Time From Infection to Disease and Infectiousness for Ebola Virus Disease, a Systematic Review

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We systematically reviewed the literature to estimate the incubation and latent periods of Ebola virus disease. We found limited epidemiological data from individuals with discrete 1-day exposures. Available data suggest that the incubation and latent periods may differ, and mathematical models may be improved by distinguishing between the two periods.

Keywords. Ebola; incubation period; latent period; transmission; systematic review.

The current Ebola outbreak in West Africa is unprecedented in size and geographic scope. Numerous mathematical models have been developed to capture the transmission dynamics and potential impact of interventions [1–7]. However, few reliable data exist on key epidemiologic features of Ebola virus disease (EVD), and most modeling parameters come from previous models or single empirical reports [8, 9]; these include time from infection to symptom onset (incubation period), time from infection to the onset of infectiousness (latent period), and duration of infectiousness. Here we systematically reviewed the literature on Ebola outbreaks to estimate these parameters.

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METHODS

Definitions

Infectious Period

Following the US Centers for Disease Control and Prevention and the World Health Organization, which report that Ebola transmission occurs primarily by direct contact with infected secretions [10, 11], we defined the EVD infectious period as the duration of any of the following wet symptoms: vomiting, diarrhea, coughing, or hemorrhage. We assumed the infectious period ends upon resolution of wet symptoms or at the time of death, and we did not consider postmortem transmission.

Incubation Period

We defined incubation period as the time from an Ebola exposure to the onset of any EVD symptoms in a probable or confirmed case. In addition to wet symptoms, we noted onset of dry symptoms including fever, myalgia, headache, oropharyngeal lesions, nausea, abdominal pain, and rash.

Latent Period

We defined the latent period as the time from an Ebola exposure to the onset of wet symptoms in a probable or confirmed EVD case. Because few sources provided a direct estimate of this period, we also considered the sum of the incubation period and the time from onset of dry to wet symptoms.

Study Selection

This systematic review conforms to PRISMA guidelines [12]. The Supplementary Material provides detail on data sources, data extraction methods, and our search strategy (Supplementary Panel 1). We reviewed all titles and abstracts identified in the specified databases excluding articles that did not report primary data on the incubation or latent periods of EVD in humans. We performed full-text reviews of the remaining articles extracting information on the incubation and latent periods and the time from onset of dry to wet symptoms. We excluded observations without a reported time of onset of any symptoms (for incubation period) or of wet symptoms (for latent period). Among the subset of articles with information on timing of wet symptoms, we also extracted the infectious period.

We considered only studies that provided a clear case definition for EVD and information about the type and timing of Ebola exposures. Because the time of a transmission event is not known from multi-day exposures, we included only data from individuals with single-day exposures.

Table 1. Ebola Virus Disease Incubation Period, Latent Period, and Time to Onset of Wet Symptoms

				Incubation Period			
Author	Reference	Outbreak Location	Year	Species	Exposure Type	Value ± SD or (Range), Days	N
Incubation period, percutaneous transmission							
Breman et al; International Commission	[9, 13]	Zaire	1976	*Zaire ebolavirus*	Contaminated needle injection	6.3 ± N/A (range 1–15)	57
Emond et al	[14]	Porton Down, England	1976	Not specified (*Zaire ebolavirus* or *Sudan ebolavirus* inferred)	Needlestick	6 ± N/A	1
Heymann et al	[15]	Tandala, Zaire	1977–1978	*Zaire ebolavirus*	Laceration	12 ± N/A	1
Khan et al	[16]	Kikwit, DRC	1995	*Zaire ebolavirus*	Contaminated needle injection	3 ± N/A (range 1–6)	11
Mean incubation period (percutaneous route)[a]						5.86 ± 1.42	70
Incubation period, person-to-person transmission							
Breman et al; International Commission	[9, 13]	Zaire	1976	*Zaire ebolavirus*	Single contact	2 ± N/A	1
Bwaka et al	[17]	Kikwit, DRC	1995	*Zaire ebolavirus*	Direct HCW contact	6.2 ± N/A (range 5–8)	5
Bitekyerezo et al	[18]	Mbarara, Uganda	2000	*Sudan ebolavirus*	Crowded accommodation contact	7 ± N/A	1
Leroy et al	[19]	Ndongo, DRC	2007	*Zaire ebolavirus*	Washed corpse	8 ± N/A	1
Incubation period, animal-to-person transmission							
Baize et al	[20]	Mayibout, Gabon	1996	*Zaire ebolavirus*	Consumed chimpanzee (decedents)	7.8 ± 0.9	12
Baize et al	[20]	Mayibout, Gabon	1996	*Zaire ebolavirus*	Consumed chimpanzee (survivors)	8.4 ± 1.3	5
Mean incubation period (non-percutaneous route)[a]						7.34 ± 1.35	25
Incubation period, unknown route of transmission							
Richards et al	[21]	Gabon/Johannesburg, RSA	1996	*Zaire ebolavirus* (inferred)	Assisted in CVC placement	3 ± N/A	1
Mean incubation period (all routes of transmission)[a]						**6.22 ± 1.57**	**96**

