# Ebola Virus Disease mathematical models and epidemiological parameters: a systematic review and meta-analysis

***Pathogen Epidemiology Review Group***

*MRC Centre for Global Infectious Disease Analysis &*
*WHO Collaborating Centre for Infectious Disease Modelling,*
*Jameel Institute, School of Public Health,*
*Imperial College London*

# Pathogen Epidemiology Review Group

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# Introduction

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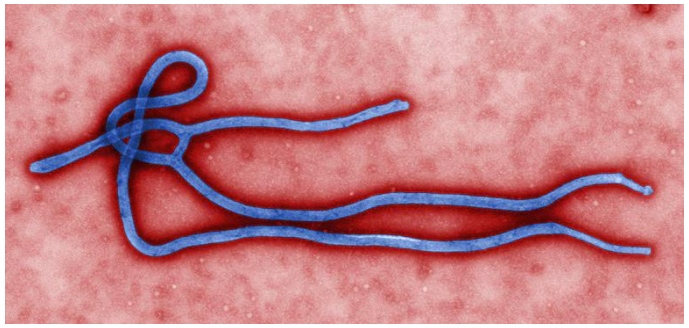
- deadly **filovirus**
- transmitted through **close contact** and **bodily fluids**
  - especially during traditional burials and caregiving.
- **38 known outbreaks** since its discovery in 1976.
  - Most in **Central and Western Africa**,
- West African (WA) Ebola epidemic, caused over 11,000 reported deaths between 2013 and 2016 mainly across Guinea, Liberia and Sierra Leone.
- Four species of Ebola Virus are known to affect humans: Zaire, Bundibugyo, Sudan and Taï Forest.
- Reston, is only known to cause disease in non-human primates and Bombali, was identified in samples taken from bats in Sierra Leone.



# Search terms

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First search until 8th March 2019. Updated until 7th July 2023.

Ebola AND ((transmissi* OR epidemiolog*) OR (model* NOT imag*) OR (severity OR ”case fatality ratio*” OR CFR OR ”case fatality rate*” OR ”mortality rate*” OR ”attack rate*”) OR (”infectious period*” OR ”serial interval*” OR ”incubation period*” OR ”generation time*” OR ”generation interval*” OR ”latent period*” OR latency) OR (heterogeneit* OR superspread* OR ”super spread*” OR super- spread* OR overdispersion OR overdispersed OR over-dispersion OR over-dispersed OR ”over dispersion” OR ”over dispersed”) OR (infectivity OR infectiousness OR ”growth rate*” OR ”reproduction number*” OR ”reproductive number*” OR R0 OR ”reproduction ratio*” OR ”reproductive rate*”) OR (”pre-existing immunity” OR serological OR serology OR serosurvey*) OR (evolution* OR mutation* OR substitution*) OR (outbreak* OR cluster* OR epidemic*) OR (”risk factor*”)).

