

Next-generation serology: integrating cross-sectional and capture–recapture approaches to infer disease dynamics

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Citation: Gamble, A., R. Garnier, T. Chambert, O. Gimenez, and T. Boulinier. 2020. Next-generation serology: integrating cross-sectional and capture–recapture approaches to infer disease dynamics. *Ecology* 101(2):e02923. 10.1002/ecy.2923

Abstract. Two approaches have been classically used in disease ecology to estimate epidemiological parameters from field studies: cross-sectional sampling from unmarked individuals and longitudinal capture–recapture setups, which generally involve more limited numbers of marked individuals due to cost and logistical constraints. Although the benefits of longitudinal setups are increasingly acknowledged in the disease ecology community, cross-sectional data remain largely overrepresented in the literature, probably because of the inherent costs of longitudinal surveys. In this context, we used simulated data to compare the performances of cross-sectional and longitudinal designs to estimate the force of infection (i.e., the rate at which susceptible individuals become infected). Then, inspired from recent method developments in quantitative ecology, we explore the benefits of integrating both cross-sectional (seroprevalences) and longitudinal (individuals histories) data sets. In doing so, we investigate the effects of host species life history, antibody persistence, and degree of a priori knowledge and uncertainty on demographic and epidemiological parameters, as those are expected to affect in different ways the level of inference possible from the data. Our results highlight how those elements are important to consider in determining optimal sampling designs. In the case of long-lived species exposed to infectious agents resulting in persistent antibody responses, integrated designs are especially valuable as they benefit from the performances of longitudinal designs even with relatively small longitudinal sample sizes. As an illustration, we apply this approach to a combination of empirical and simulated data inspired from a case of bats exposed to a rabies virus. Overall, this work highlights that serology field studies could greatly benefit from the opportunity of integrating cross-sectional and longitudinal designs.

Key words: detectability; eco-epidemiology; immunity persistence; sampling strategy; study design; wildlife.

INTRODUCTION

Understanding the ecology and evolution of infectious diseases in wildlife has been highlighted as critical for public health (Jones et al. 2008) and biodiversity conservation (Smith et al. 2006). Natural host–parasite systems also offer useful models to obtain valuable insights on evolutionary ecology processes such as coevolution and local adaptation (Gandon 2002) or host and vector movements (Boulinier et al. 2016). However, investigations in the wild have been hampered by the difficulty of collecting data allowing efficient inference of eco-epidemiological dynamics (Plowright et al. 2019). For instance, the force of infection (i.e., the rate at which

susceptible individuals acquire an infectious disease), a key eco-epidemiological parameter (Hens et al. 2012), is difficult to estimate from field data as it requires assessing how many individuals went from susceptible (e.g., non-infected and non-immunized) to infected in a given time period, which is rarely observable. Estimating these parameters is however a critical step in the characterization of epidemiological dynamics and factors impacting them. Methods allowing their estimation from field data are thus needed.

The benefits of longitudinal setups, defined here as the repeated sampling of the same individuals across time, notably using capture–recapture designs (Lebreton et al. 1992), are increasingly acknowledged in the disease ecology community (e.g., Jennelle et al. 2007, Lachish et al. 2007, Chambert et al. 2012b, Buzdugan et al. 2017, Marescot et al. 2018). However, cross-sectional data, defined here as the sampling of unmarked individuals at one or

Manuscript received 27 July 2018; revised 18 September 2019; accepted 26 September 2019. Corresponding Editor: A. Marm Kilpatrick.

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more points in time, remain largely over-represented in the literature, probably because of the inherent costs of longitudinal surveys. It requires much more time and skills to spot marked individuals and to recapture them than to capture a random sample of individuals in a target population (e.g., if a marked fur seal is spotted in the middle of a harem, field workers may have to postpone the capture to limit disturbance and biting risks, while in a cross-sectional sampling design, the capture of another, more peripheral, individual would be much easier).

Recent advances in population ecology, such as the advent of integrated modeling, may open new perspectives for the estimation of eco-epidemiological parameters. Indeed, Integrated Population Modeling (IPM) has proven effective to improve demographic parameter estimations by integrating data sets of different natures (e.g., capture–recapture and counts) on the condition that they depend partly on the same set of (demographic) parameters (Besbeas et al. 2002, Schaub et al. 2007, Abadi et al. 2010, Fletcher et al. 2019). In disease ecology, a similar approach could thus be used to integrate low-cost cross-sectional data with longitudinal data that provide key elements about processes underlying the dynamics of the considered variables (e.g., the kinetics of the immune response). IPM has been recently applied in an epidemiological context (McDonald et al. 2016) but, to our knowledge, approaches integrating cross-sectional and capture–recapture epidemiological data have never been explicitly used to estimate epidemiological parameters.

In some species, individuals can be marked and repeatedly (re)captured across time, allowing longitudinal sampling. This is particularly true for long-lived vertebrates showing seasonal and colonial breeding (such as seabirds, pinnipeds, and chiropterans) and which are often faithful to their breeding or roosting site (e.g., Chambert et al. 2012b, Robardet et al. 2017, Gamble et al. 2019a). In these systems, capture–recapture approaches have started to be used to estimate epidemiological state transition probabilities (e.g., from healthy to symptomatic) while accounting for recapture probabilities below unity, which are unavoidable in wild settings (Jennelle et al. 2007, Conn and Cooch 2009). However, longitudinal studies are usually based on relatively small sample sizes because field efforts needed to resight and recapture marked individuals tend to be intensive. In contrast, cross-sectional studies are usually less costly and may also allow the estimation of epidemiological state transition probabilities. This type of data can generally be used to monitor variations of prevalences (i.e., the proportion of infected individuals) or seroprevalences (i.e., proportions of seropositive individuals). However, linking variations of prevalences or seroprevalences to epidemiological dynamics often requires additional data seldom available in wild populations, such as knowledge on the infectious period (e.g., Hénau et al. 2010) and/or refined antibody kinetic curves (e.g., Borremans et al. 2016, Pepin et al. 2017), or strong assumptions on the host demography (e.g., Samuel et al. 2015). Both approaches (longitudinal and cross-

sectional) thus present relative pros and cons. Because cross-sectional and longitudinal data are outcomes of the same eco-epidemiological processes based on the same demographic and epidemiological parameters (notably survival, force of infection, and antibody level persistence), their combination into an integrated model should improve the estimation of these parameters.

