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Article

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Modeling of the combined dynamics of leptospirosis transmission and seroconversion in herds

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Abstract

Leptospirosis is a zoonotic disease-causing illness in both humans and animals resulting in related economic impacts due to production loss as well as prevention and control efforts. Several mathematical models have been proposed to study the dynamics of infection but none of them has so far taken into account the dynamics of seroconversion. In this study, we have developed a general framework, based on the kinetic model for animal leptospirosis, that combines both the infection and the antibody dynamics to simultaneously follows both infection and seroconversion status of leptospirosis in a herd population. It is a stochastic compartmental model (for transition rates) with time delay (for seroconversion) which describes the progression of infection by a SEIR (susceptible, exposed, infected and removed) approach and seroconversion by four-state antibody kinetics (antibody negative and three antibody positive states of different antibody levels). The model shows that it is possible to assess and follow both infection and seroconversion status through the prism of diagnostic testing. Such an approach could prove useful to assist the competent authorities in their analyzes of epidemic situations and in the implementation of strategies for controlling and managing the associated risks.

Keywords: animal leptospirosis, antibody-dependent, diagnostic test, seroconversion dynamics, time-lag model

Introduction

Leptospirosis, caused by pathogenic spirochetes belonging to the genus *Leptospira* of the family Leptospiraceae[1]. It is an infectious disease found in human and other animals across the globe. However, the disease is prevalent mainly in subtropical or tropical countries where humid climates abide[2]. Humans and animals are infected after encountering either the waste products of infected animals or exposed to an environment that is contaminated with leptospires. Leptospires can enter through the body via small cuts, mucous membranes, or through wet skin[3].

In animals, the leptospirosis associated symptoms vary with infected serovars or host adapted serovars[3,4]. Some of the infected animals remain asymptomatic, and can spread the bacteria in the urine for lifelong[5]. The carriage of leptospires in the proximal renal tubules leads to contamination of soil, water, and rivers. This becomes the main sources of transmission. Leptospirosis in animals is a disease with a major worldwide economic impact. Clinical signs of the leptospirosis infection in cattle are mainly manifested by reproductive problems such as infertility, abortion, and weak offspring[6].

Due to the variety of symptoms, diagnosis tests depend on the laboratory assays used to identify leptospirosis infection. Laboratory techniques such as the detection of specific antibodies, microscopic agglutination test (MAT), indirect hemagglutination assay (IHA), and immuno-enzymatic assays (ELISA) are keys to detect the disease. MAT is the most common and standard technique used in serological examination as it produces high sensitivity and specificity results[7]. In addition, MAT is used to identify the circulated *Leptospira* serogroups[8–10] by simultaneously detecting both immunoglobulin M (IgM) and immunoglobulin G (IgG), which are classes of agglutinating antibodies[11,12]. Nonetheless, ELISA can differentiate IgM or IgG antibodies[10,13]. To detect the antigen, PCR is an alternative. This method can directly detect leptospiral DNA in the samples. However, it cannot identify the etiological serovars[12]. The isolation and identification of *Leptospira* is possible with the culture method. Nevertheless, the method is difficult for many reasons, for examples, type of samples and the timing of taken samples[12]. Therefore, all currently available leptospirosis infection diagnostic tests could not provide a definite indication.

To study the dynamics of leptospirosis, several mathematical models have been proposed[14–16]. Those models mainly focused on the sensitivity of the transmission parameters that are related to the number of infected animals based on the simulation results. Nevertheless, the time series of infected animals are not well defined due to the limitations of current diagnosis

methods. To follow the spread of the disease animal population, serological diagnostics are broadly accepted. However, to our knowledge, seroconversion of leptospirosis has never been considered in any previous models.

This study thus aims to assess the impact of seroconversion dynamics on the results derived from serological diagnostic tests and makes it possible to illustrate the actual epidemic schemes during the outbreak. We therefore built a general framework based on the kinetic model for animal leptospirosis that combines both the infection and the antibody dynamics. Using a compartmental model with time delay, the model simultaneously follows both infection and seroconversion dynamics. The status of the population is described as a function of the basic reproduction number, which illustrates the number of infections (epizootic size) and the prevalence of antibody-positive individuals.

Results

Seroconversion dynamical model

A first key result of this study is the description of the general framework of the seroconversion dynamical model consisted of a combination of the infection and antibody dynamics. The kinetic schemes of the infection dynamics, antibody dynamics and combined model are shown in Fig. 1 and the equations are described in the Methods section.

The infection dynamics was explained following the compartmental Susceptible-Exposed-Infectious-Recovered-Susceptible (SEIRS) model. Infectious animals can transmit the disease to susceptible animals that progress to exposed animals with a transmission rate λ. Exposed animals became infectious after an incubation period of mean duration $t_e = 1/\nu$. The mean duration of infection is $t_i = 1/\alpha$. Infectious animals progress to recovered and immune state, which became susceptible again after a mean duration of immunity of $t_r = 1/\gamma$. All animals die at a mortality rate μ considered as the population renewal rate. The set of equations related to the infection dynamics were provided in the Supplement Information (S1. Methods).

Regarding the antibody kinetics, the model is based on the antibody level of animals (mainly cattle here). Primarily exposed animals developed antibody levels from negative to positive in both IgM and IgG antibodies and later only positive IgG antibodies. IgM antibodies stay for 3 to 5 weeks (in cattle)[17] while IgG antibodies, appearing at the same time or just after IgM antibodies, stay for a much longer time[17]. Subsequently, the animal IgG antibodies decrease

at a rate ω_1 and became negative again in both IgM and IgG antibodies. Afterwards, re-infection of those animals rose their IgG antibodies to a higher level[18,19] (IgG+ state).

