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1 **A framework to monitor changes in transmission and epidemiology of emerging pathogens:**

2 **Lessons from Nipah virus**

3 **Running title: Monitoring Nipah virus epidemiology**

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22

23 **Abstract**

24 It is of uttermost importance that the global health community develops the surveillance capability
25 to effectively monitor emerging zoonotic pathogens that constitute a major and evolving threat for
26 human health. Here, we propose a comprehensive framework to measure changes in (i) spillover risk,
27 (ii) interhuman transmission, and (iii) morbidity/mortality associated with infections based on six
28 epidemiological key indicators derived from routine surveillance. We demonstrate the indicators'
29 value for the retrospective or real-time assessment of changes in transmission and epidemiological
30 characteristics using data collected through a long-standing, systematic, hospital-based surveillance
31 system for Nipah virus in Bangladesh. We show that while interhuman transmission and
32 morbidity/mortality indicators were stable, the number and geographic extent of spillovers varied
33 significantly over time. Such combination of systematic surveillance and active tracking of
34 transmission and epidemiological indicators should be applied to other high risk emerging pathogens
35 to prevent public health emergencies.

36 **Key words:** Nipah virus, Emerging pathogens, Surveillance, Monitoring

37

38

39 **Introduction**

40 Emerging zoonotic pathogens represent an important and growing risk to humans. As cross-species
41 interactions increase at the human-animal interface, more opportunities arise for pathogens to
42 spillover. Large-scale epidemics of human immunodeficiency virus (HIV), Ebola, or Middle East
43 respiratory syndrome coronavirus (MERS-CoV) can trace their roots back to spillovers from a
44 zoonotic reservoir [1]. The timely deployment of targeted interventions to prevent public health
45 emergencies would clearly benefit from the real-time evaluation of temporal trends suggestive of
46 altered spillover risk or evolutionary changes linked to increased transmission or disease. Given that
47 many emerging pathogens spillover infrequently, changes in pathogen characteristics may go
48 undetected unless there exist systematic efforts to track these changes. Enhanced monitoring
49 approaches that go beyond tracking case numbers to identify changes in disease risk and underlying
50 mechanisms would therefore help improve global preparedness and response capacities. The
51 International Health Regulations and Global Health Security Agenda both call for stronger
52 surveillance and trend monitoring [2,3]. It has however rarely been possible to develop a
53 comprehensive monitoring framework for emerging zoonotic pathogens due to the lack of stable
54 surveillance collecting detailed case information.

55 Nipah virus (NiV) is an emerging zoonotic pathogen found in fruit bats throughout South and
56 Southeast Asia. NiV is considered by the World Health Organization as an important health threat to
57 humans due to the severity of disease, the absence of treatments or vaccines, and its ability to be
58 transmitted between people [4,5]. Bangladesh is the only country reporting regular spillovers of NiV,
59 which are nearly exclusively detected through a systematic, hospital-based surveillance system,
60 implemented in 2007 following the ad-hoc identification of ~100 cases during 2001-2006 [6]. The
61 surveillance system is based on three sentinel hospitals where all meningoencephalitis cases are
62 routinely tested for NiV. Identification of a NiV case triggers detailed investigations in affected
63 communities including the identification of transmission networks and the tracing of contacts. The

64 hospital-based surveillance system leverages clinical services and is therefore less expensive and
65 easier to maintain than other population-based surveillance systems.

66 Here we propose six epidemiological indicators of emerging zoonotic pathogens and their
67 transmission that can be derived from such routine surveillance data to measure changes in (i)
68 spillover risk, (ii) interhuman transmission, and (iii) morbidity/mortality associated with infections
69 (Figure 1A). Although many of these measures are commonly used in epidemiological studies, their
70 role in the routine monitoring of emerging infectious diseases is not yet defined. The NiV surveillance
71 system in Bangladesh provides a unique opportunity to collect comparable data on cases and their
72 characteristics over time. The objective of this study was to demonstrate how these indicators can be
73 obtained from routine surveillance data and used to monitor changes in disease transmission and
74 epidemiology to inform future public health policy and practice.

75 **Methods**

76 *Establishing baseline measures and assessing historical changes*

77 We used data from the systematic NiV surveillance system collected during 2007-2018 to establish
78 baseline measures of the six indicators and assess historical changes over time. Details of the
79 surveillance methods have been previously published [7,8], but in short, at three tertiary care
80 hospitals, all patients admitted with signs and symptoms consistent with febrile neurological illness
81 during December – March had clinical and epidemiological information and serum collected for
82 testing for IgM antibodies against NiV. We further assessed all six indicators using data collected
83 during 2001-2006, a time period before routine hospital-based surveillance was implemented and
84 cases were not systematically detected (see Supplementary Material). During this time period, cases
85 were detected through community investigations following the notification of case clusters and NiV
86 cases not associated with case clusters were likely to be missed.

87 *1. Spillover risk*

88 In Bangladesh, humans usually acquire NiV through drinking date palm sap contaminated with the
89 virus by fruit bats [4]. It is important to monitor spillover frequency since any increase may result in
90 higher disease burden, or may indicate emergence of new transmission pathways. In addition, each
91 spillover event represents an opportunity for more transmissible or virulent strains to emerge. A
92 spillover event is defined as a single case infected from the reservoir or a cluster of cases that can be
93 traced back to a single spillover source (i.e., one or several individuals infected through a
94 contaminated palm sap pot plus subsequent cases infected by interhuman transmission) and the
95 annual spillover rate as the number of spillover events in a given transmission season (December of
96 the previous year until May of the given year). We assumed that spillover events follow a Poisson
97 distribution and estimated the spillover rate observed in a given year with Poisson exact 95%
98 confidence intervals (95%CI) and the average annual spillover rate during a given time period (i.e. for
99 the duration of stable surveillance or time periods between change points) with approximate Poisson
100 95%CIs. We tested the statistical significance of changes in spillover frequency pre and post a specific
101 time point using exact Poisson test, where we moved the time point by one-year increments over the
102 duration of stable surveillance. If several time points resulted in significant differences, we selected
103 the time point resulting in the lowest p-value. We further assessed linear changes in annual spillover
104 rates using Poisson regression; we evaluated statistical significance of linear changes using a
105 likelihood ratio test and compare this model to step-change models using the Akaike Information
106 Criterion (AIC).

107 2. *Geographic extent*

108 The geographic extent of case occurrence informs the size and location of the population at risk.
109 Moreover, pathogen introductions into new ecological areas or populations (e.g. higher population
110 density, mobility) can affect transmission dynamics and potentially boost the spread and impact of
111 the pathogen [9]. Using surveillance data on geographic location of cases we can monitor the
112 geographic extent of NiV risk. The geographic extent of case reports is defined as the number of

113 districts from which cases are reported, we quantified the geographic extent using 3-year sliding
114 windows over the duration of the surveillance dataset and assessed spatial patterns based on
115 administrative boundaries obtained from the Database of Global Administrative Areas
116 (www.gadm.org).

