

1 Sentinel versus passive surveillance for measuring changes in dengue incidence:  
2 Evidence from three concurrent surveillance systems in Iquitos, Peru  
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34 **Abstract**

35 Monitoring changes in infectious disease incidence is fundamental to outbreak detection and  
36 response, intervention outcome monitoring, and identifying environmental correlates of  
37 transmission. In the case of dengue, little is known about how consistently surveillance data track  
38 disease burden in a population over time. Here we use four years of monthly dengue incidence  
39 data from three sources – population-based (‘passive’) surveillance including suspected cases,  
40 ‘sentinel’ surveillance with 100% laboratory confirmation and complete reporting, and door-to-  
41 door (‘cohort’) surveillance conducted three times per week - in Iquitos, Peru, to quantify their  
42 relative consistency and timeliness. Data consistency was evaluated using annual and monthly  
43 expansion factors (EFs) as cohort incidence divided by incidence in each surveillance system, to  
44 assess their reliability for estimating disease burden (annual) and monitoring disease trends  
45 (monthly). Annually, passive surveillance data more closely estimated cohort incidence (average  
46 annual EF=5) than did data from sentinel surveillance (average annual EF=19). Monthly passive  
47 surveillance data generally were more consistent (ratio of sentinel/passive EF standard  
48 deviations=2.2) but overestimated incidence in 26% (11/43) of months, most often during the  
49 second half of the annual high season as dengue incidence typically wanes from its annual peak.  
50 Increases in sentinel surveillance incidence were correlated temporally (correlation coefficient =  
51 0.86) with increases in the cohort, while passive surveillance data were significantly correlated at  
52 both zero-lag and a one-month lag (0.63 and 0.44, respectively). Together these results suggest  
53 that, rather than relying on a single data stream, a clearer picture of changes in infectious disease  
54 incidence might be achieved by combining the timeliness of sentinel surveillance with the  
55 representativeness of passive surveillance.

56 **Introduction**

57 Infectious disease surveillance in developing countries is often challenged by limited  
58 public health resources, insufficient laboratory capacity, and incomplete reporting [1]. In order to  
59 obtain high-quality data in the face of these and other challenges, the World Health Organization  
60 (WHO) has recommended sentinel surveillance for many infectious diseases [2,3]. In sentinel  
61 surveillance systems, resources are focused on collecting complete, timely data from a subset of  
62 healthcare facilities or laboratories [4], thus requiring fewer resources than would be needed to  
63 actively collect the same quality of data from all facilities (population-based active surveillance).  
64 Passive surveillance systems, in which data collection is dependent on reporting by healthcare  
65 facilities, are representative by virtue of being population-based, but are also subject to under-  
66 detection and underreporting [5]. The goal of this study is to evaluate the public health utility of  
67 sentinel surveillance compared to passive surveillance for measuring changes in an endemic  
68 infectious disease, using dengue as a case study.

69 While it is well-established that data from passive surveillance underestimate the  
70 incidence (in this study: the number of new symptomatic cases per 100,000 persons per month)  
71 of infectious diseases [5] including dengue [6], the nature of temporal variation in underdetection  
72 is less clear. Such variation could have significant public health implications if the meaning of  
73 surveillance-based incidence changes over time. Here we express variation using a monthly  
74 expansion factor (EF) (i.e., the ratio of incidence in cohort surveillance to incidence in sentinel or  
75 passive surveillance). This method has been used in previous dengue studies [7,8] to estimate  
76 annual disease burden, but there is no published evidence regarding the consistency of inter-  
77 annual EFs and thus how effectively they might be applied to estimating finer-scale changes  
78 in dengue incidence.

79           Although laboratory-based sentinel surveillance has been recommended for dengue [9],  
80 the WHO urges caution in over-interpreting these data [10] because sentinel surveillance may  
81 not adequately represent broader population trends in incidence. Assessing the added value of  
82 sentinel surveillance over passive surveillance for capturing a consistent proportion of cases and  
83 detecting seasonal increases in incidence would require that both be compared against data from  
84 a third ‘gold-standard’ system that provides an objective baseline measure of incidence [11].  
85 Thus we compared data from both systems to reference data gathered from community-based  
86 surveillance in a longitudinal cohort.

