Estimating the force of infection with *Helicobacter pylori* in Japan

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Background

Helicobacter pylori (*H. pylori*) is a bacterium as the most important cause of gastric ulcer and cancer. The long-lasting natural history of inflammation caused by chronic and atrophic gastritis is thought to be followed by carcinogenesis, and thus, the gastric cancer. While the seroprevalence against *H. pylori* in Japan has declined over the birth year [1], Japanese people have yet exhibited a relatively high risk of gastric cancer [2]. As an underlying explanation of the high incidence of gastric cancer, a high prevalence of *H. pylori* in the elderly in Japan has been considered as consistent with the natural history. Considering that the route of transmission with *H. pylori* is likely associated with direct contact and hygienic conditions during the childhood, decreased contact with environment in early ages may have occurred, leading to the decreased seroprevalence of *H. pylori* even among adults.

Objective

The hazard rate or the time and age-dependent risk of infection with *H. pylori* has yet to be explicitly reconstructed from the seroepidemiological data. The present study employed mathematical models to estimate the time- and age-dependent force of infection (FOI), i.e., the rate at which susceptible individuals are infected, with *H. pylori* in Japan, predicting the future seroprevalence by time and age.

Method

A total of 10 different seroepidemiological survery datasets in Japan was used for the analysis.

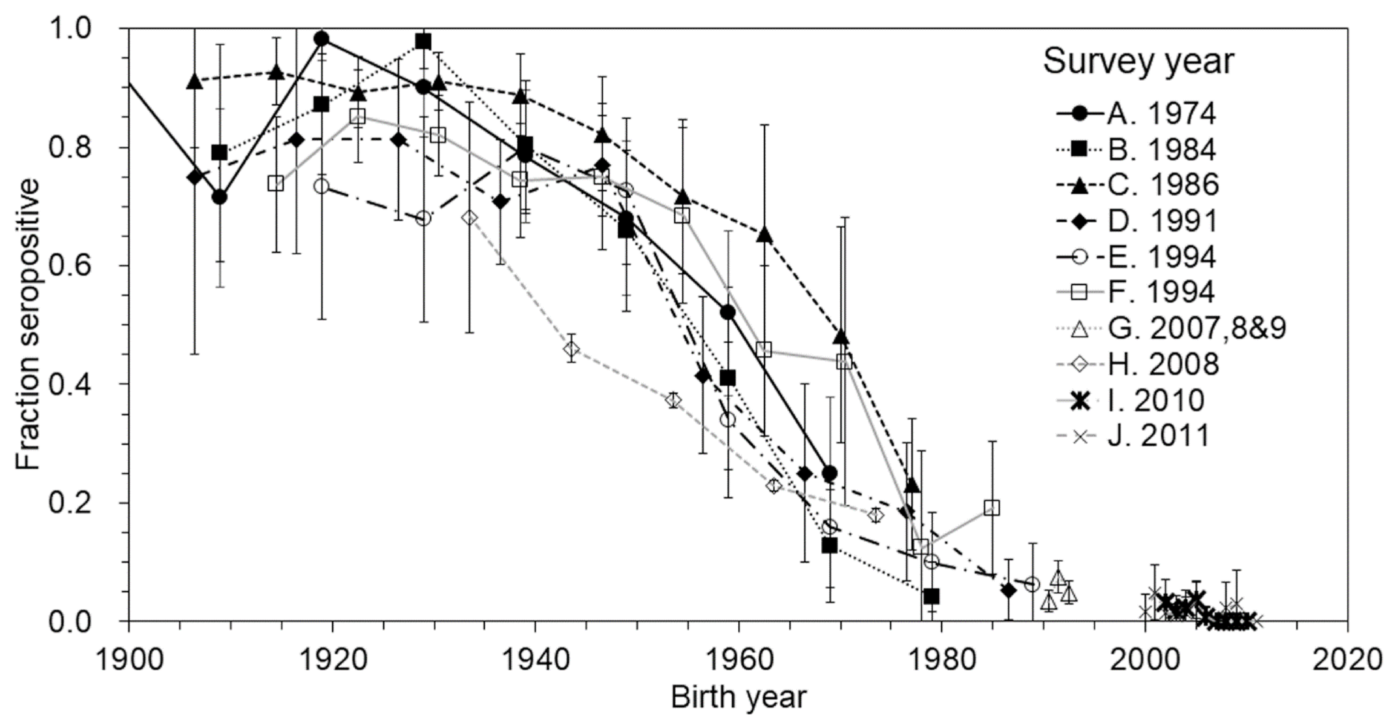
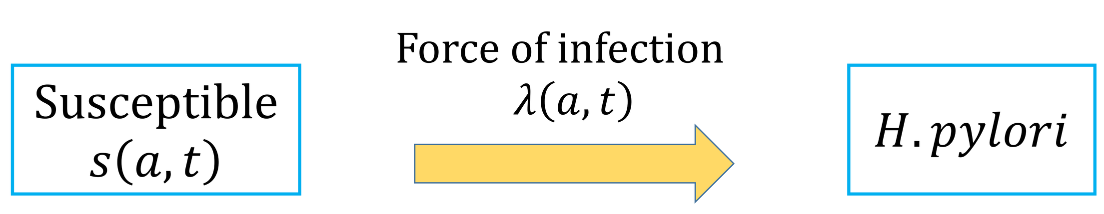


