ESTIMATING THE PROTECTIVE EFFECT OF CASE ISOLATION WITH TRANSMISSION TREE RECONSTRUCTION DURING THE EBOLA OUTBREAK IN NIGERIA, 2014 – SUPPLEMENTAL MATERIAL

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1. Data merging

The date of onset of illness for Case 1 was not described by Folarin et al. [1], while another study specified it as 17 July 2014 [2], a date referred to throughout our study as Day 0. Dates of exposure and onset of illness for Case 12 were identical in the original data [1]. This is technically impossible, and so we chose to treat this date as the date of exposure rather than that of the onset of illness. We made this decision because no onset of illness event was recorded for 23 July 2014 in any other dataset [2], and also because the most likely dates of onset for Case 12 would have been from 30 July to 10 August 2014, based on transmission tree data in [2], which would agree closely with the known incubation period distribution with mean 9.1 days and standard deviation (SD) 7.3 days [3]. By overlaying observed branches in the presence of three generations, something seen among cases infected in Port Harcourt [1, 2], the dates of onset of illness for Cases 18 and 19 were identified as 31 August 2014 and 29 July 2014, respectively. Based on visual inspection of the transmission tree [2], the date of onset of illness for Case 17 was identified as 2 August 2014 by tracing links connected to Case 13. Similarly, the date of onset of illness for Case 20 was considered to be 16 August 2014, and moreover, Case 20 was considered to have been infected by one of the first generation cases (i.e. cases infected by the index case). Thus, the possible primary cases of Case 20 are Cases 5, 6, 7, 10, 11 or 12, but it was not possible to uniquely identify any one of these on the transmission tree [2]. The resulting dataset can be found in the author's website (https://github.com/imlouischan/ebola-ng).

2. Incubation period distribution

As for the incubation period distribution, we employed the independently and identically distributed incubation period for another large-scale outbreak from 2014-2016, assuming that it followed a gamma distribution with mean 9.1 days and SD 7.3 days [3] (Fig S1A). Due to the discrete nature of our observed data, the distribution was then transformed from continuous to discrete by $f(\tau) = F(\tau + 1) - F(\tau)$ for $\tau = 0, 1, 2, ...$, where $f(\tau)$ and $F(\tau)$ represent the probability mass function (PMF) and cumulative distribution function. The sample mean of the incubation period observed in Nigeria was 9.3 days, similar to the estimate from the abovementioned larger sample study [3], while the SD was only 1.9 days, with this smaller latter value perhaps reflecting the small sample size in Nigeria. Fig S1A illustrates the mismatch between two datasets.

3. Boundaries for missing date of an event

Missing dates were quantified within intervals between observed dates and the date of emptying isolation wards and exiting follow-up on 2 October 2014 (Day77), denoted as t_{exit} [2]. The outbreak ended and the country was declared Ebola free by local authorities and WHO on 20 October 2014 (Day95), denoted as t_{end} [1]. For a case i, the dates of exposure, onset of illness, hospitalization and death are aligned as the following sequence, i.e. $t_i^e \leq t_i^s \leq t_i^h \leq t_i^d \leq t_{exit} < t_{end}$. Because we assume that human Ebola cases are not infectious before the onset of illness, the date of exposure of a case i follows the date of onset of illness of its infector v_i, i.e. $t_{v_i}^s \leq t_i^e$. Using these two inequalities, we write boundaries of missing events. The upper bound of the date of hospitalization t_i^h is $\bar{B}(t_i^h) = \min(t_i^d, t_{exit})$. Similarly, the lower and upper bounds of the date of onset of illness t_i^s are $\underline{B}(t_i^s) = \max(t_i^e, t_{v_i^n}^s, t_{v_i^n}^e)$ and $\bar{B}(t_i^s) = \min(t_i^h, t_i^d, \mathbf{t}_{u_i^n}, t_{exit})$, respectively. v_i^n represents all the 'ancestors' of case i and $\mathbf{t}_{u_i^n}$ represents all observed time events of the 'descendants' of case i. Note that the lower bound of the date of hospitalization t_i^h is the same as the lower bound of the date of onset of illness t_i^s if the latter is missing.

