae. Aegypti: Aedes aegypti

Declarations

Ethics approval and consent to participate

This protocol was reviewed and approval by Institutional Review Boards (IRBs) at SUNY Upstate Medical University (417710-27) , the Luis Vernaza Hospital in Guayaquil, Ecuador (HLV-DOF-CEISH-003), and the Ecuador Ministry of Health. Prior to study start, all study subjects engaged in a written informed consent or assent process, as applicable. In the event the subject was unable to participate in the informed consent/assent process, a recognized health-care proxy represented them in the process and documented consent. The study population included children (> 6 months) to adults who were admitted or evaluated in sentinel clinics with a clinical diagnosis of dengue illness.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests, financial or non-financial.

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Authors' contributions

MV ran the initial statistical analyses, completed the literature review and wrote the initial draft manuscript; PFR completed the statistical analysis and compiled tables, figures, and graphs in addition to manuscript preparation and feedback; CDL provided oversight on the project and provided assistance with manuscript preparation and interpretation of the data; AMSI assisted with interpretation of the data, manuscript prepararation and feedback; AKA provided assistance with data management; RJO facilitated data and our understanding of the data; TO provided oversight and local MoH involvement, access to data, interpretation of local epidemiological context; EBA coordinated local MoH and SUNY investigators, and also provided interpretation of local epidemiologic context; TPE provided guidance on active surveillance protocols and dengue disease expertise. All authors provided feedback for this manuscript, and read and approved the final manuscript.

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Tables

Table 1. Cumulative incidence of Passive Surveillance (PS) dengue illness† and PS possible dengue* per 10,000 residents Machala per year, Machala study sites only.

2014	†PS with Warning Signs N=116	*PS without Warning Signs N=650
Overall	4.12	23.49
Age-Specific		
0-4	1.86	17.11
5-19	9.44	39.72
20-64	2.26	17.58
65+	0.54	10.21

2015	†PS with Warning Signs N=61	*PS without Warning Signs N=812
Overall	2.21	29.34
Age-Specific		
0-4	2.23	15.25
5-19	4.10	34.14
20-64	1.39	29.80
65+	0.54	25.26

† Defined as symptoms, warning signs and positive laboratory test results.

* Defined as clinical symptoms only, without warning signs and without laboratory confirmation.

Table 2. Comparison of demographics of AS and PS cases in 2014; AS Dengue illness cases (symptoms, warning signs and positive test) compared to PS Dengue illness cases and, to PS Possible dengue cases (symptoms only, without warning signs or positive test).

