What is the reproductive number of yellow fever?

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**Teaser:** Our review found the average reproductive number $R_0$ for yellow fever to be 4.81 with a median of 4.21.

Yellow fever is a viral vector-borne disease caused by the yellow fever virus with its geographic distribution currently limited to sub-Saharan Africa and South America. The case fatality rate of hospitalized severe yellow fever is above 40%.\(^1\)

The basic reproductive number, $R_0$, can be used to characterize the epidemic potential of a pathogen by assessing the number of secondary cases that would be generated by one infectious case if it was to be introduced into an immunologically naïve population. $R_0$ values that are larger than 1 indicates epidemic growth; values around 1 represents endemcity; and for values below 1, the outbreak is declining and the number of new infections will be decreasing in subsequent generations. We conducted a review of published peer-reviewed literature on the estimates of the basic reproductive number of Yellow fever, and discuss the implications for herd immunity in relation to the critical vaccination levels.

We conducted searches on PubMed and Web of Science with the following search terms “yellow fever AND ($R_0$ OR basic reproductive number)” The restriction on published article language was English. We included all publications from 1950 until August 2020. Our review excluded estimates of the effective reproductive number, which depends on the background level of immunity.

A total of 31 studies were identified through the literature search based on these search terms. We excluded 23 studies because of ineligible or incomplete outcome
data. 8 studies were included in the final analysis. Overall, 11 data points were collated from the included studies. $R_0$ estimates were derived for a variety of countries, study years and methods as provided in Table 1. The estimates range from 1.35 to 11. The average $R_0$ was 4.81 with a median of 4.21 and interquartile range (IQR) of 2.19.

**Table 1.** Published estimates of $R_0$ for yellow fever

| Study               | Location          | Study year | $R_0$ estimates | Method                                                                 |
|---------------------|-------------------|------------|-----------------|-----------------------------------------------------------------------|
| Zhao et al.²        | Luanda, Angola    | 2015-2016  | 6 (range 4-8)   | Estimated from mathematical compartmental based model                |
| Kraemer et al.³     | Angola            | 2015-2016  | 4.8 (95% CI 4.0-5.6) | Formula linking to the exponential growth rate and the generation time distribution |
| Wu et al.⁴         | Angola            | 2016       | 5.2 (95% CI 4.3-6.1) | Wallinga and Teunis method, assuming mean mosquito lifespan=7 days     |
| Wu et al.⁴         | Angola            | 2016       | 7.1 (95% CI 5.5-8.7) | Wallinga and Teunis method, assuming mean mosquito lifespan=14 days    |
| Kennedy et al.⁵     | Memphis, Tennessee, USA | 1878     | 11              | Estimated from mathematical compartmental based model                |
| Johansson et al.⁶  | Asuncio´n, Paraguay | 2008     | 4.1             | Using moderate literature estimates of the parameters for the human infectious period, $R_{0a}$,average number of infectious mosquitoes produced per infectious human* the average number of infectious humans |
The $R_0$ estimates appear to vary between studies. Partly this can be related to methodological differences, but also different local susceptibility and exposure to vectors, i.e. which could be emphasized during due El Nino period and in warmer climate. A relationship between $R_0$ and climate has been observed for other viruses transmitted by the same vector (Ying Liu et al., 2020).

| Study                  | Location               | Year | $R_0$ | Notes                                                                 |
|------------------------|------------------------|------|-------|----------------------------------------------------------------------|
| Curtis’ et al.         | New Orleans, USA       | 1878 | 2.38  | $R_0$ was calculated at the neighborhood level applying a mathematical equation; Constrained |
| Curtis’ et al.         | New Orleans, USA       | 1878 | 3.59  | $R_0$ was calculated at the neighborhood level applying a mathematical equation; Unconstrained |
| Massad et al.          | Sºo Paulo State, Brazil| 2000 | 3.23 (range 1.62-6.61) | Calculate $R_0$ for yellow fever for every city that $R_0$ of dengue>1, using a mathematical function of $R_0$ for dengue with dengue cases |
| Massad et al.          | Sºo Paulo State, Brazil| 2000 | 4.21 ( range 2.39-8.59 ) | Estimate $R_0$ of yellow fever using a mathematical function of $R_0$ for dengue with the annual outbreaks of dengue in 2000 |
| Massad et al.          | Sºo Paulo State, Brazil| 1991 | 1.35 ( range 1.07-1.66 ) | Estimate $R_0$ of yellow fever using a mathematical function of $R_0$ for dengue with the annual outbreaks of dengue in 1991 |
The $R_0$ is an important number for elimination and it should be considered at a high average/aggregation level over time and space as it is the long-term elimination that is being considered.