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4. Partial reconstruction of the transmission tree

Unobserved infectors can be estimated using a transmission probability introduced by Wallinga [4]. The possible infectors are those with earlier onset of illness and the transmission probabilities of other cases are zero. This method has been extended into a partial network reconstruction given contact information that restricts a list of possible infectors with positive transmission probabilities and others are zero [5]. The transmission probability is written as

$$p_{ij}(\boldsymbol{\theta}) = \frac{\hat{s}(\tau_{ij}^{ss};\boldsymbol{\theta})}{\sum_{k\in w_i}\hat{s}(\tau_{ik}^{ss};\boldsymbol{\theta})},$$

where $\tau_{ik}^{ss} = t_i^s - t_k^s$ is the serial interval of case i and its possible infector k. w_i is a list of possible infectors of case i. The list consists of 6 infectors, namely Cases 5, 6, 7, 10, 11 and 12.

5. Reconstruction of time events

The observed dataset contained some cases for which the important time events, namely onset of illness and hospitalization, were only partially observed. The likelihood of those events was probabilistically described (Fig 1), and each event probability was considered at an individual level using convolution equations (Tables S2, S3, S4, S5). Specifically, we considered two different likelihood functions, L_r and L_s, where L_r accounts for the probability of observing a certain number of secondary transmissions per single primary case and L_s describes the probability of observing a time interval between primary and secondary cases. Theoretically, the former likelihood L_r is categorized into four types (Table S2), matching the timeline reconstruction (Table S1). On the other hand, the latter likelihood L_s is further categorized into six types due to each likelihood consisting of secondary case i and associated primary case v_i. For the description of L_s, we specifically need the date of onset of illness in both i and v_i, but only need the date of hospitalization for v_i. The observed dates are assumed to be independent and identically distributed (i.i.d.). The time from onset of illness to hospitalization is assumed to have the following two alternative distributions: Gamma and Weibull, which are discretized as the incubation period above (Fig S1). The distribution parameters were estimated using the maximum likelihood method (Fig S1B). The computation was performed using the general-purpose optimization method `stats::optim` in R version 3.4.3 (Kite-Eating Tree) on Mac OSX. The alternative distribution is selected by Akaike information criterion (AIC).

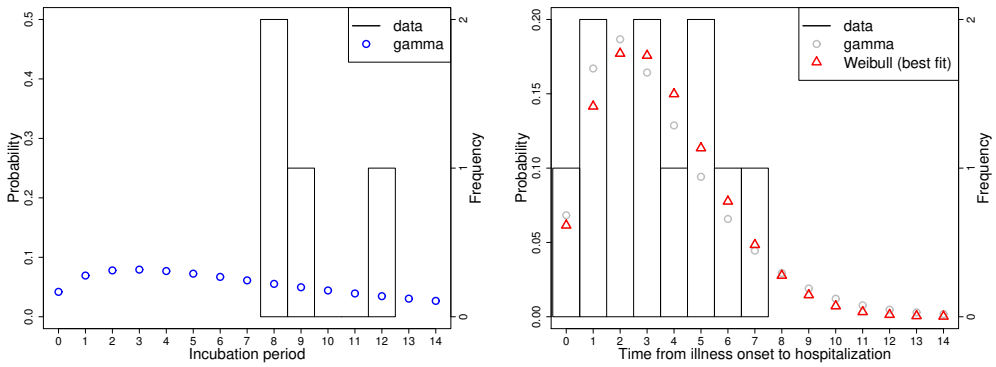


Figure 1. The probability mass functions (PMF) of (A) the incubation period and (B) the time from onset of illness to hospitalization. The observed data are shown in bars. The unfilled blue circles represent a published estimate [3]. The unfilled circles and unfilled triangles represent the predicted (fitted) values by employing two distributions, gamma and Weibull. The red and grey symbols show the best and second-best fit results, respectively. (A) The mean incubation period (with SD) was estimated as 9.1 (7.3) days. (B) The mean time from onset of illness to hospitalization (with SD) was estimated to be 4.0 (2.3) days.