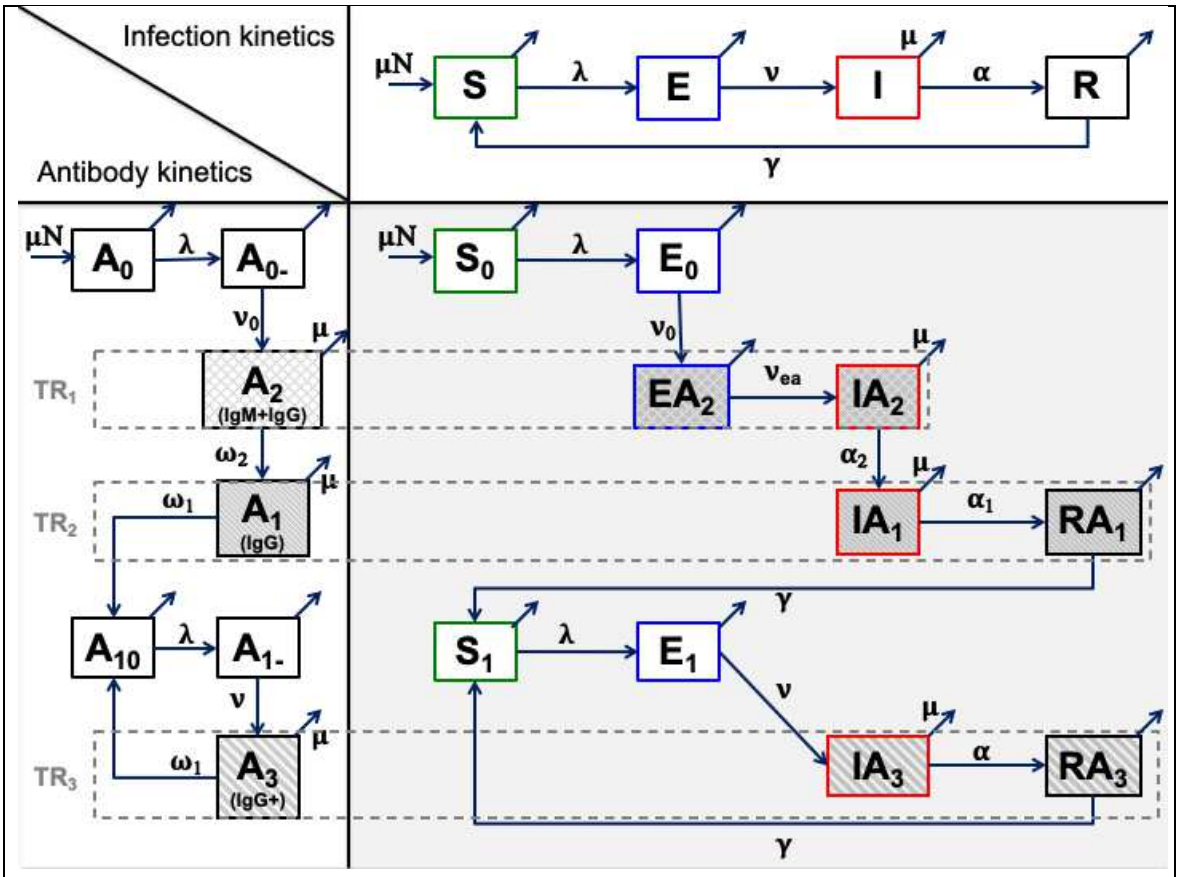

Figure 1. Kinetic scheme of the combined (right bottom) infection (top) and antibody (left bottom) dynamics. Description of population and parameters are provided in the main text and Table 1. TR_i stands for "Test Result" of a diagnostic test. Arrows tilted up correspond to the natural mortality rate μ (identical for all arrows but just indicated for some).

The infection and the antibody kinetics are combined to study the seroconversion dynamics. When susceptible animals were first infected with leptospires, they enter exposed state with negative antibodies. Subsequently, exposed animals develop IgM and IgG antibodies at a rate ν_0, and then progress to the infectious state at a rate ν_{ea}. However, infectious animals that recovered still carried IgG antibodies during the immunity period and became susceptible again with negative results in both IgM and IgG antibodies at a rate γ.

Model outcomes

The average number of infectious animals (i.e., IA_2, IA_1 and IA_3 compartments) are shown in Fig. 2 for the basic reproduction number R_0 equal to 1.5, 2.5, and 5.0. All results of the 10 compartments are shown in Fig. S1. As a check, the comparisons between the combined model and the reduced SEIRS model are shown in Fig. S2. At the beginning, there was no circulation of leptospirosis infection, the epidemic curve begins to increase and then oscillates around a plateau. The results showed that the epidemic curve could be divided into two phases: a growth phase and a stationary state. During the growth phase, the total infectious animals is mainly composed of IA_2 and IA_1. After that, the total infected population consists of the number of IA_3, IA_2, and IA_1, where most of the infectious animals came from IA_3.