117 3. *Cluster size*

118 The NiV surveillance data can also be used to monitor indicators for changes in spillover mechanisms.
119 The number of individuals who are infected from the reservoir during each spillover event, may vary
120 depending on the spillover source. For example, clusters associated with drinking palm sap may
121 differ in size from clusters associated with pig exposure, which was the main spillover route in the
122 Malaysian NiV outbreak [10]. Cluster sizes are also affected by interhuman transmission through the
123 number of secondary cases associated with a spillover event (see section below). We defined a
124 cluster of cases as individuals who acquired infection through a single spillover event (either through
125 one or more bat-to-human transmission events in one time and place or through subsequent
126 interhuman transmission). We estimated the median and interquartile range (IQR) of cluster sizes for
127 a given year, or a given time period. We used Wilcoxon rank sum test to assess changes in outbreak
128 sizes by comparing cluster size distributions pre and post a specific time point that we moved along
129 the time of stable surveillance.

130 4. *Reproduction number*

131 The reproduction number R (i.e., the average number of individuals infected by a case) is the
132 standard measure of the interhuman transmission potential of a pathogen [11]. While sustained
133 transmission of a pathogen in a population can occur only if $R \geq 1$, even increases in R to values < 1 can
134 lead to larger cluster sizes with transmission ceasing only after a substantial number of transmission
135 generations. Tracking this parameter can therefore provide an early warning sign of a change in
136 transmission [12–14]. For NiV in Bangladesh, this essential parameter can be directly estimated from
137 the transmission trees that are reconstructed during outbreak investigations. We estimated R and

138 95% CIs based on the observed number of secondary cases caused by a case, assuming that the
139 number of secondary cases follows a negative binomial distribution with mean R and a dispersion
140 parameter k [14]. We used a likelihood ratio test to assess changes in R pre and post a specific time
141 point that we moved along the duration of stable surveillance. We further assessed linear changes in
142 R by year using negative binomial regression.

143 *5. Proportion of cases who transmit infection*

144 Interhuman transmission of emerging zoonotic pathogens is often highly heterogeneous, meaning
145 that a large part of secondary cases originates from only a few superspreading events as previously
146 noted for NiV [8,15]. The mechanisms leading to superspreading events can be of social (e.g., a
147 higher number of contacts resulting in more transmission opportunities) or biological nature (e.g.,
148 higher levels of virus shedding or stronger symptoms facilitating transmission) [14]. The extent of
149 transmission heterogeneity has important implications for the optimisation of control strategies [14].
150 Where detailed information on transmission trees is available, we can quantify transmission
151 heterogeneity as the percentage of cases who transmit the pathogen [14]. For a given reproduction
152 number, a smaller percentage of cases who transmit will indicate a stronger transmission
153 heterogeneity [14]. We estimated the proportion of spreaders among NiV cases and exact binomial
154 95% CIs for a given year, or a given time period. We used an exact binomial test to assess changes in
155 the proportion of spreaders pre and post a specific time point that we moved along the time of
156 stable surveillance. We further assessed linear changes in proportion spreaders by year using logistic
157 regression. We also assessed the probability of observing multiple superspreading events (i.e. a NiV
158 case infecting ≥ 5 individuals) during outbreaks of various sizes (Supplementary material).

159 *6. Morbidity and mortality*

160 Changes in the case fatality ratio (CFR) and the prevalence of specific symptoms such as difficulty
161 breathing (a symptom previously found associated with interhuman transmission[6]), can indicate an
162 adaptation of a pathogen to the human host. We estimated the case fatality ratio (i.e. the proportion

163 of cases who died among cases) and exact binomial 95% CIs for a given year, or a given time period,
164 separately for cases infected by the reservoir (primary cases) and cases infected through interhuman
165 transmission (secondary cases). We used an exact binomial test to assess changes in the case fatality
166 rate pre and post a specific time point that we moved along the time of stable surveillance. We
167 further assessed linear changes in the case fatality rate by year using logistic regression. We applied
168 the same methods to assess changes in the proportion of cases with difficulty breathing.

169 *Real-time monitoring of indicators*

170 Changes in the transmission and epidemiology of NiV can also be assessed in real-time using the
171 proposed framework by plotting new observations against baseline distributions of indicators
172 established above. To facilitate identification of epidemiologic changes prospectively within this
173 system, we identified thresholds for “highly unlikely” events by quantifying the 2.5th and 97.5th
174 percentiles of these baseline distributions.

175 **Results**

176 *Monitoring spillover risk*

177 During 2007-2018, 76 NiV spillover events were detected in Bangladesh resulting in 166 NiV cases
178 (Figure 1B). We observed that the average annual number of spillovers detected in Bangladesh
179 varied significantly over time; it increased from 2.2 (95%CI 1.3-3.7) in 2007-2009 to 10.5 (95%CI 8.2-
180 13.4) in 2010-2015, and returned to the lower level in 2016-2018 (Figure 2A).

181 Coinciding with the temporary increase in spillover frequency, we found that the number of districts
182 reporting cases was more than two times greater in 2011-2015 compared to the other time windows
183 (Figure 2B). This increase however does not seem to reflect a gradual spread of NiV into previously
184 unaffected areas; instead there were more regular spillovers in geographic regions where NiV had
185 previously been observed (Figure S1). Two NiV cases who acquired infections in rural areas were
186 reported in Dhaka, the capital city of Bangladesh.

187 We observed a constant median cluster size of 1 case (Interquartile range [IQR] 1-2) over time (Figure
188 2C). The median cluster size was higher in 2008 (with two clusters of 6 and 4 spillover cases,
189 respectively) than in other years.

190 *Monitoring interhuman transmission*

191 Transmission potential of NiV did not vary significantly in Bangladesh during 2007-2018, with an
192 average reproduction number of 0.20 (95%CI 0.10-0.40) (Figure 2D). No interhuman transmission
193 events were observed in 2008-2009 and 2015-2018, which is consistent with the estimated average
194 reproduction number and may be explained by a smaller number of NiV cases during these years
195 (Figure S2).

196 Eight percent (95%CI 5-14) of cases transmitted NiV to another person, which was stable over time
197 (Figure 2E). During 2007-2018, two outbreaks were driven by a superspreading event. The
198 occurrence of more than one superspreading event in a single outbreak has never been observed
199 and is unlikely given the current reproduction number (Figure S3).

200 *Monitoring morbidity/mortality associated with infections*

201 We observed a stable CFR over time among cases infected by the reservoir (86%, 95%CI 79-92)
202 (Figure 2F) and those infected through interhuman transmission (46%, 95%CI 29-63) (Figure S4A).
203 The percentage of NiV cases who developed breathing difficulties also remained constant over time
204 with an average of 57% (95%CI 49-64) (Figure S4B). No significant difference in the proportion with
205 breathing difficulties were detected between cases infected by the reservoir and those infected
206 through interhuman transmission (chi-squared p-value= 0.37). The CFR was higher among cases with
207 breathing difficulty (90%) than those without (61%, chi-squared p-value <0.001).