# Inclusion / Exclusion Criteria

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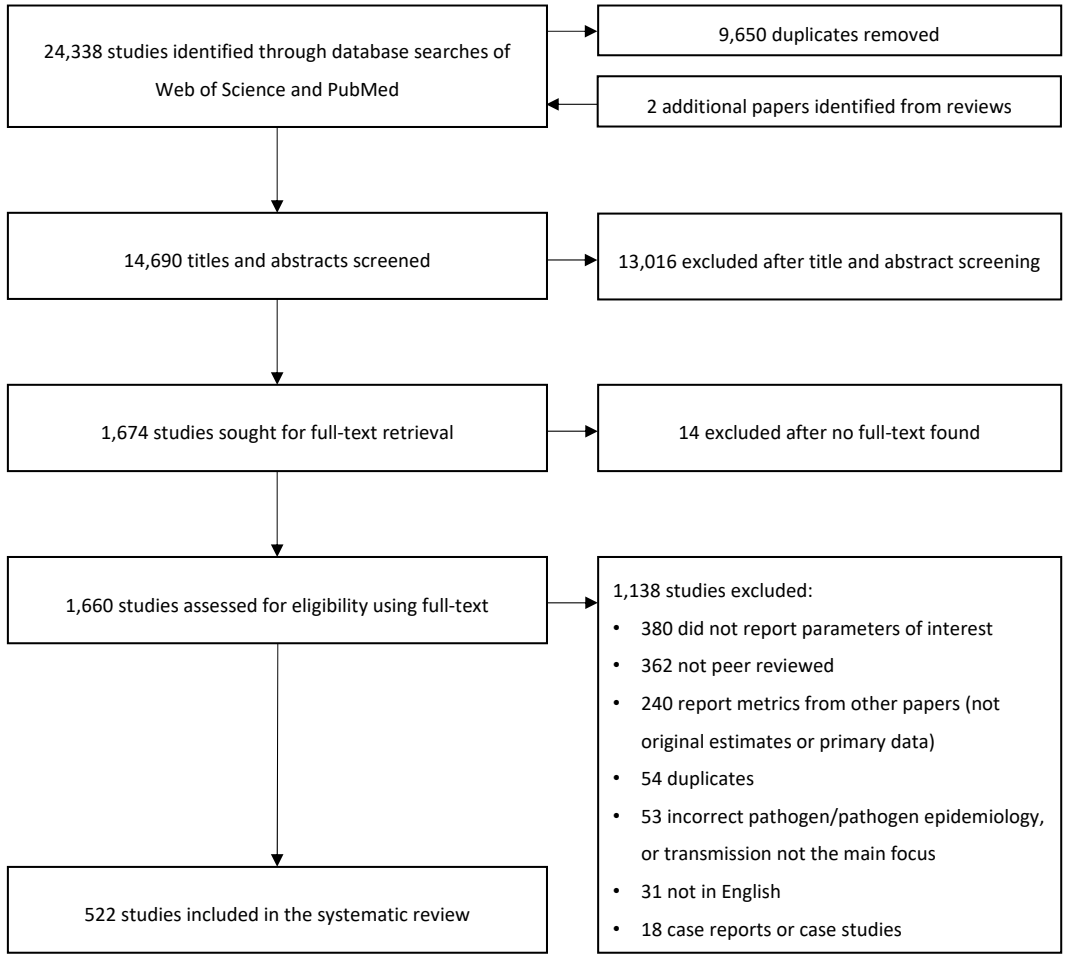
| Inclusion | Exclusion |
|---|---|
| Measures/estimates of human: Reproduction numbers (R, R0, Rt, r, Re), growth rate (r), doubling times, generation time, serial interval, incubation/latent period, case fatality ratio (CFR), attack rate, mutation rate (e.g. from phylogenetic study), overdispersion, risk factors (risk and the measure). Mathematical or statistical model of transmission. | Non-English language publication . |
| | Studies of co-infections. (local, regional, national, international). |
| | Animal studies. |
| Measures of seroprevalence and negative seroprevalence in humans. | Qualitative studies, e.g., KAP studies. |
| Nature letters. | Pathogen not the primary focus of study. |
| | Duplicates. |
| | Does not match any of the inclusion criteria. |
| | In-vitro studies. |
| | Non-peer reviewed publications, conference proceedings, abstracts, posters, letters to the editor. |