87           Dengue is an acute febrile illness (AFI) caused by any one of four serotypes of the  
88 dengue virus (DENV). It is the most prevalent mosquito-borne virus globally and is a growing  
89 health concern, with an estimated incidence of 96 million symptomatic infections per year [12].  
90 Here, dengue incidence measurement is considered in the context of Iquitos, Peru, where the  
91 disease most commonly presents as an undifferentiated, self-limiting AFI with an annual high  
92 transmission season. This scenario highlights two challenges that could potentially be addressed  
93 by sentinel surveillance data. First, because it is often clinically undifferentiated, surveillance  
94 data that include suspected cases will be influenced by physicians’ assumptions about  
95 transmission. These could potentially be improved with laboratory-confirmed sentinel  
96 surveillance, which would provide a more objective measure of the proportion of DENV cases  
97 among febrile individuals who seek treatment. Second, timely indication of increased incidence  
98 is of special concern in dengue because reactive mosquito-control activities are a common public  
99 health intervention. Rapid identification of changes in incidence based on sentinel surveillance  
100 data may result in a more effective response.

101 In Iquitos, there are three concurrent dengue surveillance systems: passive, sentinel, and  
102 door-to-door febrile surveillance in a longitudinal research cohort. Here we use cohort data as a  
103 reference to test the hypothesis that sentinel surveillance data are a more consistent – thus more  
104 ‘accurate’ – measure of incidence by month and also a more timely indicator of seasonal  
105 increases in incidence than passive surveillance data.

## 106 **Methods**

### 107 **Study area and study designs**

108 Iquitos is a geographically isolated city of ~440,000 inhabitants, located in the Amazon  
109 basin of northeastern Peru. DENV was re-introduced into the city in 1990 and was a reportable  
110 disease during our study. Beginning in 1990, each DENV serotype has been introduced and  
111 subsequently dominated transmission for multiple years before being replaced [13]. The current  
112 study includes data from three sources, detailed below: (1) ‘passive surveillance’ (confirmed and  
113 suspected cases reported by all healthcare facilities to the Dirección Regional de Salud Loreto  
114 (DRSL)), (2) sentinel surveillance (laboratory-confirmed cases from a city-wide AFI research  
115 network), and (3) door-to-door febrile surveillance in longitudinal cohorts (‘cohort  
116 surveillance’).

### 117 **Ethics statement**

118 The de-identified data used in this study were collected under four protocols  
119 (NMRC2000.0006, NMRC2010.2010, NMRC2005.009, NMRC2007.0007), all approved  
120 by the Institutional Review Boards (IRBs) of the Naval Medical Research Center and Naval  
121 Medical Research Unit No. 6 (NAMRU-6, formerly Naval Medical Research Center  
122 Detachment). The sentinel surveillance protocol (NMRC2010.2010) was also approved by the  
123 Ethics Committee for the Peruvian National Institute of Health (INS, acronym in Spanish). One

124 cohort protocol (NMRC2005.0009) was also approved by IRBs at the University of California,  
125 Davis (UC Davis), Universidad Peruana Cayetano Heredia University in Lima, Peru, and the  
126 second (NMRC2007.0007) received local approval from NAMRU-6 also registered as a  
127 Peruvian IRB, as well as the UC Davis IRB. All protocols were in compliance with regulations  
128 in the United States and Peru governing the protection of human subjects.

### 129 **Cohort surveillance**

130 Cohort surveillance data are from two spatially and temporally overlapping longitudinal  
131 cohorts. One cohort was restricted to two neighborhoods and the other cohort was distributed  
132 across the northern portion of the city. There were an average of 4,700 people under febrile  
133 surveillance during the study period. In both cohorts, phlebotomists visited participating houses  
134 three times per week to monitor all individuals  $\geq 5$  years of age for dengue-like illness. Inclusion  
135 criteria were occurrence of fever ( $\geq 38^{\circ}\text{C}$ ) for  $\leq$  five days, either by axial measurement or  
136 subject-reported in combination with the use of anti-pyretics, plus at least one other symptom  
137 consistent with DENV infection, including headache, rash, or retro-orbital pain. Positive cases  
138 were defined by DENV RNA detection by reverse transcription polymerase chain reaction (RT-  
139 PCR) or a  $\geq$  four-fold increase in DENV antibodies between acute and convalescent samples, as  
140 measured by IgM capture enzyme-linked immunosorbent assay (ELISA). RT-PCR and ELISA  
141 protocols were as previously described [14].