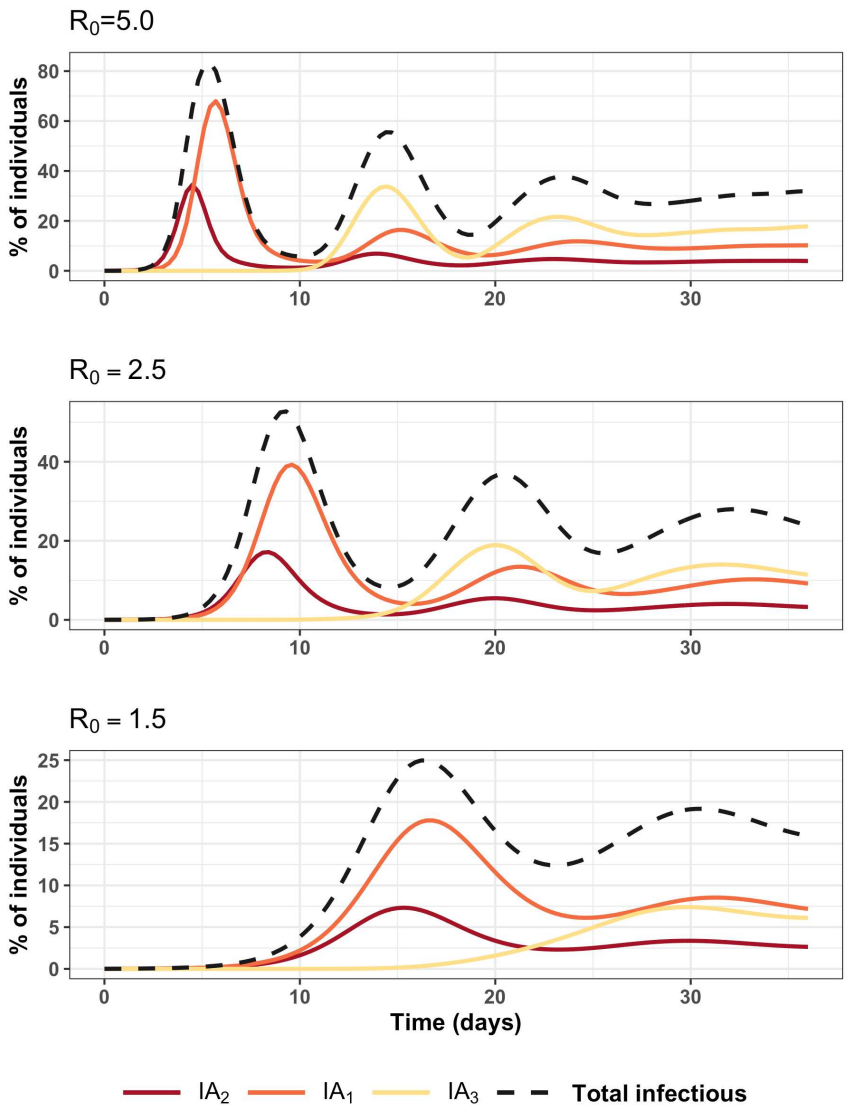

Figure 2. Average proportion of infected animals of type "i" (IA_2: carrying IgM and IgG antibodies, IA_1: only carrying IgG and IA_3 carrying high-level of IgG) as a function of time for various values of R_0. Proportion = 100 x number of animals / total population; with total population = 10,000.

For $R_0 > 1$, the first peak of infectious animals comes from the number of IA_2, carrying IgM and IgG antibodies, followed by IA_1 and IA_3 carrying IgG and high-level of IgG antibodies, respectively. The time interval between first peaks of each infectious compartments changed with R_0. For all value of R_0, the time interval between peaks of IA_2-IA_1 is about twice of the IgM duration $(1/\omega_2)$. The time interval between peaks of IA_2-IA_3 and IA_1-IA_3 decreased as R_0

increases. Increasing IgM duration leads to increase the time interval between peaks of IA_2-IA_3, and IA_1-IA_3, but does not affect the time interval between peaks of IA_2-IA_1 (data not shown). The cross-correlations of the monthly number of IA_2, IA_1 and IA_3 are plotted in Fig. S3. A positive strong correlation between IA_1 and IA_2 with a positive 4-month lag was found for all value of R_0, excepted for R_0=1.5, the lag time was 3 months. This 4-month lag corresponds to the time interval between the peaks of the number of IA_2 and IA_1 (Fig. 2). Overall, the correlation between IA_3-IA_2 and IA_3-IA_1 were similar excepted for $R_0 = 1.5$. From a -1.5 years to 1.5 years lag, the negative correlations between IA_3-IA_2 and IA_3-IA_1 were found, which implied that the high number of IA_2 and IA_1 related to the low number of IA_3. The simulation results can be used to forecast the number of IA_1 and IA_3 at later times from the number of IA_2 in the past (occurring first); that is to say, when the number of new infectious IA_2 was observed, the number of IA_1 or IA_3 can be predicted. Prior to the stationary state, Fig. 2 shows that there is no general relation in the numbers of infected animals as a function of R_0.

Characteristics of infectious

Diagnosis tests such as ELISA can be used to inform the public health about the situation concerning the number of infected in each animal herd. The number of infected animals is derived and classified as the numbers of TR_1, TR_2, and TR_3 (as shown in Fig. 6 in Methods section). The total number of infectious and that of TR_1, TR_2, and TR_3 are shown in Fig. 3. Both Figs. 2 and 3 exhibit similar trends as a function of time. During the growth phase, the total number of infectious animals is mainly composed of the number of TR_1 and TR_2, afterward it tends to be mainly TR_2 and TR_3. The cross-correlations between the number of TR_i are shown in Fig. S4. Overall, the patterns of the cross-correlations between the number of infectious animals were similar to the number of TR_i. The positive strong correlations between TR_1 and TR_2 were found to decrease as R_0 increase. This indicates that the number of TR_2 can be forecasted from the number of TR_1 with a lag time L_1. Figure 4 shows that L_1 tends to decrease a bit with R_0. However, positive weak correlations between the number of TR_3 and TR_1 were observed at lag times (L_2) of 50, 44, 37 and 35 months for R_0=1.5, 2.5, 5.0 and 7.5, respectively. As shown in Fig. 4, L_2 decreases with R_0.