Pattern	t_i^e		t_i^s		t_i^h	t_i^d	$\hat{t}_i^s$	$\hat{t}_i^h$	Observed
$i \in D^{(1)}$	$-$		O		O	$-$	t_i^s	t_i^h	10/20
$i \in D^{(2)}$	$-$		O	$\rightarrow$	M	$-$	t_i^s	$t_i^s + \tau^{sh}$	5/20
$i \in D^{(3)}$	O	$\rightarrow$	M		O	$-$	$t_i^e + \tau^{es}$	t_i^h	3/20
$i \in D^{(4)}$	M		M	$\leftarrow$	O	$-$	$t_i^h - \tau^{sh}$	t_i^h	2/20

TABLE 1. Theoretical patterns of observed and missing time events. Each case i is categorized into four different patterns for reconstructing the dates of the two important events – i.e., onset of illness and hospitalization. Four time events, the dates of exposure t_i^e, onset of illness t_i^s, hospitalization t_i^h, and death t_i^d are observed O, missing M or trivial (i.e. either is ok) $-$. The reconstructed dates of onset of illness $\hat{t}_i^s$ and hospitalization $\hat{t}_i^h$ are estimated using time lags depending on observed patterns. The last column shows the count of cases that fell into the specified pattern.

$i \in$	t_i^e		t_i^s		t_i^h	t_i^d	$L_r(\theta \mid D)$
D^{-OO-}	$-$		O		O	$-$	$\prod_{i \in D^{-OO-}} p(t_i^s, t_i^h - t_i^s)$
D^{-OM-}	$-$		O	$\rightarrow$	M	$-$	$\prod_{i \in D^{-OM-}} \frac{\sum_{\tau^{sh}=0}^{\bar{B}(t_i^h)-t_i^s} p(t_i^s, \tau^{sh}) f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=0}^{\bar{B}(t_i^h)-t_i^s} f^{sh}(\tau^{sh})}$
D^{OMO-}	O	$\rightarrow$	M		O	$-$	$\prod_{i \in D^{OMO-}} \frac{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} p(t_i^e+\tau^{es}, t_i^h - t_i^e - \tau^{es}) f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} f^{es}(\tau^{es})}$
D^{MMO-}	M		M	$\leftarrow$	O	$-$	$\prod_{i \in D^{MMO-}} \frac{\sum_{\tau^{sh}=t_i^h-\underline{B}(t_i^s)}^{t_i^h-\underline{B}(t_i^s)} p(t_i^h-\tau^{sh}, \tau^{sh}) f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=t_i^h-\bar{B}(t_i^s)}^{t_i^h-\underline{B}(t_i^s)} f^{sh}(\tau^{sh})}$

TABLE 2. Categories of the likelihood of secondary case L_r. O, M and $-$ represent observed time events, missing time events, and cases for which there are both observed and missing time events, respectively. $\underline{B}(t_i^s) = \max(t_i^e, t_{v_i^n}^s, t_{v_i^n}^e)$ is the lower bound of t_i^s. $\bar{B}(t_i^s) = \min(t_i^h, t_i^d, t_{u_i^n}^e, t_{u_i^n}^s, t_{u_i^n}^h, t_{u_i^n}^d, t_{exit})$ is the upper bound of t_i^s. $\bar{B}(t_i^h) = \min(t_i^d, t_{exit})$ is the upper bound of t_i^s. v_i^n and u_i^n represent all the 'ancestors' and 'descendants' of i, respectively. t_{exit} represents the time when the isolation wards were empty.

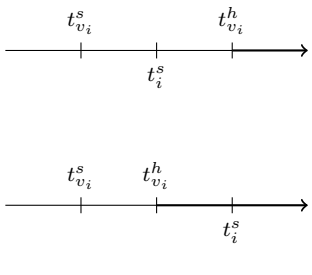
$v_i \in$	$i \in$	$L_s(\theta \mid D)$	1D timeline
D^{-OO-}	D^{-O--}	$\prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{-O--}}} \hat{s}(t_i^s - t_{v_i}^s, t_{v_i}^h - t_{v_i}^s)$	
		$= \prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{-O--} \\ t_{v_i}^h > t_i^s}} \frac{s(t_i^s - t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h - t_{v_i}^s)\right]}$	
		$\prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{-O--} \\ t_{v_i}^h \leq t_i^s}} \frac{(1-\epsilon)s(t_i^s - t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h - t_{v_i}^s)\right]}$	

TABLE 3. Categories of the likelihood of serial interval L_s. O, M and $-$ represent observed time events, missing time events, and cases for which there are both observed and missing time events, respectively. $\underline{B}(t_i^s) = \max(t_i^e, t_{v_i^n}^s, t_{v_i^n}^e)$ is the lower bound of t_i^s. $\bar{B}(t_i^s) = \min(t_i^h, t_i^d, t_{u_i^n}^e, t_{u_i^n}^s, t_{u_i^n}^h, t_{u_i^n}^d, t_{exit})$ is the upper bound of t_i^s. $\bar{B}(t_i^h) = \min(t_i^d, t_{exit})$ is the upper bound of t_i^s. v_i^n and u_i^n represent all the 'ancestors' and 'descendants' of i, respectively. t_{exit} represents the time when the isolation wards were empty.