208 Based on data collected during 2001-2006, a period before routine hospital-based surveillance was
209 implemented and cases were not systematically detected, we observed a much higher variability in

210 some of these indicators (in particular for spillover frequency, outbreak size, and reproduction
211 number) (Figure S5).

212 *Real-time monitoring of indicators*

213 The baseline measures for these six indicators that we established here can be used by public health
214 officials to detect future changes in NiV characteristics (Figure S6). Such changes can be evaluated in
215 real-time by comparing expected values (e.g., percentiles of estimated distributions) to new
216 observations, either for a single outbreak or for a transmission season. For example, based on
217 current estimates of spillover frequency, observing more than 17 spillovers in a season is very
218 unlikely (based on the 97.5th percentile of the high spillover frequency period), while half of the
219 time, more than 10 spillovers are expected to occur (Figure S6A).

220 **Discussion**

221 Systematic NiV surveillance in Bangladesh has been an important step forward in the response to the
222 emerging threat of NiV. These routinely collected data enable the establishment of baseline
223 measures that comprehensively describe current NiV spillover risk, interhuman transmission and
224 morbidity/mortality, which can now be used by public health authorities to guide rapid and reliable
225 decisions to respond to NiV outbreaks. Using these baseline measures in real-time assessments
226 allows the detection of deviations from these at early stages of a transmission season or an ongoing
227 outbreak.

228 While interhuman transmission and morbidity/mortality of NiV has been stable since the start of
229 systematic surveillance, frequency and geographic extent of spillovers temporarily increased during
230 that time period before returning to initial levels. The temporary increase may reflect NiV
231 transmission and shedding dynamics in bat populations [16], changes in bat behaviour (e.g., moving
232 to new areas to look for food), or changes in human behaviour (e.g., sap drinking, access to
233 hospitals). A study of weather associations with spillovers between 2007 – 2013 identified a
234 significant correlation between increasing spillovers and colder winter temperatures, suggesting that

235 climatic factors could be driving some of these patterns over longer time scales [17]. The monitoring
236 framework has thereby provided insights that can form the basis of studies to test different
237 hypotheses of what drives these patterns, and measure changes in patterns that could result from
238 primary or secondary prevention programs. Continuing surveillance efforts to monitor time trends or
239 cyclical dynamics in this disease system are critical and should be prioritized for funding.

240 Observed cluster sizes were stable over time, suggesting that no changes in spillover mechanisms
241 had occurred during the time period of surveillance. This finding is consistent with other
242 epidemiological evidence that identified palm sap as main spillover route over time, including during
243 spillovers in 2008 that were larger in size [18,19]. No increase in the interhuman transmission
244 potential has been suggested by any of the indicators and the reproduction number currently is
245 lower than what is required for a large outbreak. Based on the established baseline measures, the
246 occurrence of multiple superspreading events during a single outbreak is highly unlikely and may
247 therefore represent an early warning sign for the emergence of a more transmissible strain. For
248 monitoring situations where details on transmission networks are unavailable, R could also be
249 derived from the distribution of cluster sizes or the proportion of cases infected by the reservoir
250 [13,20]. The detection of two NiV cases in Dhaka, the capital of Bangladesh, demonstrates the risk of
251 virus introductions into densely populated areas where large-scale outbreaks may be more likely to
252 occur. The observed heterogeneity in some indicators during 2001-2006, a time period before
253 hospital-based surveillance started in Bangladesh, highlights that systematic surveillance for NiV, as
254 introduced in Bangladesh in 2007, is key for establishing reliable baseline estimates of transmission
255 characteristics and will remain crucial for the detection of departures from these trends in the future.
256 Based on established estimates of R it would however be highly unlikely to observe superspreading
257 events as reported before 2007 (with 11 and 22 secondary cases generated by a NiV case) (Figure
258 S6C).

259 The analysis of the collected epidemiological data also provided other insights that can be
260 investigated in future studies, such as the difference in the CFR between cases infected through the
261 reservoir and those infected through interhuman transmission. This difference may be due to a
262 higher dose of virus received through date palm sap than through contact with a patient. Developing
263 capacities to efficiently detect and respond to unusual public health events is key for improved global
264 epidemic preparedness [2,3]. The World Health Organization in 2015 therefore advocated for
265 prioritizing a number of emerging zoonotic diseases for urgent research and development that would
266 allow for improved disease control. In addition to NiV, these diseases included Crimean Congo
267 haemorrhagic fever, Ebola, Marburg, Lassa fever, Middle East respiratory syndrome and other
268 coronaviruses, and Rift Valley fever [5]. We believe that systematic surveillance for these diseases, as
269 exemplified by NiV surveillance in Bangladesh, should be implemented to enable the collection of
270 comparable and reliable data over time. The framework proposed here would also allow tracking
271 outbreaks of these diseases and targeting disease control measures. The global community would be
272 much better prepared for these threats through investments in systematic surveillance coupled with
273 active tracking and reporting of transmission and epidemiological indicators.