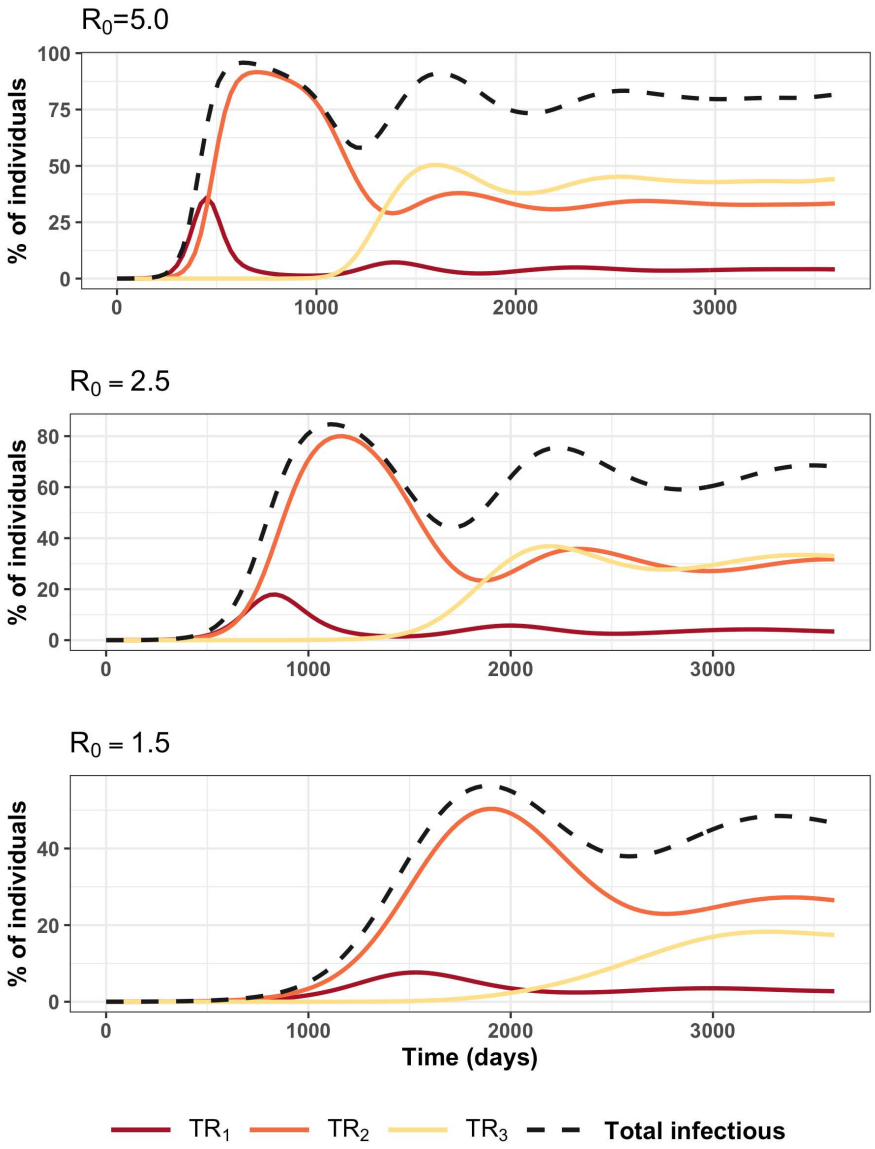

Figure 3. Average proportion of antibody positive animals of type "i" from the diagnostic test (TR_1: carrying IgM and IgG antibodies, TR_1: only carrying IgG and TR_3 carrying high-level of IgG) for 10 years. Proportion = 100 x number of animals / total population; with total population = 10,000.

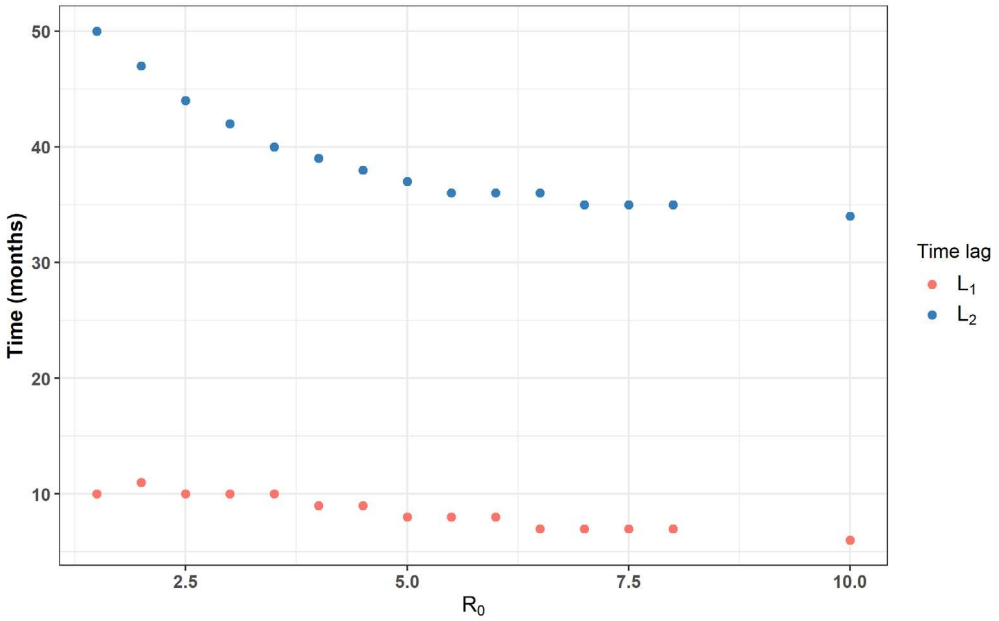

Figure 4. Lag times L_1 (between test results TR_2 and TR_1) and L_2 (between test results TR_3 and TR_1) as a function of R_0.

The comparison of results between the number of infectious IA_i and the number of TR_i for R_0= 1.5, 2.5, and 5.0 is shown in Fig. S5. The graph indicates that the number of TR_i perfectly parallel the number of infectious animals (with, $TR_1 \sim IA_2$) all the time both in the growth and stationary phases. Therefore, the number of TR_i can be used to extract the proportion of infectious animals any time. To estimate a cut-off time between growth and stationary phases, the relaxation time (time to a stationary state or a cut-off time (t_c)) is defined as the time reached at the 1st minimum of TR_i after the 1st peak of that curve. The average number of TR_i at stationary state is calculated as the average number over the period since the relaxation time to the end of simulation time (30 years). Values of t_c for TR_i are provided in Table S2.

