Sex, gender and influenza

World Health Organization

Sex, gender and influenza

July 2010

World Health Organization

WHO Library Cataloguing-in-Publication Data

Sex, gender and influenza in achieving gender equality and health equity.

1. Sex factors. 2. Gender identity. 3. Sex distribution. 4. Women. 5. Influenza, Human. 6. Disease outbreaks. 7. Pregnancy complications, Infectious. I. World Health Organization.

ISBN 978 92 4 150011 1 (NLM classification: WA 309)

Printed in France.

Photo credits courtesy of Photoshare: Kyaw Thar (p. 15); Kyaw Winn (p. 21); Suleiman Mbatiah (p. 27); Ricardo Garcia (p. 31).

Contents

Acknowledgements 5

Abbreviations 7

Summary 9

1. Introduction 11

2. Sex and gender defined 13

3. Influenza viruses 15
- 3.1 Viruses 15
- 3.2 Prevention and treatment 15

4. Male-female differences in morbidity and mortality from influenza 17
- 4.1 Incidence 17
- 4.2 Morbidity 18
- 4.3 Mortality 19

5. Male-female differences in risk factors for influenza-related morbidity and mortality 21
- 5.1 Age 21
- 5.2 Co-infection 22
- 5.3 Chronic diseases 23
- 5.4 Diabetes and obesity 24
- 5.5 Immune responses 24
- 5.6 Occupation 25
- 5.7 Caregiving 25
- 5.8 Personal hygiene 26
- 5.9 Health-seeking behaviour and access to care 26

6. Male-female differences in response to influenza virus vaccines and antivirals 27
- 6.1 Rates of vaccination 27
- 6.2 Immune responses 28
- 6.3 Adverse side effects 28
- 6.4 Antiviral therapy 29

7. Influenza infection and pregnancy 31
- 7.1 Risk to the fetus 31
- 7.2 Morbidity 32
- 7.3 Mortality 32
- 7.4 Comorbidities 32
- 7.5 Biological basis for increased morbidity and mortality 32
- 7.6 Effectiveness of antiviral therapy 33

8. Influenza vaccination and pregnancy 35
8.1 Recommendations for vaccination 35
8.2 Adverse side effects and safety 35
8.3 Vaccine efficacy 36
8.4 Pregnancy and the immune response to vaccines 36

9. Conclusions and recommendations 37

10. Statistical data 39
Table 1: **Male-female differences in response to influenza A virus infection** 39
Table 2: **Male-female differences in response to influenza virus vaccination and antivirals** 41
Figure 1: **Individuals with immunodeficiencies, including HIV, are at an increased risk for severe outcome of influenza** 42
Figure 2: **Tobacco use is associated with increased severity of influenza illness** 43
Figure 3: **Health-care workers are at an increased risk of exposure to influenza viruses** 44
Figure 4: **Rates of severe influenza disease are increased among pregnant women** 45

References 47

Acknowledgements

The World Health Organization (WHO) thanks the following individuals for the preparation of this report: Sabra L. Klein of the Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; Andrew Pekosz of the Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; Catherine Passaretti of the Department of Medicine, Infectious Diseases Division, The Johns Hopkins School of Medicine, Baltimore, USA; Martha Anker of the University of Massachusetts School of Public Health and Health Sciences, Amherst, USA; and 'Peju Olukoya of the Department of Gender, Women and Health, WHO, Geneva, Switzerland.

Thanks are also due to the following reviewers for their valuable comments: Francis Ennis of the Center for Infectious Disease and Vaccine Research, University of Massachusetts Medical School, Worcester, USA; Denise Jamieson of the Centers for Disease Control, Atlanta, USA; Saralyn Mark and Vincent Michaud of the National Aeronautics and Space Administration, Washington, USA; and John Treanor of the University of Rochester, USA.