274

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285

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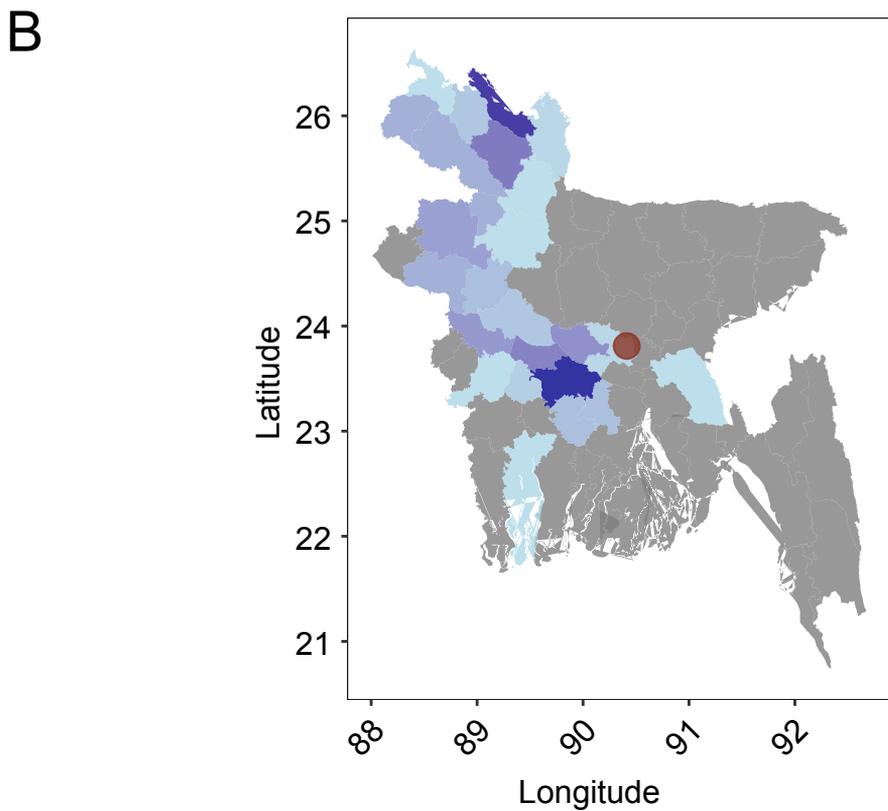
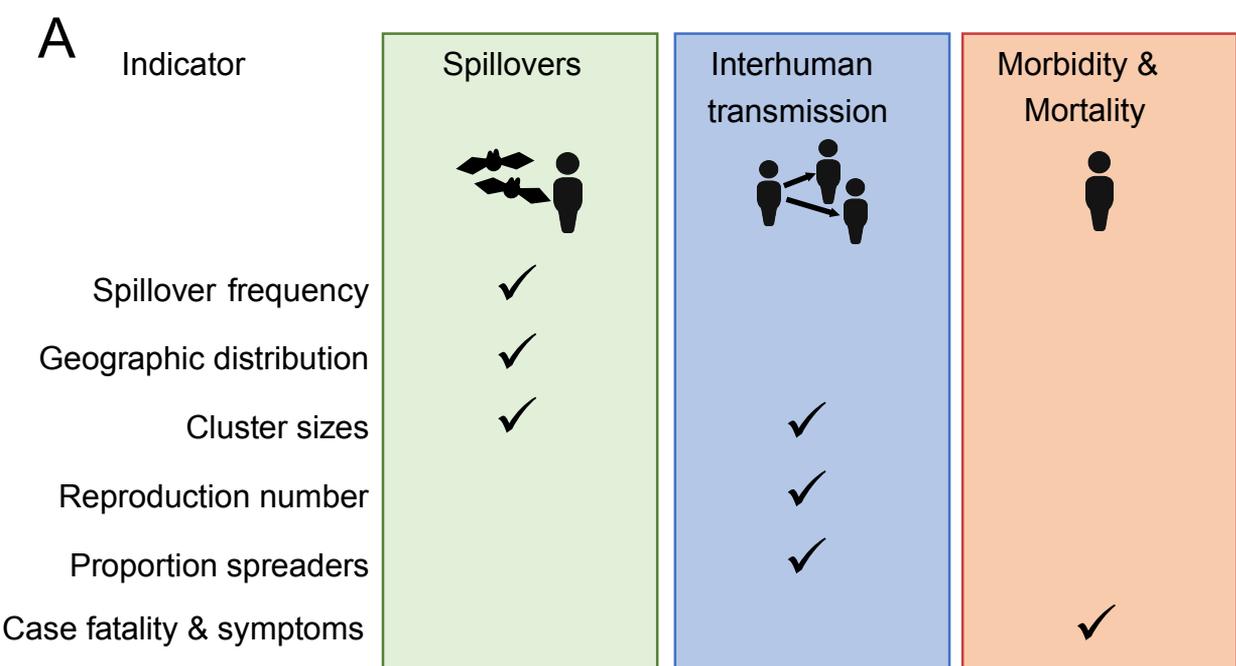
333 **Figure legends**