Serology has proven effective to detect patterns of exposure to many infectious agents and infer eco-epidemiological processes (Gilbert et al. 2013, Metcalf et al. 2016). Moreover, a wide range of approaches are now available to apply serology to wild settings (e.g., Garnier et al. 2017). However, the interpretation of serological data is not straightforward as they do not directly inform on the timing of infection. The reliability of the inference that can be made from serological data is thus dependent on the ecological and epidemiological characteristics of the considered system. Sampling schemes may need to be adjusted to reflect both these characteristics and what is possible in terms of field efforts. For instance, in some host–parasite systems, detectable antibody levels persist for many years after exposure (e.g., antibody level against the Newcastle disease virus vaccine in Ramos et al. 2014), while in other cases, they wane within a few weeks (e.g., antibody level against the avian cholera agent in [Samuel et al. 2003]), complicating interpretation of serological data. Methods allowing the estimation of the force of infection from serological data when the kinetics of the immune response is not known are needed to better characterize the factors driving epidemiological dynamics.

In the present study, we use a simulation approach to compare the performances of different sampling designs to estimate the seroconversion probability, a proxy of the force of infection, when the kinetics of the immune response after exposure is not known. This parameter can be estimated either from the temporal variations of the seroprevalence based on cross-sectional data (e.g., Samuel et al. 2015) or as the transition probability from seronegative to seropositive states in a capture–recapture model based on longitudinal data (e.g., Chambert et al. 2012b). We moreover consider the possibility of integrating both sources of data in a framework inspired from IPM. Based on data simulated under different scenarios, we notably account for several key parameters expected to have a strong impact on the observation process and the inference that can be made from serological data: host lifespan, temporal persistence of antibody levels, and detection and recapture probabilities. For instance, low annual survival will increase the turnover of individuals in the host population, which is expected to lower the benefit of longitudinal sampling designs, which rely on the repeated sampling of individuals. Finally, we illustrate how this method could be used on empirical data by considering the case of a serotine bat (*Eptesicus serotinus*) colony exposed to a rabies virus.

The results of the present study could have important implications regarding current practices in eco-epidemiology by (1) highlighting the benefits of longitudinal

sampling designs compared to cross-sectional sampling designs and (2) opening to possibility of integrating the two types of approaches to design cost-efficient sampling protocols in study systems not yet subject to longitudinal monitoring programs.

MATERIALS AND METHODS

Eco-epidemiological model

Individual data resulting from an eco-epidemiological interannual process were simulated with a set of parameters fixed to different values in order to represent different demographic and epidemiological situations (Fig. 1a): survival (ϕ), seroconversion (λ ; i.e., the probability for a seronegative individual to become seropositive, which usually corresponds to the mounting of an antibody response after exposure to an infectious agent) and seroreversion (ω ; i.e., the probability for a seropositive individual to become seronegative, which corresponds to the waning of the antibody response) probabilities. To illustrate how eco-epidemiological parameters could be quantified from serological data, we have chosen the simple situation of populations at the demographic and endemic equilibria with all individuals recruiting as seronegative and exposure having no impact on survival or detectability. Additional details and illustrations are given in Appendix S1: Section S1.

Cross-sectional sampling

Each year, n_{CS} individuals are randomly captured and sampled for serological analyses. Seroprevalence at time t (π_t) is calculated as the proportion of seropositive individuals among the tested individuals. π_t thus corresponds to the probability for a sample randomly collected in a population to be seropositive at time t . Seroprevalences at times t and $t + 1$ are linked by a function of survival, seroreversion, and seroconversion probabilities. Such approaches have previously been used to estimate seroconversion probabilities in wild populations (e.g., Hénau et al., 2010, Samuel et al. 2015). Under the eco-epidemiological model assumptions, this relation is given by

$$\pi_{t+1} = \pi_t \phi (1 - \omega) + \pi_t \phi \omega \lambda + (1 - \pi_t) \phi \lambda + r \lambda. \quad (1)$$

In equation 1, the first additive term $[\pi_t \phi (1 - \omega)]$ corresponds to seropositive individuals at time t that survive and maintain detectable antibody levels between time t and $t + 1$; the second $[\pi_t \phi \omega \lambda]$ to seropositive individuals at time t that survive, lose their antibodies and seroconvert between t and $t + 1$; the third $[(1 - \pi_t) \phi \lambda]$ to seronegative individuals at time t that survive and seroconvert between t and $t + 1$; and the last $[r \lambda]$ to individuals that recruit (here with a probability r) and seroconvert between t and $t + 1$.