Table 1 continued.

	Latent Period								
	Reference	Outbreak Location	Year	Species	Exposure Type	Initial Symptom(s)	Initial wet Symptom(s)	Value ± SD, days	N
Emond et al	[14]	Porton Down, England	1976	Not specified (*Zaire ebolavirus* or *Sudan ebolavirus* inferred)	Needlestick	Fever, central abdominal pain, nausea	Diarrhea, vomiting	9.5 ± N/A	1
Richards et al	[21]	Gabon/Johannesburg, RSA	1996	*Zaire ebolavirus* (inferred)	Assisted in CVC placement	Fever	Hematemesis, melena	14 ± N/A	1
Mean latent period[a]								**11.75**	**2**

	Time to Onset of Dry to Wet Symptoms							
	Reference	Outbreak Location	Year	Species	Initial Symptom(s)	Initial wet Symptom(s)	Value ± SD, days	N
International Commission; Isaacson et al; Sureau et al	[13, 22, 23]	Zaire	1976	*Zaire ebolavirus*	Fever, headache	Hematemesis	6 ± N/A	1
Sureau et al	[23]	Zaire	1976	*Zaire ebolavirus* (inferred)	Fever, generalized pain, vomiting	Vomiting	0 ± N/A	1
Sureau et al	[23]	Zaire	1976	*Zaire ebolavirus* (inferred)	Fever, lumbar pain, vomiting	Vomiting	0 ± N/A	1
Emond et al	[14]	Porton Down, England	1976	Not specified (*Zaire ebolavirus* or *Sudan ebolavirus* inferred)	Fever, central abdominal pain, nausea	Diarrhea, vomiting	3.5 ± N/A	1
WHO/International Study Team	[24]	Southern Sudan	1976	Not specified	Fever, headache, chest pain	Epistaxis, bloody diarrhea	4 ± N/A	1
Richards et al	[21]	Gabon/Johannesburg, RSA	1996	*Zaire ebolavirus* (inferred)	Fever	Hematemesis, melena	11 ± N/A	1
Shoemaker et al	[25]	Uganda	2011	*Sudan ebolavirus*	Mild headache	Vomiting	4 ± N/A	1
Kreuels et al	[26]	Sierra Leone	2014	*Zaire ebolavirus*	Malaise, headache, myalgia, arthralgias	Vomiting, nonbloody diarrhea	6 ± N/A	1
Lyon et al	[27]	Monrovia, Liberia	2014	*Zaire ebolavirus*	Fever, fatigue, nausea	Diarrhea, melena	5 ± N/A	1
Lyon et al	[27]	Monrovia, Liberia	2014	*Zaire ebolavirus*	Fever, fatigue, malaise	Diarrhea	8 ± N/A	1
Wolf et al	[28]	Sierra Leone	2014	*Zaire ebolavirus*	Fever, diarrhea	Diarrhea	0 ± N/A	1
Lopaz et al	[29]	Spain	2014	*Zaire ebolavirus*	Fever, malaise	Vomiting, diarrhea	7 ± N/A	1
Mean time to onset of dry to wet symptoms[a]							**6.05 ± 2.38**	**12**

Abbreviations: CVC, central venous catheter; DRC, Democratic Republic of the Congo; HCW, healthcare worker; N/A, not applicable; RSA, Republic of South Africa; SD, standard deviation; WHO, World Health Organization.

