The Old School, Brewhouse Hill, Wheathampstead,
Hertfordshire AL4 8AN, UK
www.ufaw.org.uk

Animal Welfare 2019, 28: 137-141
ISSN 0962-7286
doi: 10.7120/09627286.28.2.137

Animal welfare as preventative medicine

MS Dawkins

University of Oxford, Department of Zoology, Oxford OX1 3SZ, UK

Abstract

Antimicrobial resistance is a major threat to both human and animal health, but reduction of use raises issues of how standards of animal health and welfare can be maintained without them. This turns the spotlight onto the role of good management and higher standards of animal welfare as drug-free ways of improving immune function and increasing resistance to infection. Research is urgently needed into the relationship between animal welfare, immunity, gut microbiota and disease and we are not yet in a position to claim that improving welfare will improve resistance to disease. 'Boosting' the immune system is not straightforward and an inter-disciplinary approach is needed.

Keywords: *animal health, animal welfare, antimicrobial resistance, immunity, positive emotions, stress*

Introduction

Reduced immune function and greater susceptibility to disease are widely recognised as results of poor welfare (Gross & Siegel 1981; Moberg 1985; Broom & Johnson 1993; Cockram & Hughes 2011) and routinely used as welfare 'indicators' (Gross & Siegel 1983; Shapiro 2002; Bartomolomucci 2007; Vermette *et al* 2017). My aim here is to ask whether there is a case for viewing the relationship the other way around and seeing good welfare not just as a consequence but as a potentially major contributor to improved immune function and disease resistance.

Antimicrobial resistance is now recognised as a major threat to human health across the planet (Hudson *et al* 2017; Aidara-Kane *et al* 2018) and extensive use of antimicrobials given to farm animals has been a major contributor to this problem (Teuber 2001; McEwen & Fedorka-Cray 2002; Kemper 2008; Silbergeld *et al* 2008). Consequently, there are international calls for reduced antibiotic use on farm animals (European Centre for Disease Prevention and Control [ECDC], European Food Safety Authority [EFSA] and European Medicines Agency [EMA]) 2017; DEFRA 2017; Ying *et al* 2017) but because of concerns about how standards of animal health can be maintained without antimicrobials (Gimeno *et al* 2016) their veterinary use for livestock continues to rise across the world (Van Boeckel *et al* 2015). A major step forward would be to avoid the use of antimicrobials as growth promoters or routine prophylactics altogether (Aidara-Kane *et al* 2018) and to reserve certain types for agricultural use when they are really needed to treat actual infection. An even further step would be to find ways of reducing the risk of infection in the first place. In the context of reducing the need for antimicrobials, several different alternatives have been proposed (McEwen & Fedorka-Cray 2002), including improved management practices, wider use of vaccines, use of probiotics (Bailey & Cryan 2017; Gao *et al* 2017) and drugs that boost the ability of the immune system to kill bacteria (eg Christiansen *et al* 2017). Of these possibilities, vaccines may often not be available or are expensive, it is often not clear how probiotics and antibiotics differ in the impact they have on immune function or gut flora (Angelakis 2017; Gao *et al* 2017), and immune-boosting drugs are largely untested and may have unforeseen consequences. This means that emphasis switches onto the potential for improved management and, in particular, good welfare as a drug-free route to improved immune function. However, although the pressure for reduction in antibiotic use provides an unprecedented stimulus for research in this area, the relationship between welfare, immunity and disease resistance is more complex than often realised (Berghman 2016). Animal welfare as preventative medicine is an attractive hypothesis with worldwide implications for both human and animal health, but that hypothesis now needs to be rigorously tested.

Immunity: the biggest arms race of all time

For at least one billion years, an evolutionary battle has been raging between disease organisms and their hosts. The odds are heavily stacked against us and other animals by virtue of our large size and long generation times. For every

anti-disease mechanism our bodies evolve, bacteria and viruses can reproduce much more rapidly, allowing them, in a few hours or days, to produce new mutations and combinations of mutations that give them a whole new set of possibilities for evading our defences. Faced with a never-ending horde of newly equipped enemies, vertebrates have evolved a truly extraordinary range of defence mechanisms, collectively called the immune system, which includes the skin, specialised cells circulating in the blood and lymphatic systems and molecular pathways for detecting and destroying pathogens in cells throughout the body. In addition, an ecosystem of bacteria in the gut also has a profound effect on health in general and immune function in particular (Yeoman *et al* 2014; Bailey & Cryan 2017). Even behaviour such as grooming and avoidance of sick individuals (Zylberberg *et al* 2013; Evans *et al* 2017) can be seen as part of the body's barrage of defences against infection.

