Is disease a major causal factor in declines? An Evidence Framework and case study on koala chlamydiosis

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https://doi.org/10.1016/j.biocon.2018.03.030
Received 14 September 2017; Received in revised form 13 March 2018; Accepted 20 March 2018
Available online 05 April 2018

ARTICLE INFO
Keywords:
Declines
Koala
Phascolarctos cinereus
Conservation
Framework
Review
Misconception
Evidence
Disease
Chlamydia

ABSTRACT
Determining the role of an infectious agent in contributing to wildlife population declines is a pervasive problem in the field of conservation biology. We expand on a recently proposed broad investigative approach for disease, with a systematic framework outlining the specific types of individual- and population-scale empirical evidence required to demonstrate whether a pathogen is a component cause of declines in wild animal populations. Using koala (Phascolarctos cinereus) population declines and their putative association with the bacterial disease chlamydiosis (Family Chlamydiaceae) as a case study, we review the relevant published literature and synthesize a logical conceptual argument based on our suggested framework. Available empirical evidence supports a role for chlamydiosis contributing to host mortality and sterility, and cannot rule out a role of chlamydiosis as a component cause of koala population declines. However, the relative importance of chlamydiosis (among other threatening processes) as a driver of changes in koala demography and autecology may differ depending on the particular population or system examined, and this has yet to be elucidated over the koala's distributional range. Our approach allows us to highlight current research gaps in order to assist with future policy planning and conservation strategy. We recommend that a similar approach will assist in the evaluation of the role of disease in population declines in other ecological systems.

1. Introduction
Does a particular pathogen or disease cause declines of wild animal populations? This crucial question pervades the interface between the fields of disease ecology and conservation biology, across numerous ecosystems globally (Preece et al., 2017). Infectious diseases can have dramatic, widespread and long-term effects on ecological communities, and are increasingly being recognised as a substantial challenge in endangered species’ conservation (Daszak, 2000; Fisher et al., 2012; Jones et al., 2008; Scheele et al., 2017; Tompkins et al., 2015). Diseases that have been associated with vertebrate declines and extinctions globally include, for example, white nose syndrome in bats, West Nile Virus and avian malaria in birds, chytridiomycosis in amphibians, and chronic wasting disease in ungulates (Edmunds et al., 2016; George et al., 2015; Samuel et al., 2015; Skerratt et al., 2007; Thogmartin et al., 2012; Tompkins et al., 2015). In the applied field of conservation biology, conservation managers, ecologists, veterinarians and policy-makers are regularly being called upon to distinguish between those pathogens or diseases that deserve our attention, funding and research, and the multitude of other potential disease-causing agents. Expanding on the Disease Investigation Framework presented recently by Preece et al. (2017), in this manuscript we:

1. Specifically address pervasive misconceptions concerning the role of infectious diseases in declines
2. Present a detailed Evidence Framework outlining specific veterinary and ecological methodologies available to provide the evidence required to assess the relative role of disease
3. Demonstrate the application of this Evidence Framework with a detailed case study investigating the role of chlamydial disease in koala population declines

Please note that throughout this text we have used epidemiological terms with specific meanings. For definitions concerning our usage of these terms, please refer to the glossary provided by Preece et al. (2017).
2. Challenges in establishing the role of disease

Recent advances have been made in outlining an approach to determining the role of an infectious agent (and/or the disease it causes) in wildlife population decline and extirpation (Preece et al., 2017; Smith et al., 2009). However, substantial challenges (Table 1) and misconceptions (Table 2) remain. Even overt wildlife disease, causing epidemic or pandemic spread and associated with mass mortalities, may still take considerable time to recognise and diagnose (e.g. chytridiomycosis, white nose syndrome and dramatic mortalities of saiga antelope (Saiga tatarica) in Kazakhstan; Milner-Gulland, 2015). In contrast, our capacity for recognizing disease as a more subtle component cause (Wensink et al., 2014) of population declines, among other threatening processes, is currently limited (e.g. the sudden disappearance of the woylie (Bettongia penicillata) in Australia; Wayne et al., 2015).

