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1 **Telomere shortening as a mechanism of long-term cost of infectious**
2 **diseases in natural animal populations**

3

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5

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10

11 **Abstract**

12 Pathogens are potent selective forces that can reduce the fitness of their hosts. While studies of
13 the short-term energetic costs of infections are accumulating, the long-term costs have only just
14 started to be investigated. Such delayed costs may, at least in part, be mediated by telomere
15 erosion. This hypothesis is supported by experimental investigations conducted on laboratory
16 animals which show that infection accelerates telomere erosion in immune cells. However, the
17 generalizability of such findings to natural animal populations and to humans remains debatable.
18 First, laboratory animals typically display long telomeres relative to their wild counterparts.
19 Second, unlike humans and most wild animals, laboratory small-bodied mammals are capable of
20 telomerase-based telomere maintenance throughout life. Third, the effect of infections on
21 telomere shortening and ageing has only been studied using single pathogen infections, yet hosts
22 are often simultaneously confronted with a range of pathogens in the wild. Thus, the cost of an
23 infection in terms of telomere-shortening-related ageing in natural animal populations is likely to
24 be strongly underestimated. Here, we discuss how investigations into the links between infection,
25 immune response and tissue ageing are now required to improve our understanding of the long-
26 term impact of disease.

27

28 **Introduction**

29 Parasites are a potent selective force, as they reduce the fitness of their hosts through the
30 direct cost of parasitism itself, and the indirect cost of an immune activation^{1,2}. Costs of immune
31 responses could be both short- and long-term. Short-term costs are reduced resource availability
32 for other demanding activities such as growth, reproduction, and other forms of self-
33 maintenance³. These costs have been well documented⁴. In addition to reduced investment in
34 tissue maintenance due to trade-offs, infections can lead to accelerated ageing through direct
35 effects of inflammatory processes on telomere erosion (Figure 1). These long-term costs in terms
36 of ageing rate have until recently been largely overlooked. Telomeres are regions of non-coding
37 DNA at the end of linear eukaryotic chromosomes that shorten during each cell division and in
38 response to oxidative stress^{5,6}. While the link between ageing and telomere erosion has to be
39 interpreted with caution, since questions about mechanisms and direction of causality complicate
40 this association⁷, telomere erosion has been proposed as an essential component of the ageing
41 phenotype⁵ and a major driving force behind immunosenescence¹². In fact, telomere shortening
42 due to other natural processes (i.e. stress, cellular ageing) leading to the senescence of the
43 immune system can be viewed as an opposite, non-mutually exclusive causal pathway linking
44 ageing rate and immune responses (Figure 1).

45 The long-term costs of an infection on telomere dynamics in wild animals remain mostly
46 unclear. Most studies investigating these costs have been conducted on small laboratory
47 mammals, but the generalizability of the results obtained in these studies to natural animal
48 populations remains debatable for several reasons. First, laboratory studies usually disregard the
49 importance of individual variation in disease resistance and tolerance, yet unlike traditional
50 laboratory model species, wild animals exhibit extensive variation in responses to infection⁸.

51 Second, while laboratory studies usually focus on one type of immune challenge at a time,
52 multiple infections are the rule rather than the exception in wild animals⁹. Multiple infections
53 may, on the one hand, accumulate immune-mediated pathology. On the other hand, activation of
54 one arm of the immune system can suppress the other arm, preventing immune pathology in case
55 of coinfections⁹. We thus suggest that telomere dynamics in wild individuals might be shaped by
56 the interaction between the whole pathogen community, the inherent immune capacity, and the
57 prioritized life-history and/or immune strategy (resistance *vs* tolerance). Accordingly, we can
58 distinguish between hypotheses that should be studied in order to support either the “aging cost
59 of infections pathway” or “immunosenescence pathway” (Figure 1). In this article, we will
60 review the available evidence on the link between infections and telomere dynamics in wild
61 animals, and describe possible associated physiological mechanisms that are relevant in the
62 context of optimal fitness outcome in the wild, but would be difficult to study in laboratory
63 conditions.