Under the assumption of demographic equilibrium, recruitment exactly compensates for mortality and r can be written as $(1 - \phi)$; and under the assumption of

endemic equilibrium, seroprevalence (π^*) is stable over time (Eq. 2; intermediary steps are clarified in Appendix S1: Eqs. S1–S3). Serological states of the samples thus follow the binomial distribution given in Eq. 3:

$$\pi^* = -\frac{\lambda}{\phi(1 - \omega + \omega\lambda - \lambda) - 1} \quad (2)$$

$$y \sim B\left(n_{CS}, \frac{\lambda}{\phi(1 - \omega + \omega\lambda - \lambda) - 1}\right). \quad (3)$$

The estimation of unknown parameters will be facilitated if some of these parameters are known a priori. In this study, we thus notably considered the case when the model was informed with some values for the survival and the seroreversion probabilities (true or erroneous, e.g., based on the literature). Additional details are given in Appendix S1: Section S1.

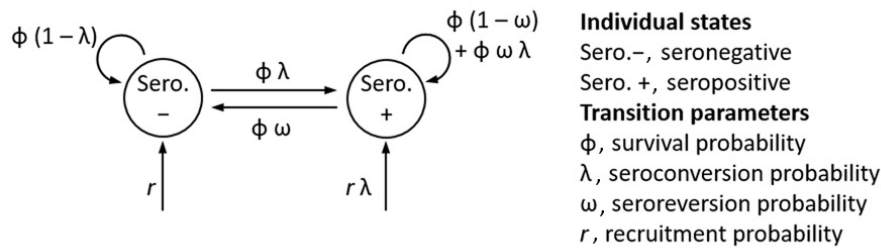
Longitudinal sampling

On the first year of the observation process, n_{LG} random individuals are captured and marked with a tag allowing individuals to be identified without recapture (e.g., rings or PIT tags). Each of the following years, each alive marked individual is resighted with a probability p then its serological state is ascertained with a probability δ corresponding to the recapture probability after resighting (the serological state being ascertained at the same time from a blood sample). A fixed number of individuals is captured each year, with a priority on marked individuals and some newly marked individuals if necessary to complete the sample size to n_{LG} . An observation event is then attributed each year to each marked individual of the study and recorded in the matrix m : 0 if not seen (for an individual either dead, alive but not present in the study site, or present but not detected), 1 if captured and ascertained as seronegative, 2 if captured and ascertained as seropositive or 3 if seen but not captured (uncertain serological state; Appendix S1: Section S1). Note that we considered no state misclassification (i.e., test sensitivity and specificity are equal to one). These assumptions are discussed in Appendix S1: Section S1. Multievent models allowing for state uncertainty (corresponding to event 3) were then fitted on the individual histories (Pradel 2005), similarly to classical applications to demographic studies (Gimenez et al. 2012). Such models are increasingly used in population ecology and in eco-epidemiology (e.g., Conn and Cooch 2009, Robardet et al. 2017, Buzdugan et al. 2017, Marescot et al. 2018).

Integrated modeling

For a given simulated population, the cross-sectional and the longitudinal data sets (y and m respectively) can be integrated together (Fig. 1b; Schaub et al. 2007). Under the assumption of independence of the two data sets (only data from unmarked individuals are included

a) Framework for the eco-epidemiological simulations



b) Framework for the integrated modelling for parameter estimation

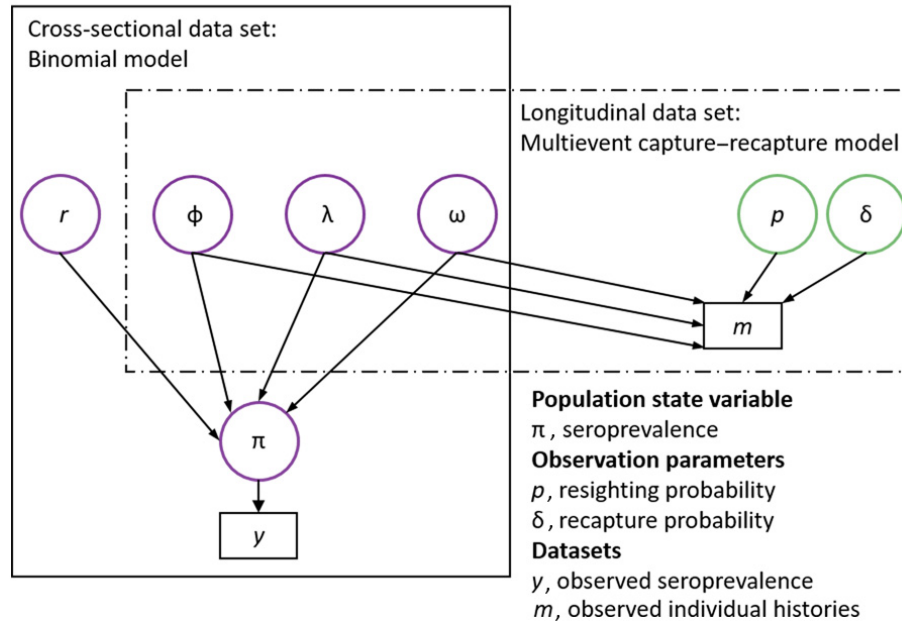


FIG. 1. Methodological framework: (a) eco-epidemiological process used for data simulation and (b) modeling framework for the estimation of the eco-epidemiological parameters.

in the cross-sectional data set), the combined likelihood function (L_{IPM}) can thus be expressed as the product of the likelihood function of the cross-sectional (L_{CS}) and longitudinal (L_{LG}) models:

$$L_{IPM}(y, m | \phi, \lambda, \omega, p, \delta) = L_{CS}(y | \phi, \lambda, \omega) \times L_{LG}(m | \phi, \lambda, \omega, p, \delta). \quad (4)$$