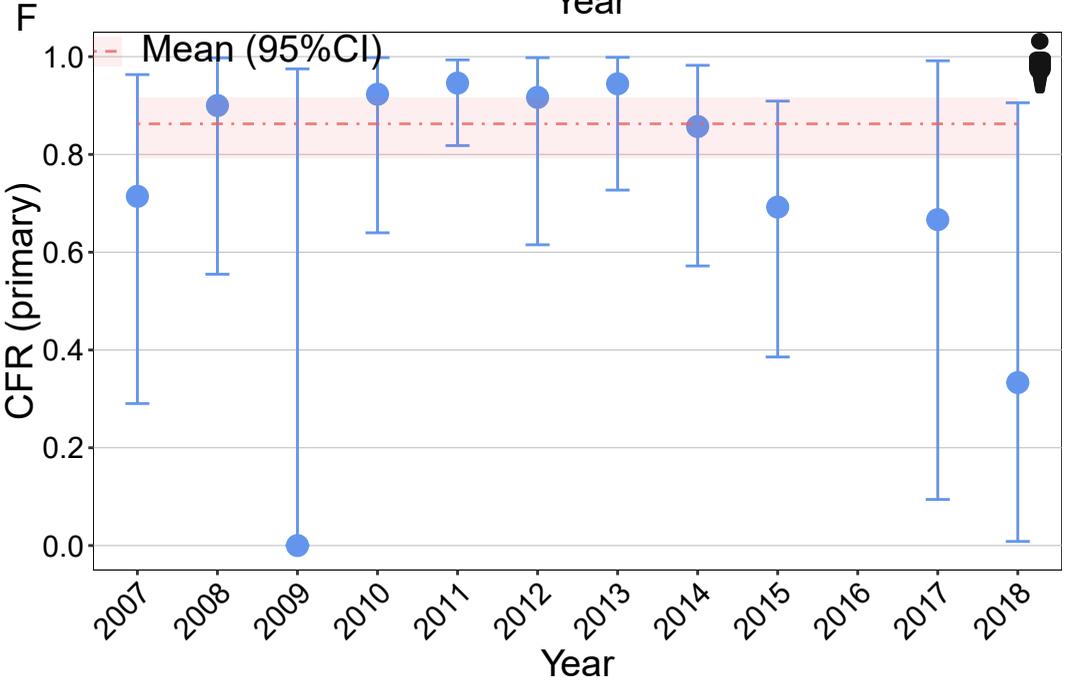
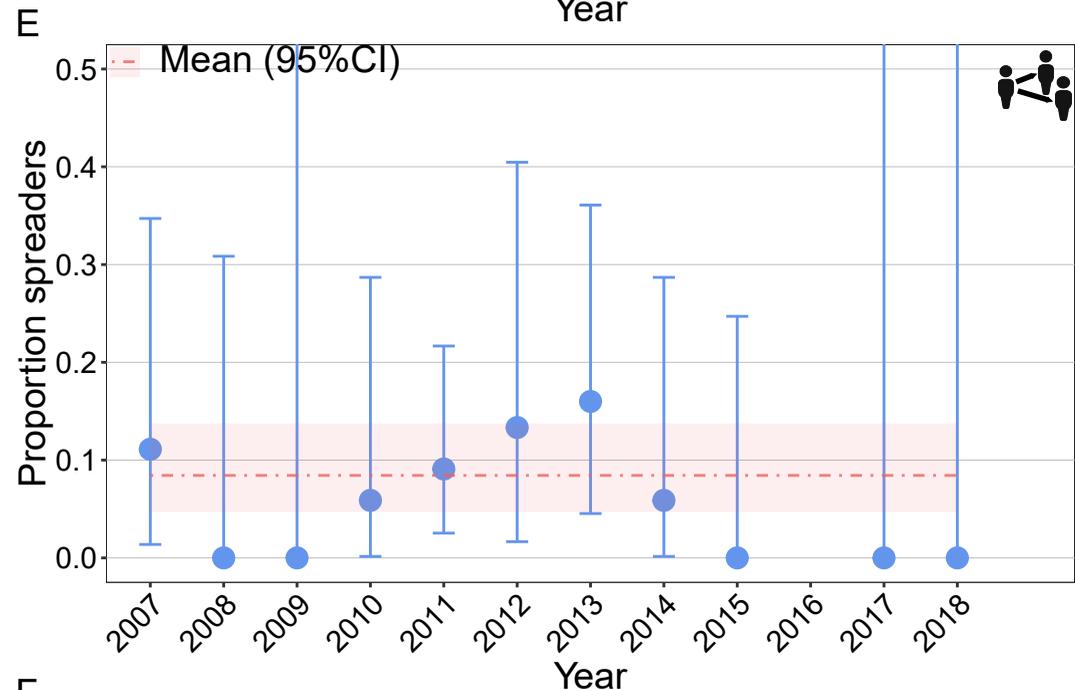
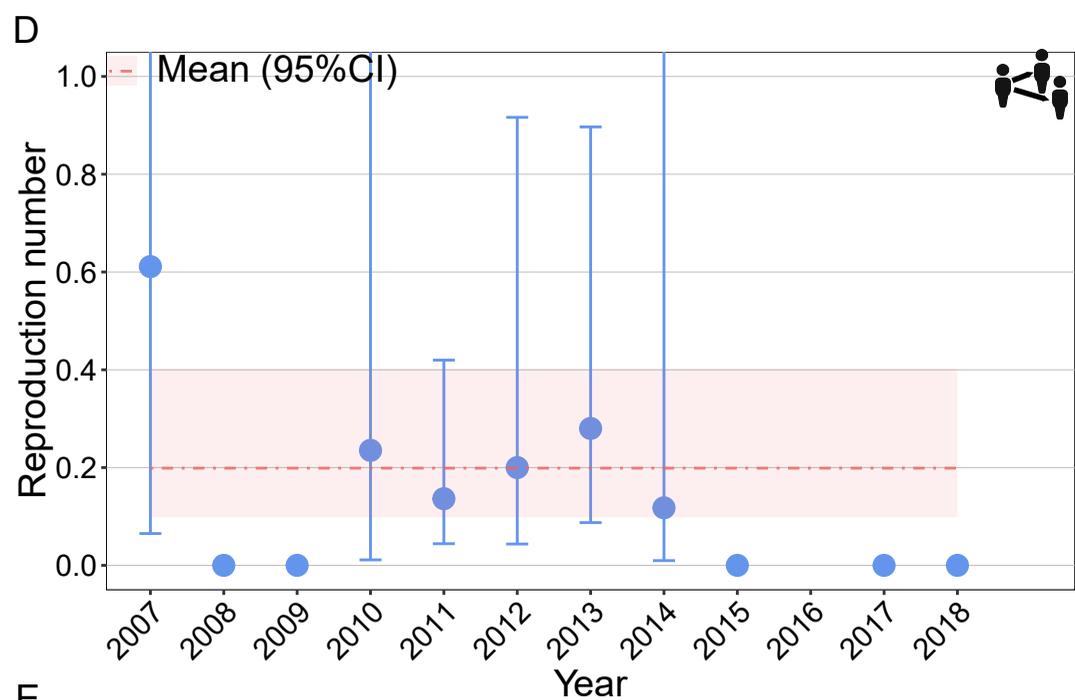
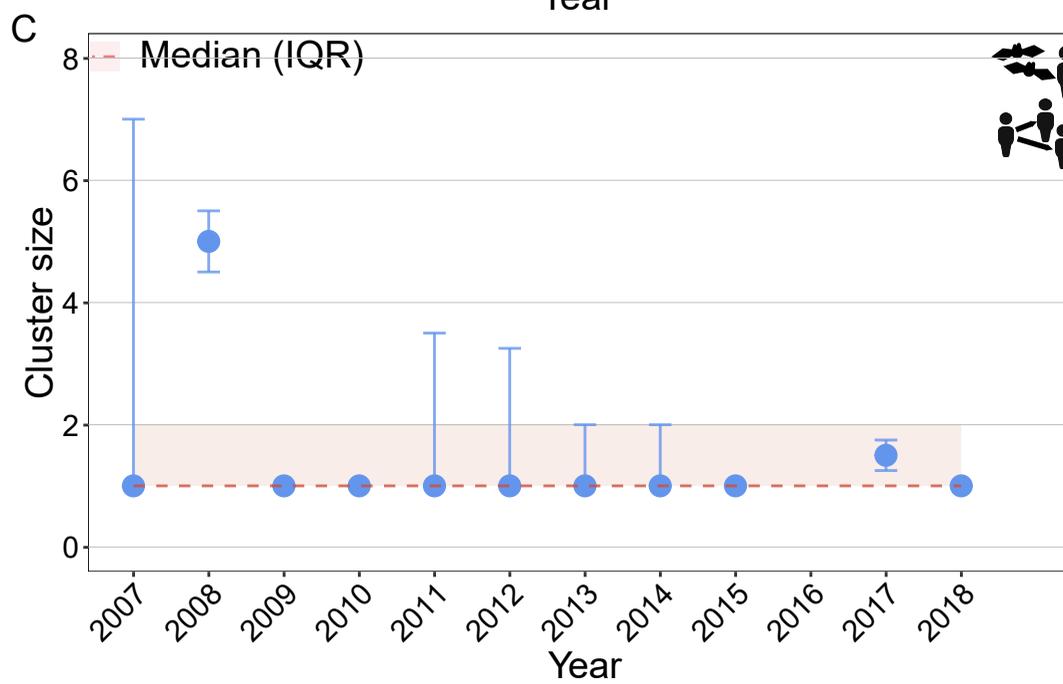
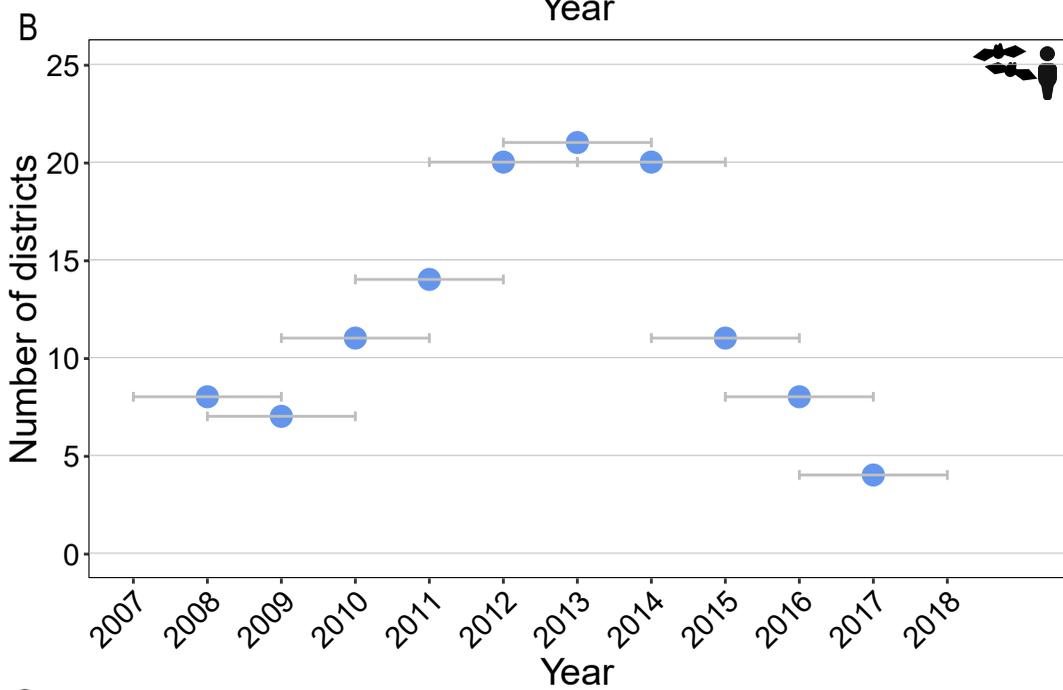
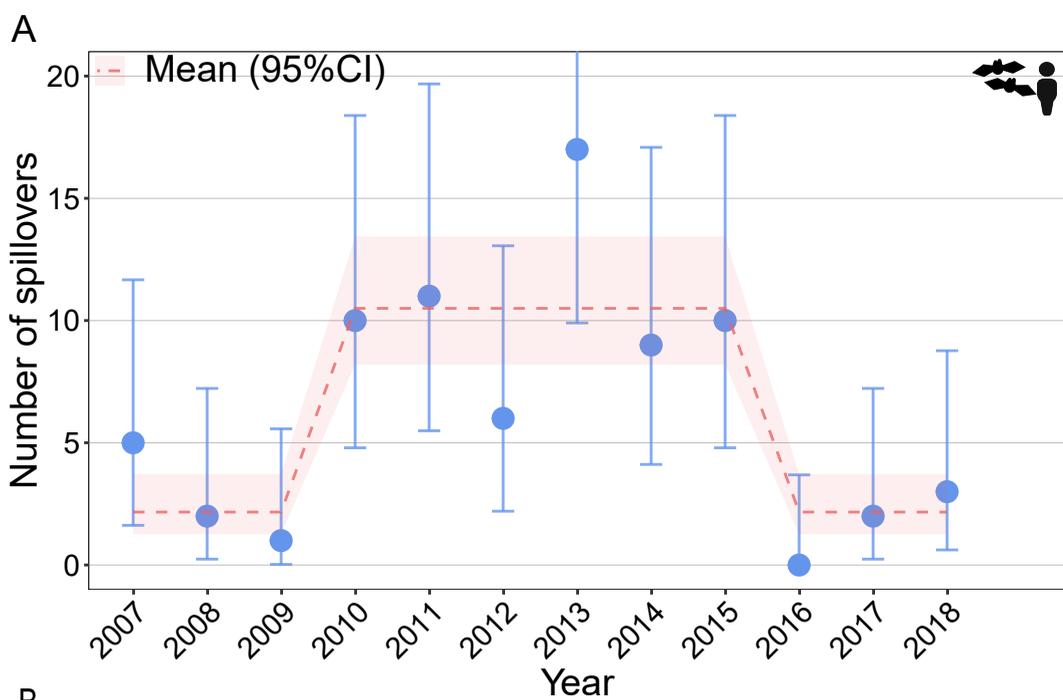
334 **Figure 1. (A) Indicators for changes in spillover risk, interhuman transmission and**
335 **morbidity/mortality of Nipah virus and other zoonotic pathogens. (B) Total number of Nipah cases**
336 **ever reported by districts in Bangladesh (2007 to 2018).**