Further contributions were received from: Anjana Bhushan of the WHO Regional Office for the Western Pacific; Julia Fitzner and Anthony Mounts of the Global Influenza Programme; Cathy Ellen Roth of the Global Alert Response unit; Gretchen Stevens of the Health Statistics and Informatics department; Marijke Velzeboer of the WHO Regional Office for the Americas; Joanna Vogel of the WHO Regional Office for the Eastern Mediterranean; and Ciro Ugarte of the WHO Regional Office for the Americas.

Diana Hopkins edited and proofread the document; and Monika Gehner, Melissa Kaminker and Milly Nsekalije of the Department of Gender, Women and Health, WHO, provided technical assistance in the finalization of the document.

Abbreviations

AIDS	acquired immunodeficiency syndrome
CI	confidence interval
COPD	chronic obstructive pulmonary disease
HIV	human immunodeficiency virus
ICU	intensive care unit
LAIV	live attenuated influenza virus
OR	odds ratio
RR	relative risk
SARS	severe acute respiratory syndrome
TB	tuberculosis
Th1	helper T cell type 1
Th2	helper T cell type 2
TIV	trivalent inactivated virus
vs.	versus
WHO	World Health Organization

Summary

Whilst sex and gender are known to have an impact on the vulnerability of people to a number of infectious diseases, the impact of sex and gender on exposure, susceptibility and immune responses to acute infections has not yet been explored comprehensively. Influenza represents a global infectious disease that can affect human populations through seasonal epidemics, pandemics and localized outbreaks. The incidence, severity and case fatality rates following influenza infection can differ between males and females, but are often age-dependent and vary between countries. The evaluation of influenza morbidity and mortality data from seasonal, outbreaks, previous pandemics and the first wave of the 2009 H1N1 pandemic reveals that the outcome of infection is generally worse for females, but that the magnitude of this difference varies across geographical regions. Although pregnancy is one factor contributing to a worse outcome in women, several additional risk factors may influence male-female differences in the outcome of influenza. For example, the severity of asthma and other chronic respiratory conditions as well as rates of diabetes and obesity is often worse in women than men.

Women are also more likely than men to be caregivers and to work in health-care occupations, which may increase their exposure rate to influenza. Immunologically, males and females respond differently to viruses, including influenza, which may reflect genetic as well as hormonal differences between the sexes. Sex and gender also have an impact on immune responses and adverse side effects following vaccination against influenza. Women mount higher antibody responses and experience more frequent and severe side effects than men, a finding that should be incorporated into the drafting of guidelines for vaccination worldwide. The effectiveness of antiviral therapies may also vary in a sex-dependent manner.

Finally, pregnancy can significantly alter responses to influenza infection and vaccination. Specifically, the severity of the disease is worse among pregnant women, especially during the second and third trimesters, than in the general population in most regions of the world. Although the increased risk of seasonal and pandemic influenza to pregnant women has been documented, the biological basis of this risk has yet to be defined. While significantly more research is required to gain a complete understanding of the complex and varied effects of sex and gender on influenza infection and vaccination, the available data demonstrate the significant impact these factors can have on an acute infection and underscore the need to consider the interplay of these factors with any infectious disease of global concern.

1 Introduction

Approximately 15 million of the 57 million deaths that occur annually worldwide are directly attributable to infectious diseases.[1] Most of the burden of morbidity and mortality occurs in developing countries.[1] The World Health Organization (WHO) has addressed infectious diseases around the globe, with consideration of the impact of sex and gender on chronic infectious diseases, including HIV and tuberculosis.[2, 3] The role of sex and gender in acute infectious diseases, such as influenza, has not been explored extensively. The global public health burden of influenza is receiving renewed attention in light of the appearance of new influenza strains (e.g. H5N1 and 2009 H1N1) and the continued circulation of seasonal influenza.

