

## FEATURE

## CHRISTMAS 2017: ALL CREATURES GREAT AND SMALL

## The science behind “man flu”

Kyle Sue explores whether men are wimps or just immunologically inferior

Kyle Sue *clinical assistant professor in family medicine*

Health Sciences Centre, Memorial University of Newfoundland, St John's, NL, Canada

“Man flu” is a term so ubiquitous that it has been included in the Oxford and Cambridge dictionaries. Oxford defines it as “a cold or similar minor ailment as experienced by a man who is regarded as exaggerating the severity of the symptoms.”<sup>1</sup> Since about half of the world’s population is male, deeming male viral respiratory symptoms as “exaggerated” without rigorous scientific evidence, could have important implications for men, including insufficient provision of care.

Despite the universally high incidence and prevalence of viral respiratory illnesses,<sup>2</sup> no scientific review has examined whether the term “man flu” is appropriately defined or just an ingrained pejorative term with no scientific basis. Tired of being accused of over-reacting, I searched the available evidence (box) to determine whether men really experience worse symptoms and whether this could have any evolutionary basis.

### Of mice and men

Mice have long been accepted as good models of human physiology for medical research,<sup>3</sup> with records dating back to William Harvey in 17th century England.<sup>4</sup> Several studies show that female mice have higher immune responses than males.<sup>5,6</sup> This led to the hypothesis that sex dependent hormones have an important role in outcomes of influenza. Further studies suggest that oestradiol is implicated in this response in mice,<sup>7</sup> with one study concluding that the hormone reduces “responses associated with immunopathology” and enhances “responses associated with recruitment of innate immune cells...into the lungs.”<sup>8</sup>

However, another mouse study suggests that stress and corticosterone levels have a role, concluding that “the increase in infection-induced corticosterone levels demonstrated in females may have suppressed the behavioural symptoms of infection.”<sup>9</sup>

Lending further weight to the oestradiol theory, an in-vitro study sniffs at an underlying reason for man flu. Using human nasal epithelial cell cultures infected with seasonal influenza A, researchers showed that exposure to oestradiol or select oestrogen receptor modulators (SERMs) decreased influenza A titres in tissue from female, but not male, donors. Oestradiol

also significantly downregulated cell metabolic processes. Adding oestrogen receptor antagonists reversed this antiviral effect.<sup>10</sup>

Another study isolated mononuclear cells from 63 healthy people grouped according to age and sex and cultured the cells with rhinovirus. Cells cultured from premenopausal women had a stronger immune response to rhinovirus than those from men of the same age. This difference was not observed when post-menopausal women were compared with men of the same age, suggesting a hormonal link.<sup>11,12</sup>

### Patterns in humans

Although animal and in-vitro studies are weak sources of evidence, human research also points to different responses to influenza in men and women. Even the World Health Organization stresses that “sex should be considered when evaluating influenza exposure and outcomes.”<sup>13</sup> Epidemiological data from 2004–10 for seasonal influenza in Hong Kong showed that adult men had a higher risk of hospital admission,<sup>14</sup> and in a US observational study of influenza mortality from 1997 to 2007, men had higher rates of influenza associated deaths compared with women in the same age groups. This was true regardless of underlying heart disease, cancer, chronic respiratory system disease, and renal disease.<sup>15</sup>

Studies of influenza vaccination suggest that women are more responsive to vaccination than men.<sup>16,17</sup> This is supported by the finding that women report more local and systemic reactions to influenza vaccine than men in questionnaires.<sup>18</sup> One study noted that men with higher testosterone levels had more down regulation of antibody response to vaccination, suggesting an immunosuppressive role for testosterone.<sup>16</sup> This is consistent with animal and in-vitro studies showing testosterone has an immunosuppressive effect<sup>19,20</sup> and a finding of higher levels of inflammatory cytokines in men with androgen deficiencies than in healthy controls.<sup>21</sup>

The sex differences extend to other respiratory infections beyond influenza. In many acute respiratory diseases, males are more susceptible to complications and exhibit a higher mortality.<sup>22</sup>

## Methods

I searched PubMed/MedLine, EMBASE, Cochrane, CINAHL, Web of Science, Scopus, and Google Scholar using combinations and variants of terms "man"/"male", "woman"/"female", "gender"/"sex", "influenza"/"flu", "viral", "respiratory", "common cold", "difference", "comparison", "intensive care." I read the abstracts of all articles found and narrowed articles down by relevance. References in each article were then hand searched to ensure comprehensiveness.