# PRISMA flow chart



# epireview

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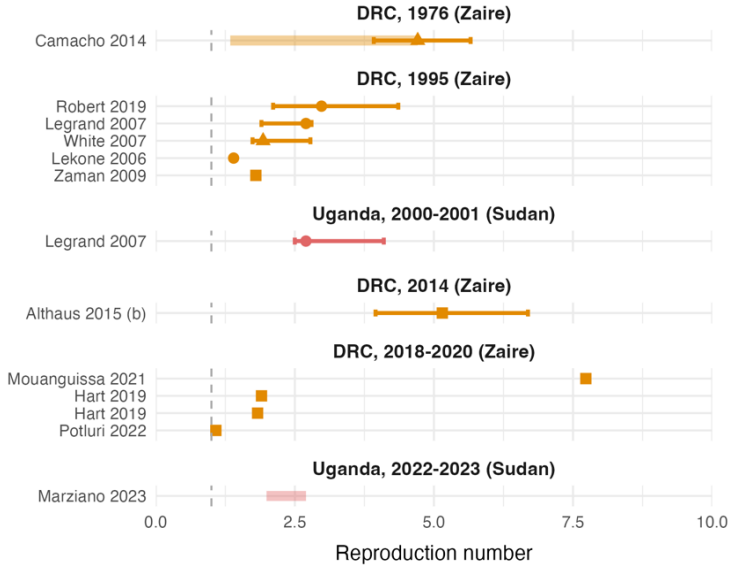
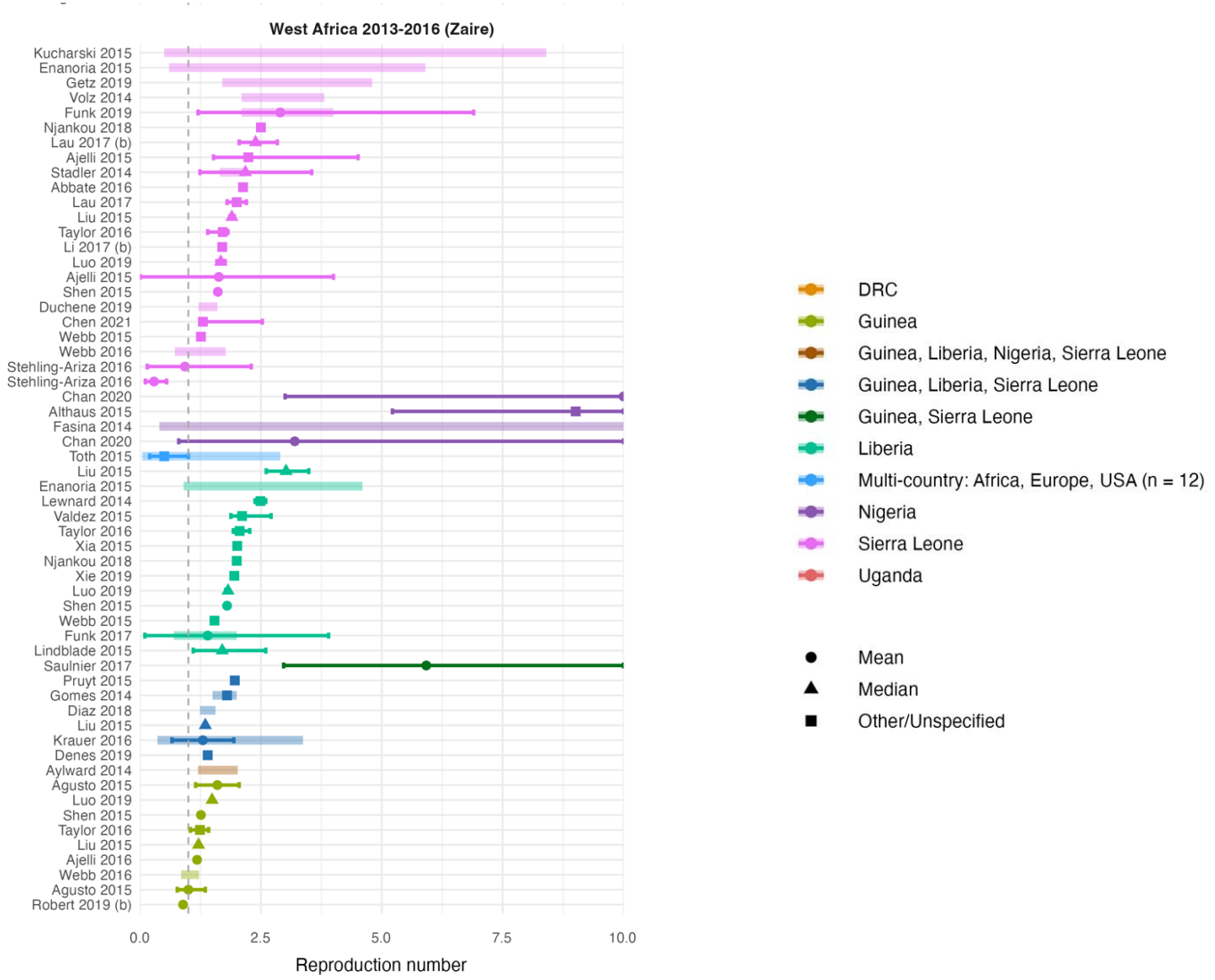
- Data package to host curated and annotated data
- Install from github
- **version 1.1.0** releases data from Lassa and Ebola review