The average number of TR_i at stationary state was used to calculate the probability p_i of finding antibody positive animals in TR_i as a function of R_0 (Fig. 5, left panel). Clearly, p_i increases with R_0 and is equal to zero for $R_0 \leq 1$. However, the probability q_i of finding infected individuals among the positive TR_i showed no variation with R_0 (Fig. 5, right panel) as predicted from Eq.(10) for the stationary state expression of $q_{i,s}$.

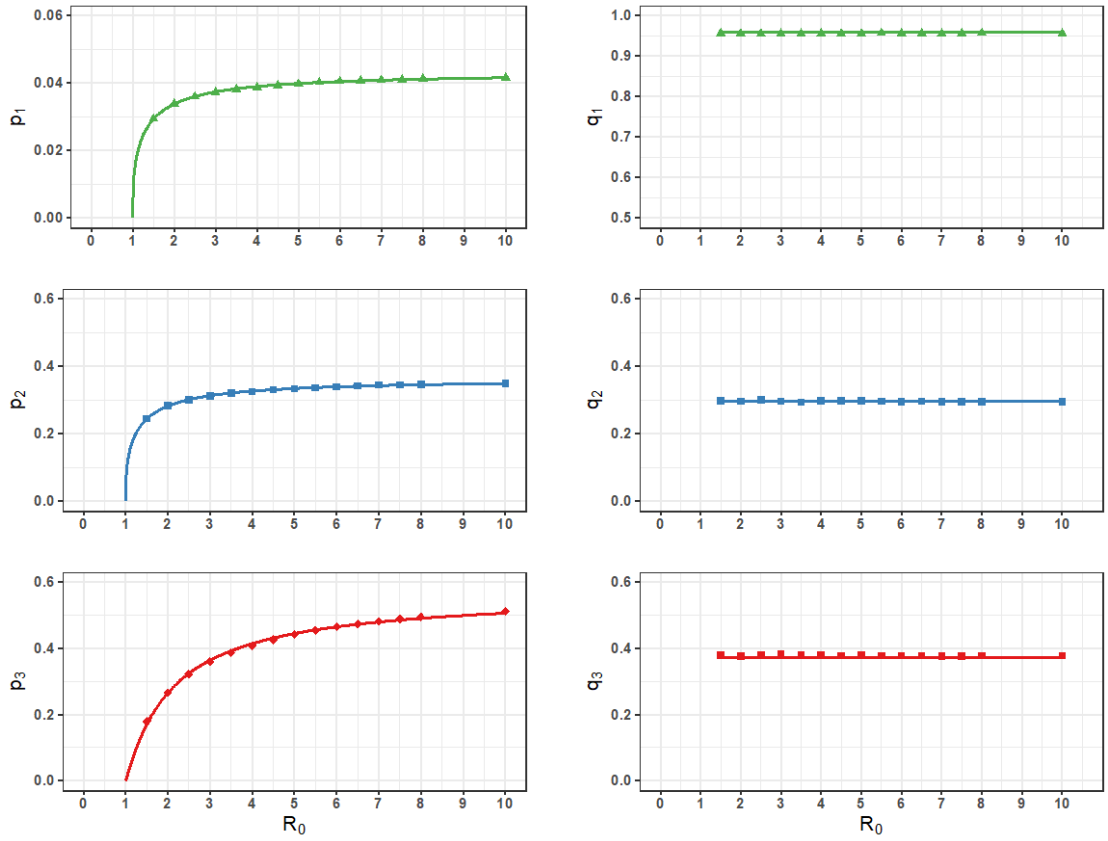

Figure 5. Fractions of antibody positive and infected animals from the diagnostic test results (1: carrying IgM and IgG antibodies, 2: only carrying IgG and 3: carrying high-level of IgG) at 10 years as a function of R_0. p_i stands for the probability of antibody positive results of type "i" and q_i for the probability of infected individuals among antibody positives of type "i". Solid lines through the data are the best-fit to the data (symbols) with Eq. (9) for p_i (left panel) and represent Eq. (10) for q_i (right panel). Dashed lines representing the 95% credible intervals are not visible.

Discussion and Conclusions

Leptospirosis is a zoonotic disease-causing illness in both humans and animals resulting in related economic impacts due to production loss as well as prevention and control efforts[20]. Several mathematical models have been constructed to study the dynamics of infection using compartment models, such as the SIR[21,22] and SEIR models[23]. These models did not consider the seroconversion dynamics. In this study, a general framework that combines both antigen and antibody dynamics was constructed to assess the state of leptospirosis in a population using diagnostic tests. To our knowledge, this model is the first compartment model built to access leptospirosis in animal considering the IgM and IgG antibody kinetics and outcomes of diagnosis tests.

It is well known that the clinical signs in animals are mild or asymptomatic[24]. Thus, the situation of leptospirosis outbreak is only described through the test results from sampling population. In our framework, a novel approach to explore the dynamics of leptospirosis in animals was proposed with the number of infected animals derived from the test results

Using IgM-ELISA, for example, with sensitivity 86% (Se_1) and specificity 84% (Sp_1)[25], the fraction of positive $T_{+,i}$ makes it possible to calculate the prevalence p_1 or the true positive antibody fraction of animals. This is helpful to uncover the actual epidemic situation rather than relying on only the serological test results. Furthermore, the basic reproduction number (R_0) is estimated using Eq.(9). In general, R_0 is a useful tool for describing and predicting the dynamics of infection. In mathematical models[15,26], R_0 is defined from the transmission rate, which is not a simple task to measure. In this study, R_0 can be prior calculated to infer the transmission rate. Subsequently, after the parameters in Eq.(10) are known, the fractions of infected states among the positive tests can be calculated. Thus, our model is useful to elucidate the picture of leptospirosis dynamics either from the parameters of Eq.(10) or from the data set from the field.