Wyke and colleagues surveyed men and women consulting general practitioners for common symptoms of minor infectious respiratory illness, finding that "women were significantly more likely to report cutting down activities in response to only one symptom in each cohort."<sup>23</sup> This contradicts the common myth that men cut down activities more than women by exaggerating the severity of symptoms.

Furthermore, in an analysis of retrospective data from a common cold unit on 1700 volunteers inoculated with virus (rhinovirus, coronavirus, influenza, etc) during 1984-89, MacIntyre postulated that "clinical observers are more ready to attribute symptoms and illness to women than to men, and...they under-rate men's symptoms."<sup>24</sup>

Finally, in an unscientific survey completed by 2131 readers of a popular magazine, men reported taking an average of three days to recover from viral respiratory illness compared with 1.5 days for women. The male authors of this study conclude that caregivers should "go that extra mile to care for us when we are stricken with it, so that future shelves can be erected, cars can be maintained and football stadia throughout the land can be well attended"<sup>25</sup>—listing only a few of the many ways male viral respiratory illnesses can affect society.

## Immunity gap

Some evidence clearly supports men having higher morbidity and mortality from viral respiratory illness than women because they have a less robust immune system. However, conclusions may be limited by author bias, inclusion of some low level evidence, and not reporting a critical appraisal of the studies cited. Additionally, the differences observed in these studies may not be representative of all respiratory viruses, and differences may be hidden within studies that did not stratify the various viruses or other differences between the sexes.

The sex difference in immunity has been suggested to be modulated by hormonal differences, with oestradiol being immunoprotective and testosterone being immunosuppressive. However, the reviewed studies did not consider other differences between the sexes—for example, men have higher rates of smoking worldwide<sup>26</sup> and are less likely to take preventive care or seek care when ill.<sup>27</sup> Hormonal influence on immune response is supported by evidence that pregnant women have more severe influenza symptoms and reduced symptoms from autoimmune diseases than non-pregnant women.<sup>28,29</sup> However, it is unclear how this is mediated or might apply to a difference between the sexes, given the changes in oestrogen, progesterone, and other hormones along with other stressors that occur during pregnancy.

If the differences found in the above studies are real, the evolutionary purpose of men's higher symptoms from viral respiratory infections remains unclear. Zuk postulates that "if males require, for example, testosterone for aggressive behaviour and the development of male secondary sexual characteristics, selection for winning at the high-stakes game males play may override the cost of any immunosuppressive effects of the hormone."<sup>30</sup> Likewise, the authors of another study speculate that reduced immunity is less important for men because males of many species are more likely to die from trauma before an

infection kills them.<sup>16</sup> Other academics agree that across species, the male strategy of "live hard, die young" arising from stronger intra-sexual competition than among females has led to less investment in immunity<sup>31</sup> and that "mounting immune responses to clear viruses requires metabolic resources that might otherwise be used for other biological processes, such as growth, maintenance of secondary sex characteristics, and reproduction."<sup>32</sup>

Avitsur and colleagues suggest that the increase in male sickness may be a strategy important for the survival since "it promotes energy conservation and reduces the risk of encountering predators."<sup>9</sup> Classic modes of energy conservation may include lying on the couch, not getting out of bed, or receiving assistance with basic activities of daily living, which could all be effective for avoiding predators.

Further higher quality research is needed to clarify other aspects of man flu. It remains uncertain whether viral titres, immune response, symptoms, and recovery time can be affected by environmental conditions. An example of future research may include a controlled trial in which men are infected with a respiratory virus, then subjected to rigorous research conditions in which all their requests are met by a healthy designated caregiver or they are left to fend for themselves. Another potential study may examine whether men with robust immune systems are less successful at mating compared with those with weaker immune systems and correspondingly higher testosterone. In other words, can the blame for man flu be shifted to the people who select these men as sexual partners rather than the men themselves?