Figure 1: Seroprevalence of anti-*Helicobacter pylori* antibody in Japan by birth year. Antibody positive fraction is reviewed as a function of birth year. Same marks represent the dataset arising from an identical publication in the same survey year. Whiskers extend to lower and upper 95% confidence intervals.

Basic concept of mathematical model



- $s(a,t)$: the fraction of susceptible individuals at age a and year t
  - Boundary condition: $s(0,t)=1$
- $\lambda(a,t)$: the FOI that depends on age a and year t
  - The rate at which susceptible individuals experience infection

$$\left(\frac{\partial}{\partial a}+\frac{\partial}{\partial t}\right)s(a,t)=-\lambda(a,t)s(a,t). \qquad (1)$$

- The FOI
  - Separable to age- and time-components

$$\lambda(a,t)=f(a)g(t). \qquad (2)$$

- The seroprevalence: $p(a,t)=1-\exp\left(-\int_{t-a}^{t}f(y-t+a)g(y)\,dy\right). \quad (3)$

Models with different assumptions of the force of infection

Model 1	Time-dependent FOI with an exponential decay
Model 2	Time-dependent FOI with a Gompertz-type decay
Model 3	Time- and age-dependent FOI with an exponential time-decay and exponential age-decay

To quantity the FOI by estimating parameters, likelihood-based approach was employed.

Results

Table: Model comparison of the time- and age-dependent force of infection to capture the transmission dynamics of *Helicobacter pylori* in Japan

Model identity	Functional assumption	Number of parameters	AIC
Model 1	Time-dependent FOI with an exponential decay	3	937.2
Model 2	Time dependent FOI with a Gompertz-type decay	4	3856.3
Model 3	Time- and age-dependent FOI with an exponential time-decay and exponential age-decay	4	2750.5

