Serocalculator: An open-source R package for estimating seroincidence from cross-sectional serosurveys

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UCDAVIS HEALTH

GOAL: Easily and reproducibly translate quantitative antibody responses at the population level into meaningful and accurate epidemiological measures of infection burden

Seroepidemiology & Environmental Surveillance for Enteric Fever (SEES)

Blood culture confirmed

Blood culture performed

Sought care at a surveillance site

Symptomatic infections

All infections (including subclinical)

THE AGA KHAN UNIVERSITY

Aiemjoy et al, Lancet Infectious Diseases, 2022

Typhoid conjugate vaccines are effective but have yet to be widely adopted

Together We Can Take on Typhoid

Within-host model of antibody dynamics

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RESEARCH ARTICLE

Estimation of seroconversion rates for infectious diseases: Effects of age and noise

This article expands

models of the serorer

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Linking the seroresponse to infection to within-host heterogeneity in antibody production

EPIDEMIC

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Statistics WILEY

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Within-host model of antibody dynamics

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Within-host model of antibody dynamics

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Within-host model of antibody dynamics

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Within-host model of antibody dynamics

Defining incidence

The **incidence rate** of a disease over a **specific time period** is the rate at which individuals in a population are **acquiring** the **disease** per **person-time at risk**.

Example: if there are 10 new cases of typhoid in a population of 1000 over a one month time period, then the incidence rate for that time period is *"10 new cases per 1000 persons per month"*.

Incidence from an individual's perspective

From the perspective of an individual in the population:

 $+$ the **incidence rate** at a given time point (t) is the instantaneous **probability** (density) of **becoming infected** at that time point, **given** that they are **at risk** at that time point. +That is, the incidence rate is a **hazard** rate.

+Notation: let's use λ_t to denote the incidence rate at time t .

Cross-sectional antibody surveys

+We recruit participants from the population of interest.

- $+$ For each survey participant, we measure antibody levels (Y) for the disease of interest
- +Each participant was **most recently infected** at some time **prior** to when we measured their antibodies.

+T is a **latent, unobserved variable**.

Modeling assumptions

We **assume** that:

+The incidence rate is approximately **constant over time** and **across the population** ("**constant and homogenous incidence**")

+Participants are always at risk of a new infection, regardless of how recently they have been infected ("**no lasting immunity**").

Time since infection and incidence

Under those assumptions:

 $+ T$ has an **exponential distribution**:

 $+p(T = t) = \lambda \exp\{-\lambda t\}$

+the rate parameter is the incidence rate

Likelihood of latent infection times

$$
+ \mathcal{L}^*(\lambda) = \prod_{i=1}^n p(T = t_i) = \prod_{i=1}^n \lambda \exp(-\lambda t_i)
$$

$$
+ \ell^*(\lambda) = \log\{\mathcal{L}^*(\lambda)\} = \sum_{i=1}^n \log\{\lambda\} - \lambda t_i
$$

$$
+ \ell^{*'}(\lambda) = \sum_{i=1}^n \lambda^{-1} - t_i
$$

$$
+ \hat{\lambda}_{\text{ML}}^* = \frac{n}{\sum_{i=1}^n t_i} = \frac{1}{\bar{t}}
$$

Likelihood of observed data

$$
f + p(Y = y) = \int_t p(Y = y, T = t) dt
$$

+p(Y = y, T = t) = p(Y = y | T = t) p(T = t)

Model for active infection period

Notation:

 $+x(t)$: Pathogen concentration at time t $+y(t)$: Antibody concentration at time t Model:

 $+x'(t) = \alpha x(t) - \beta y(t)$ $+y'(t) = \delta y(t)$

Within-host model for post-infection

antibody decay

 $+b(t) = 0$

 $\widetilde{\mathcal{L}}(t) = -\alpha y(t)^r$

Interactive Shiny app:

Open source analytical package for R available on GitHub https://github.com/UCD <u> /\$ERG/serocalculator</u>

²₆ ucd-serg.github.io/serocalculator/index.html

serocalculator 1.2.0.9006 Get started Reference Articles V Changelog

serocalculator

Antibody levels measured in a cross-sectional population sample can be translated into an estimate of the frequency with which seroconversions (infections) occur in the sampled population. In other words, the presence of many high antibody titers indicates that many individuals likely experienced infection recently and the burden of disease is high in the population, while low titers indicate a low frequency of infections in the sampled population and therefore a lower burden of disease.

The serocalculator package was designed to use the longitudinal response characteristics using a set of modeled parameters characterizing the longitudinal response of the selected serum antibodies. More details on the underlying methods can be found in Getting Started.