## Time to rest

The concept of man flu, as commonly defined, is potentially unjust. Men may not be exaggerating symptoms but have weaker immune responses to viral respiratory viruses, leading to greater morbidity and mortality than seen in women. There are benefits to energy conservation when ill. Lying on the couch, not getting out of bed, or receiving assistance with activities of daily living could also be evolutionarily behaviours that protect against predators. Perhaps now is the time for male friendly spaces, equipped with enormous televisions and reclining chairs, to be set up where men can recover from the debilitating effects of man flu in safety and comfort.

Competing interests: I have read and understood BMJ policy on declaration of interests and declare that I have no competing interests.  
Provenance and peer review: Not commissioned; externally peer reviewed.

- 1 Oxford Dictionaries. Man flu. [https://en.oxforddictionaries.com/definition/man\\_flu](https://en.oxforddictionaries.com/definition/man_flu).
- 2 Tang JW, Lam TT, Zaraket H, et al. INSPIRE Investigators. Global epidemiology of non-influenza RNA respiratory viruses: data gaps and a growing need for surveillance. *Lancet Infect Dis* 2017;doi:10.1016/S1473-3099(17)30238-4.
- 3 Perlman RL. Mouse models of human disease: an evolutionary perspective. *Evol Med Public Health* 2016;2016:170-6.pmid:27121451.
- 4 Ericsson AC, Crim MJ, Franklin CL. A brief history of animal modeling. *Mo Med* 2013;110:201-5.pmid:23829102.
- 5 Lorenzo ME, Hodgson A, Robinson DP, Kaplan JB, Pekosz A, Klein SL. Antibody responses and cross protection against lethal influenza A viruses differ between the sexes in C57BL/6 mice. *Vaccine* 2011;29:9246-55. doi:10.1016/j.vaccine.2011.09.110 pmid: 21983155.