These parameters can thus conjointly be estimated based on the cross-sectional and longitudinal data sets (y and m). As both data sets result from processes sharing some similar eco-epidemiological parameters, the integrated estimator of these parameters is expected to be less biased and more precise (Schaub et al. 2007, Abadi et al. 2010). As we considered situations in which a small proportion of the population is sampled ($\leq 10\%$ unmarked individuals and $\leq 10\%$ marked individuals) and cross-sectional and longitudinal samples were chosen randomly, leading to only a potentially small overlap of the two data sets, we made the assumption that our

cross-sectional and longitudinal data sets were independent. In addition to the assumption of independence of the two data sets typical to integrated models, the main assumptions are the ones made by the multievent capture-recapture model (see for instance Riecke et al. 2019) and when formalizing the temporal variations of the seroprevalence. These assumptions are discussed in more details in Appendix S1: Section S1.

Simulations and model fitting

For each set of parameters, 1,000 populations with a size of 600 individuals were simulated using a specifically developed individual-based model (see Appendix S2 for codes). To compare the performances of both designs under various scenarios, one cross-sectional sample and one longitudinal sample of 50 individuals ($n_{CS} = n_{LG}$) per year were then taken per simulated population following the designs described in the Cross-sectional sampling and Longitudinal sampling sections respectively. In the case of integrated

modeling, several combinations of cross-sectional ($n_{CS} = 20, 40, \text{ or } 60$) and longitudinal ($n_{LG} = 20 \text{ or } 40 \text{ or } 60$) sample sizes were tested. Unless otherwise stated, the resighting (p) and recapture (δ) probabilities were set to 0.80 and sampling was conducted over five years after having reached the endemic equilibrium (Appendix S1: Fig. S1). Within a time step, samples were collected after exposure. The performances of the estimators were then compared based first on their bias, and second on their mean square error ($MSE = \text{bias}^2 + \text{variance}$) in order to account for the bias and the precision of the estimators; the lower the bias or MSE, the more accurate the estimator. In the three cases (cross-sectional, longitudinal, and integrated), eco-epidemiological parameters were estimated from the data by maximization of likelihood using a frequentist approach. This method was preferred due to reduced computation time compared to Bayesian inference. Sensitivity analyses were conducted to explore the validity of the results for ranges of biological and observation parameters. All simulations and analyses were run within R 3.3.3 (R Core Team, 2017). Simulation codes are provided in Appendix S2, including examples of frequentist and Bayesian estimations of the parameters.

Illustrative example

The integrated estimator was then applied to a real case study of serotine bats (*Eptesicus serotinus*) exposed to a bat rabies virus (European Bat Lyssavirus type 1; EBLV-1) in Pagny-sur-Moselle, France (Robardet et al. 2017). Because we were unable to find a data set combining cross-sectional and capture–recapture setups in the literature, we chose to use this capture–recapture data set and to simulate additional cross-sectional data using the simulation model presented in the Cross-sectional sampling section and parameterized based on the demographic and epidemiological parameters estimated using a multievent model. Juvenile serotine bats from the study site are known to be exposed to EBLV-1 (Robardet et al. 2017). Thus, instead of making the assumption that individuals recruit as seronegative (as in Eq. 1), we made the assumption that females recruit in the breeder pool with the same probability of being seropositive as former breeders (i.e., seroprevalence is similar in the new recruit and former breeder pools), leading to Eq. 5 in which new recruits and former breeders are not distinguished:

$$\begin{aligned} \pi_{t+1 \text{ bats, EBLV-1}} &= \pi_{t \text{ bats, EBLV-1}} \phi (1 - \omega) + \pi_{t \text{ bats, EBLV-1}} \phi \omega \lambda \\ &+ (1 - \pi_{t \text{ bats, EBLV-1}}) \phi \lambda \end{aligned} \quad (5)$$

And seroprevalence at the equilibrium can be written

$$\pi_{\text{bats, EBLV-1}}^* = \frac{\lambda}{(\omega - \omega\lambda + \lambda)}. \quad (6)$$

The simulation of the cross-sectional data was also modified to reflect this assumption.

We considered 102 marked individuals captured between one and five times over eight capture occasions (corresponding to the empirical longitudinal data). In parallel, during each of the eight capture occasions, n_{CS} (20, 40, or 60) unmarked individuals were randomly captured and used to calculate the seroprevalence at each occasion (corresponding to the simulated cross-sectional data). We then estimated the survival, seroconversion, and seroreversion probabilities using the integrated estimator based on the best model retained in Robardet et al. (2017), in which the resighting probability varies over time: $\phi(\cdot)$, $\lambda(\cdot)$, $\omega(\cdot)$, $p(t)$, $\delta(\cdot)$. Additional details are given in Appendix S1: Section S2 and codes in Appendix S3.

RESULTS

Cross-sectional estimator

The seroconversion probability (λ) was estimated without bias (i.e., absolute difference between the true and estimated value close to zero) when using the cross-sectional estimator informed with the true values of the survival (ϕ) and seroreversion (ω) probabilities (Fig. 2a, b). In contrast, informing the cross-sectional estimator with slightly erroneous values for these parameters led to biases when lifespan and antibody persistence were long (when ϕ tends to one and ω tends to zero). The bias was smaller when lifespan or antibody persistence were short, which can easily be explained by the fact that when ϕ tends to zero and/or ω tends to one, π^* tends to λ (Eq. 2) and the seroconversion probability can thus be directly deducted from the observed seroprevalence. Hence, the cross-sectional estimator overall performed better (lower MSE independently of the a priori knowledge) when ϕ was low (i.e., short-lived host species) and/or ω was high (i.e., short-lived immune response; Fig. 2a,b and sensitivity analyses presented in Appendix S1: Fig. S4).

