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The whole iceberg: estimating the incidence of yellow fever virus infection from the number of severe cases

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Abstract

Background—Like many infectious agents, yellow fever (YF) virus only causes disease in a proportion of individuals it infects and severe illness only represents the tip of the iceberg relative to the total number of infections, the more critical factor for virus transmission.

Methods—We compiled data on asymptomatic infections, mild disease, severe disease (fever with jaundice or hemorrhagic symptoms) and fatalities from 11 studies in Africa and South America between 1969 and 2011. We used a Bayesian model to estimate the probability of each infection outcome.

Results—For YF virus infections, the probability of being asymptomatic was 0.55 (95% credible interval [CI] 0.37– 0.74), mild disease 0.33 (95% CI 0.13–0.52) and severe disease 0.12 (95% CI 0.05–0.26). The probability of death for people experiencing severe disease was 0.47 (95% CI 0.31–0.62).

Conclusions—In outbreak situations where only severe cases may initially be detected, we estimated that there may be between one and seventy infections that are either asymptomatic or cause mild disease for every severe case identified. As it is generally only the most severe cases that are recognized and reported, these estimates will help improve the understanding of the burden of disease and the estimation of the potential risk of spread during YF outbreaks.

Keywords

Case fatality rate; Epidemiology; Flavivirus; Yellow fever

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Introduction

Yellow fever (YF) virus causes intermittent epidemics of severe illness and death affecting thousands of people.[1] Human and non-human primates are the main amplifying hosts of YF virus with both species experiencing sufficient viremia to infect naïve mosquitoes, predominantly of *Aedes* and *Haemagogus* species.[1] Therefore, knowing the number of infected individuals is important for estimating the scope of an outbreak, the potential for amplification and spread of the virus and the potential burden of disease cases on the healthcare system. However, like many infectious agents, YF virus only results in disease in some of the individuals whom it infects. Thus, while deaths and severe illness with characteristic signs like jaundice and hemorrhage are good indicators of a case or an outbreak, they actually only represent the tip of the iceberg relative to the total number of infections, the more critical factor for the dynamics of transmission and spread.

To determine the relationship between severe disease and the incidence of YF virus infection, it is important to simultaneously measure the incidence of infection, mild disease, severe disease and death. However, identifying asymptomatic or mild infections require active surveillance, cohort studies or seroprevalence studies. This typically does not happen during YF outbreaks that generally occur in areas with limited health resources that are often difficult to access. In outbreaks, severe cases of YF are the primary indicator of risk as they can be fairly easily identified in healthcare facilities and communities.

Monath et al. used data from a 1978–79 outbreak in The Gambia to estimate that there were 12 inapparent YF virus infections for every severe case with fever and jaundice.[2] Additional data from the 1986 and 1987 outbreaks in Nigeria led to a revision of this estimate to approximately seven inapparent infections per severe case.[3–5] In Brazil, Vasconcelos et al. estimated a similar ratio of severe disease to mild or asymptomatic infections.[6] Thus, across several outbreaks in different countries and continents, approximately one out of every eight (13%) YF virus infections resulted in severe disease. These estimates, however, are all point estimates and thus do not capture the uncertainty associated with the very limited data used, and do not fully utilize other data sources or define the range of disease experienced, such as fever without jaundice or other symptoms associated with severe YF.

There is also uncertainty about the case fatality rate (CFR) for YF, with estimates varying from approximately 1–15% in Nigerian villages[7] to over 80% among hospitalized cases in Senegal.[8] Part of this wide range is likely attributable to small sample sizes and differences in case definitions and how cases are identified.

To better define the probabilities of asymptomatic infection, mild disease, severe disease and death associated with YF virus infection, we identified 11 studies with detailed information on the prevalence of a variety of these outcomes.[2–4,6–12] These studies involve a variety of methods and study populations, including varying case definitions, survey designs, diagnostic methods, locations, underlying rates of vaccination and previous exposure. We combined the data from these studies in a Bayesian model to estimate the number of YF virus infections occurring in the populations where these outbreaks occurred,

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and the probability of asymptomatic infection, mild disease, severe disease and death for persons infected by YF virus.