64

65 **What do we know?**

66 Studies in humans have repeatedly shown that patients with chronic infections have
67 shorter telomeres in immune cells than healthy individuals, and that individuals with shorter
68 telomeres have increased mortality rates¹⁰. This literature in humans has established a
69 relationship between health status and the rate of ageing, but the causal role of immune
70 activation on telomere shortening and human longevity remains elusive owing to obvious
71 experimental limitations with human subjects¹¹. A handful of experimental studies in animal
72 model species have demonstrated that exposure to pathogens results in accelerated telomere
73 erosion in immune cells. The generalizability of these results to humans and wild animals has

74 been questioned, since laboratory strains are often heavily inbred and display unusually long
75 telomeres relative to their wild counterparts^{12,13}. In addition, humans (characterized by short
76 telomeres and repressed telomerase in somatic tissues) and some smaller-bodied mammals
77 including laboratory rats and mice (characterized by long telomeres and telomerase-based
78 telomere maintenance in somatic tissues) do not present the same telomere dynamics throughout
79 life¹⁴. Accordingly, similar experimental setups that have been used on classical laboratory
80 models should be applied in wild animal species.

81 According to the hypothesis suggested in the current study (the aging cost of infections
82 pathway), infections should lead to faster aging. According to the alternative hypothesis (the
83 immunosenescence pathway), aging should lead to weaker immunity (Figure 1). How much
84 support can we find for either of these hypotheses from studies in wild populations? Non-
85 experimental studies showing age-related declines in telomere length and immunity (i.e.¹⁵) do
86 not allow to determine the direction of causality that is important for distinguishing between the
87 two pathways. It is noteworthy that while the immunosenescence hypotheses seems to be the
88 “null hypothesis” here, there is a lack of studies experimentally manipulating aging rate and/or
89 telomere shortening rate and recording the resulting changes in immune responses or infection
90 rates. This shortage can be explained with the scarcity of experimental approaches allowing to
91 manipulate telomere length (but see¹⁶ for a possible method). Current knowledge of the
92 consequences of infections on telomere dynamics in wild populations remains also limited. In a
93 cross-sectional study that, by definition, cannot measure telomere erosion and the pre-infection
94 variation in telomere length, Watson *et al* (2017)¹ did not find a significant relationship between
95 gastrointestinal nematode parasites load and leucocyte telomere length in Soay sheep (*Ovis*
96 *aries*). In contrast, using the same approach, Karell *et al.* (2017)¹⁸ found that tawny owls (*Strix*

97 *aluco*) carrying *Leucocytozoon* disease had shorter telomeres than uninfected individuals.
98 Longitudinal studies have shown associations between telomere erosion and bovine tuberculosis
99 infection status in wild European badgers (*Meles meles*)¹⁸ and with malaria in great reed warblers
100 (*Acrocephalus arundinaceus*)¹⁹. The study on badgers is also noteworthy in the context of the
101 current hypothesis, because it showed that age-related declines in immune response are unrelated
102 to immune cell telomere length in a wild mammal¹⁸. On the one hand, it does not provide direct
103 support for the hypothesis that immune responses can lead to accelerated ageing, on the other
104 hand, it indicates that at least in this model system, the alternative pathway (the
105 immunosenescence pathway, Figure 1) is not supported.

106 The discrepancies between these studies could be attributed to different types of
107 pathogens studied, time scales, and levels of infection. Only three studies have, so far, used an
108 experimental approach to investigate this topic in wild animals. In a study performed in captivity
109 with the F2 offspring of wild-caught house mice, where animals were exposed to an infectious
110 agent (*Salmonella enterica*), infected animals showed faster telomere erosion compared to non-
111 infected individuals¹². Inversely, in a field experiment, an antimalarial treatment administered to
112 adult blue tits had no effect on telomere shortening rates²⁰. Finally, in a study combining field
113 and captive experimental approaches, Asghar *et al.* showed the long-term costs of a malaria
114 infection on life span and survival in great reed warblers, potentially mediated through a
115 significantly greater rate of telomere shortening in six tissues^{19,29}. Given the higher inter-
116 individual than intra-individual variability in telomere length, any cross-sectional study will
117 have a very low power to detect any cost of infection. Thus, in addition to experimental studies
118 manipulating infection status in non-model animals, we recommend longitudinal and long-term

119 studies to understand these costs in the context of ageing (with telomere measurement in blood
120 samples).