Sex and gender have an impact on people's vulnerability to influenza, as well as the course and outcome of infection and vaccination. The impact of sex and gender on the outcome of infection is influenced by a number of global, social and biological factors. Recent scientific advances are providing insights into the immunological and behavioural differences between males and females[4, 5], which allow for a detailed discussion of how sex and gender impact emerging infectious diseases.[6] The WHO Gender Strategy[7] mandates that "the different needs of women and men are considered at all stages of policy and programme development". Despite this mandate, consideration of sex and gender in emerging infectious disease programmes is still the exception rather than the rule. A greater understanding of how sex and gender influence the epidemiology of influenza may impact clinical, public health and government activities that are critical in the prevention and control of influenza.

2 Sex and gender defined

Sex. While the terms sex and gender are often used interchangeably, it is important to note that they refer to very different aspects of human biology and behaviour. The term **sex** refers to biological and physiological characteristics that define males and females. Males and females differ at every biological level, with differences occurring in cells, organs, organ systems and anatomy.[8] For example, the basic organization of chromosomes is different between male and female cells. Male cells have one X and one Y chromosome, whereas female cells have two X chromosomes. This is critical for infectious diseases because many genes involved in immune responses are encoded on the X chromosome. The biological process of inactivation of one X chromosome results in mosaic expression of either the paternal or maternal X chromosome in each cell in females. If an X-linked mutation occurs, it will be expressed in approximately half of the cells from females and all of the cells in males, resulting in increased X-linked immunodeficiencies in males as compared with females.[4, 9]

Reproductive organs and circulating sex steroid hormone concentrations differ between males and females, with males having testes that generally secrete high concentrations of androgens and females having ovaries that produce high concentrations of estrogens and progesterone.[8] The hormonal differences between males and females can vary according to age (e.g. increased circulating concentrations of sex steroids after puberty and reduced circulating concentrations with older age) and reproductive status (e.g. concentrations of estrogens and progesterone increase over the course of pregnancy and change over the menstrual cycle). The anatomical differences between males and females are particularly important during pregnancy and for susceptibility to a number of infectious diseases.[10]

Gender. The term **gender** refers to the roles, behaviours, activities and attributes that individual societies consider appropriate for men and women. Examples of gender differences include differences in societal rules and norms that, to a large extent, determine what men and women believe and value, and how they behave.[8] Gender norms often differentially impact the health practices of men and women. For example, norms about smoking differ widely between men and women, with smoking generally being more common in men than women.[11, 12] Norms for the education of boys and girls traditionally tended to favour education of boys over girls; these norms, however, have been changing in many countries resulting in greater educational opportunities for women of all ages.[13, 14] Education of women is beneficial for reducing both malnutrition and child mortality in developing countries.[15] In some cultures, masculine gender norms impact whether men seek out health care and comply with medical treatments.[16]

In almost all societies, gender differences also impact the responsibilities for earning money, occupations, and the roles and responsibilities in a variety of family-related activities (e.g. food preparation, cooking, shopping, chores, and care of children and family members, including when they become ill). Societies also differ with respect to the relative status of men and women, the value society puts on male and female contributions to society, the ability of men and women to make decisions concerning their own health and the health of other family members, and access of men and women to and control over resources, all of which can have important effects on infectious diseases, including influenza.[6]

Interaction of sex and gender with infectious disease. Sex and gender differences can affect exposure to pathogens, vulnerability to infectious diseases, health-seeking behaviours, and immune responses to pathogens[5, 6], resulting in differences between males and females in the incidence, duration, severity and case fatality rates following infection.[5] The way in which sex and gender interact with infectious diseases depends on the specific pathogen. It is not unusual for both sex and gender to jointly impact differences between males and females in ways that make

it difficult to attribute the observed effects to either sex or gender alone. For example, pregnancy is a biological factor because only women can become pregnant. Yet gender often has a large impact on the nutritional status of women by influencing, for example, the information available to women on nutrition and available resources, access to economic resources and decision-making authority, especially in low-income societies.[15] The influence of sex and gender on responses to an infection can vary considerably around the world and this can make generalizations and extrapolation of data from one country to another complicated. The interaction of sex and gender with infectious diseases also can change throughout the life-course. Because both sex and gender influence the manifestation and consequence of infectious diseases in men and women, these factors need to be considered in order to have more effective public health programmes for infectious diseases, including influenza.