Longitudinal estimator

When using the longitudinal estimator, the seroconversion probability (λ) was estimated without bias without any a priori knowledge of the true survival (ϕ) and seroreversion (ω) probabilities, except when the survival probability was close to zero (Fig. 2a). In addition to the higher bias, precision was also lower at low survival probabilities. The lower performances observed for low survival probabilities are expected when using capture–recapture models as fewer individuals can be recaptured over the years, reducing the effective sample size. Precision was also slightly decreased when antibody level persistence was longer (low ω). This could be explained by the model not being able to distinguish individuals that maintained their antibody levels (at a probability $1 - \omega$) from individuals that were observed seropositive once and then seroreverted and got exposed again (at a

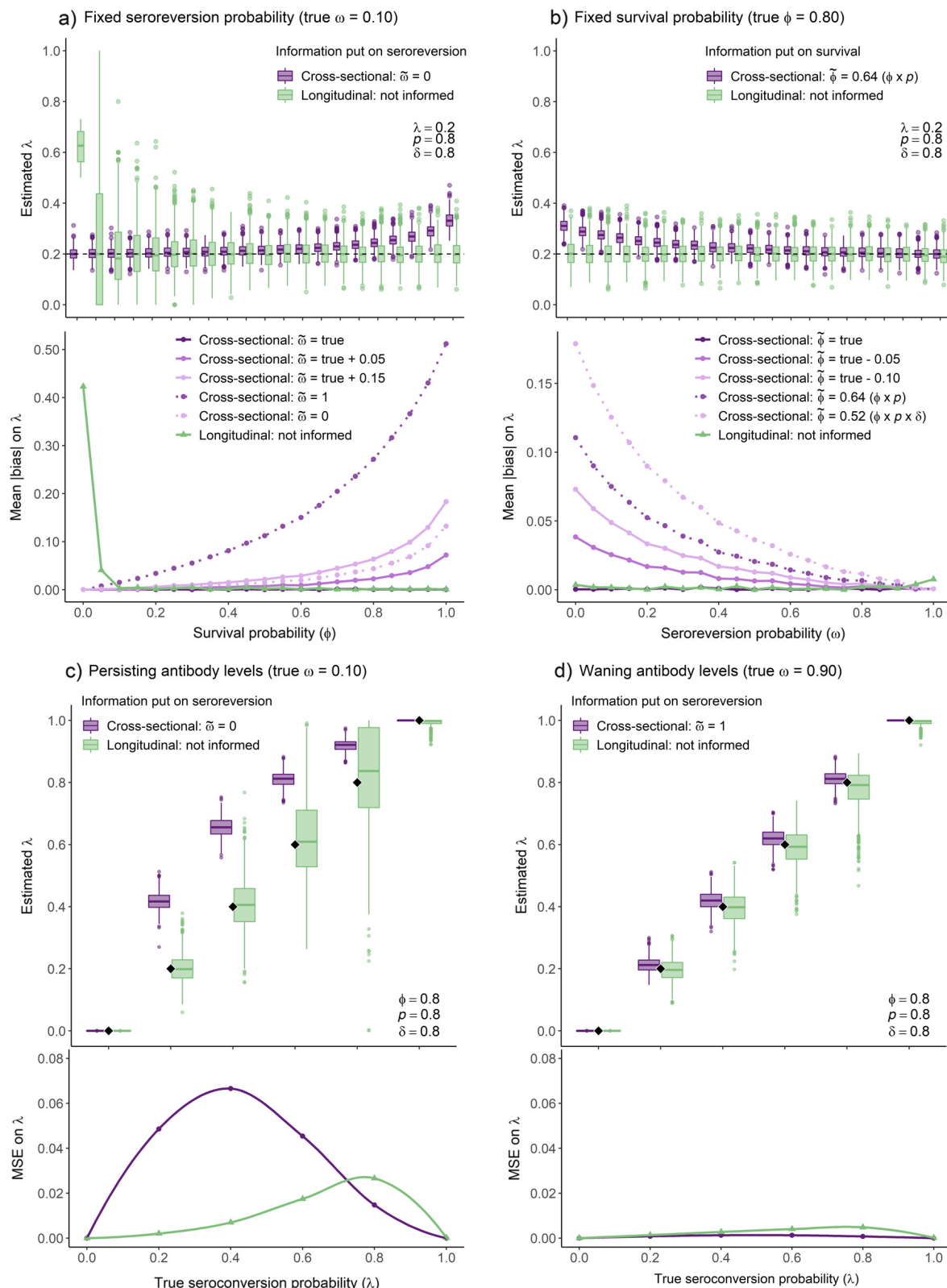


FIG. 2. The longitudinal design overall leads to no bias but low precision in the estimation of the seroconversion probability (λ) while small errors in a priori fixed seroreversion ($\tilde{\omega}$) or survival ($\tilde{\phi}$) probabilities can lead to strong biases in cross-sectional designs,