Materials and methods

Case definitions

For the purpose of surveillance in the context of an outbreak, a probable YF case has been defined as an acute febrile illness with hemorrhagic symptoms or jaundice.[13] We utilized this definition to develop three disease categories of persons infected with YF virus: asymptomatic (A): no symptoms; mild (M): some symptoms but no hemorrhagic symptoms or jaundice and severe (S): fever with hemorrhagic symptoms or jaundice or death.

We opted not to include more specific information on severe symptoms or manifestations, other than jaundice and hemorrhage, because most studies did not include that level of detail.

Data

Using expert knowledge, literature searches and chains of references, we identified 11 studies with detailed information on the prevalence of different disease outcomes in populations where confirmed YF outbreaks had recently occurred or were ongoing. The nature of the data was highly varied, with some data being directly relatable to infection or disease on the population level (Table 1). We have presented this in terms of the classifications above: A, M and S, as well as F (fatal cases), YF virus-related deaths and N, any person in the population. For each pair of columns in Table 1, the left column represents the number of people in a given category sampled from the population in the right column. For example, in Okwoga-Okpudo, there were 21 mild and severe cases among a sample of 131 people from the general population. Among the whole population, of 201 people, there were 1–5 deaths attributable to YF virus. Further details of the data selected from each study are presented in the Supplementary data.

Other data measured infection or disease among a group of people that was not directly related to a general population (Table 2); for example, the number of fatalities among severe cases of unknown or unreported provenance. For this analysis, we considered all reported YF deaths as resulting from severe illness, even if neither jaundice nor hemorrhagic fever was reported. Many YF cases die due to renal failure or cardiac arrest,[14] and do not develop hemorrhagic symptoms or jaundice before dying.[7] It is likely that most fatal cases would have developed jaundice or hemorrhagic symptoms if they had lived longer.

Because all cases were reported in the context of outbreaks, we included all individuals meeting the severe case definition with or without evidence of laboratory confirmation. For asymptomatic infections, mild infections and deaths without severe manifestations, we included only persons with YF virus infection demonstrated by: 1. detection of YF virus antibodies using an IgM ELISA or immunofluorescent antibody test (IFA), complement fixation or plaque reduction neutralization test; 2. detection of YF virus by culture; 3. detection of viral antigens using immunohistochemistry; or 4. detection of viral genome by RT-PCR. Antibody-based testing was considered confirmed only if previous vaccination

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coverage in the studied population was non-existent or low, or if it was clearly stated that the individuals being tested had not been vaccinated. Further details about the data selected for analysis are available in the Supplementary data. All data used in this study were collected from previously published material and thus did not require ethical review.

Model description

For each population that was sampled, we assumed that there was a community-wide probability of infection (p_I) during the outbreak. We assumed that the probability of infection for each outbreak population (i) was independent, as transmission dynamics may vary due to local environmental, human, mosquito or virus characteristics:

$$I_i \sim \text{Binomial}(p_{I,i}, N_i)$$

Where I_i is the number of people infected and N_i is the total population size.

Among those infected, we assumed that a proportion experienced asymptomatic infection ($p_{A|I}$), mild disease ($p_{M|I}$) or severe disease ($p_{S|I}$), with $p_{A|I}+p_{M|I}+p_{S|I}= 1$. These proportions may vary between studies (s), depending on how cases were defined and sought and depending on the characteristics of the human, mosquito and virus populations associated with the outbreak. Therefore, we assume that there may be some study-to-study variation in observed disease proportions, which we account for using a random effect:

$$\text{logit}(p_{A|I,s}) \sim \text{N}(\text{logit}(p_{A|I}), \sigma_A^2),$$

$$\text{logit}(p_{M|I,s}) \sim \text{N}(\text{logit}(p_{M|I}), \sigma_M^2),$$

and

$$\text{logit}(p_{S|I,s}) \sim \text{N}(\text{logit}(p_{S|I}), \sigma_S^2).$$

The three probabilities were then standardized by dividing by their sum ensuring that they sum to one, i.e. that every infected individual has one of these outcomes.