337

338 **Figure 2. Baseline estimates and historical changes of key indicators to monitor Nipah virus**
339 **epidemiology and transmission.** Average number of spillovers (Poisson exact 95%CI) (A), number of
340 districts reporting NiV cases within 3 year window (time windows are indicated as grey bars) (B),
341 median cluster size (interquartile range) (C), reproduction number (negative binomial 95%CI) (D),
342 proportion spreaders (binomial exact 95%CI) (E), CFR among primary cases, i.e. cases infected by the
343 reservoir (binomial exact 95%CI) (F). The year represents a transmission season, which lasts from
344 December of the previous year until May of the indicated year.

345





346 **Supplementary Material**
347 **A framework to monitor changes in transmission and epidemiology of emerging pathogens:**
348 **Lessons from Nipah virus**

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353 **Erreur ! Signet non défini.**

354

355 **1. Probability of no spreaders and superspreaders**

356 The probability of not observing any NiV spreading events by increasing number of cases is shown in
357 Figure S2. For example, the probability of not observing any spreading event is 41% among 10 NiV
358 cases and 17% among 20 cases.

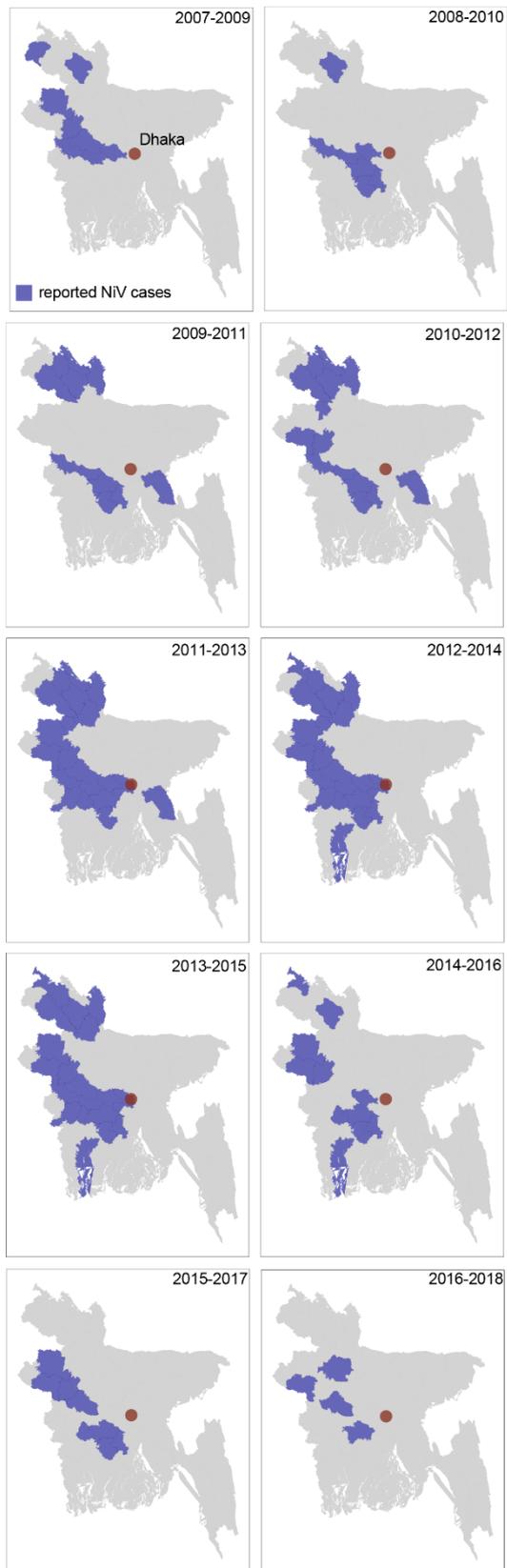
359 The probability of observing at least one, at least two, or at least three superspreading events (i.e. a
360 NiV case infecting ≥ 5 individuals) is shown in Figure S3. Among 10 cases, the probability of observing
361 at least one superspreading event is 10%; however as low as 0.4% and 0.01% for observing at least 2
362 or 3 superspreading events.