[a] Combined parameter values were fitted to the normal distribution and weighted by observation frequency.

Statistical Analysis

We performed all analyses in MATLAB (MathWorks, Natick, Massachusetts). Where appropriate, we fit a normal distribution to the point estimates extracted from the literature, weighted by the observation frequency. We calculated the latent period by summing the mean incubation period and the mean time from onset of dry to wet symptoms. We calculated the variance of this composite value as the sum of the variances.

We performed a sensitivity analysis in which we included publications that provided estimates of the incubation period based on multi-day exposures or unspecified timing and type of exposure. We also performed a sensitivity analysis of infectious period in which we considered that infectiousness ended with the resolution of plasma viremia.

RESULTS

After reviewing the titles and abstracts of 1204 citations that met our search criteria, we excluded 1113 citations that did not contain primary data regarding transmission or clinical symptoms of EVD in humans and 3 citations for which the abstracts or full texts could not be located (Supplementary Figure 1). After a full-text review of the remaining 88 citations, we excluded 70 as detailed in Supplementary Table 4. Ten publications reported an incubation period, 2 reported a latent period, and 11 reported the time from the onset of dry symptoms to the onset of wet symptoms (Table 1). We were unable to quantify heterogeneity because the majority of publications did not report the parameter variance.

The mean incubation period was 6.22 ± 1.57 days for all routes of transmission (n = 96, Table 1). The 5 publications on the incubation period following percutaneous transmission yielded a mean of 5.86 ± 1.42 days (n = 70) and the 6 following person-to-person transmission or contact with infected animals yielded a mean of 7.34 ± 1.35 days (n = 25). The mean of the latent period in individual patients was 11.75 (Table 1). The mean time from onset of dry to wet symptoms was 6.05 ± 2.38 days (n = 12). When we summed this mean with the time from exposure to onset of dry symptoms, we estimated a mean latent period of 12.27 ± 2.85 days. Stratified by exposure type, we calculated a mean latent period of 11.91 ± 2.77 days after percutaneous exposure, and 13.39 ± 2.74 days after non-percutaneous exposure. From 9 publications that reported the duration of wet symptoms, we calculated a mean infectious period of 9.40 ± 5.50 days for EVD survivors (n = 5) and a mean time from onset of wet symptoms to death of 5.33 ± 4.03 days (n = 6, Supplementary Table 3). Figure 1 summarizes these findings.

The sensitivity analysis of incubation period included 6 publications covering an additional 1189 patients (Supplementary Table 4) previously excluded due to multi-day exposures (n = 2), unspecified exposure type (n = 3), or unreported timing (n = 1). The mean incubation period for all routes of transmission was 10.07 ± 1.95 days (n = 1274), and the mean non-percutaneous