The immune system has two parts that operate together but have very different implications for animal welfare (Berghman 2016). The initial response to infection or injury is mobilisation of responses known as the 'innate' or non-specific cellular immune response, such as production of bacteria-destroying granulocytes, release of cytokines, local inflammation and generalised sickness behaviour. This emergency response 'holds the fort' long enough for the second stage immune response — adaptive or acquired immunity — to develop specific antigens against particular pathogens, which may take several days. The two immune systems have been likened to an initial grenade that causes general destruction followed by a sniper with a single target (Berghman 2016).

The emergency response of the innate immune system mobilises many different parts of the body and needs so many nutrients to keep it functioning that it may compete with other vital processes such as reproduction, growth rate and tissue repair. For example, leukocytes may compete for the same amino acids as are needed by liver cells (Kogut & Klasing 2009) or bone cells (Humphrey & Klasing 2004). Animals have therefore been seen as having to allocate scarce resources optimally between a nutrient-hungry immune system and other systems in competition with it (Houston *et al* 2007; McKean *et al* 2008). For example, wild animals that are at high risk of predation or have to deal with unpredictability of food supply are less able to combat infection (Best & Hoyle 2013; Boots *et al* 2013; Stephenson *et al* 2015) and males that put resources into elaborate ornaments and displays may be more susceptible to disease than females (Zuk & Stoehr 2010). Conversely, major disease challenge may result in more resources being put into immune function and less into growth (Brock *et al* 2013). In response to changing risk of disease, animals change where and how much they forage (Houston *et al* 2007) and how likely they are to explore new places (Zylberberg *et al* 2013).

The later-acting acquired immunity, by contrast, comes at very little nutritional cost (Iseri & Klasing 2013) and so is very much less in competition with other systems. A relatively small number of specific antigens provide long-lasting protection against infection but selecting and cloning the right ones takes time, which is why the initial holding response by the innate system is so important. It is quite clear, then, that very different approaches are needed to 'boosting' immunity depending whether innate or acquired immunity is being considered (Berghman 2016).

'Boosting' the immune system(s)?

For farm animals, the concept of a resource-hungry (innate) immune system competing, sometimes unsuccessfully, for resources has led to the practice of adding extra nutrients to the diet to boost immune function (Kidd 2004; Klasing 2007; Ingvarten & Moyes 2013), in particular, amino acids such as arginine, glutamine and cysteine (Li *et al* 2007). However, adding single nutrients to a diet, particularly if given in excess, can upset the balance of the immune system and gut flora and actually make the body more vulnerable to infection by opportunistic pathogens (Kogut & Klasing 2009). Nevertheless, the idea that the body can switch resources away from or towards the immune system depending on circumstances is a powerful one and has led to the view that a more holistic approach to management, such as reducing stress and positively improving welfare, could free up much-needed resources for the immune system (Broom & Johnson 1993; Ekkel *et al* 1995; Hoerr 2010).

Support for this idea comes from studies on humans, where good immune function is closely related to peoples' subjective reports of being happy and satisfied with their lives (Nakata *et al* 2010; Takao *et al* 2018) while, conversely, impaired immune function has been found in people distressed by circumstances such as homelessness (Arranz *et al* 2009). But it is not clear exactly how being happier is related to better immunity and there is every reason to be cautious about the interpretation of an increase in 'immune function'. Much research is still needed but there is now increasing evidence that mental illnesses such as schizophrenia and depression are also associated with an increase in the cellular immune response (Maes 2011; Horsdal *et al* 2017) and neuronal cell surface antibodies (Steiner *et al* 2012; Lennox *et al* 2017). Depression is associated both with chronic inflammation and compensatory responses to combat inflammation (Berk *et al* 2013) and there are clear parallels to stress responses in non-human animals (Dantzer *et al* 2008). For example, mice that are repeatedly subjected to stress, such as being defeated in social encounters, show an inflammation response throughout the body including enhanced neutrophil and cytokine activity (Lafuse *et al* 2017). To follow the military analogy, just because there are many grenades exploding does not mean that all is well. On the contrary, it could indicate a situation that is pathologically out of control.