363 **2. Importance of systematic surveillance for baseline establishment**

364 We also estimated the indicators for each year during 2001-2006, a time period before routine
365 hospital-based surveillance was implemented and cases were not systematically detected. During
366 2001-2006, we observe a much higher variability in some of these key measures: the observed
367 annual spillover frequency ranged from 0 to 14, annual median outbreak sizes from 1 to 13, and the
368 annual estimated reproduction number from 0 to 0.85 (Figure S5). This demonstrates the difficulties
369 for establishing some of these baseline measures in the absence of stable surveillance.

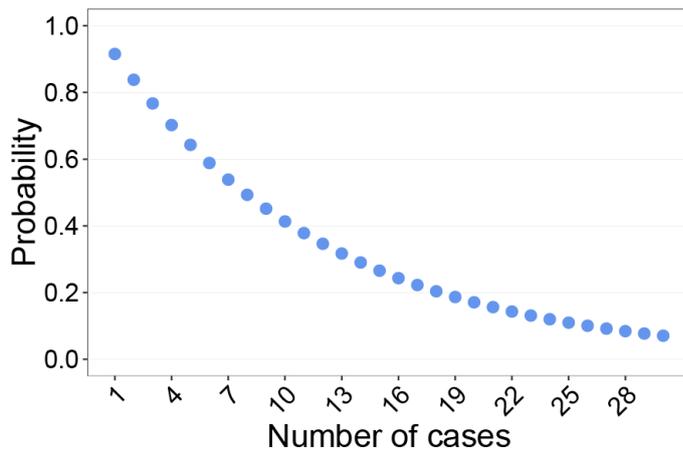
370 **3. Supplementary Figures**

371 **Figure S1. Location of districts reporting Nipah cases within moving 3-year time intervals during**
372 **2007-2018.**



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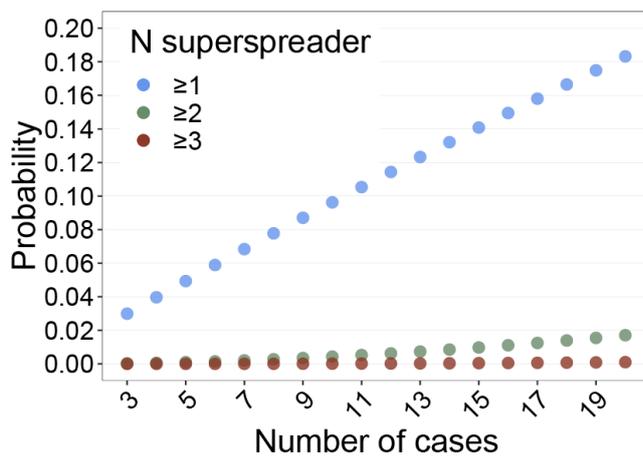
374 **Figure S2. Probability of observing zero spreading events by number of cases.**



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377 **Figure S3. Probability of observing at least 1, at least 2, and at least 3 superspreading events by**
378 **number of cases.**



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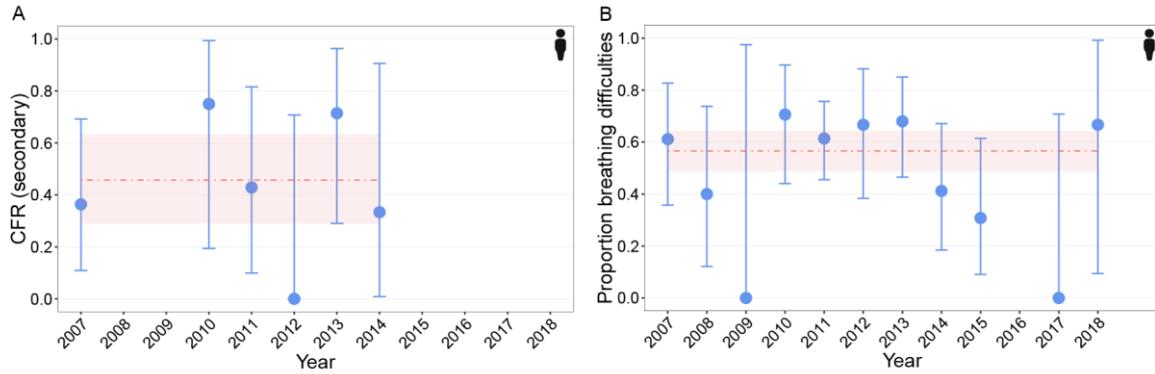
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391 **Figure S4. Baseline estimates and historical changes of key indicators to monitor Nipah virus**
 392 **epidemiology and transmission- additional measures.** CFR among secondary cases, i.e. cases
 393 infected by interhuman transmission (binomial exact 95%CI); no secondary cases occurred during
 394 2015-2018 (A), proportion of cases with difficulty breathing (binomial exact 95%CI) (B). The year
 395 represents a transmission season, which lasts from December of the previous year until May of the
 396 indicated year.