Furthermore, the cross-correlation of the number of TR_i was studied to provide better understanding on the time lag of infection. Animals with positive antibody is anticipated in later time after the outbreak. Using the time lag, for example, if the number of $TR_1$is estimated, the number of TR_2 and TR_3 can be then predicted. Reversely, if the high titer level of IgG is known by other means the number of TR_3 can be calculated and the TR_1 and TR_2 in the past can be tracked back. The time lag output is based on the input parameters and is flexible to change. Thus, this model is also applicable for leptospirosis in humans once data collected from human outbreaks and relevant diagnostic tests is available.

The developed model that we have just described is based on only on few assumptions and the outcomes depend on the quality of the parameters used. The model considered a closed system with a homogeneously well-mixed population with the parameters used obtained from the literature (see Table 1). To take account for the uncertainties in the parameters we used distributions to sample the parameters. It was assumed that the parameters were constant over the entire study period. The model can be embellished in several directions including age structure and precise renewal pattern of populations, spatio-temporal aspects or other factors that may have an impact like weather conditions.

In conclusion, we developed and constructed a general and generic modeling framework allowing to describe the transmission dynamics of animal leptospirosis in which antibody kinetics is taken into account. The model also makes it possible to describe the outbreak situations through the prism of diagnostic tests. This proposed new approach could prove useful to the competent authorities in their analyzes of real outbreak situations and, consequently, in the implementation of disease control and associated risk management strategies.

Methods

Seroconversion dynamical model. The set of equations underlying the seroconversion model has been described as follows. Let N denotes the total and constant population and $\lambda(t) = (\beta/N) \times [IA_2(t) + IA_1(t) + IA_3(t)]$ represents the time-dependent force of infection. The combined kinetics of infection and antibodies dynamics, according to Fig. 1, can be described by the-set of ten delayed differential equations as:

$$
\begin{cases}
\dfrac{dS_0}{dt} = \mu N - [\lambda(t) + \mu]S_0 \\
\dfrac{dE_0}{dt} = \lambda(t)S_0 - [\nu_0 + \mu]E_0 \\
\dfrac{dEA_2}{dt} = \nu_0[E_0(t) - \phi(t_{ea})E_0(t - t_{ea})] - \mu EA_2 \\
\dfrac{dIA_2}{dt} = \nu_0\phi(t_{ea})[E_0(t - t_{ea}) - \phi(t_{ia2})E_0(t - t_{ea} - t_{ia2})] - \mu IA_2 \\
\dfrac{dIA_1}{dt} = \nu_0\phi(t_{ea})\phi(t_{ia2})[E_0(t - t_{ea} - t_{ia2}) - \phi(t_{ia1})E_0(t - t_{ea} - t_{ia2} - t_{ia1})] - \mu IA_1 \\
\dfrac{dRA_1}{dt} = \nu_0\phi(t_{ea})\phi(t_{ia2})\phi(t_{ia1})[E_0(t - t_{ea} - t_{ia2} - t_{ia1}) - \phi(t_{ra1})E_0(t - t_{ea} - t_{ia2} - t_{ia1} - t_{ra1})] - \mu RA_1 \\
\dfrac{dS_1}{dt} = \nu_0\phi(t_{ra1})\phi(t_{ea})\phi(t_{ia2})\phi(t_{ia1})E_0(t - t_{ea} - t_{ia2} - t_{ia1} - t_{ra1}) + \nu\phi(t_{ia3})\phi(t_{ra3})E_1(t - t_{ia3} - t_{ra3}) - [\lambda(t) + \mu \\
\dfrac{dE_1}{dt} = \lambda(t)S_1 - [\nu + \mu]E_1 \\
\dfrac{dIA_3}{dt} = \nu[E_1(t) - \phi(t_{ia3})E_1(t - t_{ia3})] - \mu IA_3 \\
\dfrac{dRA_3}{dt} = \nu\phi(t_{ia3})[E_1(t - t_{ia3}) - \phi(t_{ra3})E_1(t - t_{ia3} - t_{ra3})] - \mu RA_3
\end{cases}
$$

where $\phi(t_k) = \phi_k = e^{-\mu t_k}$ and μ is the natural mortality rate; The summation of all equations equals to zero due to the total population N is kept constant. From the combined models, the meaning of variables for the kinetics of infection according to a SEIRS epidemiological model are given by using the following equations (See S1. Methods for the reduced model),

$$
\begin{cases}
S = S_0 + S_1 \\
E = E_0 + EA_2 + E_1 \\
I = IA_2 + IA_1 + IA_3 \\
R = RA_1 + RA_3
\end{cases} \tag{2}
$$

and the antibody classes are defined as:

$$
\begin{cases}
\text{Negative} = S_0 + S_1 + E_0 + E_1 \\
\text{IgM+IgG} = EA_2 + IA_2 \\
\text{IgG} = (EA_2 + IA_2) + (IA_1 + RA_1) + (IA_3 + RA_3) \\
\text{IgG+} = IA_3 + RA_3
\end{cases}. \tag{3}
$$

The basic reproduction number R_0 for this system is given b:

$$R_0 = \left(\frac{\beta}{\beta+(\alpha+\mu)N}\right)\left(\frac{\alpha}{\alpha+\mu}\right)N. \quad (4)$$