https://doi.org/10.7120/09627286.28.2.137 Published online by Cambridge University Press

Animal welfare implications

The interactions between brain, gut microbiome and immune system are highly complex (Dantzer *et al* 2008; Bailey & Cryan 2017; Leonard 2018) and there is consequently no simple relationship between measures of immune activity and welfare (Boissy *et al* 2007). Improving the ability of the acquired immune system to produce specific antigens through vaccination has obviously been one of the most important steps forward in the battle against disease, but even vaccines can trigger an unwanted innate inflammatory response ('vaccine reaction') especially with live attenuated vaccines so that there is still much work to be done (Kaiser 2010). However, it is the essential but volatile innate immune responses that we understand least and where we need to be particularly careful in our interpretations or desire to 'boost' it. Emergency innate immune responses, such as inflammation, are essential because they provide the first defence against infection and, without them, we could not survive. But the constant battle between host and pathogen, with viruses and bacteria evolving ever better ways of evading host defences can lead to unwanted side-effects, such as autoimmune diseases including rheumatoid arthritis and multiple sclerosis in which the innate immune system turns on its own body as the enemy. As mentioned above, even depression is now seen by some as an inflammatory disease arising through an over-active innate immune system (Maes 2011; Berk *et al* 2013).

The interactions between welfare, immune responses and disease resistance represent an immensely exciting area of research, given extra urgency by the need to reduce dependence on antimicrobials and the growing acknowledgement that animal health and human health are inextricably bound together (Murtaugh *et al* 2017). Animal welfare scientists have much to contribute by way of how to assess good welfare and, in particular, how to use behaviour to put 'valence' on mood and emotion (Boissy *et al* 2007; Dawkins 2008; Mendl *et al* 2010). However, animal welfare is now an interdisciplinary science (Veissier & Miele 2015) and co-operation with immunologists, physiologists and microbiologists is essential for the best research. We need to keep a clear separation between innate and acquired immunity because the implications for welfare are very different (Berghman 2016) and to be mindful of ethical and economic implications for the findings to be widely adopted.

We do not yet have clear evidence that improving welfare would improve disease resistance and so we cannot yet claim it is an important part of preventative medicine. But there are many pointers in this direction and, if confirmed, this hypothesis would have major implications for living without antimicrobials but also for the priority that the world is prepared to give to improving animal welfare. The path is not easy, but it is one well worth following.

References

Aidara-Kane A, Angulo FJ, Conly J, Minato Y, Silbergeld EK, McEwen SA and Collignon PJ 2018 World Health Organisation (WHO) guidelines on use of medically important microbials in food-processing animals. *Antimicrobial Resistance and Infection Control 7*: AR7. https://doi.org/10.1186/s13756-017-0294-9

Angelakis E 2017 Weight gain by gut microbiota manipulation in production animals. *Microbial Pathogenesis 106*: 162-170. https://doi.org/10.1016/j.micpath.2016.11.002

Arranz L, de Vicente A, Munoz M and de la Fuente M 2009 Impaired immune function in a homeless population with stress-related disorders. *Neuroimmunomodulation 16*: 251-260. https://doi.org/10.1159/000212386

Bailey MT and Cryan JF 2017 The microbiome as a key regulator of brain, behaviour and immunity. *Brain Behavior and Immunity 66*: 18-22. https://doi.org/10.1016/j.bbi.2017.08.017

Bartolomucci A 2007 Social stress, immune function and disease in rodents. *Frontiers in Neuroendocronology 28*: 28-49. https://doi.org/10.1016/j.yfrne.2007.02.001

Berghman LR 2016 Immune responses to improving welfare *Poultry Science 95*: 2216-2218. https://doi.org/10.3382/ps/pew159

Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML and Maes M 2013 So depression is an inflammatory disease, but where does the inflammation come from? *BMC Medicine 11*: AR 200. https://doi.org/10.1186/1741-7015-11-200

Best A and Hoyle A 2013 The evolution of costly acquired immune memory. *Ecology and Evolution 3*: 2223-2232. https://doi.org/10.1002/ece3.611