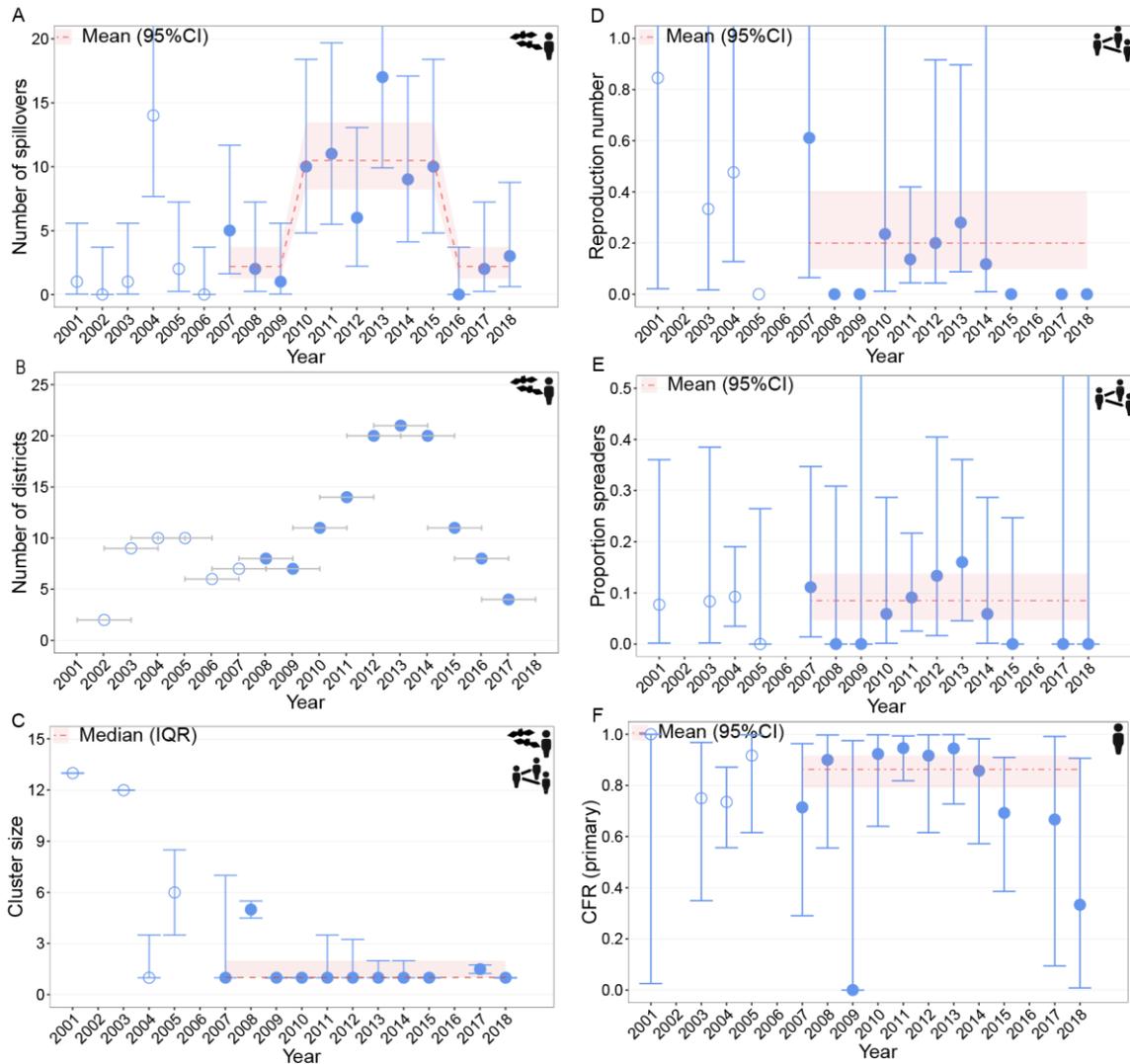


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400 **Figure S5. Comparing key indicators before (2001-2006) and after implementation of systematic**
 401 **hospital-based surveillance (2007- 2018).** Average number of spillovers (Poisson exact 95%CI) (A),
 402 number of districts reporting NiV cases within 3 year window (time windows are indicated as grey

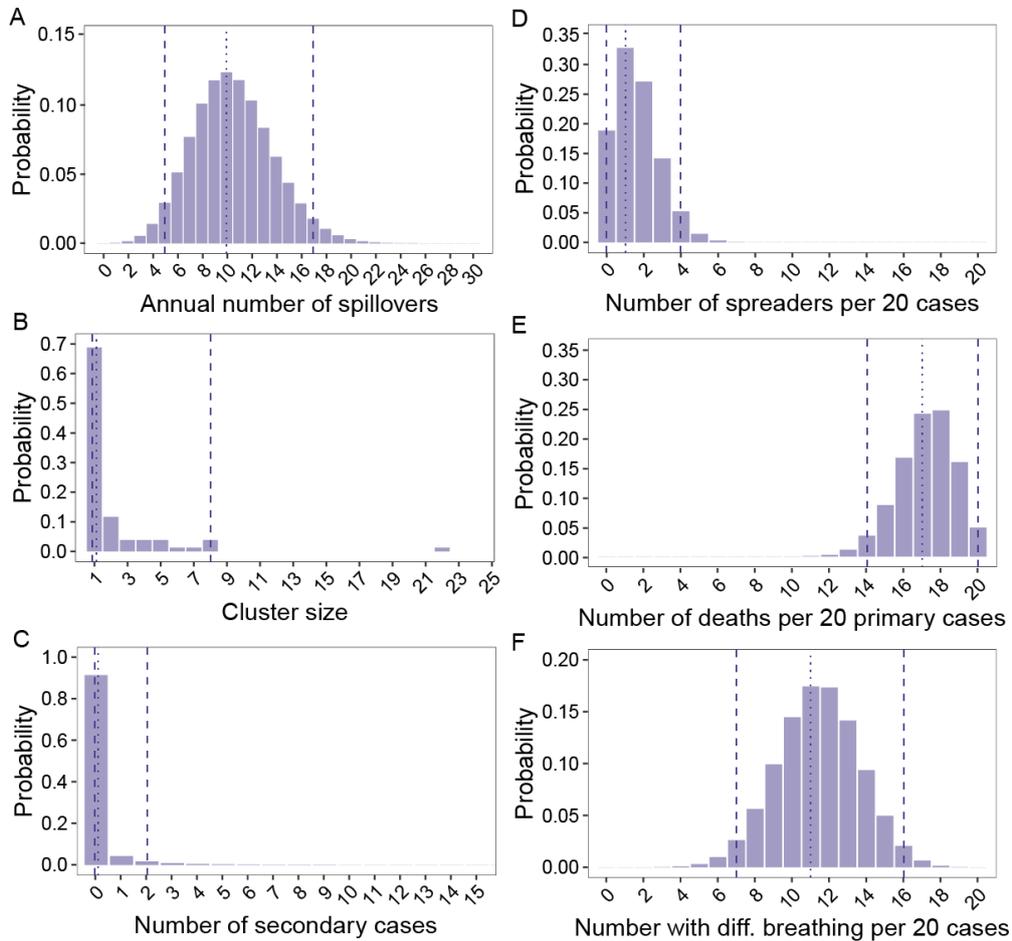


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410 **Figure S6. Detecting outliers in Nipah virus transmission and epidemiology using baseline**
411 **estimates.** Distribution of annual number of outbreaks (A). Empirical distribution of observed
412 outbreak sizes (B). Distribution of number of individuals infected by a case (C). Distribution of
413 number of spreaders among 20 cases (D). Distribution of number of deaths among 20 primary cases
414 (E). Distribution of number of cases with difficulty breathing among 20 cases (F). The dotted lines
415 indicate the 50th percentile; the dashed lines indicate the 2.5th and 97.5th percentile.



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