Note that when $\beta = 0$, the $R_0 = 0$, and when $\beta \to \infty$, $R_0 = \alpha N/(\alpha+\mu)$. In the absence of any information on β, the R_0 can be inverted to express the contact-transmission rate β as a function of R_0, population size N and other parameters of the system as:

$$\beta = \frac{R_0(\alpha+\mu)^2 N}{\alpha N - R_0(\alpha+\mu)}. \quad (5)$$

The meaning and values of parameters for the combined model are provided in Table 1, retrieved from the literature (Table S1). Time lags in Eq.(1) for SEIRS and antibody kinetics are constrained as shown in Fig. 1 by the following relations:

$$\begin{cases} t_e = \frac{1}{\nu} = \frac{1}{\nu_0} + \frac{1}{\nu_{ea}} \;;\; t_{ea} = \frac{1}{\nu_{ea}} \\ t_i = \frac{1}{\alpha} = t_{ia2} + t_{ia1} = t_{ia3} \\ t_r = \frac{1}{\gamma} = t_{ra1} = t_{ra3} \\ t_{ea} + t_{ia2} = \frac{1}{\omega_2} \\ t_{ia3} + t_{ra3} = \frac{1}{\omega_1} = \frac{1}{\omega_2} + t_{ia1} + t_{ra1} \end{cases} . \quad (6)$$

To account for the variability and uncertainty in durations $d = t_{ea}, t_i, t_r$ and $1/\omega_2$ in Table 1, the d were all sampled using a Weibull distribution, $W(d) = \frac{k}{\lambda_d}\left(\frac{d}{\lambda_d}\right)^{k-1} \exp\left[-\left(\frac{d}{\lambda_d}\right)^k\right]$, with the shape parameter $k = 2$ and scale parameter, $\lambda_d = \frac{2}{\sqrt{\pi}} \times \left(\widehat{t_{ea}}, \widehat{t_i}, \widehat{t_r}, \widehat{1/\omega_2}, \right)$, where $\widehat{\cdots}$ designates the corresponding mean value given in Table 1. The other parameters were calculated using the relations in Eq.(6).

Table 1: Parameters and time durations of the infection and antibody dynamics.

Definitions	**Symbol**	**Mean [min, max]**	**Unit**	**References**
Transmission rate	β	varying	1/day	From Eq.(5)
Duration of incubation	$t_e = 1/\nu$	10	day	Baker, 1948[27]
Duration of infection	$t_i = 1/\alpha$	240 [200,280]	day	Leonard, 1993[28]
Duration of immunity	$t_r = 1/\gamma$	542 [360,720]	day	Estimated
Natural mortality rate	μ	6.85×10^{-4}	1/day	Estimated
Onset of IgM and IgG: primary infection	$1/\nu_0$	7	day	Cousins, 1985; Smith, 1994[17,29]
Onset of IgG+: subsequent infection	$1/\nu$	10	day	Estimated
Duration of IgM	$1/\omega_2$	65 [60,70]	day	Leonard, 1993[28]

Duration of IgG	$1/\omega_1$	782	day	Estimated
Duration of incubation ($EA_2 \rightarrow IA_2$)	$t_{ea} = 1/\nu_{ea}$	3 [1,5]	day	Estimated
Duration of seroconversion from IgM to IgG ($IA_2 \rightarrow IA_1$)	$t_{ia2} = 1/\alpha_2$	$1/\omega_2 - t_{ea}$	day	Calculated
Duration of infection ($IA_1 \rightarrow RA_1$)	$t_{ia1} = 1/\alpha_1$	$t_i - t_{ia2}$	day	Calculated
Duration of immunity and IgG (RA_1)	t_{ra1}	t_r	day	Calculated
Duration of infection for IA_3 state	t_{ia3}	t_i	day	Calculated
Duration of immunity and IgG+ (RA_3)	t_{ra3}	t_r	day	Calculated
Basic reproduction number	R_0	varying	–	Eq.(4)

Data analysis. The diagnosis of leptospirosis is complicated and depends on the laboratory test. To detect antibodies, there are tests such as microscopic agglutination test (MAT) and immuno-enzymatic assays (ELISA) that are well-known methods. Here, we consider a diagnostic test that would provide one, two or all three of the following outcomes or test results (TR) as shown in Fig. 1: TR_1 – detecting only IgM (and assuming that IgG are also present) and corresponding to the total number of EA_2 and IA_2 as A_2; TR_2 – detects low levels of IgG corresponding to the number of IA_1 and RA_1 as A_1; and TR_3 – detects high levels of IgG corresponding to the number of IA_3 and RA_3 as A_3.