Boissy A, Manteuffel G, Jensen MB, Oppermann M, Spruijt B, Keeling LJ, Winckler C, Forkman B, Dimitrov I, Langbein J, Bakken M, Veissier I and Aubert A 2007 Assessment of positive emotions in animals to improve their welfare. *Physiology & Behavior 92*: 375-397. https://doi.org/10.1016/j.physbeh.2007.02.003

Boots M, Donnelly R and White A 2013 Optimal immune defence in the light of variation in lifespan. *Parasite Immunology 35*: 331-338. https://doi.org/10.1111/pim.12055

Brock PM, Hall AJ, Goodman SJ, Cruz M and Acevedo-Whitehouse K 2013 Immune activity. Body condition and human-associated environmental impacts in a wild marine mammal. *PLOS One 8*: AR E67132

Broom DM and Johnson KG 1993 *Stress and Animal Welfare*. Chapman and Hall: London, UK. https://doi.org/10.1007/978-94-024-0980-2

Christiansen SH, Murphy RA, Juul-Madsen K, Fredborg M, Hvam ML, Axelgaard E, Skovdal SM, Meyer RL, Skov Sørensen UB, Möller A, Nyengaard JR, Nørskov-Lauritsen N, Wang M, Gadjeva M, Howard KA, Davies JC, Petersen E and Vorup-Jensen T 2017 The immunomodulatory drug glatiramer acetate is also an effective antimicrobial agent that kills gram negative bacteria. *Nature Scientific Reports* article no 15653. https://doi.org/10.1038/s41598-017-15969-3

Cockram S and Hughes BO 2011 Health and disease. In: Appleby MC, Mench JA, Olsson IAS and Hughes BO (eds) *Animal Welfare, Second Edition* pp 12-137. CABI: Wallingford, UK. https://doi.org/10.1079/9781845936594.0120

Dantzer R, O-Connor JC, Freund GG, Johnson RW and Kelley KW 2008 From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience 9*: 46-57

Dawkins MS 2008 The science of animal suffering. *Ethology 114*: 937-945. https://doi.org/10.1111/j.1439-0310.2008.01557.x

DEFRA 2017 https://www.gov.uk/government/collections/antimicrobial-resistance-amr-information-and-resources

ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), and EMA (European Medicines Agency) 2017 ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals – Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. *EFSA Journal 15(7)*: 4872. https://doi.org/10.2903/j.efsa.2017.4872

Ekkel ED, Hessing MJC and Tielen MJM 1995 The specific-stress-free housing system has positive effects on productivity, health and welfare of pigs. *Journal of Animal Science 73*: 1544-1551. https://doi.org/10.2527/1995.7361544x

Evans K, Buchanan KL, Griffith SC, Klasing KC and Addison BA 2017 Ecoimmunology and microbial ecology: Contributions to avian behavior, physiology, and life history. *Hormones and Behavior 88*: 112-121. https://doi.org/10.1016/j.yhbeh.2016.12.003

Gao P, Ma C, Sun Z, Wang L, Huang S, Su X, Xu J and Zhang H 2017 Feed-additive probiotics accelerate yet antibiotics delay intestinal microbiota maturation in broiler chicken. *Microbiome 5*: AR UNSP9 https://doi.org/0.1186/s40168-017-0315-1

Gimeno C, Postma M, Dewulf J, Hogeveen H, Laywers L and Wauters E 2016 Farm-economic analysis of reducing antimicrobial use while adopting improved management strategies on farrow-to-finish pig farms. *Preventative Veterinary Medicine 129*: 74-87. https://doi.org/10.1016/j.prevetmed.2016.05.001

Gross WB and Siegel PB 1981 Long-term exposure of chickens to three levels of social stress. *Avian Disease 25*: 312-326. https://doi.org/10.2307/1589925

Gross WB and Siegel HS 1983 Evaluation of the heterophil lymphocyte ratio as a measure of stress in chickens. *Avian Diseases 27*: 972-979. https://doi.org/10.2307/1590198

Hoerr FJ 2010 Clinical aspects of immunosuppression in poultry. *Avian Disease 54*: 2-15. https://doi.org/10.1637/8909-043009-Review.1