# Basic Reproduction Number



# Epidemiological delays

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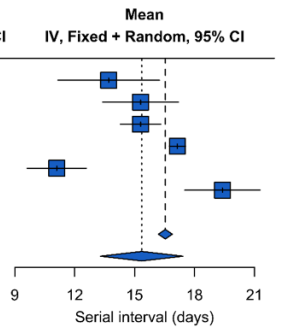
*serial interval*

**A**

| Study | Mean | SD | Total | Weight (common) | Weight (random) | Mean IV, Fixed + Random, 95% CI |
|---|---|---|---|---|---|---|
| Ajelli 2015 | 13.70 | 4.50 | 12 | 1.87% | 14.52% | 13.70 [11.15; 16.25] |
| Aylward 2014 | 15.30 | 9.30 | 92 | 3.36% | 16.09% | 15.30 [13.40; 17.20] |
| Chan 2020 | 15.30 | 2.30 | 20 | 11.96% | 17.82% | 15.30 [14.29; 16.31] |
| Dowell 1999 | 17.14 | 2.93 | 200 | 73.91% | 18.48% | 17.14 [16.74; 17.55] |
| Muoghalu 2017 | 11.10 | 5.20 | 47 | 5.50% | 16.98% | 11.10 [ 9.61; 12.59] |
| Pettey 2017 | 19.40 | 5.10 | 28 | 3.40% | 16.11% | 19.40 [17.51; 21.29] |
| **Total (common effect, 95% CI)** | | | **399** | **100.00%** | **--** | **16.54 [16.19; 16.89]** |
| **Total (random effect, 95% CI)** | | | | **--** | **100.00%** | **15.36 [13.29; 17.42]** |

Heterogeneity: $Tau^2 = 5.9835$; $Chi^2 = 80.94$, df = 5 ($P < 0.01$); $I^2 = 94\%$

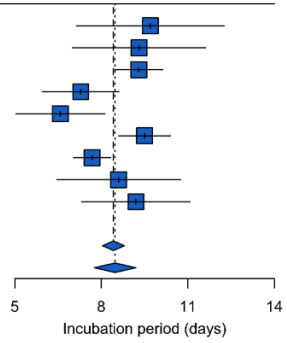



*incubation period*

**B**

| Study | Mean | SD | Total | Weight (common) | Weight (random) | Mean IV, Fixed + Random, 95% CI |
|---|---|---|---|---|---|---|
| Ajelli 2015 | 9.70 | 3.70 | 8 | 2.19% | 5.70% | 9.70 [7.14; 12.26] |
| Althaus 2015 | 9.31 | 5.28 | 20 | 2.69% | 6.58% | 9.31 [6.99; 11.63] |
| Chan 2020 | 9.30 | 1.90 | 20 | 20.79% | 16.07% | 9.30 [8.47; 10.13] |
| Dowell 1999 | 7.28 | 3.50 | 27 | 8.26% | 12.12% | 7.28 [5.96; 8.61] |
| Francesconi 2003 | 6.58 | 3.85 | 24 | 6.07% | 10.57% | 6.58 [5.04; 8.12] |
| Muoghalu 2017 | 9.50 | 4.00 | 76 | 17.82% | 15.51% | 9.50 [8.60; 10.40] |
| Wamala 2010 | 7.68 | 3.53 | 116 | 34.96% | 17.60% | 7.68 [7.04; 8.32] |
| Xu 2016 | 8.60 | 6.10 | 31 | 3.13% | 7.27% | 8.60 [6.45; 10.75] |
| Yan 2015 | 9.20 | 6.70 | 49 | 4.10% | 8.58% | 9.20 [7.32; 11.08] |
| **Total (common effect, 95% CI)** | | | **371** | **100.00%** | **--** | **8.42 [8.04; 8.80]** |
| **Total (random effect, 95% CI)** | | | | **--** | **100.00%** | **8.48 [7.76; 9.20]** |

Heterogeneity: $Tau^2 = 0.6616$; $Chi^2 = 25.46$, df = 8 ($P < 0.01$); $I^2 = 69\%$