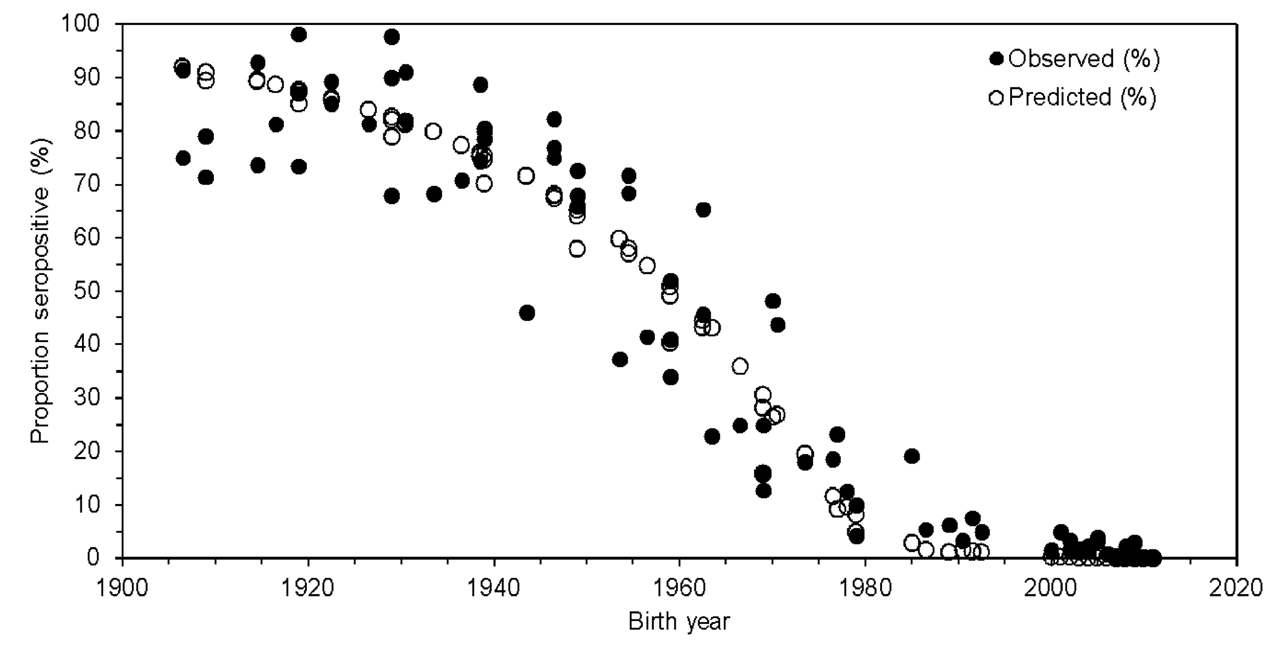


Figure 2: Comparison between observed and predicted seroprevalence against *Helicobacter pylori* in Japan by birth year. Observed data are plotted by birth year and compared against model prediction assumes time dependence in the force of infection with an exponential decay. Predictions were made as a function of survey year and age.

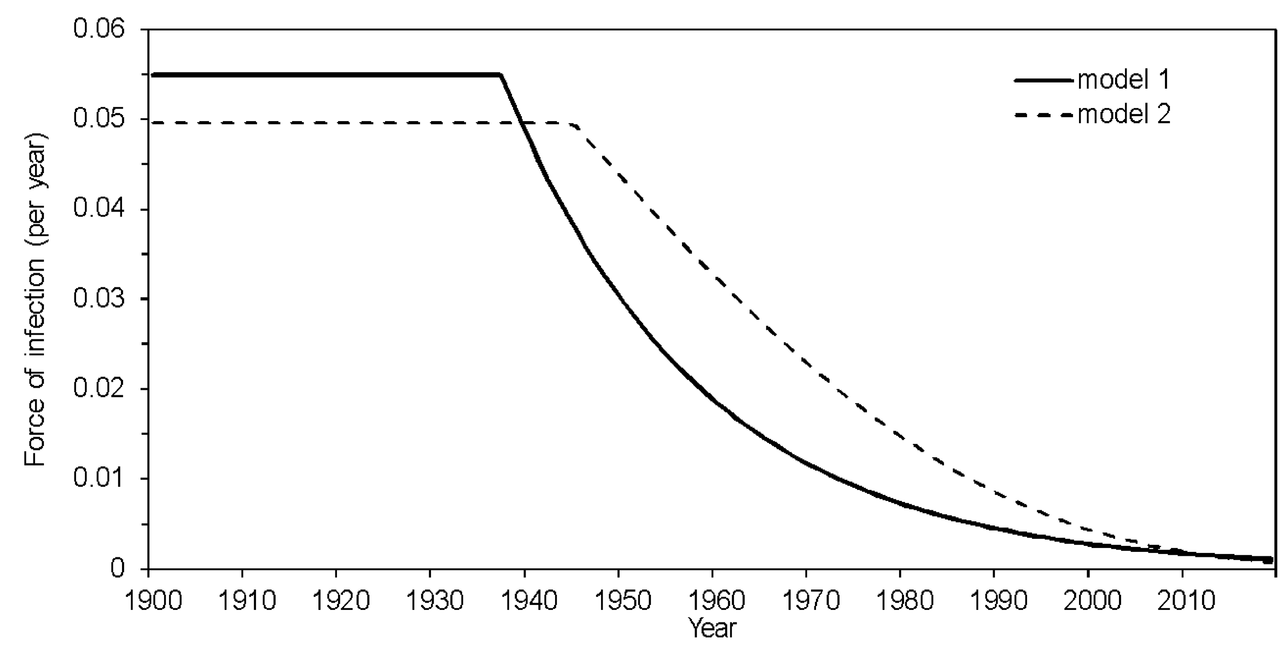


Figure 3: Estimated force of infection of *Helicobacter pylori* as a function of calendar time in Japan. Model 1 is the estimate of time-dependent force of infection with an exponential decay. Model 2 is the estimate of time-dependent force of infection with Gompertz-type decay.