As described above, we assumed that all fatalities came from among the severe cases. We assumed that this probability of fatality ($p_{F|S}$) may also be influenced by study methods or differences in local transmission characteristics:

$$\text{logit}(p_{F|S,s}) \sim \text{N}(\text{logit}(p_{F|S}), \sigma_F^2).$$

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We designed a hierarchical Bayesian model to specify each of the observed components in Table 1 as a binomial sample of the relevant population, related to the probabilities of each disease classification across studies. In studies with an observed number of asymptomatic infections (*A*), mild and severe cases (*M*+*S*), severe cases (*S*) or fatal cases (*F*) in a random sample population (*N*) the parameters are related to the probabilities of infection and disease outcome as follows:

$$A_{i,s} \sim \text{Binomial}(p_{I,i}p_{A|I,s}, N_i),$$

$$M_{i,s}+S_{i,s} \sim \text{Binomial}(p_{I,i}(p_{M|I,s}+p_{S|I,s}), N_i),$$

$$S_{i,s} \sim \text{Binomial}(p_{I,i}p_{S|I,s}, N_i)$$

and

$$F_{i,s} \sim \text{Binomial}(p_{I,i}p_{S|I,s}p_{F|S,s}, N_i).$$

In studies with an observed number of asymptomatic infections (*A*) in a sample of individuals with no history of disease (N_A):

$$A_{i,s} \sim \text{Binomial}(p_{I,i}p_{A|I,s}/(1-p_{I,i}(p_{M|I,s}+p_{S|I,s})), N_{A,i}).$$

In studies reporting asymptomatic infections and mild cases (*A*+*M*) among people with a history of no severe disease ($N_{!S}$):

$$A_{i,s}+M_{i,s} \sim \text{Binomial}(p_{I,i}(p_{A|I,s}+p_{M|I,s})/(1-p_{I,i}p_{S|I,s}), N_{!S,i}).$$

For the data that was not directly linked to a population sample (Table 2), we used the following distributions:

$$M_s \sim \text{Binomial}(p_{M|I,s}/(p_{A|I,s}+p_{M|I,s}), N_{AM,S}),$$

where N_{AM} is the number of people with asymptomatic or mild infections,

$$M_s+S_s \sim \text{Binomial}(p_{M|I,s}+p_{S|I,s}, I_s)$$

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and

$$F_s \sim \text{Binomial}(p_{F|S,s}, S_s).$$

We fitted the model using Markov Chain Monte Carlo methods in OpenBUGS Version 3.2.1[15] using the R2OpenBUGS package[16] in R Version 2.15.13.[17] We used vague beta priors (Beta[1, 1]) for each probability and vague gamma priors for each local precision parameter ($1/\sigma^2 \sim$Gamma[1, 1]). Three chains were initialized with different initial probability values and checked for convergence and autocorrelation. We discarded the initial 20 000 samples, and used over relaxation and thinning at every 300 samples to obtain 1000 uncorrelated samples of each parameter. Posterior distributions for unobserved quantities were estimated conditionally on other location-specific observed components and on the global parameter posterior distributions.

Results

For individual studies, the estimated YF virus infection outcome probabilities varied, falling between the estimated overall mean and the observed proportion in studies where it was available (Figure 1). The estimated variances for the random effects on the logit-transformed probabilities were 0.9 (95% credible interval [CI] 0.3–9.3) for $p_{A|I}$, 1.2 (95% CI 0.3–13.9) for $p_{M|I}$, 0.55 (95% CI 0.2–3.7) for $p_{S|I}$ and 0.6 (95% CI 0.3–2.5) for $p_{F|S}$. This variability may arise from natural variation, differences in study methods or a combination of both. We thus estimated the credible intervals for the average probabilities across studies and for the expected probability for an unknown area with unknown study methods (Table 3). The overall estimate for the probability of a YF virus infection being asymptomatic was 0.55 (95% CI 0.37–0.74) (Figure 2). The probability of infection resulting in mild disease was 0.33 (95% CI 0.13–0.52) and severe disease was 0.12 (95% CI 0.05–0.26). The probability of severe disease resulting in death or CFR was 0.47 (95% CI 0.31–0.62). Overall, 5% (95% CI 2–12%) of infections and 13% (95% CI 5–28%) of those with mild or severe disease, i.e. any sign of disease, resulted in death.