### 142 **Sentinel surveillance**

143 Sentinel febrile surveillance was carried out by NAMRU-6. Here we include dengue case  
144 counts from two public hospitals and eight public outpatient clinics located throughout Iquitos,  
145 together serving  $\sim 208,000$  residents ( $\sim 47\%$  of the population during the study period) (DRSL,  
146 unpub. data). A febrile case was defined as an individual  $\geq 5$  years old experiencing a fever of  $\geq$

147 38°C for a maximum of five days. These individuals were invited to participate, regardless of  
148 clinical diagnosis. An acute blood sample was collected at the time of enrollment and a  
149 convalescent sample was collected two to four weeks later, when possible. Criteria for positive  
150 cases were the same as for the cohorts, as described above, and infection detection protocols  
151 were as previously described [15].

## 152 **Passive surveillance**

153 Passive surveillance data are based on case counts reported to the DRSL. These include  
154 suspected and laboratory-confirmed dengue cases from the four districts that comprise the city of  
155 Iquitos, located in the Department of Loreto. Iquitos is estimated to account for ~64% of all  
156 dengue cases in the region [16]. The total number of reported cases was scaled accordingly. Case  
157 data were restricted to individuals  $\geq 5$  years of age, to correspond with the cohort and sentinel  
158 surveillance study protocols.

## 159 **Study period characteristics**

160 Two successive DENV introductions occurred during the study period of 1 July 2008 to  
161 30 June 2012. A virgin-soil invasion of dengue virus 4 (DENV-4) occurred in October 2008 [17]  
162 and a novel genotype of DENV-2 American/Asian lineage II (DENV-2) was introduced in  
163 November 2010 [18]. Both introductions resulted in replacement events, so that by the second  
164 year of circulation ('inter-epidemic' years), the introduced virus accounted for  $\geq 90\%$   
165 symptomatic DENV infections identified in both cohort and health-center based surveillance.

166 Based on ten years of data, high dengue incidence in Iquitos was observed between  
167 September and April; peak incidence occurred at various points in that interval. We used  
168 trimester transmission season designations: (1) low, May to August, (2) early high, September to  
169 December, and (3) late high, January to April [12]. While these designations do not reflect

170 observed incidence pattern for every year, they delineate periods of transmission as perceived by  
171 patients, physicians, and public health officials.

## 172 **Analyses**

173 All analyses were conducted by month (July to June, annually) to minimize the number  
174 of time periods with zero in the denominator of the incidence rate ratio (i.e., sentinel  
175 surveillance/cohort surveillance). Out of a possible 48 months, 43 were included in the analysis  
176 of passive surveillance data. Five months were excluded because no dengue cases were identified  
177 in the cohorts. Analysis using sentinel surveillance excluded two additional months: one because  
178 no cases were identified by sentinel surveillance and another when the participants were not  
179 enrolled for most of the month. Null months were distributed across transmission season  
180 categories, with three in the low season and two in each of the other seasons.

181 Cohort incidence was defined as dengue cases per 100,000 persons per month. The  
182 surveillance population included all persons residing in houses monitored three times per week  
183 by door-to-door febrile surveillance in the longitudinal cohorts. Sentinel surveillance incidence  
184 was defined as dengue cases per 100,000 persons per month in the combined catchment  
185 populations of participating hospitals and clinics. Catchment areas were estimated in 2008 by the  
186 DRSL (unpub. data). Passive surveillance incidence included both suspected and confirmed  
187 dengue cases per 100,000 persons per month in the total estimated 2008 population of Iquitos  
188 [19]. To match the restrictions in cohort case data, population estimates used to calculate  
189 incidence for sentinel and passive surveillance were restricted to persons  $\geq 5$  years of age. All  
190 individuals under surveillance by any of the three methods were assumed to contribute person-  
191 time to the incidence estimate



192 We calculated annual and monthly EFs for passive and sentinel surveillance to describe  
193 the range of healthcare based case detection, relative to cohort surveillance, within each year and  
194 between years. EFs were calculated as cohort incidence divided by either passive or sentinel  
195 incidence. Ratio of standard deviations was used to compare variation in data by year and  
196 season.

197 To compare the relative timing of passive versus sentinel surveillance systems for early  
198 identification of seasonal increases in dengue incidence, we performed a cross-correlation  
199 analysis of both systems with cohort surveillance for the full time series and by transmission  
200 season. This method quantifies the strength of the temporal association between the cohort  
201 surveillance incidence rate at month  $t$  and the passive or sentinel surveillance incidence rate at  
202 month  $t+h$  (where the sign of  $h$  indicates a temporal lag or lead).

203 Statistical analysis was performed using R version 3.1.1 [20]. Statistical significance was  
204 assessed at  $\alpha = 0.05$ .

