

Correspondence

Demographic Evidence of Sex Differences in Vulnerability to Infectious Diseases

TO THE EDITOR—The journal's recent supplement on sex differences in susceptibility and response to infectious diseases was an excellent initiative for promoting research on a neglected topic of major interest [1–8]. If, in general, males show a higher susceptibility to many infectious diseases, the reviews displayed a number of infectious and autoimmune diseases for which females are more vulnerable. Differential vulnerability between males and females may come from exposure, infection (local or systemic), immune reaction, or a combination of these factors. Evidence came mainly from medicine, epidemiology (direct observation), and biology (animal models and *in vivo* observation). I address another dimension: demographic evidence.

We directed a population observatory in Niakhar, Senegal, West Africa, in which a comprehensive demographic surveillance system (DSS) monitored causes of death, as well as family behavior. In this population, there was no evidence of any differential behavior between boys and girls, as is generally true in African countries [9]. But mortality was higher

for girls than for boys for selected diseases (measles and pertussis), despite similar incidences. Furthermore, a randomized controlled trial of the Edmonston-Zagreb high-titer measles vaccine demonstrated a higher susceptibility to measles virus among girls [10].

Following these observations, my colleagues and I reviewed death statistics published by the World Health Organization (WHO), with special attention to measles [11, 12]. These are medically certified causes of death, gathered and standardized by the WHO. In this huge sample of 15.8 million deaths, there was clear evidence that female mortality was higher from some infectious and parasitic diseases but not from others. Furthermore, female mortality was higher at certain ages, especially among older children and young adults, but not at other ages (Table 1). For most diseases, exposure and infection could be considered similar for males and females, so that mortality variations suggested differential resistance to severe infection.

The higher female mortality from selected causes and in certain age groups in high-mortality populations was documented earlier, although with fewer details [13]. In our study, the age groups

with higher female mortality were highly specific. Excess female mortality was rarely found among individuals aged <1 year, was common at ages 1–11 years, very common at ages 12–24 years, common at ages 25–49 years, but rare at ages ≥ 50 years, and it varied by disease.

In 1997, we proposed a theory to explain sex differences in mortality based on the T-helper type 1 (Th1)/Th2 balance [11]. In brief, it states that hormones interfere with immunity, so that females appear to be more vulnerable to diseases for which an excessive Th2 response is deleterious. This may explain why sex differences vary with age: childhood is an age of mini-puberty, 12–24 years is the age of puberty and early adulthood, and age ≥ 50 years is beyond the occurrence of menopause, all with very different hormonal profiles.

A few examples will illustrate the changing pattern by age. Higher female mortality from tuberculosis and leprosy is found among women aged <25 years but not among those aged ≥ 25 years [11]. Human immunodeficiency virus (HIV) is also interesting: in African heterosexual epidemics, the lifetime risk of contracting the virus is about the same for men and women. However, young

Table 1. Select Diseases With Marked Sex Differences in Mortality

Etiologic Agent	Higher Male Mortality, All Ages	Higher Female Mortality	
		Ages 1–49 y	Young Adults
Viruses	Poliomyelitis, hepatitis C	Smallpox, measles, rubella	Hepatitis B, influenza
Bacteria	Typhoid fever, anthrax, meningococcal infection, tetanus	Pertussis, streptococcal infection (scarlet fever, erysipelas)	Cholera, shigellosis, diphtheria, paratyphoid fever, syphilis
Mycobacteria	Tuberculosis, leprosy
Parasites	Malaria, trypanosomiasis, schistosomiasis	Ancylostomiasis	...

Data are from the World Health Statistics Database (http://www.who.int/gho/publications/world_health_statistics/2014/en/).

women (ie, those aged 15–24 years) seem to be more susceptible, with major consequences for the dynamics of the epidemics [14]. Furthermore, hormonal contraception could interfere with susceptibility to HIV, and this applies to those aged <25 years but not to those aged ≥25 years [15].

The genetic characteristics of the organisms seem to play an independent role. In another study, based on causes-of-death statistics in the United States, my colleagues and I showed that Spanish influenza virus had a different tropism by age and sex than other influenza viruses: it killed proportionately more young males and fewer older persons [16]. So, a minor change in the genetic characteristics of the virus may have a huge effect on age-specific and sex-specific mortality. The precise mechanisms remain unknown.

Last, various other factors may interact with the Th1/Th2 responses and change the outcome of infection. In a randomized trial, my colleagues and I showed that zinc supplementation, known to affect the Th1/Th2 balance, had a differential effect on childhood diseases among boys and girls [17].

During the past 150 years, most infectious diseases for which females were more vulnerable have been controlled, so that females gained a serious advantage over males. This may not last forever if other diseases with higher male mortality are also controlled, so that autoimmune diseases may become a leading cause of death. In the current situation, however, males are paying a price for their different hormonal system and continue to be more

vulnerable to many infectious diseases, to many noncommunicable diseases, and to accidents and violence.

Note

Potential conflict of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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