3 Influenza viruses

3.1 Viruses

Influenza is caused by one of three viruses – influenza A, B or C – with influenza A and B being responsible for the vast majority of the 200 000 to 500 000 deaths and billions of US dollars in economic losses attributed to annual infections globally.[17, 18] Influenza impacts the human population through three kinds of outbreaks. Seasonal influenza is caused by strains of influenza that circulate continuously in the human population, resulting in a portion of the population that has pre-existing immunity due to prior exposure or exposure to similar influenza strains and is, therefore, protected from infection. Currently, there are two influenza A viruses (H1N1 and H3N2) and one influenza B virus which are responsible for annual epidemics.

An influenza pandemic occurs when an influenza A virus strain that is antigenically different from the seasonal virus strains enters the human population. There have been four documented pandemics in the past 100 years (1918, 1957, 1968 and 2009). The lack of pre-existing immunity to the pandemic strain in the human population leads to a substantial increase in the total number of influenza cases and, therefore, the number of influenza-related deaths, even if the newly emerged virus does not cause more severe disease than seasonal influenza. Finally, there are outbreaks of influenza where limited numbers of humans in defined geographical areas are exposed to novel influenza viruses.

The ongoing outbreaks of H5N1 influenza are an example of this type of exposure. In the temperate zones of the northern and southern hemispheres, influenza cases peak in the winter months, but in the tropical and subtropical zones, cases appear over much longer periods of time.[19] With the emergence of the 2009 H1N1 influenza virus strain, the first influenza pandemic of this century, we once again face a time of increased disease burden from

A woman receives medical care in Myanmar.

influenza. In this report, data regarding the 2009 H1N1 pandemic are limited to the so-called 'first wave' of cases in the northern hemisphere and the winter influenza season in the southern hemisphere, roughly covering April to September 2009.

3.2 Prevention and treatment

There are two types of vaccines capable of eliciting a protective immune response to influenza.[20] The trivalent, inactivated virus (TIV) vaccine is composed of three virus strains that are administered via intramuscular injection and have been inactivated and partially puri-

fied. The live attenuated influenza virus (LAIV) vaccine consists of the same three influenza virus strains but in weakened forms that are no longer capable of causing disease. However, it can replicate and induce an immune response in vaccines. There also are two classes of antivirals that are effective against influenza[21] – the ion channel blockers (amantadine, rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Both classes of drugs are effective if administered within 48 hours of symptom onset, but antiviral resistance to each class is highly prevalent in seasonal influenza virus strains.[22]

4 Male-female differences in morbidity and mortality from influenza

4.1 Incidence

Whether the precise incidence rates of influenza differ for males and females is difficult to ascertain, especially with the paucity of data from developing countries. The symptoms of influenza are similar to those of other diseases, which makes influenza difficult to distinguish from other diseases on this basis alone. Laboratory diagnosis is required to confirm influenza, which requires utilization of health-care services. Because seasonal influenza typically lasts 3–5 days, a small proportion of cases result in utilization of health care and an even smaller percentage of those cases are confirmed. Utilization of health-care services, confirmation of cases and misdiagnosis, for example, can differ between men and women as a result of physician or patient biases as has been demonstrated for other diseases.[23]

In developed countries, such as the United States of America and Spain, the reported incidence of infection with seasonal influenza viruses is higher in males (up to 60% in the United States) than females of diverse ages, ranging from infants to elderly adults[24, 25] (see Table 1). Available data on male-female differences in the number of cases of seasonal influenza are limited and, therefore, conclusions are difficult to draw. Most reports of cases of seasonal influenza do not analyze data for male-female differences and, if they do, they often do not consider the interaction between sex and age. There also is a paucity of data from developing countries.