## 205 Results

### 206 Incidence

207 In each of the four transmission years (July to June) studied, the highest annual and  
208 seasonal incidence occurred in cohort surveillance, followed by passive surveillance, and the  
209 lowest incidence occurred in sentinel surveillance (Figure 1, Table 1). An exception was the  
210 DENV-2 introduction (2010-11), when passive surveillance case numbers surpassed cohort  
211 surveillance in the late high season (January-April).

212 At least 80% of cases were identified between September and April in each surveillance  
213 system. Peak incidence generally occurred in the early high season (September-December) or  
214 early in the late high season (January-April) (Figure 1, Table 1).

215 **Time-varying incidence**

216 Annual EFs from 2008-2012 based on passive surveillance relative to cohort surveillance  
217 were consistently lower than those based on sentinel surveillance data: 1.9 vs. 6.8, 14.2 vs. 25.0,  
218 1.2 vs 14.2, 2.4 vs. 30.7 (Table 1). Both data series were highly variable by month, compared to  
219 annual figures (Figure 2, Table 1). The overall relationship of sentinel surveillance data to cohort  
220 data was more variable than that of passive surveillance data to cohort data, as measured by the  
221 relative standard deviation of monthly EFs (ratio of sentinel/passive EF standard deviations =  
222 2.2). This pattern was also observed by year (ratio of standard deviations = 1.1, 1.4, 2.2, 10.8)  
223 and season (ratio of standard deviations = 13.2, 2.6, 1.8 for low, early high, and late high  
224 seasons, respectively).

225 Passive surveillance overestimated dengue incidence in 26% (11/43) of months (indicated  
226 by EF values <1). Low (May-August), early high (September-December), and late high  
227 (January-April) seasons contained four, one and six of these overestimated months, respectively.  
228 Sentinel surveillance always underestimated incidence (i.e., EF >1).

229 Monthly increases in sentinel surveillance incidence were correlated with increases in  
230 cohort surveillance cases during the same month, across the time series (correlation coefficient =  
231 0.86), as well as early (0.87) and late (0.84) high transmission seasons (Figure 3). Increases in  
232 passive surveillance incidence were also associated with increases in cohort incidence overall  
233 and by transmission season. The full time series showed statistically significant associations both  
234 in the same month and with a one-month lag (0.63 and 0.44, respectively). The strongest  
235 association in the early high season was at a one-month lag (correlation=0.57). In the late high  
236 season, incidence was highly correlated without any lag (correlation=0.65). Both systems

237 showed mixed positive and negative correlations in the low season, none of which were  
238 significant.

## 239 **Discussion**

240  
241 Here we use four years of data from three concurrent dengue surveillance systems in  
242 Iquitos, Peru, to assess the relative performance of monthly data from sentinel surveillance and  
243 passive surveillance, based on the criteria of consistency and timeliness in relation to a referent  
244 cohort incidence time series. Sentinel surveillance data generally reflected seasonal increases in  
245 dengue incidence earlier than in passive surveillance – in the same month as the cohort, as  
246 opposed to a lag of up to two months – but were not a reliable indicator of the magnitude of the  
247 increase. Data from passive surveillance, on the other hand, were generally more consistent, in  
248 that they had a lower range of EF values, but overestimated incidence in 26% (11/43) of months,  
249 most often during the second half of the annual high transmission season.

250 An annual EF, calculated by comparing cohort incidence to population-based  
251 surveillance data, can be used to estimate total disease burden and set public health priorities.  
252 Here, we found that passive surveillance data were a closer estimate of annual disease burden as  
253 measured using cohort data. In three of the four years, passive surveillance data included  
254 approximately half of all cases expected based on the cohort incidence, resulting in an EF of ~2.  
255 During 2009-2010, the EF rose to ~1. This change may have been driven by a lower sense of  
256 reporting urgency because DENV-4 had circulated in the previous year and was perceived to  
257 cause only mild illness. We extended the analysis to consider monthly EFs, with the goal of  
258 understanding how consistently sentinel surveillance data captures finer-scale trends when the  
259 objective is to monitor intervention outcomes or understand temporal changes in transmission

260 patterns. Compared to passive surveillance, monthly data from the sentinel study had an overall  
261 wider range of EF values (ratio of sentinel/passive standard deviations = 2.2).