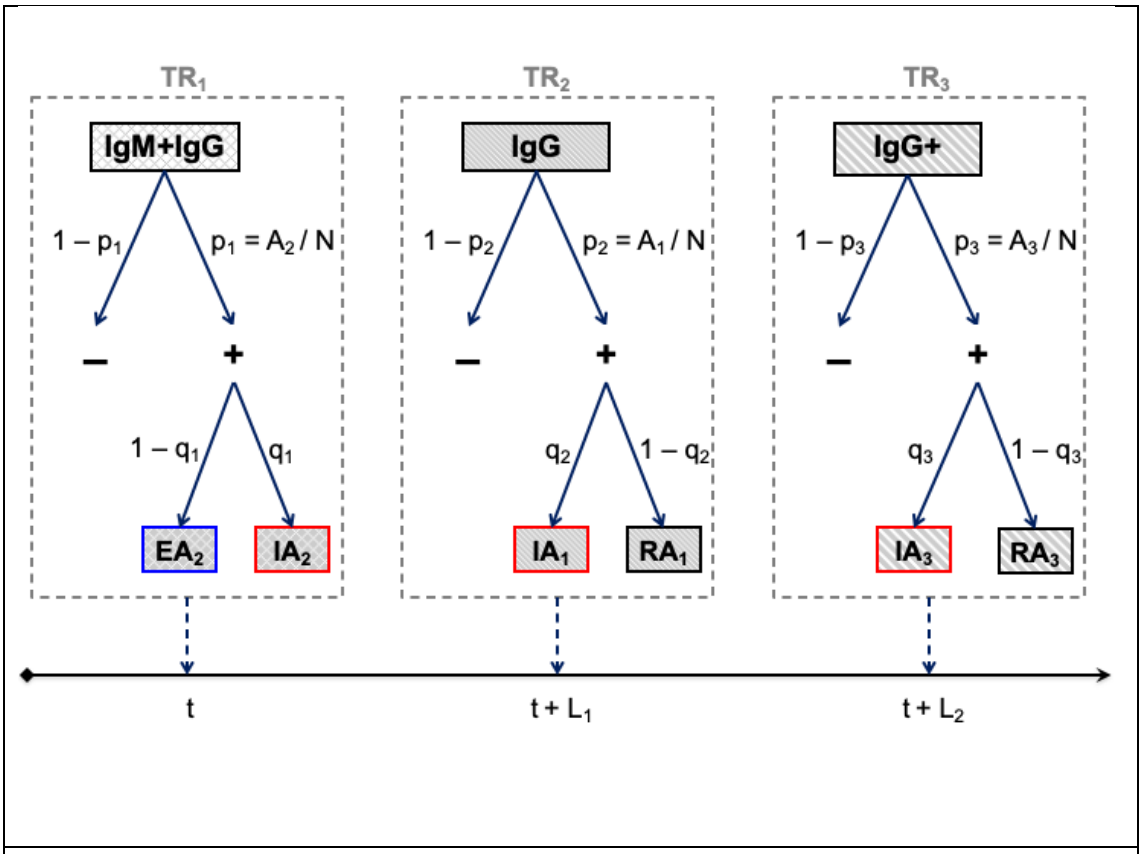

Figure 6. Results of a diagnostic test. TR_i stands for test result. The prevalence p_i corresponds to the true fraction of positive individuals carrying targeted antibodies and q_i the fraction of them that are infected. L_1 and L_2 represent the lag times between associated antibody states of the population.

As shown in Fig.6, such a diagnostic test provides information regarding the prevalence p_i or the fraction of (real or true) positive animals carrying targeted antibodies, the fraction q_i of positive animals that are infected, and the lag time (L_1 and L_2) since infection. To extract that information, the reasoning below goes as follows.

- *Prevalence of antibody positive:* any diagnostic test is characterized by a sensitivity Se and specificity Sp. Therefore, the fraction of positive $T_{+,i}$ from the diagnostic test result is given by,

$$T_{+,i} = Se_i \times p_i + (1 - Sp_i) \times (1 - p_i), \tag{7}$$

where p_i is the prevalence or the fraction of real or true positive from test i. Now, inverting Eq.(7) provides p_i as,

$$p_i = \left(T_{+,i} + Sp_i - 1\right)/(Se_i + Sp_i - 1). \tag{8}$$

Then, using outputs of simulations, we can use the determined prevalence p_i to infer the value of R_0.

- *Fraction of infected:* using simulation outputs, we can determine the fraction of infected q_i corresponding to the determined R_0.
- *Time lag since infection (for a test performed at time t)*: TR_1 identifies freshly infected populations A_2, and A_1 and A_3 positive populations should be observed later at L_1 and L_2, respectively. TR_2 reflects populations A_1 infected about L_1 ago that is expected to be A_3 positive later at $L_2 - L_1$. TR_3 identifies populations A_3 infected at least about L_2 ago.

At the steady state, the expressions of p_i are given in Eq.(S5). However, we found that simulations can be fitted as well with the power law,

$$p_i = a_i(1 - 1/R_0)^{k_i}, \tag{9}$$

where a_i and k_i are given in Table 2.

Table 2: The parameters for $p_i = a_i(1 - 1/R_0)^k$.

p_i	a_i (95% CI)	k_i (95% CI)	r^2
p_1	0.0431(0.0430-0.0432)	0.3530(0.3442-0.3618)	0.9985
p_2	0.3626(0.361-0.3642)	0.3625(0.3502-0.3748)	0.9973
p_3	0.5680(0.5614-0.5746)	1.1000(1.0580-1.1410)	0.9976

Likewise, the expressions of q_i at the steady state are given in Eq.(S6) as,

$$\begin{cases} q_{1,s} = \frac{IA_2}{IA_2+EA_2} = \frac{\phi_{ea}[1-\phi_{ia2}]}{1-\phi_{ea}\phi_{ia2}} \\ q_{2,s} = \frac{IA_1}{IA_1+RA_1} = \frac{1-\phi_{ia1}}{1-\phi_{ia1}\phi_{ra1}} \\ q_{3,s} = \frac{IA_3}{IA_3+RA_3} = \frac{1-\phi_{ia3}}{1-\phi_{ia3}\phi_{ra3}} \end{cases} \tag{10}$$

Clearly, the $q_{i,s}$ are constant as a function of R_0.

Simulations details and Statistical analyses. Stochastic simulations numerically solve Eq.(1) with parameters in Table 1 at daily time step and with initial 10,000 individuals over a 30 year

period. Unless stated otherwise, all the parameters are kept the same in all simulations except for the contact-transmission β value that is varied via R_0 using Eq.(5). 1,000 simulations were used for statistical analysis. The average numbers of each compartment in Eq.(1) were recorded every 30 days to generate a monthly data series. All simulations were performed using the MATLAB R2016b and statistical analyses were performed using R version 4.0.2.

Data availability

The datasets generated during analyzed and/or the current study were made available from the corresponding author based on reasonable requests.

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Author Contributions

SC: performed the analysis, conceptualized, wrote the manuscript and revising it critically for important content.

KCM: participated in its design and involved in drafting the manuscript.

AK: participated in framing the antibody kinetic model and involved in drafting the manuscript.

AW: participated in its design and involved in drafting the manuscript.

DJB: supervised the work, conceptualized, developed the model, wrote the manuscript and revising it critically for important content.

All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional Information

Supplementary Information is available for this paper at ???

Ethics declarations

NA. Our research does not include any human or animal subjects.

Approval for animal experiments

NA. Our research does not involve any animal experiments.

Approval for human experiments

NA. Our research does not involve any human experiments (or tissue samples).

Consent to participate/Consent to publish

NA. Our research does not involve any participants.

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