The transmission of H5N1 is most often from infected poultry to humans, with very limited human-to-human transmission; thus, the patterns of exposure and associated risk factors are different from those for seasonal or pandemic influenza viruses. As of November 2009, there had been 444 confirmed H5N1 cases and 262 deaths reported to WHO. Worldwide, cases of H5N1 occur equally between males and females; there are, however, significant male-female differences in individual countries. In Thailand, females account for 36% of the laboratory confirmed H5N1 cases, whereas in Egypt females account for 68% of the cases.[26] In Indonesia, there were significantly more cases of H5N1 among young adult women in 2007 (female odds ratio (OR): 2.6, 95% confidence interval (CI): 1.2–5.6), but not in other years examined from 2003–2008.[26] The mean age of male and female cases are generally not different, except in Thailand where males have been significantly younger than females (16 vs. 33 years of age).[26] Many behaviours, including those associated with occupation or responsibilities in the home, change at the time of puberty and could impact the risk of exposure to H5N1 influenza; thus, age-associated differences in rates of exposure should be considered separately for males and females. The limited number of H5N1 cases in several geographical regions also makes definitive conclusions difficult to draw.

As the 2009 H1N1 pandemic continues to evolve, whether or not the incidence of infection differs between the sexes remains unresolved. Evaluation of the first wave of 2009 H1N1 through the northern hemisphere and during the winter influenza season in the southern hemisphere reveals male-female differences that vary between countries. Available data from Canada (April–May 2009) indicate that male-female differences in the incidence of infection vary with age to the extent that the incidence of infection with 2009 H1N1 is higher in males than females 10–19 years of age, higher in females than males 20–39 years of age, and is equal between the sexes after 40 years of age.[27] Argentina (April–May 2009) also reports age-dependent differences between the sexes, in which the incidence of infection with 2009 H1N1 was higher in females 20–39 years of age, but was higher in males 40–59 years of age.[28] In France, early reports (May–July 2009)

suggested a higher incidence of infection among females than males 0–19 years of age for non-imported cases (i.e. people who had not travelled to other countries with confirmed 2009 H1N1) (n = 90).[29] In Brazil (April–August 2009), the number of laboratory confirmed 2009 H1N1 cases was higher for females (56.5%), a majority of whom were of reproductive age (15–49 years of age; 2256 of 3249 women with confirmed 2009 H1N1), and of whom 23.3% were pregnant.[30] Other countries, including Belgium (May–June 2009; n = 130), Italy (April–June 2009; n = 54), and Peru (May–September 2009; n = 4263), reported no male-female differences in the number of cases of 2009 H1N1 during the first few months of surveillance, but these countries also did not report analyzing data stratified by age group.[31–33] Unfortunately, many reports from countries, including Spain (April–May 2009), the Netherlands (May–June 2009), and Thailand (May–July 2009), as well as aggregated case reports from several European countries (April–June 2009), do not stratify or compare the incidence of 2009 H1N1 by sex.[34–37] Analysis of male-female differences in incidence data stratified by age group is necessary to properly evaluate whether these differences are conserved across the life-course and in diverse regions of the world. For studies conducted in Argentina, Brazil, Canada and France in which male-female differences in the incidence of 2009 H1N1 are stratified by age, it appears that there are more cases of young adult females than males of comparable ages.