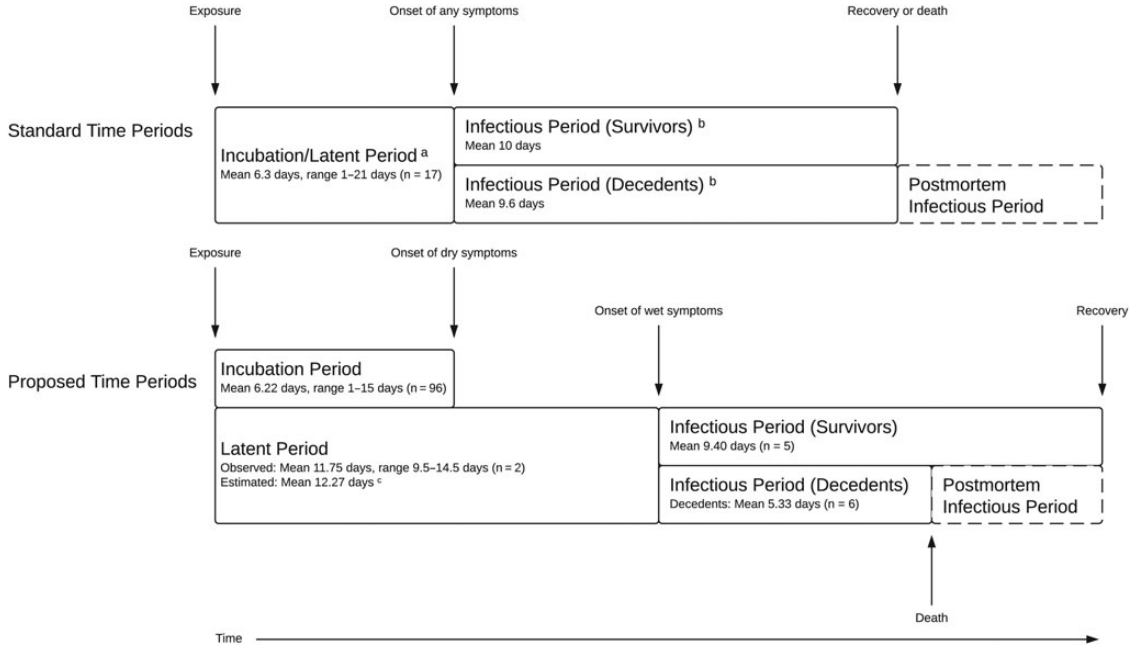

Figure 1. Standard vs proposed time periods for Ebola virus disease. [a]Source: [9]; [b]Source: [8]; [c]The mean latent period was estimated by summing the mean time from exposure to onset of dry symptoms with the mean time from onset of dry to wet symptoms.

incubation period was 10.32 ± 1.67 (n = 1203). The sensitivity analysis of infectious period including 5 publications reporting time from onset of wet symptoms to resolution of plasma viremia (Supplementary Table 3) yielded a mean infectious period of 14.00 ± 5.55 days among EVD survivors (n = 6).

DISCUSSION

We found limited data from individuals with discrete 1-day exposures with which to estimate the incubation and latent periods for EVD. A 1976 report on the first known Ebola outbreak gave an incubation period of 1 to 21 days, and this range has been used in many modeling studies [9]. In contrast, the studies that met our inclusion criteria provided support for a mean incubation period of 6.2 days with a range of 1 to 15 days. It is important to note that the standard errors we report are measures of uncertainty in the point estimate of each population mean and are not measures of the degree of individual-level variation in the population. The standard errors should not be used to infer the optimal length of quarantine during an Ebola outbreak.

Many modeling studies assume that the EVD latent period is equal to its incubation period [1, 5, 6]. The studies reviewed here suggest that dry symptoms precede wet ones by a mean of 6.1 days. This means that the incubation period likely underestimates the time to infectiousness, and that models using the incubation period as the latent period may capture a slower dynamic. More important, however, are our findings on the infectious period of EVD. The infectious periods used in many models have come from limited empirical data [2–6, 8], fitted estimates from prior models [1], or relied on models that estimated serial intervals rather than infectious periods [7]. If these estimates were based on empirical data on the time from onset of any symptoms until either death or clinical recovery, then the infectious periods may have been systematically overestimated.

Our stringent inclusion criteria represent a potential source of selection bias. The mean incubation period estimated in our sensitivity analysis was longer than that estimated in our primary analysis, consistent with our expectation that reports on multi-day exposures may overestimate the incubation period. Recall bias may introduce misclassification of the timing of exposure to EVD and the incubation period in either direction, as patients may recall exposures to known EVD patients more than with unrecognized infectious sources.

The assumption that Ebola is only transmitted from patients with wet symptoms may underestimate the infectious period if Ebola can be transmitted by fomites, droplets, or aerosols that hosts may generate when they have dry symptoms. Postmortem Ebola transmission is also well recognized, and therefore the duration of the infectious period is likely underestimated for decedents. When we considered the end of infectiousness to be the resolution of plasma viremia, this sensitivity analysis yielded a mean infectious period of 14.0 days in contrast to the 9.4 days until resolution of wet symptoms.

In summary, we demonstrate that limited epidemiological data from individuals with discrete 1-day exposures underpins estimates for the EVD incubation period used in the current modeling literature, and we summarized empirical data suggesting that the time to symptoms underestimates the time to infectiousness for EVD. These findings may have important implications for models of EVD intervention strategies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute on Drug Abuse, the National Institute of General Medical Sciences, or the National Institutes of Health (NIH).

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