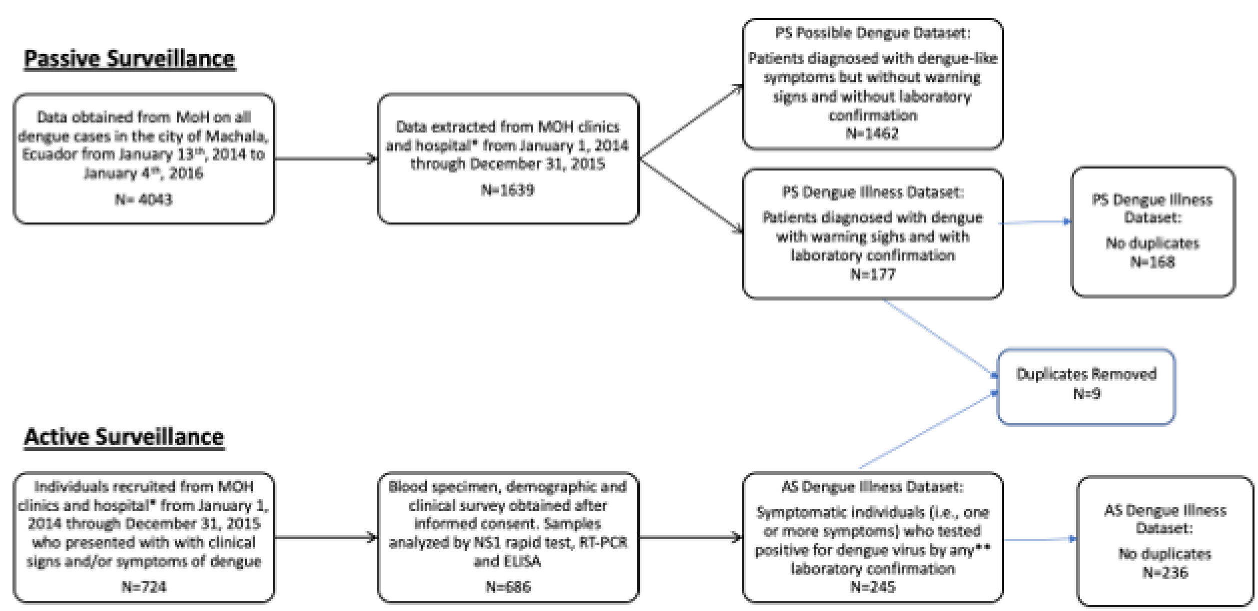
2014		**AS, Dengue Illness**		**PS, Dengue Illness**		**AS vs PS, Illness**	**Possible Dengue**		**AS vs PS vs Possible**
		N	**(%)**	**N**	**(%)**	***p value***	**N**	**(%)**	***p value***
Sex	**Male**	96	(47)	55	(51)	*0.70*	323	(49.5)	*0.79*
	Female	109	(53)	57	(49)		329	(50.5)	
Age	**< 5**	11	(5.4)	5	(4.5)	*0.004*	46	(7.1)	*0.003*
	5-9	21	(10.2)	14	(12.5)		76	(11.7)	
	10-14	44	(21.5)	44	(39.3)		130	(20)	
	15-19	29	(14.1)	18	(16.1)		114	(17.5)	
	20-64	94	(45.9)	30	(26.8)		265	(40.8)	
	65 plus	6	(2.9)	1	(0.9)		19	(2.9)	

Table 3. Comparison of demographics of AS and PS cases in 2015; AS Dengue illness cases (symptoms, warning signs and positive test) compared to PS Dengue illness cases and, to PS Possible dengue cases

(symptoms only, without warning signs or positive test).

2015		AS, Dengue Illness N	(%)	PS, Dengue Illness N	(%)	AS vs PS, Illness *p value*	Possible Dengue N	(%)	AS vs PS vs Possible *p value*
Sex	**Male**	16	(40)	24	(43)	*0.78*	356	(44)	*0.85*
	Female	24	(60)	32	(57)		448	(56)	
Age	**< 5**	1	(2.5)	6	(7.0)	*0.11*	41	(4.4)	*<0.001*
	5-9	7	(17.5)	33	(38.4)		71	(8.7)	
	10-14	7	(17.5)	12	(14)		121	(14.9)	
	15-19	5	(12.5)	15	(17.4)		83	(10.2)	
	20-64	19	(47.5)	19	(22.1)		449	(55.3)	
	65 plus	1	(2.5)	1	(1.2)		47	(5.8)	

Figures



*MoH clinics: Brisas del Mar, Rayito de Luz, Mabel Estupiñan, and El Paraiso and MoH Teófilo Dávila Hospital
**Positive laboratory confirmation for dengue virus by RT-PCR, NS1 rapid test, NS1 ELISA or IgM ELISA