121

122 **What to measure?**

123 A significant part of the studies on the long-term costs of an infection on ageing in the wild have
124 used avian species with telomere length measured in red blood cells^{19,20}, where it is supposed to
125 reflect telomere length in haematopoietic tissues (but see²²). The next step, in birds but also in
126 other organisms, is thus to measure telomere shortening in immune cells in order to study how
127 the type and extent of immune response mounted impact the rate of ageing of the immune
128 system. Immune cells are expected to be particularly vulnerable to telomere shortening under an
129 infection because of their rapid proliferation. In addition, the enzymes and enzyme complexes of
130 immune cells such as phagocytes and lymphocytes can rapidly produce large amounts of ROS
131 (reactive oxygen species)²³. Due to their cytotoxic character, ROS can directly contribute to the
132 degradation of the pathogen but this increased production of ROS may also be costly by
133 impacting immune cells through DNA damage and telomere shortening⁶.

134 Recent studies in humans have shown that the rate of telomere attrition and telomerase activity
135 are significantly different between cell types, suggesting cell-specific susceptibility and telomere
136 length regulation mechanisms^{24,25}. Even more, it has been recently shown in a wild mammal
137 (mandrill, *Mandrillus sphinx*) that leukocyte composition varies temporally and that these
138 variations are mirrored by change in blood telomere length²⁶. Thus, any conclusion based on
139 whole blood or total white blood cells are likely to be biased, especially in the case of infections
140 that affect white blood cell count and composition²⁷. A next step will therefore involve
141 measuring telomere shortening in specific populations of immune cells¹⁸. This approach would

142 also make it possible to discern whether any effects of infection on telomeres were due to
143 changes in circulating immune cell sub-types, which may differ in mean telomere length (e.g. an
144 increasing representation of memory T-cells with shorter telomeres relative to naive T-cells with
145 longer telomeres) versus within-cell telomere erosion in response to infection²⁵. However, since
146 sample amounts are generally small in studies of wild animals, methodological advancements
147 would be needed before this approach can be used, since cell sorting would have to be followed
148 by DNA extraction and the analysis of telomere length.

149

150 **Living in the real world: tolerance, resistance and coinfections**

151 Defense against parasites can be divided into two conceptually different components: resistance,
152 the ability to limit parasite burden, and tolerance, the ability to limit the disease severity induced
153 by a given parasite burden²⁸. Tolerance does not reduce the parasite burden, but decreases the
154 host susceptibility to tissue damage²⁹. Currently, very little is known about the full spectrum of
155 tolerance mechanisms. However, studies on mice with malaria infection have demonstrated that
156 protecting tissues from the toxic byproducts of immune responses is one of the mechanisms²⁹.
157 Telomere shortening accompanies strong responses to chronic parasite exposure from both
158 innate and acquired arms of the immune system¹². Preventing telomere shortening caused by
159 inflammation could be one of the molecular mechanisms behind parasite tolerance. Accordingly,
160 individuals exhibiting tolerance to parasites should also demonstrate lower telomere shortening
161 rate and have longer telomeres in comparison with individuals that apply immune responses for
162 to fighting off parasites. In line with this hypothesis, in a natural population of juvenile brown
163 trout (*Salmo trutta*), individuals that were less sensitive to parasite-induced impaired growth (and
164 therefore demonstrated higher tolerance), showed longer telomeres³⁰. We therefore predict that

165 host phenotypes that demonstrate higher levels of tolerance also show reduced telomere attrition
166 rate during the infection when compared to host phenotypes that are more prone to fight off the
167 parasites (higher resistance phenotypes), and suggest that host telomere attrition rate should be
168 an important trait to analyse in future studies of disease tolerance in the wild.

169 Wild animals are usually affected by several pathogens at the same time. While this could lead to
170 amplified long-term costs of infection, multiple infections can sometimes lead to lowered
171 inflammatory responses to specific type of parasites⁹. For example, chronic helminth infections
172 typically induce an anti-inflammatory type 2 immune response that limits damage to host tissues
173 by down-regulated inflammatory type 1 immune response usually triggered by bacterial
174 infections⁹. The possible amplifying or subduing effects of co-infections on telomere shortening
175 have so far not been studied, partly because the already complex dynamics of an immune
176 response through time will be compounded by immunological variation among hosts in their
177 pathogen exposure, age, nutrition and other varying aspects found in natural populations¹⁰. At the
178 same time, natural variation among individuals should be viewed as an unused potential for new
179 discoveries, rather than a nuisance. We therefore encourage studies on telomere dynamics
180 looking at the simultaneous effect of co-infections, as these could give more reliable answers to
181 the question about long-term costs of infection for wild animals.