Based on these results, 9 (95% CI 1–70) mild and asymptomatic infections would be expected for every severe case during a new outbreak; with the credible interval including the variability associated with the random effects. For each death due to YF virus, there may be 21 other infections (95% CI 3–239), including 12 asymptomatic infections (95% CI 1–145), 8 mild cases (95% CI 0–100) and 1 non-fatal, severe case (95% CI 0–9).

Discussion

For most pathogens, observed disease only represents a small fraction of all infections. Furthermore, estimation of the true infection rate generally relies on limited data of varied quality with potential cofactors that are unknown or unobserved. Our Bayesian approach to YF virus infections and disease allows for controlling for different study designs and study populations, while exploiting all available data, and accounting for uncertainty.

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Using data from 11 YF investigations, we described the proportion of YF virus infections in humans that are likely to be asymptomatic or result in mild or severe disease. Approximately 55% of infections were asymptomatic, 33% resulted in mild disease and 12% resulted in severe illness characterized by fever with jaundice or hemorrhagic symptoms. These estimates are generally in-line with previous estimates of severe versus inapparent (i.e. asymptomatic or mild) infections.[2–6]

Our estimated CFR of 47% among severe cases is similar to previous estimates of 40–50%.[3,9,10,14,18] However, CFR did vary substantially from other point estimates, likely due to sample size limitations, different methods and case definitions. Observations from Nigeria, The Gambia and Uganda, for example, had only a handful of known deaths in each community, so the observations of 1–25% CFR are based on very few severe cases.[2,7,12] In the 1978 Nigeria outbreak, the overall estimated CFR was 21%, but included substantial underreporting in the largest study population.[4] In the two more thoroughly assessed communities, the observed CFR was much higher, 50% and 75%, but again the sample size was very limited in those populations.[4] In other studies from Brazil[6] and Senegal,[8,11] CFRs of 16–28% were reported, but the denominators included at least some people with mild rather than severe disease as we have defined it here. When we included mild disease in our case definition, the CFR decreased to 12%. Studies may also overestimate the CFR if they capture mostly hospitalized cases, as deaths may be more likely to be captured than non-fatal severe cases.[14] The CFR may also appear higher when there is overrepresentation of the most severe cases, such as in routine surveillance systems, where only the most severe diseases are likely to be captured. For example, among 4066 cases reported to the Pan American Health Organization between 1985 and 2012, 58% died, almost the upper limit of the credible interval estimated here.[17]

Despite using carefully screened data from 11 different studies, all of our estimates contain a high amount of uncertainty as reflected in the large credible intervals. These intervals reflect both uncertainty due to data limitations, as discussed above, and natural variability that may be intrinsic or related to heterogeneities between the outbreaks. Uncertainty in the data comes from the paucity of published YF outbreak studies, the limited amount of data from small samples in those studies, varying study designs and difficulty in measuring outcomes. For example, the number of deaths due to YF virus may be overestimated if it includes all deaths with fever and jaundice (including hepatitis fatalities, for example) or underestimated if only laboratory-confirmed cases are accepted.[9] Factors contributing to spatiotemporal heterogeneity in infection rates and potentially disease rates include: the local environment,[19,20] characteristics of the human, vector and virus populations,[21] pre-existing YF virus immunity due to previous exposure or vaccination, interventions in response to outbreaks, and the prevalence of other health conditions that may influence the severity of disease (such as malnutrition or HIV infection). In fact, most of the investigations reviewed here were accompanied or immediately followed by vaccination campaigns.[2–4,6–8,10–12]

There are several limitations to the approach we have used to estimate the probability of each infection outcome. In the model, intra-study variability was captured in the random effects as there was not enough information to assess differences related to specific sources of heterogeneity. The credible intervals for individual studies and the expected credible

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intervals for a new study were particularly large, implying that estimation from individual studies was highly dependent on the characteristics of the study and the study population. The random effects do not allow us to distinguish between these factors, but do allow the estimation of average global rates given the presence of local differences across the diverse group of outbreaks included in the analysis.