# Epidemiological delays

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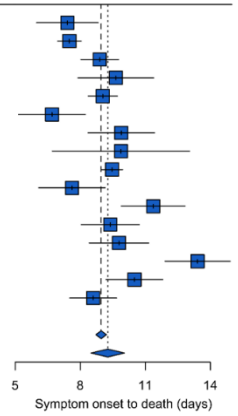
*time from symptom onset to death*

C

| Study | Mean | SD | Total | Weight (common) | Weight (random) | Mean IV, Fixed + Random, 95% CI |
|---|---|---|---|---|---|---|
| Althaus 2015 | 7.41 | 3.24 | 20 | 2.98% | 6.15% | 7.41 [ 5.99; 8.83] |
| Aylward 2014 | 7.50 | 6.80 | 594 | 20.09% | 7.49% | 7.50 [ 6.95; 8.05] |
| Faye 2015 | 8.90 | 4.00 | 82 | 8.01% | 7.09% | 8.90 [ 8.03; 9.77] |
| Francesconi 2003 | 9.64 | 3.46 | 15 | 1.96% | 5.55% | 9.64 [ 7.89; 11.39] |
| Lanini 2015 | 9.04 | 3.17 | 84 | 13.07% | 7.34% | 9.04 [ 8.36; 9.72] |
| Muoghalu 2017 | 6.70 | 4.10 | 27 | 2.51% | 5.92% | 6.70 [ 5.15; 8.25] |
| Nanclares 2016 | 9.89 | 3.92 | 25 | 2.54% | 5.94% | 9.89 [ 8.36; 11.43] |
| Roddy 2012 | 9.88 | 5.36 | 11 | 0.60% | 3.36% | 9.88 [ 6.71; 13.05] |
| Rosello 2015 | 9.47 | 4.44 | 317 | 25.14% | 7.55% | 9.47 [ 8.98; 9.96] |
| Rosello 2015 | 7.62 | 4.44 | 32 | 2.54% | 5.94% | 7.62 [ 6.08; 9.16] |
| Rosello 2015 | 11.37 | 5.41 | 52 | 2.78% | 6.06% | 11.37 [ 9.90; 12.84] |
| Rosello 2015 | 9.39 | 5.67 | 68 | 3.31% | 6.28% | 9.39 [ 8.04; 10.74] |
| Schieffelin 2014 | 9.79 | 4.32 | 38 | 3.19% | 6.24% | 9.79 [ 8.42; 11.16] |
| Uyeki 2016 | 13.42 | 1.72 | 5 | 2.64% | 5.99% | 13.42 [11.91; 14.92] |
| Wamala 2010 | 10.50 | 4.19 | 39 | 3.48% | 6.35% | 10.50 [ 9.19; 11.82] |
| Xu 2016 | 8.60 | 4.80 | 76 | 5.16% | 6.75% | 8.60 [ 7.52; 9.68] |
| **Total (common effect, 95% CI)** | | | **1485** | **100.00%** | **--** | **8.97 [ 8.72; 9.21]** |
| **Total (random effect, 95% CI)** | | | | **--** | **100.00%** | **9.27 [ 8.50; 10.04]** |

Heterogeneity: $Tau^2$ = 1.9793; $Chi^2$ = 101.06, df = 15 (P < 0.01); $I^2$ = 85%

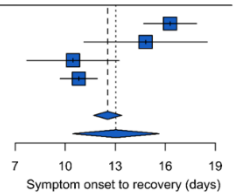



*time from symptom onset to recovery*

D

| Study | Mean | SD | Total | Weight (common) | Weight (random) | Mean IV, Fixed + Random, 95% CI |
|---|---|---|---|---|---|---|
| Kangbai 2021 | 16.29 | 8.26 | 105 | 28.40% | 28.11% | 16.29 [14.71; 17.87] |
| Nanclares 2016 | 14.82 | 9.42 | 25 | 5.21% | 19.14% | 14.82 [11.13; 18.51] |
| Roddy 2012 | 10.47 | 5.47 | 15 | 9.25% | 23.08% | 10.47 [ 7.70; 13.24] |
| Wamala 2010 | 10.82 | 4.99 | 77 | 57.14% | 29.67% | 10.82 [ 9.70; 11.93] |
| **Total (common effect, 95% CI)** | | | **222** | **100.00%** | **--** | **12.55 [11.71; 13.39]** |
| **Total (random effect, 95% CI)** | | | | **--** | **100.00%** | **13.04 [10.46; 15.63]** |

