A Bayesian Weibull survival model for time to infection data measured with delay

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Rational

Unless a perfect diagnostic test exists, time to detection of infection is systematically longer than time to infection. Hence, to infer about the time-to-infection risk, survival analysis models should adjust for the delayed detection of infection. We developed a Bayesian Weibull survival model that adjusts for infection risk, survival analysis models should adjust for the delayed detection of infection. Hence, to infer about the time-to-infection, we need to consider the observation of a positive test result as an event that occurs with a delay. To use our model we needed to specify prior information about the time it takes from MAP infection to get a milk ELISA positive result. Based on available information and expert opinion (N.S.S.), we chose a prior value of \( u \) as 1300 days (3.5 years) extending from 1000 (2.7 years) to 1600 (4.4 years) days.

Definitions

Time to infection (tr): The time interval required for the specific component cause to induce infection. The specific component cause comprises of a set of minimal conditions and events (e.g. the single, continuous or repetitive adequate exposure to the pathogen) sufficient to inevitably produce infection.

Time to detection of infection (t): The time required for detection of the pathogen and/or the immune response of the host.

Detection delay (u): The time interval between (tr) and (t).

Bayesian model

For the \( i \)th individual, let the unobserved \( tr_i \) (e.g. time to MAP infection) be equal to:

\[
tr_i = t_i - u_i \tag{Eq. 1}
\]

We assume that detection delay follows an approximately normal distribution:

\[
u_i \sim N(m_u, \tau u) \tag{Eq. 2}
\]

with \( m_u \) the expected mean of \( u \) and \( \tau u \) the precision of the normal distribution.

For either censored or uncensored observations, we assume that \( tr_i \) follow a truncated Weibull distribution, with the lower bound (lb) corresponding to zero or the censoring time:

\[
tr_i \sim W(\lambda_i, \rho), [lb, +\infty) \tag{Eq. 3}
\]

with \( \lambda_i = e^{\lambda u / \mu} \), and \( \rho \) the shape parameter of the Weibull distribution.

Given the observed distribution of the \( t_i \) and specifying the prior information on \( u \), the model is fully specified. Adjusted median survival times (\( m_i \)) for individuals with specific covariate information \( z_i \) can be estimated by:

\[
m_i = (\ln 2 e^{-b z_i})^{-1 / \rho} \tag{Eq. 5}
\]

Simulation- Sensitivity analysis

The impact of ignoring \( u \) on \( \rho \) and the regression coefficients depended on (a) the longevity and (b) the presence of differential or non-differential detection delay, (c) the prevalence and (d) the strength of association with the risk factor.

In all considered scenarios model parameters were accurately estimated as long as the true \( u \) value was included in the central 90th prior probability space.

Application

We utilized the proposed model to assess the risk of MAP infection in Danish dairy cattle by analyzing available time to milk seropositivity data. Detailed data information are in Nielsen and Ersbol (2006).

We first ran a standard Weibull model and subsequently our (II) model. Models were run in the freeware program WinBUGS. For all simulations and applications convergence diagnostics of the MCMC chain revealed no convergence problems.

Results

Low or heavy shedders posed a higher risk to test milk-ELISA positive and were infected earlier in their lives than non-shedders. There was no difference between heavy and low shedders.

Heavy or low MAP shedders are likely to get infected earlier in their lives than non-shedders.

The shape parameter \( \rho \) of the weibull distribution was \( \rho > 2.67 \) and \( \rho < 0.56 \).

Thus, the incidence of seroconversion increases (Fig. 1), while the incidence of infection decreases with age (Fig. 2), respectively.

Discussion

Young calves are more susceptible to MAP infection and resistance to infection increases with aging (Fig. 2), while older animals are more likely to become seropositive (Fig. 1).

Ignoring detection delay can have a severe impact on the estimated risk and median survival time. The proposed model led to corrected estimates and can be particularly useful in the case of chronic infections with a long latent infection period.

Simulations

We estimated the risk of MAP infection in Danish dairy cattle by analyzing available time to milk seropositivity data.