- 6 Hoffmann J, Otte A, Thiele S, Lotter H, Shu Y, Gabriel G. Sex differences in H7N9 influenza A virus pathogenesis. *Vaccine* 2015;33:6949-54. doi:10.1016/j.vaccine.2015.08.044 pmid:26319064.
- 7 Pazos MA, Kraus TA, Muñoz-Fontela C, Moran TM. Estrogen mediates innate and adaptive immune alterations to influenza infection in pregnant mice. *PLoS One* 2012;7:e40502. doi:10.1371/journal.pone.0040502 pmid:22792357.
- 8 Robinson DP, Hall OJ, Nilles TL, Bream JH, Klein SL. 17 $\beta$ -estradiol protects females against influenza by recruiting neutrophils and increasing virus-specific CD8 T cell responses in the lungs. *J Virol* 2014;88:4711-20. doi:10.1128/JVI.02081-13 pmid:24522912.
- 9 Avitsur R, Mays JW, Sheridan JF. Sex differences in the response to influenza virus infection: modulation by stress. *Horm Behav* 2011;59:257-64. doi:10.1016/j.yhbeh.2010.12.002 pmid:21167165.
- 10 Peretz J, Pekosz A, Lane AP, Klein SL. Estrogenic compounds reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors. *Am J Physiol Lung Cell Mol Physiol* 2016;310:L415-25. doi:10.1152/ajplung.00398.2015 pmid:26684252.
- 11 Antrobus C. Gender differences in flu severity: fact or fiction? *Australian Pharmacist* 2012;31:288-92.
- 12 Carroll ML, Yerkovich ST, Pritchard AL, Davies JM, Upham JW. Adaptive immunity to rhinoviruses: sex and age matter. *Respir Res* 2010;11:184-91. doi:10.1186/1465-9921-11-184 pmid:21194432.
- 13 World Health Organization. *Sex, gender, and influenza*. WHO Press, 2010.
- 14 Wang X-L, Yang L, Chan K-H, et al. Age and sex differences in rates of influenza-associated hospitalizations in Hong Kong. *Am J Epidemiol* 2015;182:335-44. doi:10.1093/aje/kwv068 pmid:26219977.
- 15 Quandelacy TM, Viboud C, Charu V, Lipsitch M, Goldstein E. Age- and sex-related risk factors for influenza-associated mortality in the United States between 1997-2007. *Am J Epidemiol* 2014;179:156-67. doi:10.1093/aje/kwt235 pmid:24190951.
- 16 Furman D, Hejblum BP, Simon N, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *Proc Natl Acad Sci U S A* 2014;111:869-74. doi:10.1073/pnas.1321060111 pmid:24367114.
- 17 Engler RJ, Nelson MR, Klote MM, et al. Walter Reed Health Care System Influenza Vaccine Consortium. Half- vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses. *Arch Intern Med* 2008;168:2405-14. doi:10.1001/archinternmed.2008.513 pmid:19064822.
- 18 Beyer WE, Palache AM, Kerstens R, Masurel N. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. *Eur J Clin Microbiol Infect Dis* 1996;15:65-70. doi:10.1007/BF01586187 pmid:8641306.
- 19 Olsen NJ, Kovacs WJ. Gonadal steroids and immunity. *Endocr Rev* 1996;17:369-84. pmid:8854050.
- 20 Rettew JA, Huet-Hudson YM, Marriott I. Testosterone reduces macrophage expression in the mouse of toll-like receptor 4, a trigger for inflammation and innate immunity. *Biol Reprod* 2008;78:432-7. doi:10.1095/biolreprod.107.063545 pmid:18003947.
- 21 Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Chanher KS, Jones TH. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men. *J Clin Endocrinol Metab* 2004;89:3313-8. doi:10.1210/jc.2003-031069 pmid:15240608.
- 22 Giefing-Kröll C, Berger P, Lepperdinger G, Grubeck-Loebenstien B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. *Aging Cell* 2015;14:309-21. doi:10.1111/ace.12326 pmid:25720438.
- 23 Wyke S, Hunt K, Ford G. Gender differences in consulting a general practitioner for common symptoms of minor illness. *Soc Sci Med* 1998;46:901-6. doi:10.1016/S0277-9536(97)00217-7 pmid:9541075.
- 24 Macintyre S. Gender differences in the perceptions of common cold symptoms. *Soc Sci Med* 1993;36:15-20. doi:10.1016/0277-9536(93)90301-J pmid:8424180.
- 25 Boynton P. Are reports of "man flu" just Nuts? *BMJ* 2006;333:1128doi:10.1136/bmj.39041.590556.59.
- 26 Guindon GE, Boisclair D. *Past, current and future trends in tobacco use: HNP discussion paper*. The World Bank, 2003.
- 27 Baker P, Dworkin SL, Tong S, Banks I, Shand T, Yamey G. The men's health gap: men must be included in the global health equity agenda. *Bull World Health Organ* 2014;92:618-20. doi:10.2471/BLT.13.132795 pmid:25197149.
- 28 Yudin MH. Risk management of seasonal influenza during pregnancy: current perspectives. *Int J Womens Health* 2014;6:681-9. doi:10.2147/IJWH.S47235 pmid:25114593.
- 29 Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. *Immunol Invest* 2008;37:631-44. doi:10.1080/08820130802205886 pmid:18716941.
- 30 Zuk M. The sicker sex. *PLoS Pathog* 2009;5:e1000267. doi:10.1371/journal.ppat.1000267 pmid:19180235.
- 31 Restif O, Amos W. The evolution of sex-specific immune defences. *Proc Biol Sci* 2010;277:2247-55. doi:10.1098/rspb.2010.0188 pmid:20335214.
- 32 Klein SL, Hodgson A, Robinson DP. Mechanisms of sex disparities in influenza pathogenesis. *J Leukoc Biol* 2012;92:67-73. doi:10.1189/jlb.0811427 pmid:22131346.

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>