Heterogeneity: $Tau^2$ = 5.5347; $Chi^2$ = 34.42, df = 3 (P < 0.01); $I^2$ = 91%



# Ebola species analysis

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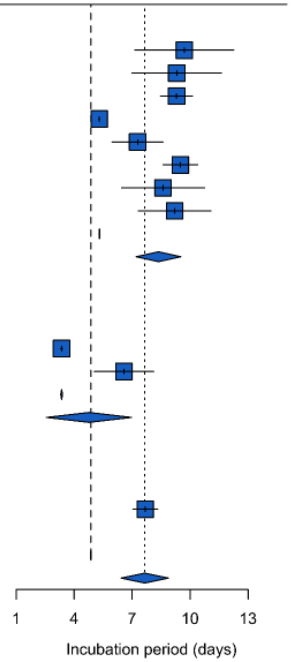
## *Onset to death*

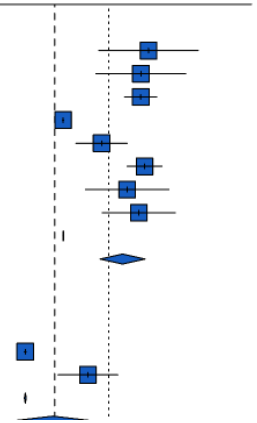
| Study or Subgroup | Mean | SD | Total | Weight (common) | Weight (random) | Mean IV, Fixed + Random, 95% CI |
|---|---|---|---|---|---|---|
| **Ebola virus species = Zaire** | | | | | | |
| Ajelli 2015 | 9.70 | 3.70 | 8 | 0.01% | 7.15% | 9.70 [7.14; 12.26] |
| Althaus 2015 | 9.31 | 5.28 | 20 | 0.01% | 7.59% | 9.31 [6.99; 11.63] |
| Chan 2020 | 9.30 | 1.90 | 20 | 0.07% | 9.94% | 9.30 [8.47; 10.13] |
| Chowell 2004 | 5.30 | 0.23 | 315 | 76.82% | 10.42% | 5.30 [5.27; 5.33] |
| Dowell 1999 | 7.28 | 3.50 | 27 | 0.03% | 9.29% | 7.28 [5.96; 8.61] |
| Muoghalu 2017 | 9.50 | 4.00 | 76 | 0.06% | 9.86% | 9.50 [8.60; 10.40] |
| Xu 2016 | 8.60 | 6.10 | 31 | 0.01% | 7.89% | 8.60 [6.45; 10.75] |
| Yan 2015 | 9.20 | 6.70 | 49 | 0.01% | 8.37% | 9.20 [7.32; 11.08] |
| Total (common effect, 95% CI) | | | 546 | 77.02% | -- | 5.31 [5.28; 5.34] |
| Total (random effect, 95% CI) | | | | -- | 70.52% | 8.36 [7.21; 9.52] |
| Heterogeneity: $Tau^2$ = 2.1488; $Chi^2$ = 229.02, df = 7 (P < 0.01); $I^2$ = 97% | | | | | | |
| **Ebola virus species = Sudan** | | | | | | |
| Chowell 2004 | 3.35 | 0.49 | 425 | 22.84% | 10.41% | 3.35 [3.30; 3.40] |
| Francesconi 2003 | 6.58 | 3.85 | 24 | 0.02% | 8.94% | 6.58 [5.04; 8.12] |
| Total (common effect, 95% CI) | | | 449 | 22.86% | -- | 3.35 [3.31; 3.40] |
| Total (random effect, 95% CI) | | | | -- | 19.36% | 4.77 [2.57; 6.98] |
| Heterogeneity: $Tau^2$ = 2.2591; $Chi^2$ = 16.85, df = 1 (P < 0.01); $I^2$ = 94% | | | | | | |
| **Ebola virus species = Bundibugyo** | | | | | | |
| Wamala 2010 | 7.68 | 3.53 | 116 | 0.12% | 10.13% | 7.68 [7.04; 8.32] |
| **Total (common effect, 95% CI)** | | | **1111** | **100.00%** | -- | **4.87 [4.84; 4.89]** |
| **Total (random effect, 95% CI)** | | | | -- | **100.00%** | **7.65 [6.43; 8.88]** |
| Heterogeneity: $Tau^2$ = 3.7533; $Chi^2$ = 5552.03, df = 10 (P = 0); $I^2$ = 100% | | | | | | |
| Test for subgroup differences (common effect): $Chi^2$ = 5306.15, df = 2 (P = 0) | | | | | | |
| Test for subgroup differences (random effects): $Chi^2$ = 8.02, df = 2 (P = 0.02) | | | | | | |