4.2 Morbidity

Rates of hospitalization (see Table 1) from seasonal influenza viruses are consistently higher in males than females of all ages, where data are available. This is especially true among young children (male OR: 1.9, 95% CI: 1.0–3.7) and the elderly (1393 per 100 000 for males and 969 per 100 000 for females), as demonstrated by data from Canada.[38–40] Data from Denmark suggest that male-female differences in the risk of hospitalization from seasonal influenza virus shift at puberty, such that males are more likely to be hospitalized before puberty (relative risk (RR) for males: 1.64, 95% CI: 1.29-2.08), whereas females are more likely to be hospitalized after puberty (RR for males: 0.61, 95% CI: 045-081).[41]

The first cases of the 2009 H1N1 pandemic in the United States were in California (April–May 2009), where 553 cases were reported, of which 26 required hospitalization with confirmed 2009 H1N1 virus. Of the confirmed hospitalized cases, a majority (21/26) were women, five of whom were pregnant.[42] More recent analyses of cohorts of the first patients hospitalized with 2009 H1N1 infection in Australia/New Zealand (June–August 2009; n = 722), Mexico (March–June 2009; n = 58) and the United States (April–June 2009; n = 272) reveal that similar proportions of males and females (females = 52.1% in Australia and New Zealand, 53.4% in Mexico and 49% in the United States) were hospitalized.[43–45] Evaluation of the differences between males and females in hospitalization and development of critical illness following infection with 2009 H1N1 influenza is confounded by age, as most studies do not report male-female differences according to age group.[43–45] In Canada (April–August 2009), there were 168 critically ill patients with confirmed or probable 2009 H1N1 influenza, a majority of whom were young adult females (67.3% with 7.7% pregnant).[43] The reason for the greater proportion of hospitalized women than men in Canada is not known, but many cases involve comorbid conditions, including chronic lung disease (e.g. asthma), which is typically more severe in females than males.[46–49] In Brazil (April–August 2009), rates of hospitalization with severe acute respiratory illness have been higher among females (57.5%) than males, with a majority of the females being of reproductive age (15–49 years of age), of which 20.8% were pregnant.[30] Similarly, in Victoria, Australia (May–September 2009), although approximately half of the hospitalized cases with confirmed 2009 H1N1 were males, of the 108 2009 H1N1 cases that required intensive care unit (ICU) admission, 55% were females.[50] Further, in New South Wales, of the 225 ICU admissions with confirmed 2009 H1N1 (June–August 2009), 53% were females.[51]

As the 2009 H1N1 pandemic evolves, it will be important to consider whether biases exist in the collection or reporting of data, which may influence whether or not male-female differences are observed. Examination of these differences in larger, more complete datasets will be necessary, especially if data are further disaggregated by age. Consideration of age-associated effects on the differences between males and females in the development of critical illness and hospitalization is important as several biological (e.g. hormonal) and behavioural transitions occur after puberty in individuals of many cultures. One

trend that appears consistent across several countries is that more females of reproductive age are hospitalized with critical illness than males. Finally, the presentation of disease and constellation of symptoms expressed following infection may differ between males and females and should be considered in clinical settings.

4.3 Mortality

Fatality due to influenza viruses differs between males and females (see Table 1). Mortality from seasonal influenza viruses is most common among children (i.e. <5 years of age) and the elderly (i.e. 65+ years).[52] In elderly populations, crude mortality rates are higher in women in Portugal (21 per 100 000 for women and 14 per 100 000 for men), but higher in men in Switzerland.[53, 54] Because women tend to live longer than men, age-adjusted death rates from influenza should be analyzed. In the United States, during the 1957 pandemic and two subsequent epidemic years of H2N2 influenza, mortality was higher among females than males in the 1–44 age group, but was higher among males than females among individuals over the age of 44.[55] Importantly, when mortality data were not stratified by age group, no male-female differences were observed during these H2N2 epidemics.