FIG. 2. Continued

especially for long-lived host species and persisting antibody levels. Estimated values of (a, b) the seroconversion probability and corresponding bias or (c, d) MSE in relation to (a) survival, (b) seroreversion, and (c, d) seroconversion probabilities using cross-sectional or longitudinal estimators. For the cross-sectional design, results are shown for a realistic gradient of error on the a priori fixed value of seroreversion ($\hat{\omega}$) or survival ($\hat{\phi}$), while the longitudinal design does not require those parameters to be set a priori (not informed). The true seroconversion probability is represented by a black dashed line (a, b) or black diamonds (c, d). Notes that, in panel a, a null seroreversion value corresponds to a lifelong persistence of antibody levels; in panel b, a survival value of $\phi \times p$ corresponds to an underestimated survival probability comparable to the raw return rate probability, which is sometimes used in the literature (the <1 resighting probability being ignored). Box plot components are mid line, median; box edges, first and third quartiles; whiskers, minimum and maximum values (after outlier removal); and points, outliers.

probability $\omega \times \lambda$) as both situations fit with the observation of the individuals as seropositive during two consecutive occasions. This is supported by the fact that the precision was lower for higher seroconversion probabilities when the seroreversion was low but not when it was high (Fig. 2c,d). Hence, the longitudinal estimator overall performed better when ϕ was high (i.e., long-lived host species) and/or ω was high (i.e., short-lived immune response; sensitivity analyses presented in Appendix S1: Fig. S4).

Integrated estimator

Similarly to the longitudinal estimator, the integrated estimator of the seroconversion probability (λ) was unbiased without having to rely on any a priori knowledge on the survival (ϕ) and/or seroreversion (ω) probabilities (Fig. 3). In addition, integrating cross-sectional data to longitudinal data increased the precision of the estimator for any fixed longitudinal sample size. For instance, when antibody level persistence was long, adding 20 unmarked individuals to 20 marked individuals at each sampled occasion allowed the standard error of the estimated values to be divided by 1.7. The results are not trivial though: for instance, for intermediate antibody level persistence, sampling longitudinally 20 marked individuals and a novel batch of 20 unmarked individuals at each yearly sampling occasion gives a more accurate estimation than sampling longitudinally 40 marked individuals (Fig. 3b), while this is not the case for persisting antibody levels (Fig. 3a). In such comparisons, one need to keep in mind the relative field costs (in time spent and skills required) associated with (re)capturing marked versus unmarked individuals (see Appendix S1: Fig. S9 for illustrative examples). Additional results are presented in the Appendix S1: Section S3, notably considering the effects of various biological (host lifespan and antibody persistence; Appendix S1: Fig. S5) and observations parameters (resighting and recapture probabilities, study duration, sample sizes; Appendix S1: Figs. S6–S8).

Illustrative example

The estimation of seroconversion probability was improved (smaller confidence interval) when longitudinal and cross-sectional data were integrated together (compared to using only longitudinal data; Table 1). For

instance, the seroconversion probability [95% confidence interval] was estimated at 0.085 [0.033; 0.201] using the longitudinal design and 0.079 [0.043; 0.139] using the integrated design including data from 60 unmarked individuals each year. The estimates of survival, resighting and recapture probabilities were unchanged, as expected considering that these parameters were not expected to impact seroprevalence (Eq. 5).

DISCUSSION

Based on an eco-epidemiological model and simulations under different sampling scenarios, our results suggest that longitudinal data analyzed in capture–recapture frameworks are preferable to cross-sectional data when poor a priori knowledge (for instance on the survival and seroreversion probabilities) is available on the system, which is the case with most wild host–parasites systems. The cross-sectional estimator can nonetheless be accurate for hosts with short lifespan and/or short antibody level persistence or when informed with reliable a priori knowledge on these parameters. In contrast, the longitudinal approach provided accurate estimates and also allowed survival and seroreversion probabilities to be estimated along with observation parameters (resighting and recapture probabilities; e.g., the serotine bat example). Finally, the integrated estimator benefited from the performances of longitudinal designs, notably it did not rely on any a priori known parameters, even with relatively small longitudinal sample sizes. Based on these results, we hope to encourage researchers to think about the benefits of implementing longitudinal setups, potentially of relatively small scope depending on the system characteristics, in parallel to already existing cross-sectional studies. We also propose a method to integrate these two types of data, which we believe could be useful in the future to motivate researchers to switch from cross-sectional to integrated designs. The method we present here also offers the possibility to integrate data sets that were previously analyzed independently, and thus to improve the inference of eco-epidemiological processes made from these data. For instance, multi-site cross-sectional data could be integrated with single-site longitudinal data (e.g., Picard-Meyer et al. 2011, Robardet et al. 2017) to overcome the need of a priori knowledge on the host kinetics of the immune response, which is likely conserved within a species sampled across sites.