182

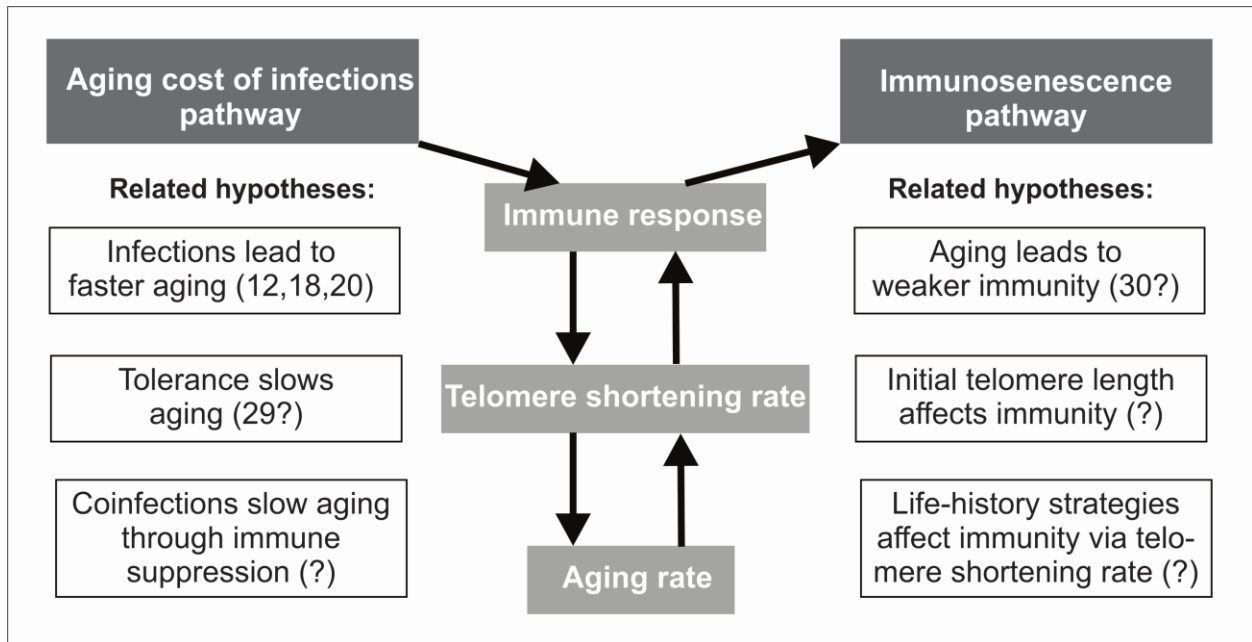
183 **Conclusion**

184 While our understanding of the short-term energetic costs of infection are accumulating, the
185 longer-term consequences of infection on ageing remain to be explored. Tissue damage and
186 intense cell proliferation associated with infection is likely to accelerate ageing, a process
187 possibly mediated by increased rates of telomere shortening. Studying the impact of infection on

188 telomere dynamics in natural animal hosts is thus essential, since natural selection has optimized
189 these processes in the context of lifetime fitness, and the costs and benefits associated with
190 telomere shortening cannot be understood outside the ecological context. Experimental studies
191 manipulating infection levels and immune responses, and measuring telomere dynamics in the
192 wild could shed light on the causality. However, longitudinal and long-term studies are crucial
193 for understanding the telomere-mediated effect of infectious diseases on ageing in wild
194 populations, with important implications for our understanding of the long-term cost of infection
195 in humans.
196

197 **Figure legend:**

198 Two non-mutually exclusive pathways with reversed causality directions that link responses to
199 infections with aging rate. Numbers indicate references supporting related hypotheses in wild
200 populations, question marks indicate either indirect support or missing support in wild
201 populations.



202

203

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