Horsdal HT, Kohlerorsberg O, Benros ME and Gasse C 2017 C-reactive protein and white blood cell levels in schizophrenia, bipolar disorders and depression-associations with mortality and psychiatric outcomes: a population-based study. *European Psychiatry 44*: 164-172. https://doi.org/10.1016/j.eurpsy.2017.04.012

Houston A, McNamara JM, Barta Z and Klasing KC 2007 The effect of energy reserves and food availability on optimal immune defence. *Proceedings of the Royal Society B274*: 2835-2847. https://doi.org/10.1098/rspb.2007.0934

Hudson JA, Frewer LJ, Jones G, Brereton PA, Whittingham MJ and Stewart G 2017 The agri-food chain and antimicrobial resistance: a review. *Trends in Food Science and Technology 69*: 131-147. https://doi.org/10.1016/j.tifs.2017.09.007

Humphrey BD and Klasing KC 2004 Modulation of nutrient metabolism and homeostasis by the immune system. *World's Poultry Science Journal 60*: 90-100. https://doi.org/10.1079/WPS20037

Ingvarten KL and Moyes K 2013 Nutrition, immune function and health in dairy cattle. *Animal 7*: 122-122

Iseri VJ and Klasing KC 2013 Dynamics of the systemic components of the chicken (*Gallus gallus domesticus*) immune system following activation by *Escherichia coli*: implications for the cost of immunity. *Developmental Comparative Immunology 40*: 248-257. https://doi.org/10.1016/j.dci.2013.02.005

Kaiser P 2010 Advances in avian immunology: prospects for disease control. A review. *Avian Pathology 39*: 309-324. https://doi.org/10.1080/03079457.2010.508777

Kemper N 2008 Veterinary antibiotics in the aquatic and terrestrial environment. *Ecological Indicators 8*: 1-13. https://doi.org/10.1016/j.ecolind.2007.06.002

Kidd MT 2004 Nutritional modulation of immune function in broilers. *Poultry Science 83*: 650-657. https://doi.org/10.1093/ps/83.4.650

Klasing KC 2007 Nutrition and the immune system. *British Poultry Science 48*: 529-537. https://doi.org/10.1080/00071660701671336

Kogut MH and Klasing K 2009 An immunologist's perspective on nutrition, immunity, and infectious diseases: Introduction and overview. *Journal of Applied Poultry Research 18*: 103-110. https://doi.org/10.3382/japr.2008-00080

Lafuse WP, Gearinger R, Fisher S, Nealer C, Mackos AR and Bailey MT 2017 Exposure to a social stressor induces translocation of commensal *Lactobacilli* to the spleen and priming of the innate immune system. *Journal of Immunology 198*: 2383-2393. https://doi.org/10.4049/jimmunol.1601269

Lennox BR, Palmer-Cooper EC and Pollak T 2017 Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. *Lancet Psychiatry 4*: 42-48. https://doi.org/10.1016/S2215-0366(16)30375-3

Leonard BE 2018 Inflammation and depression: causal or coincidental link to the pathophysiology? *Acta Neuropsychiatrica 30*: 1-16. https://doi.org/10.1017/neu.2016.69

Li P, Yin Y, Li D and Wu G 2007 Amino acids and immune function. *British Journal of Nutrition 98*: 237-252. https://doi.org/10.1017/S000711450769936X

Maes M 2011 Depression as an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Progress in Neuro-psychopharmacology and Biological Psychiatry 35*: 664-675. https://doi.org/10.1016/j.pnpbp.2010.06.014

McEwen SA and Fedorka-Cray PJ 2002 Antimicrobial use and resistance in animals. *Clinical Infectious Diseases 34*: S93-S106. https://doi.org/10.1086/340246.