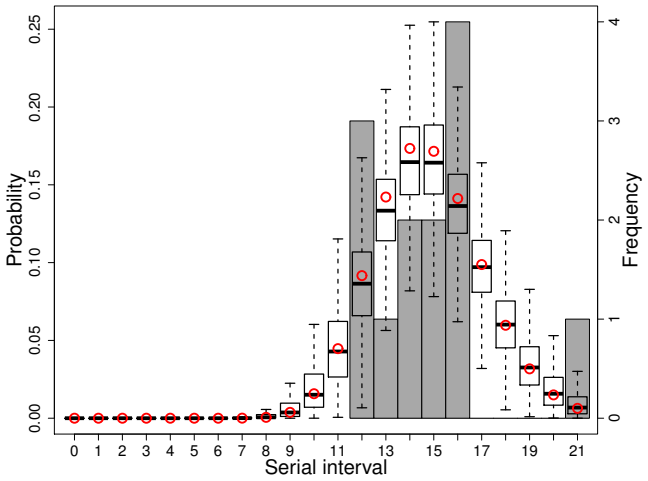


FIGURE 2. The serial interval distribution. The unbiased distribution $s(\tau)$ (i.e. in the absence of case isolation) is represented by using boxes as shown in Fig 2C. The mean and SD were 15.3 (95%CI: 14.2-16.6) and 2.3 (95%CI: 1.6-3.5) days. The corresponding biased distribution $\hat{s}(\tau)$ (i.e. in the presence of case isolation) is not shown due to various individual time from illness onset to hospitalization. As an alternative, the frequency of observed serial interval (biased; i.e. in the presence of case isolation) is shown as histogram using gray bars. The sample mean and SD were 14.8 and 2.5 days. The red circles represent the MLE fitted values by employing gamma distribution, as Fig S1B. The MLE mean and SD were 15.3 and 2.3 days. As isolation was taken place during the first week since the time of illness onset for most of the individuals, the unbiased $s(\tau)$ and biased (data and MLE) serial interval distributions are similar.

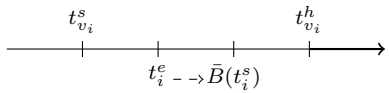
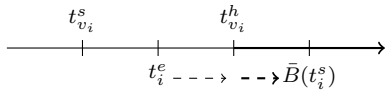
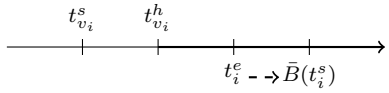
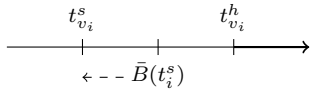
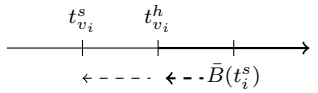
$v_i \in$	$i \in$	$L_s(\theta \mid D)$	1D timeline
D^{-OO-}	D^{OM--}	$\prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{OM--}}} \frac{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} \hat{s}(t_i^e+\tau^{es}-t_{v_i}^s, t_{v_i}^h-t_{v_i}^s) f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} f^{es}(\tau^{es})}$	
		$= \prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{OM--} \\ t_{v_i}^h > \bar{B}(t_i^s)}} \frac{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} \frac{s(t_i^e+\tau^{es}-t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h-t_{v_i}^s)\right]} f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} f^{es}(\tau^{es})}$	
		$\prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{OM--} \\ t_i^e < t_{v_i}^h \le \bar{B}(t_i^s)}} \frac{\sum_{\tau^{es}=0}^{t_{v_i}^h-t_i^e} \frac{s(t_i^e+\tau^{es}-t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h-t_{v_i}^s)\right]} f^{es}(\tau^{es}) + \sum_{\tau^{es}=t_{v_i}^h-t_i^e}^{\bar{B}(t_i^s)-t_i^e} \frac{(1-\epsilon)s(t_i^e+\tau^{es}-t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h-t_{v_i}^s)\right]} f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} f^{es}(\tau^{es})}$	
		$\prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{OM--} \\ t_{v_i}^h \le t_i^e}} \frac{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} \frac{(1-\epsilon)s(t_i^e+\tau^{es}-t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h-t_{v_i}^s)\right]} f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t_i^s)-t_i^e} f^{es}(\tau^{es})}$	
D^{-OO-}	D^{MMO-}	$\prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{MMO-}}} \frac{\sum_{\tau^{sh}=t_i^h-\bar{B}(t_i^s)}^{t_i^h-t_{v_i}^s} \hat{s}(t_i^h-\tau^{sh}-t_{v_i}^s, t_{v_i}^h-t_{v_i}^s) f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=t_i^h-\bar{B}(t_i^s)}^{t_i^h-t_{v_i}^s} f^{sh}(\tau^{sh})}$	
		$= \prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{MMO-} \\ t_{v_i}^h > \bar{B}(t_i^s)}} \frac{\sum_{\tau^{sh}=t_i^h-\bar{B}(t_i^s)}^{t_i^h-t_{v_i}^s} \frac{s(t_i^h-\tau^{sh}-t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h-t_{v_i}^s)\right]} f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=t_i^h-\bar{B}(t_i^s)}^{t_i^h-t_{v_i}^s} f^{sh}(\tau^{sh})}$	
		$\prod_{\substack{v_i \in D^{-OO-} \\ i \in D^{MMO-} \\ t_{v_i}^h \le \bar{B}(t_i^s)}} \frac{\sum_{\tau^{sh}=t_i^h-\bar{B}(t_i^s)}^{t_i^h-t_{v_i}^h} \frac{(1-\epsilon)s(t_i^h-\tau^{sh}-t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h-t_{v_i}^s)\right]} f^{sh}(\tau^{sh}) + \sum_{\tau^{sh}=t_i^h-t_{v_i}^h}^{t_i^h-t_{v_i}^s} \frac{s(t_i^h-\tau^{sh}-t_{v_i}^s)}{1-\epsilon\left[1-S(t_{v_i}^h-t_{v_i}^s)\right]} f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=t_i^h-\bar{B}(t_i^s)}^{t_i^h-t_{v_i}^s} f^{sh}(\tau^{sh})}$	