| Study or Subgroup | Mean | SD | Total | Weight (common) | Weight (random) | Mean IV, Fixed + Random, 95% CI |
|---|---|---|---|---|---|---|
| **Ebola virus species = Zaire** | | | | | | |
| Althaus 2015 | 7.41 | 3.24 | 20 | 1.68% | 4.70% | 7.41 [ 5.99; 8.83] |

## *Onset to recovery*

| Study or Subgroup | Mean | SD | Total | Weight (common) | Weight (random) | Mean IV, Fixed + Random, 95% CI |
|---|---|---|---|---|---|---|
| **Ebola virus species = Zaire** | | | | | | |
| Ajelli 2015 | 9.70 | 3.70 | 8 | 0.01% | 7.15% | 9.70 [7.14; 12.26] |
| Althaus 2015 | 9.31 | 5.28 | 20 | 0.01% | 7.59% | 9.31 [6.99; 11.63] |
| Chan 2020 | 9.30 | 1.90 | 20 | 0.07% | 9.94% | 9.30 [8.47; 10.13] |
| Chowell 2004 | 5.30 | 0.23 | 315 | 76.82% | 10.42% | 5.30 [5.27; 5.33] |
| Dowell 1999 | 7.28 | 3.50 | 27 | 0.03% | 9.29% | 7.28 [5.96; 8.61] |
| Muoghalu 2017 | 9.50 | 4.00 | 76 | 0.06% | 9.86% | 9.50 [8.60; 10.40] |
| Xu 2016 | 8.60 | 6.10 | 31 | 0.01% | 7.89% | 8.60 [6.45; 10.75] |
| Yan 2015 | 9.20 | 6.70 | 49 | 0.01% | 8.37% | 9.20 [7.32; 11.08] |
| Total (common effect, 95% CI) | | | 546 | 77.02% | -- | 5.31 [5.28; 5.34] |
| Total (random effect, 95% CI) | | | | -- | 70.52% | 8.36 [7.21; 9.52] |
| Heterogeneity: $Tau^2$ = 2.1488; $Chi^2$ = 229.02, df = 7 (P < 0.01); $I^2$ = 97% | | | | | | |
| **Ebola virus species = Sudan** | | | | | | |
| Chowell 2004 | 3.35 | 0.49 | 425 | 22.84% | 10.41% | 3.35 [3.30; 3.40] |
| Francesconi 2003 | 6.58 | 3.85 | 24 | 0.02% | 8.94% | 6.58 [5.04; 8.12] |
| Total (common effect, 95% CI) | | | 449 | 22.86% | -- | 3.35 [3.31; 3.40] |



# Case Fatality Ratio

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# Transmission models

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- We extracted 295 models.
  - 71% compartmental,
  - 6% branching process,
  - 6% agent-based models,
  - 17% other model types or combinations of models.
- Various assumptions were made in the models including homogenous mixing, heterogeneity in transmission rates between groups or over time and the latent period being the same as the incubation period.
- Only 13% of models (n=37) have any publicly available code associated with them, limiting re-usability.

# Conclusions

- Much is already known about the Ebola Zaire species; however, our review highlights a critical lack of evidence for other species such as Sudan, Bundibugyo and Taï forest.
- Initial analyses suggest statistically significant differences in key parameters between species such as the incubation period and delays from onset to death or recovery.
- There is high variability across studies, likely driven by differences in epidemic context.

## pre-print on medRxiv