Figure 1

Flowchart of active surveillance and passive surveillance recruitment methods

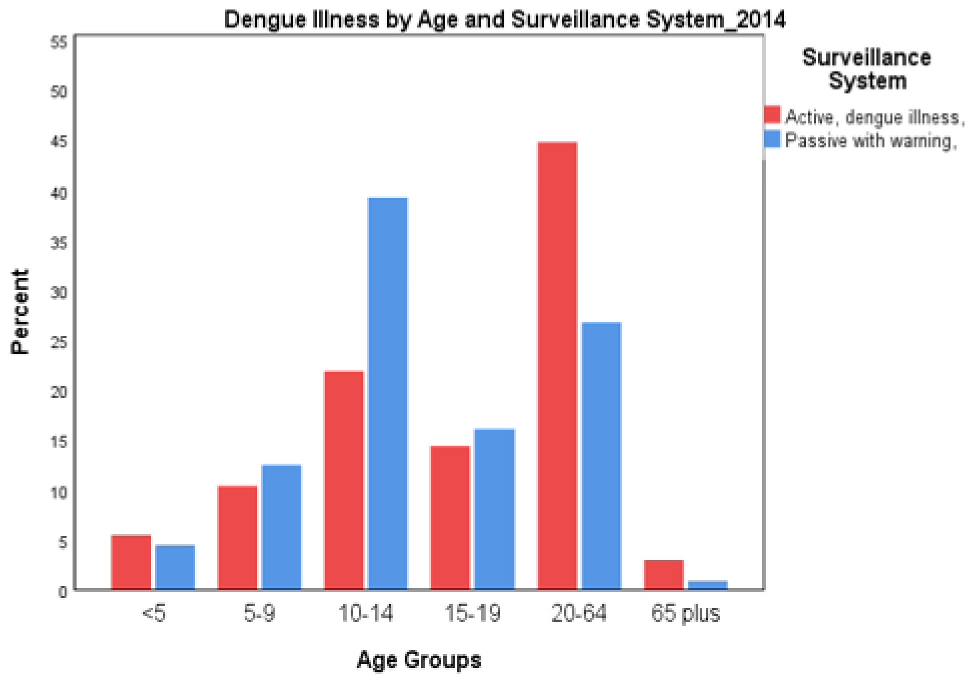


Figure 2

Dengue illness by age group and surveillance system, 2014 .

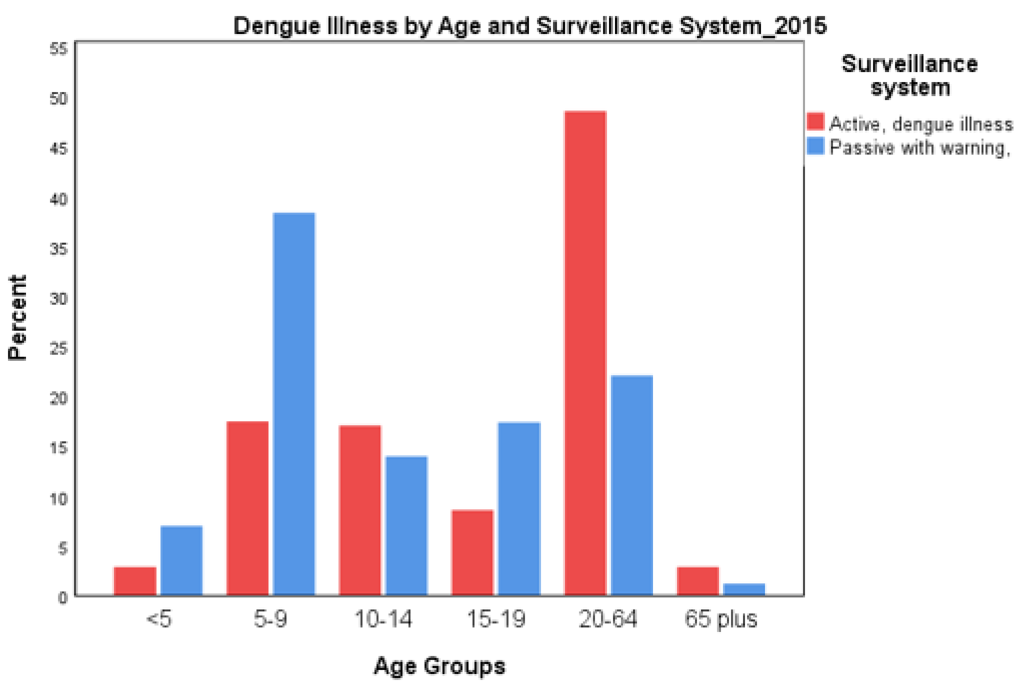


Figure 3

Dengue illness by age and surveillance system in 2015.