TABLE 4. Categories of the likelihood of serial interval L_s.

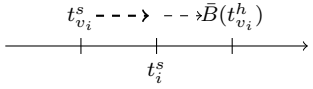
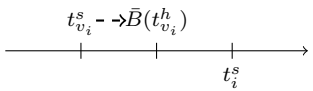
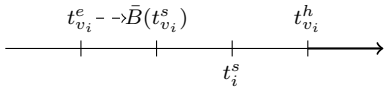
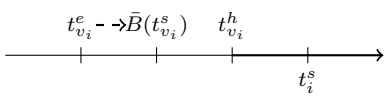
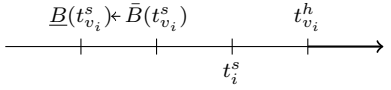
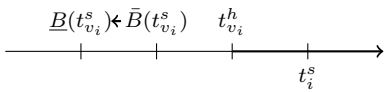
$v_i \in$	$i \in$	$L_s(\theta \mid D)$	1D timeline
D^{-OM-}	D^{-O--}	$\prod_{\substack{v_i \in D^{-OM-} \\ i \in D^{-O--}}} \frac{\sum_{\tau^{sh}=0}^{\bar{B}(t^h_{v_i})-t^s_{v_i}} \hat{s}(t^s_i - t^s_{v_i}, \tau^{sh}) f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=0}^{\bar{B}(t^h_{v_i})-t^s_{v_i}} f^{sh}(\tau^{sh})}$	
		$= \prod_{\substack{v_i \in D^{-OM-} \\ i \in D^{-O--} \\ t^s_i < \bar{B}(t^h_{v_i})}} \frac{\sum_{\tau^{sh}=0}^{t^s_i - t^s_{v_i}} \frac{(1-\epsilon) s(t^s_i - t^s_{v_i})}{1-\epsilon\left[1-S(\tau^{sh})\right]} f^{sh}(\tau^{sh}) + \sum_{\tau^{sh}=t^s_i - t^s_{v_i}}^{\bar{B}(t^h_{v_i})-t^s_{v_i}} \frac{s(t^s_i - t^s_{v_i})}{1-\epsilon\left[1-S(\tau^{sh})\right]} f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=0}^{\bar{B}(t^h_{v_i})-t^s_{v_i}} f^{sh}(\tau^{sh})}$	
		$\prod_{\substack{v_i \in D^{-OM-} \\ i \in D^{-O--} \\ t^s_i \geq \bar{B}(t^h_{v_i})}} \frac{\sum_{\tau^{sh}=0}^{\bar{B}(t^s_{v_i})-t^s_{v_i}} \frac{(1-\epsilon) s(t^s_i - t^s_{v_i})}{1-\epsilon\left[1-S(\tau^{sh})\right]} f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=0}^{\bar{B}(t^h_{v_i})-t^s_{v_i}} f^{sh}(\tau^{sh})}$	
D^{OMO-}	D^{-O--}	$\prod_{\substack{v_i \in D^{OMO-} \\ i \in D^{-O--}}} \frac{\sum_{\tau^{es}=0}^{\bar{B}(t^s_{v_i})-t^e_{v_i}} \hat{s}(t^s_i - t^e_{v_i} - \tau^{es}, t^h_{v_i} - t^e_{v_i} - \tau^{es}) f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t^s_{v_i})-t^e_{v_i}} f^{es}(\tau^{es})}$	