Conclusions

For many disease outbreaks, it is usually the severe cases that are first detected, as they are more recognizable.[22–25] For YF virus, the severe form of the disease is more recognizable, but may represent an additional three to twenty asymptomatic or mild infections. For any observed case, there is likely a larger problem with appreciable potential for further infections, a fact that has long been implicitly recognized. The International Health Regulations accordingly state that a single observed YF case is sufficient to trigger an assessment of global risk.[26] As for other infectious diseases, understanding how the incidence of YF virus infection relates to the occurrence of severe cases is critical to decision-making and the implementation of appropriate responses and interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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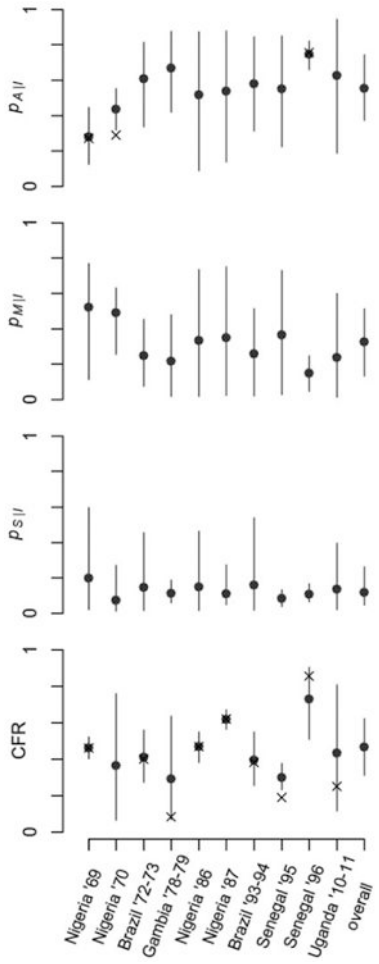

Figure 1.

Estimates for yellow fever virus infection outcomes for individual studies and the overall averages. For each individual study and the overall model, the mean estimates (points) and 95% credible intervals (lines) are shown for the probabilities of being asymptomatic ($p_{A|I}$), having mild symptoms ($p_{M|I}$) or severe symptoms ($p_{S|I}$) given yellow fever virus infection. The case fertility ratio (CFR) is the probability of a severe case resulting in a fatality. For the studies with relevant observed data (Table 1), the crude rates from those observations are indicated by an x.

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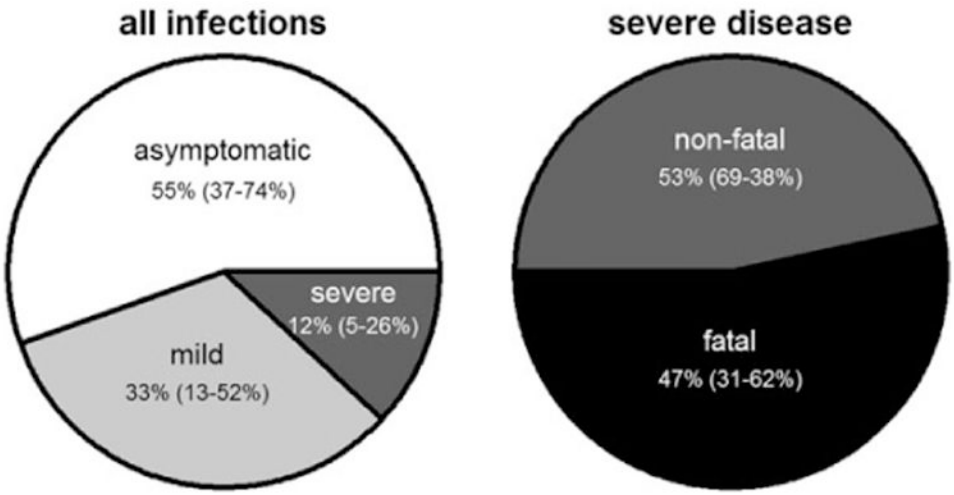

Figure 2.