Case fatality rates for avian influenza have ranged widely between countries from 33% to 88%. Within most countries, males and females have similar case fatality rates; when data from all countries are combined, however, females are less likely to survive than males. An analysis of all reported H5N1 cases through May 2008 revealed that the risk of mortality from H5N1 is 1.6 times higher for females than males.[26] Analyses of H5N1 cases in Indonesia reveal that case fatality rates are higher in females (89%) than males (73%).[56] In Egypt, females are 10 times more likely to die from H5N1 than males.[57]

Mortality rates during the 1918 H1N1 pandemic were higher in adult males (15–44 years of age) in the United States (672 per 100 000 for males and 498 per 100 000 for females) as well as in 12 other countries (Australia, Denmark, Finland, France, Italy, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland and the United Kingdom) for which age-adjusted mortality data are available.[58–60] Mortality from 2009 H1N1 is not common, but data from South Africa, where the incidence of co-infection with HIV and tuberculosis (TB) is high, reveal that 59 of 91 fatal cases from April–October 2009 were female and, of the 59 females, 45 were young adults of reproductive age, 25 of whom were pregnant.[61] As noted in Sections 5 and 7, co-infection with HIV or TB as well as pregnancy can significantly impact the outcome of influenza virus infection. In contrast, in Victoria, Australia (May–September 2009), 58% of fatal 2009 H1N1 cases were males[51], and in Brazil (April–August 2009) and Peru (May–September 2009) case fatality rates from 2009 H1N1 were equal between males and females.[30, 33] To date, no consistent pattern of male-female differences in mortality from the 2009 H1N1 has emerged.

Most epidemiological studies do not exhaustively assess male-female differences in the clinical features, age of the patient, severity or outcome of influenza virus infections. Future studies aimed at identifying the biological as well as behavioural factors that impact male-female differences in response to influenza viruses are necessary. Consideration of differences in health-seeking behaviours, access to health-care services, comorbid conditions, behavioural risk factors, and immunological differences between males and females must continue to be incorporated into statistical analysis models.

5 Male-female differences in risk factors for influenza-related morbidity and mortality

Certain risk factors predispose patients to increased morbidity and mortality following exposure to influenza viruses.[20] The severity and prevalence of these underlying conditions that predispose individuals to increased influenza-related morbidity often differ between males and females resulting in the potential for differential burden from influenza between the sexes. The constellation of risk factors for increased morbidity also differs between seasonal influenza, avian influenza, past pandemic strains, and the 2009 H1N1 pandemic strain. Male-female differences in the risk factors for increased severity of seasonal, outbreak and pandemic influenza are hypothesized to contribute to male-female differences in the outcome of infection.

An elderly woman with health-care providers from the Myanmar Women's Association Kan Thar Lay, Myanmar.

5.1 Age

Age is the most significant risk factor for increased seasonal influenza-related mortality, with 90% of seasonal influenza-related deaths occurring in individuals over the age of 65 years.[62] In contrast, during the 1918 H1N1, 1957 H2N2, and 1968 H3N2 pandemics as well as during the 1957–1958 H2N2 epidemic, half of the influenza-related deaths occurred among individuals less than 65 years of age.[55, 60, 63] In most countries around the world, mortality rates from all causes are higher for males than females in all age groups with the proportion of the population that is female increasing with age.[64] In 2007, United Nations estimates showed 275 million women above the age of 65 as compared with 217 million males in the same age range worldwide. Worldwide, women over the age of 65 outnumber men 4 to 3 and, over the age of 80, women outnumber men by 2 to 1.[65] Despite the fact that women over the age of 65 outnumber men, examination of the 1957 H2N2 pandemic and two subsequent H2N2 epidemic influenza seasons in the United States still showed higher influenza/pneumonia-related mortality rates per 100 000 males as compared with females in this age range.[55]