262         The temporal relationship between increased case counts in surveillance data and what  
263 actually happens in the population is of primary interest when the surveillance objective is to  
264 detect and rapidly respond to potential outbreaks. For infectious diseases with a seasonal pattern,  
265 such as influenza and dengue, the period of greatest interest is early in the annual high season.  
266 We found that sentinel surveillance data show a strong positive correlation to cohort data (i.e.,  
267 both have rising case counts) within the same month during the trimester when increased  
268 incidence might first be expected. Conversely, the strongest correlation for passive surveillance  
269 was observed at a one-month lag, although there were similar correlations at zero and two  
270 months. Our finding that > 50% (6/11) of the months in which incidence was overestimated by  
271 passive surveillance data occurred later in the ‘expected’ high season suggests that this temporal  
272 variation in identifying increased incidence may be due to seasonal differences in case reporting  
273 and/or physicians’ index of suspicion, so that detection rates are a product of both expectation of  
274 dengue and actual incidence.

275         The advantage of early indication of potential outbreaks provided by sentinel surveillance  
276 data is tempered by their inconsistent proportional relationship to incidence in the community. In  
277 the early high season, the monthly EF for sentinel surveillance data varied much more than for  
278 passive surveillance data (ratio of sentinel/passive standard deviations = 2.6). Identifying  
279 increased incidence, when that might typically be expected, is necessary but likely not sufficient  
280 for triggering a costly vector control response in most dengue-endemic areas, depending on  
281 public health resources a public health department for responding to what may be a false alarm.

282           Observational study data only approximate ‘true’ surveillance or population incidence  
283 data. While this analysis is the first comparison of sentinel surveillance data with cohort data for  
284 dengue, the sentinel surveillance data considered here are based on hospital and clinic patients  
285 agreeing to participate in the study, rather than the total number of those seeking medical  
286 treatment. However, this sampling effect may be offset by complete data reporting in the context  
287 of a scientific study. These sentinel data might also introduce an age-related bias by consistently  
288 capturing a lower proportion of pediatric patients, based on observations by our study  
289 phlebotomists that children are generally less willing than adults to consent to a venous blood  
290 draw (unpub. data).

291           Another limitation is that cohort surveillance may not be measuring the same population  
292 as was sampled by the other two surveillance systems. Passive and sentinel surveillance data in  
293 Iquitos are drawn from healthcare facilities throughout the city, whereas one of the cohorts was  
294 distributed across the northern portion of the city and the other focused in two neighborhoods.  
295 However, strong temporal correlation between increased incidence in the cohort and in sentinel  
296 surveillance suggests that, at least early in the high transmission season, these data are not being  
297 significantly biased by the spatial heterogeneity of DENV transmission that has been observed in  
298 Iquitos [21].

299           Passive surveillance data are generally a more consistent measure of dengue incidence in  
300 the community, compared to sentinel surveillance, while sentinel surveillance data provide a  
301 more timely indicator of potential seasonal outbreaks, in the context of Iquitos. In other places  
302 where data from both types of surveillance systems are available, these findings can guide  
303 decisions about which data to use for specific public health objectives. For example, sentinel  
304 surveillance data may be useful in the context of an early outbreak warning system, but do not

305 appear to be reliable for monitoring long-term pathogen transmission trends, due to their overall  
306 inconsistent relationship with population-based incidence. On the other hand, passive  
307 surveillance data more accurately measure overall incidence trends, yet often overestimate  
308 monthly incidence late in the transmission season when they include suspected cases, suggesting  
309 that physician suspicion and reporting are driving surveillance measures. An integrated  
310 surveillance system could trigger low-resource public health actions based on sentinel  
311 surveillance, such as alerting all healthcare facilities specifically to encourage timely reporting  
312 and increase healthcare awareness. This could reduce delays in passive surveillance data, while  
313 retaining their population-level representativeness. To improve the understanding, and thus the  
314 application, of surveillance data there is a need for objective measures of how human behavioral  
315 factors such as physician suspicion, case reporting, and treatment seeking influence  
316 measurements of incidence. Results of this study highlight the need to explicitly consider the  
317 implications of inconsistent detection when using infectious disease incidence data for outbreak  
318 detection and trend monitoring.