View on CRAN Browse source code

License

 $GPL-3$

Links

Community Contributing quide Code of conduct

Citation Citing serocalculator

National Institute of Allergy and **Infectious Diseases** **R CODE OUTPUT**

Import longitudinal antibody parameters from OSF curves <- "https://osf.io/download/rtw5k/" %>% load curve params()

Visualize curve parameters curves %>% autoplot()

Import sample population data from OSF xs_data <- "https://osf.io/download//n6cp3/" %>% load pop data()

Visualize antibody data xs_data %>% $autoplot(strata = "Country", type='density')$

R code using serocalculator

Estimate seroincidence stratified by country and age

```
est Country ageCat = est.incidence.by(strata = c("Country", "ageCat"),
    pop data = xs data,
    curve params = curves,
    noise_params = noise, 
    antigen_isos = c("HlyE_IgG", "HlyE_IgA")
)
```
summary(est Country ageCat)

Stratum Country ageCat n est.start incidence.rate SE CI.lwr CI.upr Stratum 1 Bangladesh <5 101 0.1 0.39998293 0.0395 0.3297 0.4853 Stratum 2 Bangladesh 5-15 256 0.1 0.47701125 0.032 0.4183 0.544 Stratum 3 Bangladesh 16+ 44 0.1 0.44929893 0.0763 0.3221 0.6267 Stratum 4 Nepal <5 171 0.1 0.02026628 0.0044 0.0132 0.0311 Stratum 5 Nepal 5-15 378 0.1 0.0354936 0.0031 0.0299 0.0421 Stratum 6 |Nepal | 16+ | 211 | 0.1 | 10.0935101| 0.0078| 0.0795| 0.11 Stratum 7 Pakistan <5 126 0.1 0.10592089 0.0136 0.0823 0.1363 Stratum 8 Pakistan 5-15 261 0.1 0.1145304 0.0084 0.0991 0.1323 Stratum 9 Pakistan 16+ 107 0.1 0.19011951 0.0204 0.1541 0.2346

Results

Serocalculator

The serocalculator R package provides a rapid and computationally simple method for calculating seroconversion rates, as originally published in Simonsen (2009) and Teunis (2012), and further developed in subsequent publications by de Graaf (2014), Teunis (2016), and Teunis (2020).

In short, longitudinal seroresponses from confirmed cases with a known symptom onset date are assumed to represent the time course of human serum antibodies against a specific pathogen. Therefore, by using these longitudinal antibody dynamics with any cross-sectional sample of the same antibodies in a human population, an incidence estimate can be calculated.

Further details on the methodology can be found on the main package website.

This app provides a user-friendly interface to use the serocalculator methodology without the need for specialized coding knowledge. Users should follow the steps to:

- · Import the required datasets
- · Inspect their data
- · Estimate seroincidence
- Prepare a report (optional)

Required datasets:

- · Cross-sectional population-based dataset with age and quantitative antibody results
- · Noise parameters
- · Longitudinal curve parameters

If you need assistance or encounter a clear bug, please file an issue with a minimal reproducible example on GitHub

https://ucdserg.shinyapps.io/shiny serocalculator/

e-illing the gaps with erocalculator

Stanford
University

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SEACTN

South and Southeast Asian **Community-based-Trials Network**

International *Accine* **nstitute**

World Health
Organization

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South Sudan

TyVAC Typhoid Vaccine
Acceleration Consortium

CENTER FOR VACCINE DEVELOPMENT . OXFORD VACCINE GROUP . PATH

ACKNOWLEDGEMENTS

BILL&MELINDA **GATES** foundation

Fogarty International Center

Toronto General
Toronto Western
Princess Margaret
Toronto Rehab

International Vaccine Institute

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CHRF

Extra slides

Biological noise

When we measure antibody concentrations in a blood sample, we are essentially counting molecules (using biochemistry).

We might miss some of the antibodies (undercount, false negatives) and we also might incorrectly count some other molecules that aren't actually the ones we are looking for (overcount, false positives, cross-reactivity).

We are more concerned about overcount (cross-reactivity) than undercount. For a given antibody, we can do some analytical work beforehand to estimate the distribution of overcounts, and add that to our model $p(Y = y | T = t)$.

Measurement noise

There are also some other sources of noise in our bioassays; user differences in pipetting technique, random ELISA plate effects, etc. This noise can cause both overcount and undercount. We can also estimate the magnitude of this noise source, and include it in $p(Y = y | T = t)$.

Variation in antibody kinetics by:

