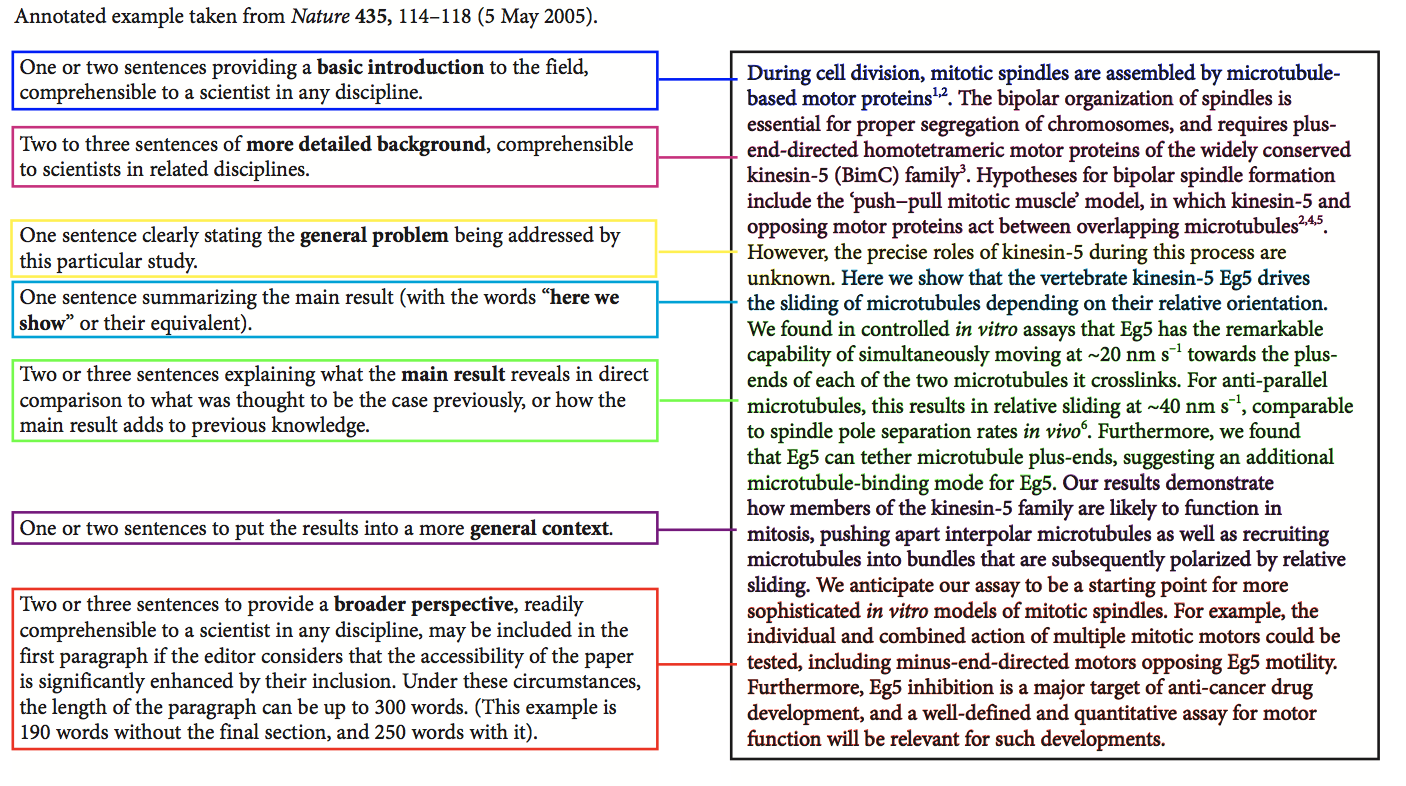
**Testing the generality of host-symbiont cophylogeny**

Alexander Hayward, Robert Poulin & Shinichi Nakagawa

**Abstract**

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**Main**

Symbioses are prolonged and intimate associations between organisms of different species (Wilkinson 2001). Symbiotic relationships may be mutualistic, where both partners benefit from the interaction, parasitic, where one partner benefits and the other suffers a cost, or commensalistic where one partner benefits while the other neither benefits nor suffers a loss (Leung & Poulin 2008) (Fig. 1). Symbioses are extremely common and exert a substantial influence in the living world with significant evolutionary and ecological impacts for disease (Schmid Hempel 2011; Hopkins *et al.* 2016), for driving major evolutionary transitions (Margulis & Fester 1991; Szathmáry & Smith 1995; Kiers & West 2015), and for influencing the structure and function of ecological communities (Reynolds *et al.* 2003; Thrall *et al.* 2007). Symbioses are also of considerable applied importance, due to the benefits provided by ecosystem services such as pollination and biocontrol, and the costs associated with harmful pests and agents of disease (Haines-Young & Potschin 2010; Gunn & Pitt 2012). Yet, despite their widespread biological and applied relevance, much remains unknown about the fundamental mechanisms that govern symbioses.

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| **Fig. 1: Examples of host-symbiont relationships.**   |  |  |  |  | | --- | --- | --- | --- | |  |  | elated image |  | |  |  |  |  |   Examples of symbiosis illustrating their pervasive nature across the diversity of life on earth. Clockwise from top-left: figwasp and fig tree pollination mutualism – the wasp gains a habitat and food resource for young, the tree gains pollination; mycorrhizal fungus and tree nutritional mutualism – the fungus gains carbohydrates for growth, while the tree gains increased water and nutrient absorption capabilities; bacteria and ruminant mutualism – the bacteria gain a hospitable environment for growth and reproduction, the ruminant gains nutrition from digesting bacteria; clownfish and anemone mutualism – the clownfish gains protection from predatory fish and the anemone gains protection from anemone feeding organisms; isopod and fish parasitism – the isopod feeds on fish tissue; louse and seabird parasitism – the louse feeds on albatross feathers; virus and vertebrate parasitism, the virus reproduces and spreads using host resources; plant and fungus parasitism – the fungus uses host resources to reproduce. |

Symbioses are typically defined in terms of a host organism that provides the habitat for a smaller symbiont (ref), and a key unanswered question in the study of symbiosis is the degree to which symbiont phylogenies track those of their hosts (Fig. 2). Elucidating this question offers potential insights into the processes that drive symbiont diversification, and hence the generation of a large proportion of Earth’s biodiversity, given that symbionts represent a considerable proportion of total species diversity (Windsor 1998; Poulin 2014). Unravelling the factors that influence host-symbiont phylogenetic congruence is also crucial for improving understanding of host-switching, a major research focus in host-parasite interactions, with direct implications for the prediction and mitigation of zoonoses, emerging infections, and the control of agricultural pests (Morens *et al.* 2004; Woolhouse *et al.* 2005).

The idea that symbionts track their hosts over evolutionary timescales, cospeciating in synchrony, is encapsulated by ‘Fahrenholz’s Rule’, which states that parasite phylogeny should reflect host phylogeny (Fahrenholz 1913; Eichler 1942). Fahrenholz’s Rule was formulated over one hundred years ago, yet a persistent assumption of host-specialization and accompanying host-parasite phylogenetic congruence remains within the field of host-symbiont interactions (Nylin *et al.* 2018), despite apparently limited support from the literature (de Vienne *et al.* 2013). Given the availability of statistical methods to compare host-symbiont phylogenetic congruence (e.g. Brooks 1981; Page 1990), and a recent accumulation of studies that apply these approaches (see 196 analyses listed in Supplementary Tables 1 and 2), opportunities now exist to examine the generality of Fahrenholz’s Rule within a formal quantitative framework.

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| **Fig. 2: Example of congruent and incongruent host-symbiont phylogenies.**    Hypothetical host (left) and symbiont (right) evolutionary trees, illustrating: (a) perfect phylogenetic congruence between hosts and symbionts, and, (b) incongruent tree topologies between hosts and symbionts. Taken from Poulin (2007). |

We apply meta-analytical methods to analyse a large body of published studies that quantify phylogenetic congruence for particular symbioses. We consider reported test statistics (*p values*) from two widely applied approaches for estimating host-symbiont phylogenetic congruence: one based on estimations of shared discrete macroevolutionary events (i.e. 'TreeMap', Page 1994), and one based on branch-length comparisons to estimate overall similarity (i.e. 'Parafit', Legendre *et al.* 2002). Firstly, we examine the extent to which symbiont phylogeny tracks host phylogeny, providing a broadscale analysis of cophylogeny. We then test the validity of Fahrenholz’s Rule specifically, by testing the generality of the prediction that parasite phylogeny mirrors host phylogeny across multiple host and parasite taxa. If parasites are specialized and tightly coevolved to single host species (Summers *et al.* 2003), we expect a strong signal of phylogenetic congruence between host and parasite phylogenies. Alternatively, if parasites commonly shift to new host species, either with parasite speciation following host-switching events (Rundle & Nosil 2005; Giraud *et al.* 2010), or without speciation (Clayton *et al.* 2015), we expect a weak or absent signal of phylogenetic congruence. Next, we compare the findings for parasites to those for mutually beneficial symbiotic interactions (sensu Bronstein 2015). Mutualism can be viewed within the framework of ‘reciprocal exploitation’ (Herre *et al.* 1999). Within this framework, the incentive to cheat (Trivers 1971; Leigh 2010) may destabilise the longevity of mutualisms over protracted evolutionary timescales, resulting in no greater overall phylogenetic congruence between hosts and mutualists than that observed for parasites. Conversely, mutualisms may be robust to such challenges and thus evolutionarily persistent (Ferriere *et al.* 2007; Douglas 2008), which would result in a pattern of tight host-mutualist phylogenetic congruence. To distinguish between these alternatives, we test host-mutualist phylogenetic congruence across host and mutualist taxa, while simultaneously providing a general comparison of host-symbiont phylogenetic congruence between mutualism and parasitism.

Given the paucity of formal testing of the drivers of host-symbiont phylogenetic congruence, we extend our analyses to consider the influence of several classic traits of relevance for host-symbiont interactions. Host specificity is a central aspect of symbiont life history with widespread ecological and evolutionary implications (Poulin 2007; Thrall *et al.* 2007), and may exert an independent effect on host-symbiont phylogenetic congruence beyond the mutualist-parasite divide. Under the prediction that specialist symbionts are evolutionarily or ecologically ‘tied-in’ to their host associations and hence undergo few host shifts(Hafner *et al.* 1994; Clayton & Johnson 2003; Hafner *et al.* 2003), host-symbiont phylogenetic congruence is expected to be high given specialism. Similarly, if generalist symbionts are relatively independent from associations with particular host lineages, host-symbiont phylogenetic congruence is expected to be low given generalism. Alternatively, if specialists remain associated with one or few hosts, but retain the ability to make host-shifts of varying frequency and magnitude (Krumbholz *et al.* 2009; Hall *et al.* 2016), then phylogenetic congruence is predicted to be low given specialism. Meanwhile, if dominant host-symbiont interactions occur within a context of host generalism (Charleston & Robertson 2002), then host-symbiont phylogenetic congruence may actually be high given generalism. Finally, no consistent pattern may be apparent between host specificity and host-symbiont phylogenetic congruence. We also consider the relevance of mode of transmission, to test the general expectation that vertical transmission promotes greater phylogenetic congruence (Nieberding & Olivieri 2007; Moran *et al.* 2008; Ebert 2013). Lastly, we examine the influence of endosymbiosis versus ectosymbiosis. Given that endosymbionts are fully enclosed within the host, they may be subject to greater selection for specialization than ectosymbionts (Poulin 2007; Schmid Hempel 2011), which may translate into tighter associations, and higher levels of phylogenetic congruence. Taken together, our study constitutes the first broadscale test of host-symbiont phylogenetic congruence across modes of symbiosis and key aspects of host and symbiont life-history, providing general implications for understanding of the factors underlying symbiont host-shifts and speciation.

Considering 196 published host-symbiont cophylogeny studies, including a wide spectrum of host and symbiont taxa, we found support that host phylogeny and symbiont phylogeny show a general tendency to reflect one another (*r* = \*\*, *Zr* = 0.342, 95% CI = 0.301, 0.383, *p*  = 0.0142)(Fig. 3A), with moderate variation in the strength of phylogenetic congruence among studies (*I*2 = 59.69). While positive, this tendency for cophylogeny is fairly low, corresponding to a mean *p-*value for phylogenetic congruence of *p =* 0.\*\*, versus a value of *p* = 0.5 if host-symbiont phylogeny is no more likely to reflect host phylogeny than by chance alone.

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| **Fig. 3: Forest plots of effect size for host-symbiont cophylogeny.**    **A**, Forest plot illustrating the overall effect size (±95% CI) of host-symbiont cophylogeny from a meta-analysis of 196 individual studies. The plot shows support for significantly greater phylogenetic congruence than is expected by chance. **B**, Forest plot showing separate effect sizes for host-parasite cophylogeny and host-mutualist cophylogeny, with the effect size of congruence for host-mutualist cophylogeny significantly greater than that for host-parasite cophylogeny. |

Next, we examined parasitism and mutualism separately. We found that while both modes of symbiosis display a positive effect for host-symbiont cophylogeny, our results support significantly greater congruence between host and mutualist phylogenies, than between host and parasite phylogenies (Contrast: *r* = \*\*, *Zr* = -0.104, 95% CI = -0.187, -0.021) (Fig. 3B). These findings have several implications. Firstly, our results do not support Fahrenholtz’s Rule; while we find that host and parasite phylogenies show greater similarity than expected by chance, the point estimate for congruence across studies is relatively weak, and host and parasite phylogenies cannot be said to be reflective of each other. Secondly, taking a large number of studies into consideration that sample a wide breadth of host and mutualist diversity, significant phylogenetic congruence for hosts and mutualists supports the hypothesis that host-mutualist relationships are in general evolutionary persistent, and are not routinely destabilised by reciprocal exploitation over evolutionary timescales. Thirdly, our results suggest that hosts and their mutualists show significantly greater phylogenetic congruence than hosts and their parasites.

To further dissect the identified cophylogenetic pattern between symbiont and host phylogenies, we examined if taxonomy exerted an effect by partitioning studies according to host and symbiont taxonomy. Variation in effect size among host taxa was highly variable, with microbe hosts sharing greatest phylogenetic congruence with their symbionts (*r* = \*\*, *Zr* = 0.558, 95% CI = 0.392, 0.725), followed by invertebrate hosts, vertebrate hosts (*r* = \*\*, *Zr* = 0.410, 95% CI = 0.330, 0.490), and lastly plant hosts (*r* = \*\*, *Zr* = 0.265, 95% CI = 0.180, 0.350) (Fig. 4A). In contrast, variation in phylogenetic congruence among symbiont taxa was lower, with microbe (*n* = 101) and invertebrate (*n* = 91) symbionts showing a very similar effect size for phylogenetic congruence (microbes: *r* = \*\*, *Zr* = 0.347, 95% CI = 0.291, 0.403; invertebrates: *r* = \*\*, *Zr* = 0.325, 95% CI = 0.263, 0.387), while poor sampling for vertebrate (*n* = 2) and plant (*n* = 3) symbionts precludes detailed comparisons (Fig. 4B). Splitting host taxonomy by mode of symbiosis revealed that differences in effect size for phylogenetic congruence originate largely from differences in mutualist host taxonomy, rather than parasite host taxonomy (Fig. 4C). Microbial hosts of mutualists show by far the strongest phylogenetic congruence with their symbionts (*r* = \*\*, *Zr* = 0.856, 95% CI = 0.617, 1.095, *p* < 0.0001) (Fig. 4C). Excluding vertebrate hosts with mutualistic symbionts (which are represented by only a single example in the dataset), the next highest level of phylogenetic congruence involves invertebrate hosts (*r* = \*\*, *Zr* = 0.431, 95% CI = 0.342, 0.519, *p* < 0.0001), while plant hosts show the lowest level of phylogenetic congruence with their mutualist symbionts, with an effect size slightly lower than that observed across parasite host taxonomy (*r* = \*\*, *Zr* = 0.246, 95% CI = 0.130, 0.363, *p* < 0.0001) (Fig. 4C).

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| **Fig. 3: Forest plots of effect size for host-symbiont cophylogeny, split by taxonomy.**    **A**, Forest plot illustrating the overall effect size of host-symbiont phylogenetic congruence, split by host taxonomy. All categories of hosts show a positive effect for phylogenetic congruence, with microbe, followed by invertebrate hosts showing the greatest effect. **B**, Forest plot illustrating the overall effect size of host-symbiont phylogenetic congruence, split by symbiont taxonomy. The effect is positive for microbe and invertebrate symbionts, while too few replicates exist for vertebrate and plant symbionts to allow other meaningful comparisons. **C**, Forest plot illustrating the overall effect size of host-symbiont phylogenetic congruence, split by host taxonomy and by mode of symbiosis. Differences in effect size are largely accounted for by the high effect size for microbe hosts of mutualists, and to a lesser extent, by the relatively high effect size for invertebrate hosts of mutualists. |

Host specificity is a fundamental aspect of host-symbiont interactions, and we next examined if this trait is associated with host-symbiont phylogenetic congruence. For this, we considered correlations with two different estimators of specificity: (i) host range, calculated as the total number of links between a set of hosts and their symbionts, divided by the total number of host taxa (i.e. perfect host specificity for each symbiont = 1, with the index increasing with each additional link between symbionts and hosts), and, (ii) host taxonomic breadth, where specificity decreases as symbionts are associated with hosts from successively higher ranks of Linnean taxonomy. Interestingly, no association was identified for either measure of host specificity, (slope for host range: *r* = \*\*, *Zr*= -0.026, 95% CI = -0.065, 0.012; slope for host taxonomic breadth: *r* = \*\*, *Zr*= -0.015, 95% CI = -0.053, 0.023), suggesting that host specificity is not an important general determinant of host-symbiont cophylogeny.

A major prediction for host-symbiont cophylogeny is that vertical transmission should promote phylogenetic congruence (Nieberding & Olivieri 2007; Moran *et al.* 2008; Ebert 2013). In line with this prediction, we found that mode of transmission was a significant correlate of host-symbiont phylogenetic congruence, with the strongest effect observed for vertical transmission, followed by the effect observed for mixed modes of transmission (symbionts are transferred via either route), with horizontal transmission showing the lowest effect size (vertical transmission: : *r* = \*\*, *Zr*= 0.521, 95% CI = 0.433, 0.609; mixed modes of transmission: : *r* = \*\*, *Zr*= 0.358, 95% CI = 0.272, 0.445; horizontal transmission: *r* = \*\*, *Zr*= 0.286, 95% CI = 0.237, 0.334; vertical transmission vs horizontal transmission = ??) (Fig. 4). \*\*[Discussion inserted here about whether the above effect of mutualism is totally explained by vertical transmission]. - Can we quantify the extent to which the effect of vertical transmission underlies the difference between parasitism and mutualisms here? It would be helpful to be able to disentangle this considering the bias in the dataset of vertical transmission showed by mutualists. Also maybe we should add a figure for mode of transmission split by type of symbiosis (i.e. 35 mutualists have vertical transmission, 22 mutualists have horizontral transmission, –is there a significance difference in congruence between the two groups?)\*\*.

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| **Fig. 4: Forest plot of effect size for host-symbiont cophylogeny, partitioned by mode of transmission (vertical, horizontal, mixed).**    Symbionts that are transmitted vertically share a significantly higher level of phylogenetic congruence with their hosts, compared to symbionts that are transmitted horizontally, or via both modes of transmission. |

Lastly, we examined whether an endosymbiotic versus an ectosymbiotic lifestyle has any relationship with host-symbiont cophylogeny. Endosymbionts, which live inside the host, experience a considerably more intimate relationship with the host than ectosymbionts, which interact with the host at the host’s surface. A major prediction is that the more intimate relationship associated with endosymbiosis may translate into greater congruence between host and symbiont phylogenies. Contrary to this hypothesis, we find that the distinction between endosymbiosis and ectosymbiosis has no influence on the degree of phylogenetic congruence observed between hosts and their symbionts (endosymbiosis: *r = \*\*, Zr*= 0.334, 95% CI = 0.283, 0.384; ectosymbiosis: *r = \*\*, Zr*= 0.364, 95% CI = 0.288, 0.441) (Fig. 5). There was only one example of a symbiont that was able to associate both as an endosymbiont and ectosymbiont with the same host, and the estimate for congruence in this case was again highly similar to that observed for endo- and ectosymbiosis individually (mixed endo- and ectosymbiosis: *r = \*\*, Zr*= 0.325, 95% CI = -0.204, 0.854).