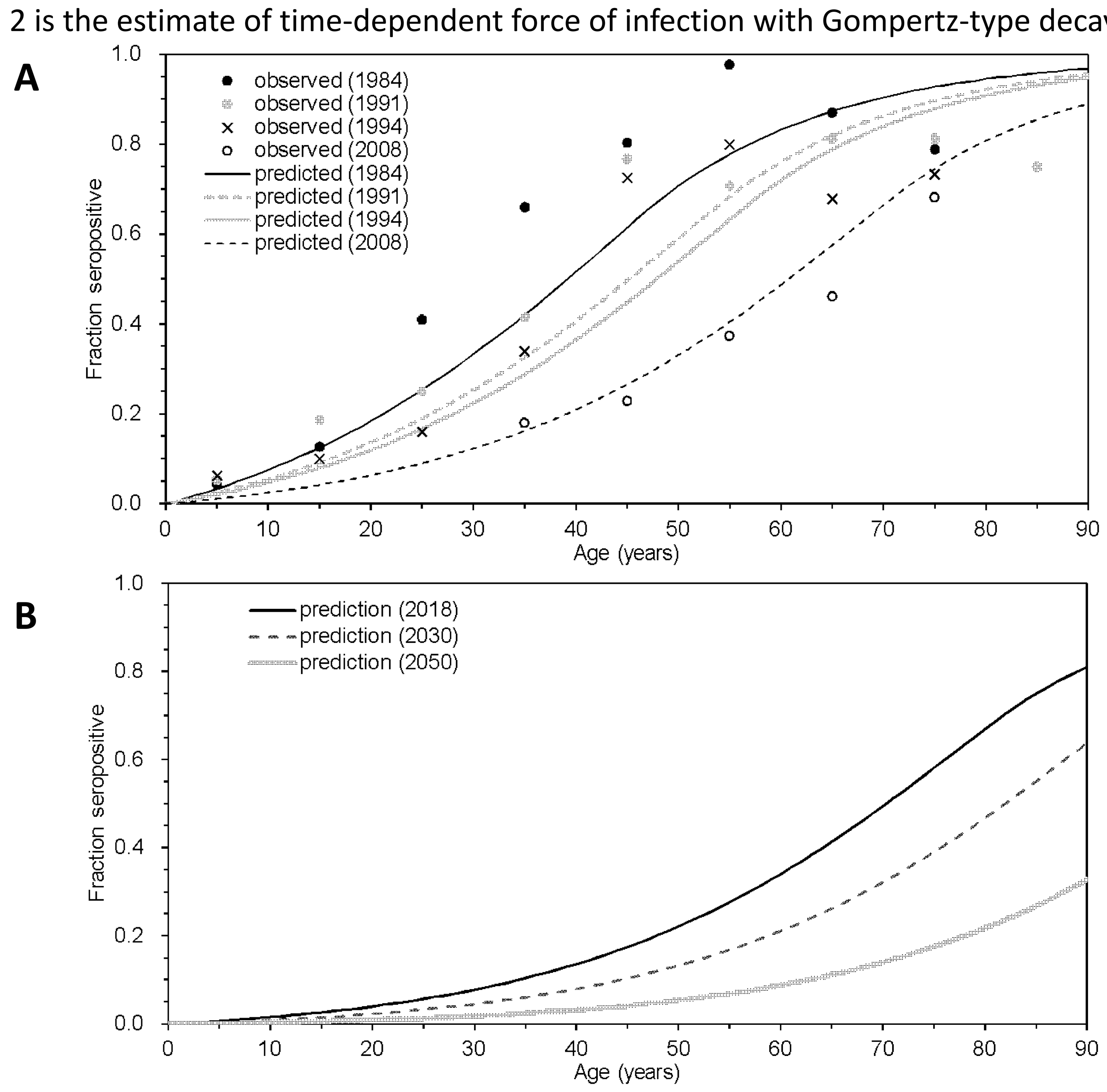


Figure 4: Prediction of the seroprevalence against *Helicobacter pylori* in the past and the future in Japan. (A) Comparison between observed and predicted seroprevalence by age and survey year. Lines are the expected values derived from the time-dependent force of infection with an exponential decay. (B) Prediction of the future seroprevalence against *Helicobacter pylori* in Japan. Gradual right shift in the seroprevalence is captured by our time-dependent force of infection with an exponential decay.

Conclusions

- ◆Time-dependent FOI with exponential decline was selected as the best fit model
- ◆FOI started decreasing during and/or shortly after World War Ⅱ (1937 vs 1945)
  - Consistent improvement in hygienic condition led to diminished transmission (e.g. reduction in infection opportunities through outdoor water or bath)
- ◆ Seroprevalence against *H. pylori* has continuously declined over time in Japan
- ◆Age of seropositive individuals would be shifted to older groups in the future
  - It anticipates the future decline in gastric ulcer and cancer incidence

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Conflict of Interest (COI): We declare that there is no conflict of interests between authors