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437 **Table 1:** Incidence per 100,000 persons per time period, and associated expansion factors (EFs).  
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	<b>Cohort surveillance</b>	<b>Sentinel surveillance</b>	<b>Passive surveillance</b>
<b>2008-09</b>			
Annual total	2324.6	339.9	1220.4
Low season total	90.5	27.6	82.1
Early high season total	1725.3	204.6	691.3
Late high season total	508.8	107.7	447.1
Monthly range <sup>b</sup>	16.6 – 1128.1	5.3 – 106.9	4.6 – 233.3
Peak incidence month	October	October	December
Annual EF	NA	6.8	1.9
Monthly EF range	NA	2.1 – 10.6	0.14 – 7.2
<b>2009-10</b>			
Annual total	3341.4	133.5	236.08
Low season total	363.5	25.0	72.7
Early high season total	1020.5	19.2	97.5
Late high season total	1957.4	89.3	65.9
Monthly range <sup>a</sup>	18.2 – 788.0	1.4 – 29.8	11.2 – 33.2
Peak incidence month	March	February	November
Annual EF	NA	25.0	14.2
Monthly EF range	NA	4.2 – 75.9	0.60 – 55.2
<b>2010-11</b>			
Annual total	3461.8	244.0	2810.0
Low season total	400.4	13.9	81.5
Early high season total	836.0	51.9	76.5
Late high season total	2225.4	177.7	2651.9
Monthly range <sup>b</sup>	19.2 – 1554.0	1.4 – 128.7	4.6 – 1272.8
Peak incidence month	January	January	January
Annual EF	NA	14.2	1.2
Monthly EF range	NA	2.5 – 93.6	0.20 – 31.4
<b>2011-12</b>			
Annual total	1015.8	33.1	427.3
Low season total	128.0	6.2	141.0

Early high season total	135.3	12.0	38.6
Late high season total	752.5	14.9	247.7
Monthly range <sup>b</sup>	19.3 – 501.7	1.4 – 4.3	8.8 – 120.7
Peak incidence month	January	December-March <sup>b</sup>	April
Annual EF	<b>NA</b>	30.7	2.4
Monthly EF range	<b>NA</b>	13.4 – 116.1	0.4 – 11.3

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440 <sup>a</sup> Does not include months in which no cases were detected