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| **Fig. 5: Forest plot of effect size for host-symbiont cophylogeny, partitioned by whether the symbiont has an endosymbiotic or ectosymbiotic lifestyle.**    Endosymbiosis and ectosymbiosis share a very similar effect for phylogenetic congruence. Consequently, living within a host as an endosymbiont, as opposed to at the surface of the host as an ectosymbiont, does not appear to influence the degree of cophylogeny between hosts and symbionts. |

Employing a large quantitative and systematic review of the cophylogeny literature, we examined major hypotheses regarding the drivers of host-symbiont phylogenetic congruence. We found support for a general pattern of congruence between host and symbiont phylogenies. Significant congruence was observed for both hosts and their parasites, and for hosts and their mutualists, but it is was found to be significantly stronger in the latter case. Yet, while the observed pattern is indicative of a general tendency for symbionts to show phylogenetic congruence with their hosts, it does not support widespread mirroring of host and symbiont phylogenies, for either parasites or mutualists. Thus, we do not find evidence to support a strict interpretation of Fahrenholtz’s Rule (whereby hosts and symbionts exhibit strict cophylogenesis), either for parasites or mutualists. Such a result is not altogether unexpected, as events that generate phylogenetic incongruence between hosts and symbionts, such as host-switching and a failure of symbionts to cospeciate with their hosts (ref), are considered to be fairly common across parasite diversity. However, this study represents a first quantitative appraisal of this fundamental aspect of host-symbiont evolution. Importantly, considerable variation in congruence exists among host phylogenies and both parasite and mutualist phylogenies. Therefore, a central challenge is to identify which factors are of importance in fostering close cophylogeny.

One explanation for the greater strength of phylogenetic congruence between mutualists and their hosts could be that the reciprocal benefits that define mutualisms provide a stronger ‘cophylogenetic glue’ to unite partners, compared to the antagonistic interactions involved in parasitism. Meanwhile, within the context of host-parasite co-evolutionary dynamics, because the red queen never stops running, there is a constant possibility that one partner trips up, potentially resulting in a greater likelihood of lineage extinction and host-switching and accompanying phylogenetic discordance. However, by breaking down the observed tendency for phylogenetic congruence between hosts and symbionts, we found that mode of symbiont transmission is a key correlate of phylogenetic congruence, due to the positive effect of vertical transmission. The explanation for this pattern may be that symbionts that rely on vertical transmission are generally much more closely tied to the host, whereas those that use more broadcast means of transmission typically have a much greater potential to switch onto a new host. Interestingly we found no relationship with host-specificity in our study. However, we did not examine cases of host switching from a single host to another single host, as this in itself is a means of generating phylogenetic discordance, and this may vary between symbionts that undergo vertical and horizontal transmission.

\*\*Are we able to say how much of the effect mode of transmission accounts for? Is there any evidence at all for the reciprocal benefits argument?\*\*

With this study, we initiate a new direction in the study of symbiosis, towards formal quantitative analyses that seek to address fundamental questions regarding the nature of host-symbiotic evolutionary relationships. As the number of individual cophylogenetic studies increases, the power of these analyses will increase, permitting more detailed approaches to tease apart patterns and underlying mechanisms. Crucially, meta-analyses are only as good as the studies upon which they are based. A continued accumulation of taxonomically well-sampled, multi-locus host and symbiont phylogenies, ideally taking phylogenetic uncertainty into account, will provide a powerful platform on which to base further analyses. \*\*summing up couple of lines?\*\*

**Methods**

**Measures of host-symbiont phylogenetic congruence**

-More detailed description of how the tests for phylogenetic congruence work.

**Data collection**

-How the literature was searched systematically. At the macroevolutionary scale (i.e. discounting within-species studies)

-How data were categorised e.g. classification of the mode of symbioses was taken from the authors. In cases where this was not mentioned, the literature was consulted.

**Meta-analysis**

-How done, how bias avoided, etc.

**Data availability**

A copy of the dataset analysed in this study is included in the supplementary information.

**Author information**

**Affiliations**

Alexander Hayward1, Robert Poulin2, Shinichi Nakagawa3

1 Centre for Ecology and Conservation, University of Exeter, Penryn Campus, Penryn, TR10 9FE, Cornwall, UK.

2 Department of Zoology, University of Otago, P.O. Box 56, Dunedin, 9054, New Zealand.

3 Evolution & Ecology Research Centre, School of Biological, Earth & Environmental Sciences, University of New South Wales, Sydney NSW 2052, Australia.

**Contributions**

RP conceived the study. All authors designed the study. SN performed the analyses. AH collected the data and drafted the manuscript, and RP and SN provided comments and contributed to the final manuscript.

**Competing interests**

The authors declare no competing interests.

**Corresponding author**

Correspondence to ?

**Supplementary Information**

-Data table of mined information from cophylogeny studies.

-All figures and tables from Shinichi’s Analysis document.

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