McKean KA, Yourth CP, Lazzaro BP and Clark AG 2008 The evolutionary costs of immunological maintenance and deployment. *Evolutionary Biology 8* AR 76. https://doi.org/10.1186/1471-2148-8-76

https://doi.org/10.7120/09627286.28.2.137 Published online by Cambridge University Press

Mendl M, Burman OHP and ES Paul 2010 An integrative and functional framework for the study of animal emotion and mood. *Proceedings of the Royal Society B277*: 2895-2904. https://doi.org/10.1098/rspb.2010.0303

Moberg GP 1985. Biological responses to stress: Key to assessment of animal well-being? In: Moberg GP (eds) *Animal Stress* pp 27-49. American Philosophical Society: Bethesda, Maryland, USA. https://doi.org/10.1007/978-1-4614-7544-6_3

Murtaugh MP, Steer CJ, Sreeevatsan S, Patterson N, Kennedy S and Sriramaran P 2017 The science behind One Health: at the interface of humans, animals and the environment. *Annals of the New York Academy of Sciences 1395*: 12-32. https://doi.org/10.1111/nyas.13355

Nakata A, Takahashi M, Irie M and Swanson NG 2010 Job satisfaction is associated with elevated natural killer cell immunity among healthy, white-collar employees. *Brain, Behavior and Immunity 24*: 1268-1275. https://doi.org/10.1016/j.bbi.2010.05.004

Shapiro SJ 2002 Effects of social manipulations and environmental enrichment on behaviour and cell-mediated immune responses in rhesus macaques. *Pharmacology, Biochemistry, and Behavior 73*: 271-278. https://doi.org/10.1016/S0091-3057(02)00779-7

Silbergeld EK, Graham J and Price LB 2008 Industrial food animal production, antimicrobial resistance and human health. *Annual Review of Public Health 29*: 151-169. https://doi.org/10.1146/annurev.publhealth.29.020907.090904

Steiner J, Bogerts B, Sarnyai Z, Walter M, Bernstein H-G and Myint A-M 2012 Bridging the gap between the immune and glutamate hypotheses of schizophrenia and major depression: potential role of glial NMDA receptor modulators and impaired blood-brain barrier integrity. *World Journal of Biological Psychiatry 13*: 482-492. https://doi.org/10.3109/15622975.2011.583941

Stephenson JF, van Opsterhout C and Cable J 2015 Pace of life, predators and parasites: predator-induced life-history evolution in Trinidadian guppies predicts decrease in parasite tolerance. *Biology Letters 11*: AR 20150806

Takao Y, Okuno Y, Mori Y, Asasa H, Yamanishi K and Iso H 2018 Associations of perceived mental stress, sense of purpose in life, and negative life events with the risk of incident herpes Zoster and postherpetic neuralgia. *American Journal of Epidemiology 187*: 251-259. https://doi.org/10.1093/aje/kwx249

Teuber M 2001 Veterinary use and antibiotic resistance. *Current Opinion in Microbiology 4*: 493-499. https://doi.org/10.1016/S1369-5274(00)00241-1

Van Boeckel TP, Brower C, Gilbert M, Grenfell, Levin SA, Robinson TP, Teillant A and Laxminarayan R 2015 Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Science 112*: 5649-5654. https://doi.org/10.1073/pnas.1503141112

Veissier I and Miele M 2015 Short historical overview of animal welfare sciences: how a societal concern has become a transdisciplinary subject. *INRA Productions Animales 28*: 399-409

Vermette CJ, Henrikson ZA, Schwean-Lardner KV and Crowe T G 2017 Influence of hot exposure on 12-week-old turkey hen physiology, welfare, and meat quality and 16-week-old turkey tom core body temperature when crated at transport density. *Poultry Science 96(11)*: 3836-3843. https://doi.org/10.3382/ps/pex220

Yeoman CJ, White BA, Lewis HA and Roberts RM 2014 Gastrointestinal tract microbiota and probiotics in production animals. *Annual Review of Animal Biosciences 2*: 469-486. https://doi.org/10.1146/annurev-animal-022513-114149

Ying GG, He LY, Ying AJ, Zhang QQ, Liu YS and Zhao JI 2017 China must reduce its antibiotic use. *Environmental Science Technology 51*: 1072-1073. https://doi.org/10.1021/acs.est.6b06424

Zuk M and Stoehr AM 2010 Sex differences in susceptibility to infection: an evolutionary perspective. In: Klein SL and Roberts CW (eds) *Sex Hormones and Immunity to Infection* pp 1-10. Springer-Verlag: Berlin, Germany. https://doi.org/10.1007/978-3-642-02155-8_1

Zylberberg M, Klasing KC and Hahn TO 2013 House finches (*Carpodacus mexicanus*) balance investment in behavioural and immunological defences against pathogens. *Integrative and Comparative Biology 53(S1)*: E400