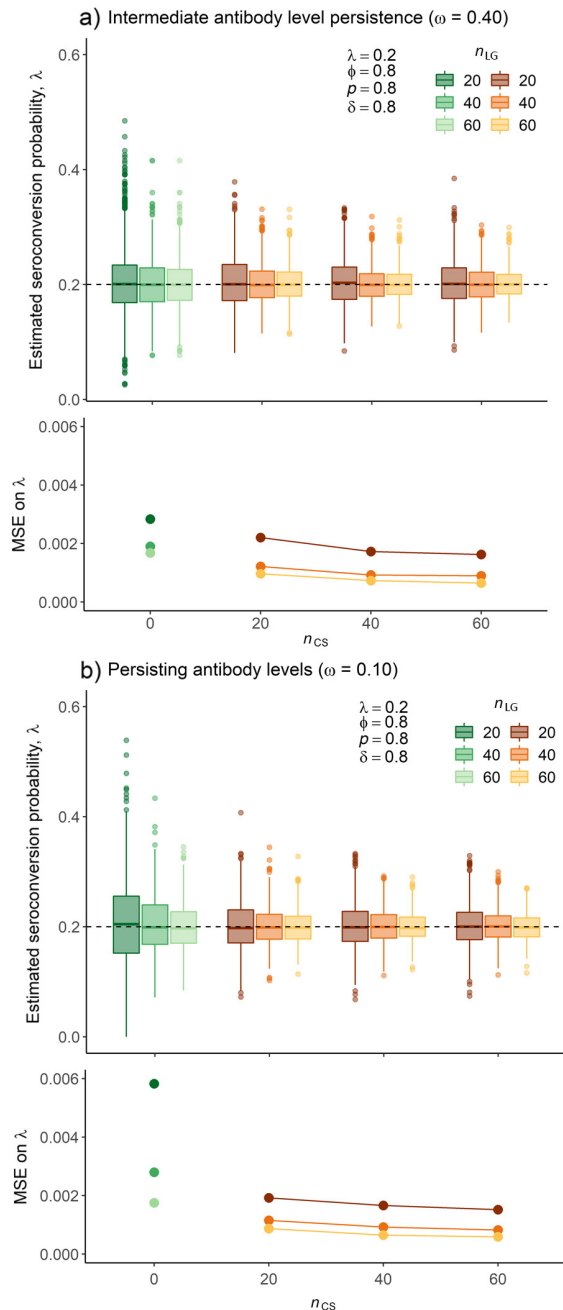


FIG. 3. The integrated estimator leads to higher precision in the estimation of the seroconversion probability (λ) compared to the longitudinal estimator. Estimated values of the seroconversion probability and corresponding MSE for different combinations on data sets analyzed with the longitudinal ($n_{CS} = 0$) or the integrated ($n_{CS} > 0$) model. Two situations were explored: (a) intermediate or (b) long persistence of the antibody levels. The true seroconversion probability is represented by a black dashed line. The cross-sectional model is not represented on this figure as it requires a priori reliable knowledge on ϕ and ω . The parameter n_{CS} is the number of individuals randomly captured and sampled for serological analyses each year; n_{LG} is the number of random individuals captured and marked with a tag the first year of the observation process.

Although the benefits of longitudinal setups are increasingly acknowledged in the disease ecology community, our study is the first to our knowledge to explore the conditions in which these benefits are actually found. Overall, the results highlight that the key elements to determine an optimal sampling design are (1) host species life history, (2) the degree of antibody persistence, and (3) the degree of a priori knowledge and uncertainty on demographic and epidemiologic parameters. This work also stresses the potential benefits of incorporating data from capture–recapture sampling designs in eco-epidemiological analyses, often largely based on cross-sectional field surveys. In practice, this integrated approach would be particularly beneficial in systems in which (1) individuals can be recaptured over several years (relatively long lifespan and high site faithfulness) and (2) large numbers of unmarked individuals can be sampled without increasing too much the cost of the study. This is, for instance, the case when samples can be collected when accidental capture is frequent (e.g., when using non-targeted capture methods such as mist nets, harp, or Sherman traps; e.g., Robardet et al. 2017, Mariën et al. 2018), or as part of harvesting practices (e.g., Rossi et al. 2005), or from the offspring of colonial breeders (e.g., Chambert et al. 2012b). In such cases, seroprevalence data from unmarked individuals may be collected with minimal additional effort in parallel to capture–recapture setups. For instance, particularly efficient cross-sectional sampling designs may not even require the capture of adults if the sampling of offspring, or eggs, can be used as a reliable alternative to adult blood sampling (Aleksseev et al. 2014, Hammouda et al. 2014, Gamble et al. 2019b; discussed in Appendix S1: Section S4). Further simulation work could aim at optimizing designs (e.g., sample sizes, sampling frequencies, study duration...) for various scenarios, similar to work performed for occupancy models (Mackenzie and Royle 2005, Guillera-Aroita and Lahoz-Monfort 2012).

The present study illustrates that setting up a capture–recapture program, potentially in parallel to extensive cross-sectional sampling, to estimate epidemiological parameters may be particularly rewarding in long-lived host species and when specific antibody level persistence is unknown, which is often the case for non-model species (e.g., seabirds [Chambert et al. 2012b] or marine mammals [Chambert et al. 2012a]). Conversely, in a species expected to be subjected to high yearly mortality probabilities (e.g., small passerines [Grosbois et al. 2006] or rodents [Mariën et al. 2018]), cross-sectional surveys may be the most efficient way to explore interannual processes. Nevertheless, implementing longitudinal, or integrated, setups can still be valuable in short-lived species to study processes occurring at smaller time scales (e.g., monthly; Mariën et al. 2018). In case of doubt about annual survival and/or the temporal persistence of antibody levels, it is always advisable to implement a capture–recapture program at a time scale adapted to

TABLE 1. Eco-epidemiological parameters estimated from a bat colony exposed to a rabies virus using the longitudinal or integrated design.