Estimates for yellow fever (YF) virus infection outcomes. The left panel indicates the expected percentage of YF virus infected people in each disease category with 95% credible intervals in parentheses. The right panel indicates the probability of fatal outcomes among severe cases with 95% credible intervals in parentheses.

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Table 1

Data directly related to population-level incidence for yellow fever (YF) virus infections, clinical cases and deaths

Study	Ref.	Location	S	N	M+S	N	A	N	A	N_A	A+M	$N_{!S}$	F	N
Nigeria, 1970	1	Okwoga-Okpudo	_[a]	–	21	131	11	131	–	–	–	–	1 to 5	201
Nigeria, 1970	1	Aidogodo	–	–	29	72	5	72	–	–	–	–	2 to 3	317
Nigeria, 1970	1	2 villages combined	–	–	–	–	–	–	15	126	–	–	–	–
Gambia, 1978–79	2	Sambuldu	4	73	–	–	–	–	–	–	8	24	0	73
Gambia, 1978–79	2	Sukuta	8	86	–	–	–	–	–	–	26	38	1	86
Gambia, 1978–79	2	2 villages combined	–	–	–	–	–	–	26	51	–	–	–	–
Nigeria, 1987	3	Ejigbo	8	133	–	–	–	–	–	–	–	–	6	133
Nigeria, 1987	3	Igbeti	2	57	–	–	–	–	–	–	–	–	1	57
Brazil, 1993–94	4	Mirador	–	–	–	–	–	–	28	840	40	852	–	–
Senegal, 1995	5	Koungheul	110	8678	–	–	–	–	45	450	–	–	46	8678
Senegal, 1996	6	Dougounbene	–	–	16	167	21	167	–	–	–	–	–	–
Senegal, 1996	6	Katiawane	–	–	4	78	12	78	–	–	–	–	–	–
Senegal, 1996	6	Lanta	–	–	1	67	8	67	–	–	–	–	–	–
Senegal, 1996	6	M'Bollop	–	–	1	42	9	42	–	–	–	–	–	–
Senegal, 1996	6	Nianghene	–	–	0	83	19	83	–	–	–	–	–	–
Senegal, 1996	6	5 villages combined	–	–	–	–	–	–	–	–	–	–	36	2166
Uganda, 2010–11	7	Aremo Central & Golgota	4	1100	9	1100	–	–	–	–	–	–	1	1100

A: asymptomatic infections; F: fatal cases; M: mild cases; N: anyone (not infected+A+M+S); N_A: anyone with no history of illness; $N_{!S}$: anyone with no history of severe disease; S: severe cases.

[a]Data not available or redundant, in the case of combined villages.

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Table 2

Outcome data not directly related to population-level incidence for yellow fever (YF) virus infection

Study	Reference	Location	M	A+M	M+S	I	F	S
Nigeria, 1969	8	Jos	-[a]	–	22	28	116	252
Nigeria, 1970	1	Adiga	–	–	6	13	–	–
Brazil, 1972–73	9	Goias	4	16	–	–	16	40
Nigeria, 1986	10	Oju	–	–	–	–	59	126
Nigeria, 1987	3	Oyo	–	–	–	–	202	325
Brazil, 1993–94	4	Maranhao	–	–	–	–	13	34
Senegal, 1995	5	Koungheul	–	–	–	–	15	79
Senegal, 1996	6	Kaffrine		–	–	–	12	14
Brazil, 1998–2002	11	National	–	–	–	–	92	140

A: asymptomatic infections; F: fatal cases; I: infected (A+M+S); M: mild cases; S: severe cases.

[a]Data not available.

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Table 3
Probability of yellow fever (YF) virus infection outcomes

	Mean	Overall 95% CI[a]	New study 95% CI[b]
Among infected			
Asymptomatic $p_{A\|I}$	0.55	0.37–0.74	0.1–0.87
Mild $p_{M\|I}$	0.33	0.13–0.52	0.02–0.75
Severe $p_{S\|I}$	0.12	0.05–0.26	0.01–0.45
Among severe			
Fatal $p_{F\|S}$	0.47	0.31–0.62	0.10–0.84

[a] 95% credible interval for overall mean.

[b] 95% credible interval for a new study in an unknown location.