441 <sup>b</sup> Equal incidence across four months

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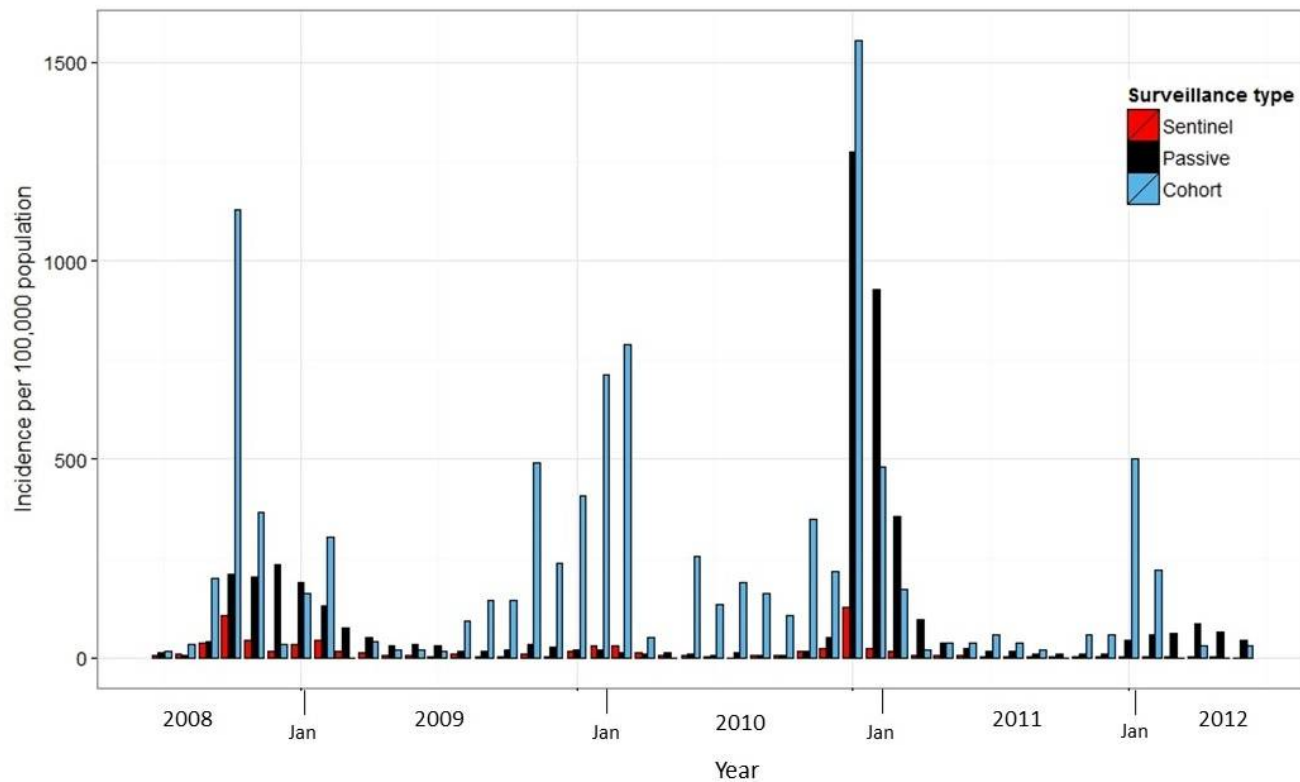
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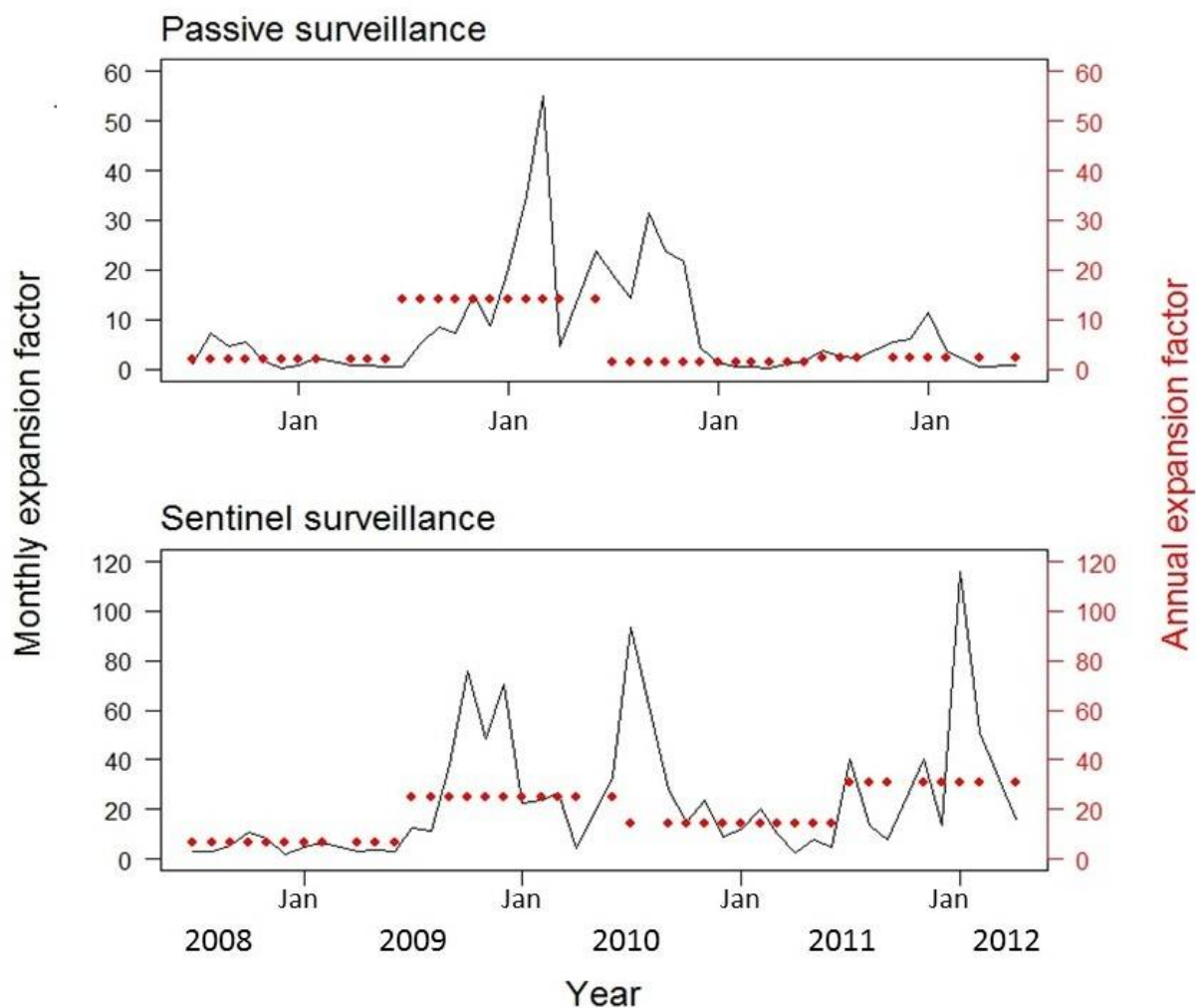
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452 **Figure 1:** Incidence measured as per 100,000 population per month by sentinel, passive, and  
453 cohort surveillance. Bars are grouped by month to represent incidence as measured by each of  
454 the three surveillance systems.