With increasing global travel patterns (at least before the COVID-19 pandemic), the risk of importation of yellow fever to vulnerable countries where the vector is present but no adequate vaccination coverage exists is high.\(^\text{10}\) The critical vaccination level corresponds to the proportion of population that need to be vaccinated to achieve herd immunity assuming the population is vaccinated at random and that the population is mixing homogenously. Therefore, in the hypothetical situation when a vaccine is 100% effective (i.e. $E=1$) the critical vaccination level equals the herd immunity level, $V_c = 1 - \frac{1}{R_0}$; otherwise it is, $V_c = 1 - \frac{1}{R_0 E}$. Assuming a vaccine efficacy of 99% (30 days after vaccination (WHO, 2019)), we calculated the critical vaccine coverage levels need to be between 26.2%, 77.0% and 91.8% according to the minimum, median and maximum $R_0$ values respectively. Reaching very high $V_c$ levels, such as 91.8%, for herd immunity is logistically not feasible in many current settings.

We conclude that vaccine coverage thresholds may vary between areas and countries as the basic reproductive number can vary substantially in different localities.

**Author contributions**

J.R. had the idea, and Y.L. did the literature search and created the table. Y.L. wrote the first draft; Y.L and J.R. drafted the final manuscript. All authors contributed to the final manuscript.

**Conflict of interest**

None declared.

**References**

1. Ho YL, Joelsons D, Leite G F C, et al. Severe yellow fever in Brazil: clinical characteristics and management[J]. Journal of Travel Medicine, 2019, 26(5).

2. Zhao S, Musa SS, Hebert JT, et al. Modelling the effective reproduction number of vector-borne diseases: the yellow fever outbreak in Luanda, Angola 2015-2016 as an example. PeerJ. 2020;8:e8601. Published 2020 Feb 27. doi:10.7717/peerj.8601
3. Kraemer MUG, Faria NR, Reiner RC Jr, et al. Spread of yellow fever virus outbreak in Angola and the Democratic Republic of the Congo 2015-16: a modelling study [published correction appears in Lancet Infect Dis. 2019 Apr;19(4):e109]. *Lancet Infect Dis.* 2017;17(3):330-338. doi:10.1016/S1473-3099(16)30513-8

4. Wu JT, Peak CM, Leung GM, Lipsitch M. Fractional dosing of yellow fever vaccine to extend supply: a modelling study. *Lancet.* 2016;388(10062):2904-2911. doi:10.1016/S0140-6736(16)31838-4

5. S. Wright Kennedy, Andrew J. Curtis & Jacqueline W. Curtis (2015). Historic Disease Data as Epidemiological Resource: Searching for the Origin and Local Basic Reproduction Number of the 1878 Yellow Fever Epidemic in Memphis, Tennessee, *Annals of the Association of American Geographers,* 105:5, 1-16, DOI: 10.1080/00045608.2015.1059167

6. Johansson M A , Arana-Vizcarrondo N , Biggerstaff B J , et al. Assessing the Risk of International Spread of Yellow Fever Virus: A Mathematical Analysis of an Urban Outbreak in Asunción, 2008[J]. *American Journal of Tropical Medicine & Hygiene,* 2012, 86(2):349.

7. Curtis, A., J. W. Mills, and J. K. Blackburn. 2007. A spatial variant of the basic reproduction number for the New Orleans yellow fever epidemic of 1878. *The Professional Geographer* 59 (4): 492–502.

8. Massad, Eduardo & Burattini, Marcelo & Coutinho, Francisco & Fernandez Lopez, Luis. (2003). Dengue and the risk of urban yellow fever reintroduction in Sao Paulo State, Brazil. *Revista de saúde pública.* 37. 477-84. 10.1590/S0034-89102003000400013.

9. Massad, Eduardo & Coutinho, Francisco & Burattini, Marcelo & Fernandez Lopez, Luis. (2001). The Risk of Yellow Fever in a Dengue-Infested Area. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 95. 370-374.

10. Gubler D J . Pandemic Yellow Fever: A Potential Threat to Global Health via Travelers[J]. *Journal of Travel Medicine,* 2018(1):1.