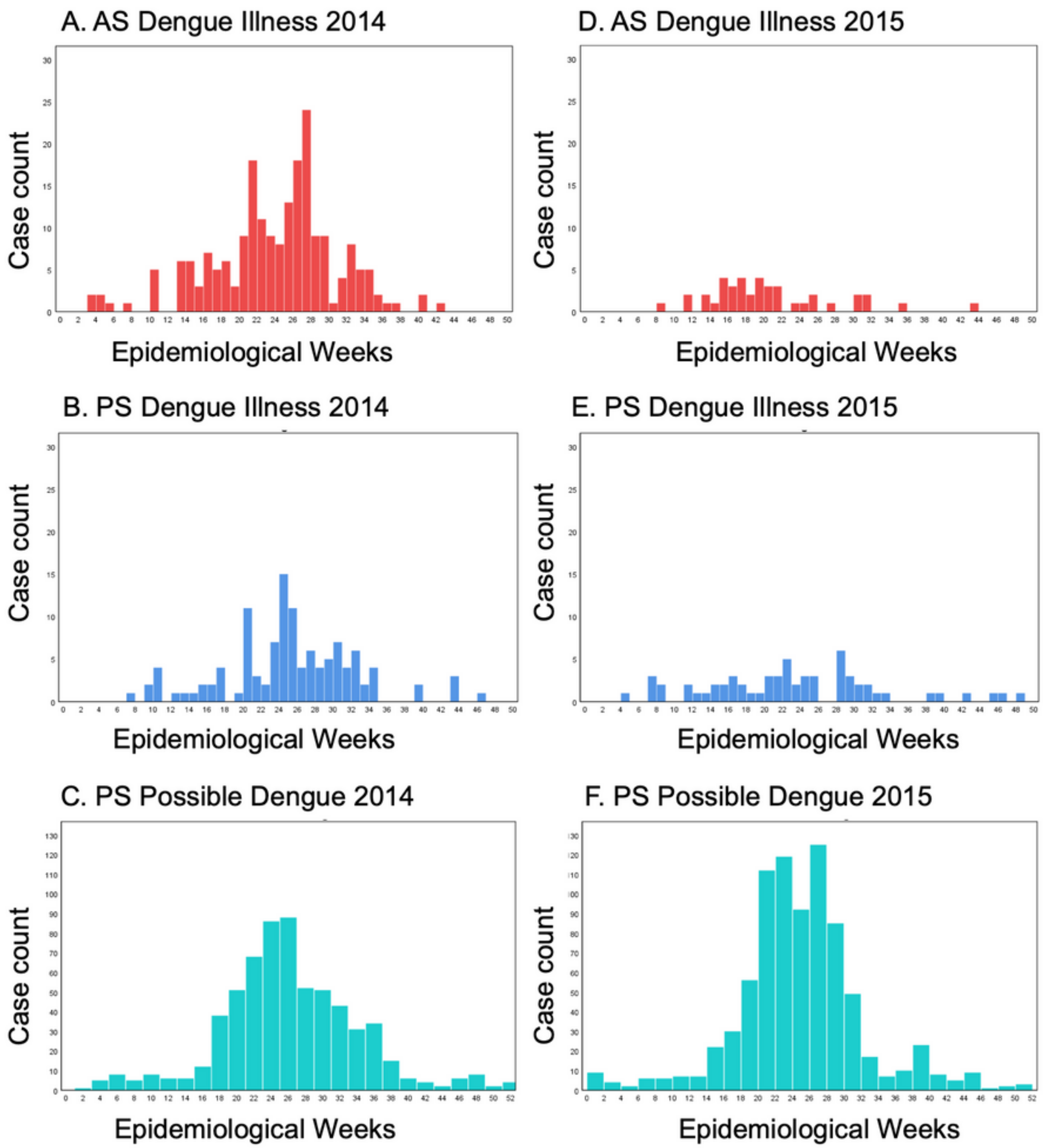


Figure 4

Dengue illness and possible dengue in both systems in 2014 and 2015 by epidemiologic weeks