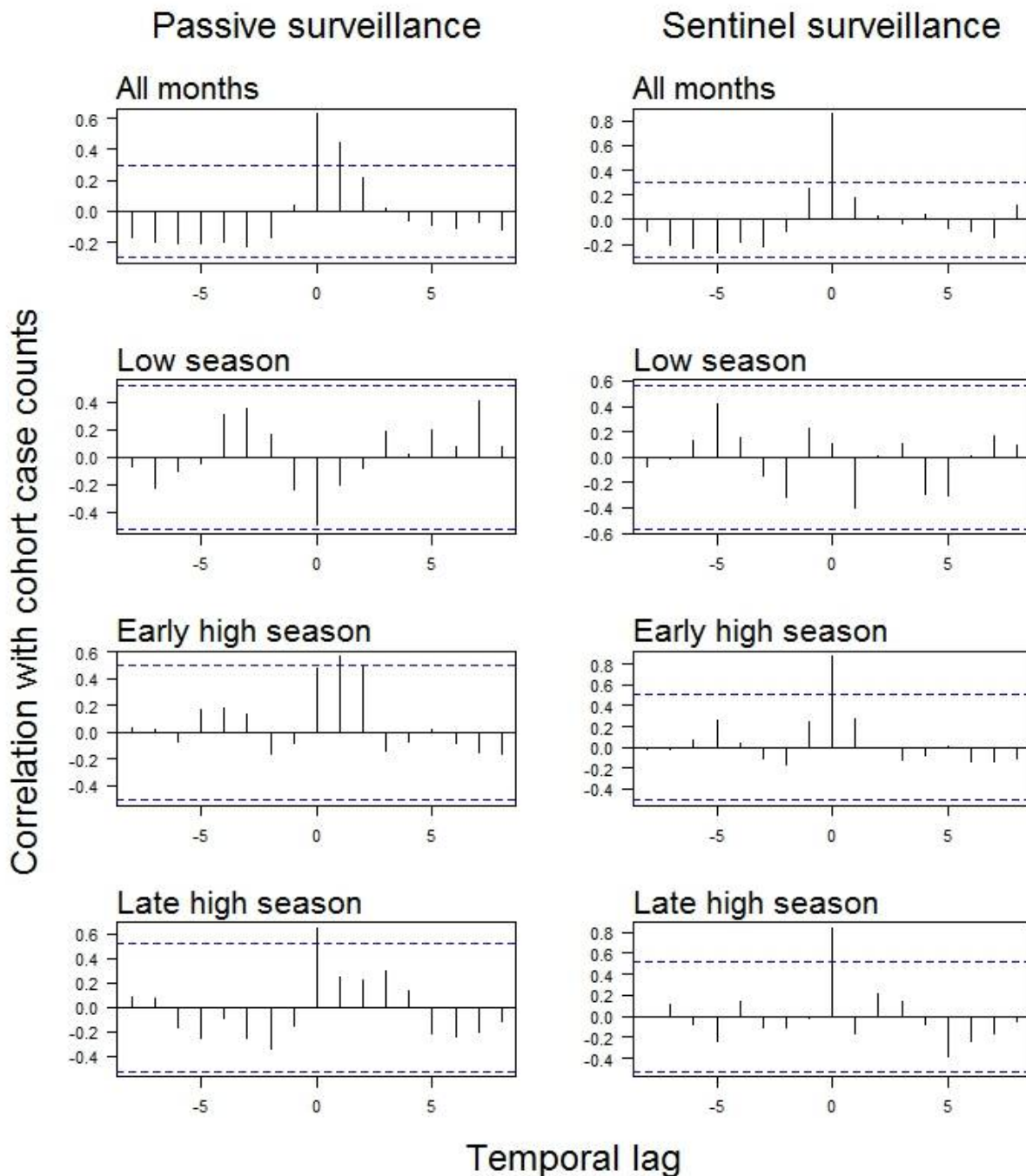
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456 **Figure 2:** Monthly and annual expansion factors calculated as the ratio of cohort to passive (top  
457 panel) and sentinel (bottom panel) incidence (monthly or annual cases per 100,000 population).  
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465 **Figure 3:** Temporal correlation of case detection for passive surveillance and sentinel  
466 surveillance relative to cohort surveillance. Positive numbers on the x-axis indicate a delayed  
467 increase in cases. Positive numbers on the y-axis indicate a positive relationship (i.e., sentinel or  
468 passive surveillance case numbers increase as active surveillance case numbers increase).  
469 Horizontal dotted lines represent statistical significance at  $\alpha = 0.05$