Parameter	Design			
	Longitudinal	Integrated $n_{CS} = 20$	Integrated $n_{CS} = 40$	Integrated $n_{CS} = 60$
Survival probability, ϕ	0.750 [0.684; 0.807]	0.750 [0.684; 0.807]	0.750 [0.684; 0.807]	0.750 [0.684; 0.807]
Seroconversion probability, λ	0.085 [0.033; 0.201]	0.072 [0.038; 0.130]	0.085 [0.046; 0.151]	0.079 [0.043; 0.139]
Seroconversion probability, ω	0.145 [0.072; 0.271]	0.152 [0.080; 0.269]	0.145 [0.075; 0.261]	0.148 [0.078; 0.265]
Resighting probability at $t = 1, p_1$	0.793 [0.733; 0.843]	0.793 [0.733; 0.843]	0.793 [0.733; 0.843]	0.793 [0.733; 0.843]
Resighting probability at $t = 2, p_2$	0.152 [0.049; 0.383]	0.152 [0.049; 0.383]	0.152 [0.049; 0.383]	0.152 [0.049; 0.383]
Resighting probability at $t = 3, p_3$	0.865 [0.630; 0.960]	0.865 [0.630; 0.960]	0.865 [0.630; 0.960]	0.865 [0.630; 0.960]
Resighting probability at $t = 4, p_4$	0.138 [0.062; 0.277]	0.138 [0.062; 0.277]	0.138 [0.062; 0.277]	0.138 [0.062; 0.277]
Resighting probability at $t = 5, p_5$	0.365 [0.218; 0.542]	0.365 [0.218; 0.542]	0.365 [0.218; 0.542]	0.365 [0.218; 0.542]
Resighting probability at $t = 6, p_6$	0.702 [0.477; 0.859]	0.702 [0.477; 0.859]	0.702 [0.477; 0.859]	0.702 [0.477; 0.859]
Resighting probability at $t = 7, p_7$	0.646 [0.421; 0.821]	0.646 [0.421; 0.821]	0.646 [0.421; 0.821]	0.646 [0.421; 0.821]
Recapture probability δ	0.659 [0.385; 0.856]	0.659 [0.385; 0.856]	0.659 [0.385; 0.856]	0.659 [0.385; 0.856]

Notes: The estimates are presented with their 95% confidence interval between brackets. Note that the confidence interval of seroconversion probability (in boldface type) is smaller when using the integrated design. The parameter n_{CS} is the number of individuals randomly captured and sampled for serological analyses each year; t is time.

the host species phenology. The interannual time scale we considered here may be particularly suited to the long-term monitoring of seasonally breeding species or to investigate the potential impact of diseases on long-lived populations (e.g., Lachish et al. 2007, Robardet et al. 2017). In disease systems with strong expected within- and between-year dynamics, the approach would need to incorporate some temporal hierarchy in considered eco-epidemiological parameters and in the corresponding timing of sampling.

Overall, given the relatively realistic situations we considered and the possibility to tailor the approach to more specific cases, the present study could have important implications regarding current practices in eco-epidemiology. For instance, the presented approach could be adapted to consider the time variations of the force of infection to account for epidemic cases or to incorporate parameters to account for a potential disease-induced mortality (discussed in Appendix S1: Section S1). Our study continues to expand the currently proposed framework to improve inference of the circulation of infectious agents in wild populations using serological data (see Appendix S1: Section S5). The sampling design will of course have to be adapted to the main objective of the survey (Yoccoz et al. 2001). For instance, if the main objective of the study is to estimate the seroconversion probability in a long-lived host species, putting important efforts on recapture (to insure a high δ) as part of a longitudinal setting, and integrating additional cross-sectional data could greatly improve the precision of the seroconversion estimators (Appendix S1: Fig. S6b, top panel). In contrast, if the main interest is on the survival probability, putting more effort on resighting (independently of recapture) could improve the precision of the estimates (Lahoz-Monfort et al. 2014, Lieury et al. 2017), but integrating cross-sectional data will provide no added benefit (Appendix S1: Fig. S6a, middle panel).

In any case, as already advocated in other papers (Albert et al. 2010, Garnett et al. 2011, Restif et al. 2012), but still seldom done (Herzog et al. 2017), we recommend a priori modeling based on available knowledge when designing eco-epidemiological studies, notably to account for host demography, immune response characteristics and sampling costs (Appendix S1: Fig. S9).

In addition to the assumption of independence of the data sets, the approach we used relies on the same assumptions as the ones classically made by the chosen capture–recapture and compartmented epidemiological models, and thus the same limitations apply. Notably, it is important to note that, because we used a simulated data set, the performances of the three presented approaches could have been overestimated. For instance, we did not consider the effect of potential heterogeneities between individuals included in the cross-sectional and longitudinal data sets (e.g., mean age differences or differences in age variances between the marked and unmarked individuals). If they cannot be avoided, these sources of heterogeneities could be accounted for in the modeling process (e.g., Péron et al. 2010). Finally, considering the recent advances made in quantitative ecology, this approach could be applied to more complex scenarios than the one we considered here, by being combined with methods accounting for state misclassification by repeating sampling (McClintock et al. 2010, Lahoz-Monfort et al. 2016), using the information contained in quantitative measurements (Choquet et al. 2013), combining assays such as serology and direct detection (Viana et al. 2016, Buzdugan et al. 2017) or by integrating individual traits more explicitly (Plard et al. 2019).

ACKNOWLEDGMENTS

We are thankful to Rémi Choquet and Roger Pradel for discussions, to Emmanuelle Robardet, Evelyne Picard-Meyer, and

Florence Cliquet for the serotine bat data, and to three anonymous reviewer's for their suggestions. This work used computational and storage services associated with the shared clusters provided by CEFÉ-CNRS and UCLA Institute for Digital Research and Education's Research Technology Group (Hoffman2). This paper is a contribution to the French Polar Institute IPEV programs ECOPATH 1151 and PARASITO-ARCTIQUE 333 and to the ECOPOP observation service of the OREME scientific observatory. A. Gamble was supported by a PhD fellowship from French Ministry of Research and the DARPA, project PREEMPT # D18AC00031. The content of the article does not necessarily reflect the position or the policy of the U.S. government, and no official endorsement should be inferred. T. Chambert was supported by a CeMEB LabEx post-doctoral fellowship and O. Gimenez by the ANR, project DEMOCOM # 16-CE02-0007.

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