Addressing these challenges in practice requires a transdisciplinary approach bridging veterinary science, epidemiology/disease ecology, general ecology, and conservation biology fields. It requires not only recognizing and appreciating the tools and expertise utilized by the various disciplines in solving these problems, but respecting the validity of these various methodologies. Discipline-specific jargon and research silos can result in ineffective transdisciplinary communication and interpretation of data and results, as well as misconceptions surrounding the potential role of pathogens and disease in host population declines (Table 2).

There is a long history of the development of criteria for causal inference, from the early work of David Hume (Hume 1739–1740) to the well-known Henle-Koch Postulates (Box 1; Evans, 1976), to more recent applications (Plotwright et al., 2008). While these methods for “testing” the plausibility of causal associations are essential and extremely valuable, no single set of “rules” will be suitable for all scenarios, and all have their exceptions. For example, the Henle-Koch Postulates (Box 1), widely used for identifying and confirming the causative agent of an infectious disease within an individual, are inappropriate criteria for non-infectious, multifactorial, and chronic diseases due to their focus on pathogen isolation (Evans, 1976). Furthermore, no single study is able to definitively prove an association between a pathogen and population declines, and thus contemporary scientific inference demands corroboration of the results via multiple studies.

3. Evidence framework

The Disease Investigation Framework provided by Preece et al. (2017) (see Box 2) outlines a series of steps for investigating cases of wildlife population decline where disease is a putative cause. Here, we expand on the three components of this process (steps 6, 7 and 9 in Box 2) that are most challenging in subtle cases of disease-associated decline (i.e. where pathogens are present, but mass mortalities are not observed). Our Evidence Framework (Fig. 1) provides a structure for identifying disease-associated wildlife declines where disease cannot be clearly ruled out as a causal factor.

In our Evidence Framework (Fig. 1) we separate disease processes into two scales – the individual host scale (Fig. 1A) and the host population scale (Fig. 1B). To confirm that a pathogen may potentially contribute to population declines, it should be demonstrated to be having an effect at both of these scales. In the figure columns we outline the main effects that pathogens can have on individual fitness (Fig. 1Ai) and population size (Fig. 1Bi), together with evidence required to demonstrate these effects (Fig. 1AII and 1BII), and a suite of veterinary and ecological methods by which this evidence can be provided (Fig. 1AIII, BIII and examples provided in Fig. 1AIV, BIV). We define “individual fitness” following Barrows (2011) as “an individual's relative contribution to the gene pool of its next and future generations”.

To use the Evidence Framework, at the individual host scale (Fig. 1A), it is important that a pathogen of interest should both be proven to be present (Fig. 1AIi), and demonstrated as causally associated with one or more of the listed effects (Fig. 1Alb–d) on individual hosts. It should be noted that lack of proof of pathogen presence does not confirm its absence without appropriate test sensitivity, sample sizes and study power (Skerratt et al., 2011b). Veterinary pathologists are well situated to collect appropriate evidence (Fig. 1AI) for causally associating tissue or organ dysfunction (Fig. 1AIlc) with pathogen presence (Fig. 1AIIa) and consistent clinical signs (Fig. 1AIIb). Their expertise may be called upon to confirm lack of a more plausible cause. Specific laboratory diagnostic testing is usually required to provide evidence for consistent host physiological and immune responses. Ecologists may be best suited to provide evidence concerning other forms of reduced fitness (Fig. 1Ald) and behavioural changes (Fig. 1Alf) in individuals with evidence of disease. While evidence for these latter effects is supportive, it is not in itself sufficient, and veterinary examinations are still required.

At the host population scale (Fig. 1B), the effects of negative population growth (Fig. 1Bla) and/or increased population vulnerability (Fig. 1Blb) should be demonstrated in association with the presence of disease in individuals (Fig. 1BIIa). Although not essential for confirming disease as a potential component cause of declines, identifying and examining the relative importance of other threatening processes putatively contributing to population declines can help elucidate the relative role of disease, and/or the presence of any synergisms or interactions between threatening processes and their effects on populations. It is also important to recognise that population decline need not be