		$= \prod_{\substack{v_i \in D^{OMO-} \\ i \in D^{-O--} \\ t^s_i < t^h_{v_i}}} \frac{\sum_{\tau^{es}=0}^{\bar{B}(t^s_{v_i})-t^e_{v_i}} \frac{s(t^s_i - t^e_{v_i} - \tau^{es})}{1-\epsilon\left[1-S(t^h_{v_i} - t^e_{v_i} - \tau^{es})\right]} f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t^s_{v_i})-t^e_{v_i}} f^{es}(\tau^{es})}$	
		$\prod_{\substack{v_i \in D^{OMO-} \\ i \in D^{-O--} \\ t^s_i \geq t^h_{v_i}}} \frac{\sum_{\tau^{es}=0}^{\bar{B}(t^s_{v_i})-t^e_{v_i}} \frac{(1-\epsilon) s(t^s_i - t^e_{v_i} - \tau^{es})}{1-\epsilon\left[1-S(t^h_{v_i} - t^e_{v_i} - \tau^{es})\right]} f^{es}(\tau^{es})}{\sum_{\tau^{es}=0}^{\bar{B}(t^s_{v_i})-t^e_{v_i}} f^{es}(\tau^{es})}$	
D^{MMO-}	D^{-O--}	$\prod_{\substack{v_i \in D^{MMO-} \\ i \in D^{-O--}}} \frac{\sum_{\tau^{sh}=t^h_{v_i} - \bar{B}(t^s_{v_i})}^{t^h_{v_i} - \underline{B}(t^s_{v_i})} \hat{s}(t^s_i - t^h_{v_i} + \tau^{sh}, \tau^{sh}) f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=t^h_{v_i} - \bar{B}(t^s_{v_i})}^{t^h_{v_i} - \underline{B}(t^s_{v_i})} f^{sh}(\tau^{sh})}$	
		$= \prod_{\substack{v_i \in D^{MMO-} \\ i \in D^{-O--} \\ t^s_i < t^h_{v_i}}} \frac{\sum_{\tau^{sh}=t^s_i - \underline{B}(t^s_{v_i})}^{t^h_{v_i} - \underline{B}(t^s_{v_i})} \frac{s(t^s_i - t^h_{v_i} + \tau^{sh})}{1-\epsilon\left[1-S(\tau^{sh})\right]} f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=t^s_i - \underline{B}(t^s_{v_i})}^{t^h_{v_i} - \underline{B}(t^s_{v_i})} f^{sh}(\tau^{sh})}$	
		$\prod_{\substack{v_i \in D^{MMO-} \\ i \in D^{-O--} \\ t^s_i \geq t^h_{v_i}}} \frac{\sum_{\tau^{sh}=t^h_{v_i} - \bar{B}(t^s_{v_i})}^{t^h_{v_i} - \underline{B}(t^s_{v_i})} \frac{(1-\epsilon) s(t^s_i - t^h_{v_i} + \tau^{sh})}{1-\epsilon\left[1-S(\tau^{sh})\right]} f^{sh}(\tau^{sh})}{\sum_{\tau^{sh}=t^h_{v_i} - \bar{B}(t^s_{v_i})}^{t^h_{v_i} - \underline{B}(t^s_{v_i})} f^{sh}(\tau^{sh})}$	

TABLE 5. Categories of the likelihood of serial interval L_s.

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