Age also might impact the outcome of influenza virus infection differently between males and females through notable physiological and behavioural changes that occur over the life-course. Sex determination and differentiation occur during prenatal development and involve

genetic and hormonal factors that cause the primordial reproductive system to become either feminized or masculinized. These biological sex differences are present at the time of birth and probably impact the development of the respiratory system and susceptibility to respiratory tract infections.[66] Previously, it had been shown that susceptibility to severe acute respiratory diseases was greater for infant boys than girls[66, 67], but these studies did not consider whether infants were breastfed or formula-fed. Recent evidence from Argentina reveals that infant feeding regimens determine the severity of acute respiratory illness differentially between the sexes. Specifically, among formula-fed infants, the severity of respiratory diseases, including influenza, is significantly higher for girls than boys.[68, 69] Breastfeeding can protect against severe respiratory diseases, but this protection appears to be restricted to girls.[68, 69] Despite the advantage of breastfeeding for girls, rates of breastfeeding (i.e. the proportion of individuals breastfed), at least in Argentina, are still higher for boys than girls.[69] These data illustrate the complex interactions between sex and gender that are a likely influence on susceptibility to influenza viruses among children.

During the pubertal period, hormonal and behavioural changes result in different expressions of secondary sex characteristics, fertility and behaviours that reinforce gender identity through adolescence and into adulthood.[8] Many of the biological differences between the sexes are reflective of the hormonal changes that occur during puberty, resulting in increased synthesis of androgens in the testes of males and estradiol in the ovaries of females. There also is normal variation in the timing of puberty that can vary according to genetic, ethnic, and cultural differences.[8] Physiological and hormonal changes at puberty do not occur in isolation and often coincide with significant changes in behaviour and social roles. As individuals progress through adulthood (approximately 40 years), their occupations, social roles and lifestyles change. Further, adult women, but not men, experience fluctuations in their reproductive condition associated with reproductive cycles and pregnancy. As women age, there is a five to 10 year time period of menopause-related changes in hormone patterns and fertility.[8] Although less well characterized, there is a decline in androgen production that occurs in men between the ages of 48–70.[70] At each stage over the course of the lifespan, these hormonal, physiological and behavioural changes can impact both exposure to and the outcome of infection. As noted in Section 4, many of the male-female differences in morbidity and mortality from influenza virus infection are age-dependent.

5.2 Co-infection

Influenza-related mortality is highest in those at the extremes of age, either the very young or the very old.[20] This age-associated pattern is seen annually with seasonal influenza and also was noted in the 1957 and 1968 pandemics.[71] The influenza-related mortality curve during the 1918 pandemic, however, was notably different from seasonal and other influenza pandemics in that increased mortality was observed not only in the very young and the very old, but also among young adults, particularly young men aged 25–44 years, based on data collected in Japan, the United Kingdom and the United States.[52, 72] Prevalence studies also have shown a male predominance in the number of cases of TB during the 1918 influenza pandemic.[73] One hypothesis for the increased mortality rates among males during the 1918 influenza pandemic is that co-infection with influenza and TB may have led to a higher likelihood of influenza-related deaths among males[58, 74]; this hypothesis, however, is still debated.[58, 75–77]

Influenza in immunocompromised individuals is associated with increased disease severity and is recognized as a comorbidity for seasonal influenza.[20] Rates of HIV in females are approaching that of males worldwide.[78] In 2007, it was estimated that of the 30.8 million individuals living with HIV around the world, 15.5 million were women. The greatest increase in HIV prevalence in women is occurring in sub-Saharan Africa, where females acquire HIV at a younger age than males (see Figure 1). Following infection with HIV, women progress to AIDS faster than men, suggesting that disease severity is worse in women.[79] Studies in Africa, India, the Middle East and the United States have shown disparities in access to care for women with HIV.[80–83] Women also traditionally have a more difficult time accessing treatment for HIV, possibly predisposing them to worse outcomes.[80, 83, 84] Whether infection with HIV and progression to AIDS differentially affects the outcome of influenza virus infection in males and females has not been reported.

5.3 Chronic diseases

Chronic respiratory and cardiovascular diseases are two major comorbid conditions that predispose patients to increased seasonal influenza-related morbidity[20] and male-female differences in chronic respiratory conditions have been reported. Data from Canada and the United States illustrate that, prior to puberty, males have higher numbers of asthma exacerbations than females; this trend, however, is reversed in adulthood.[85] Several studies indicate that rates of asthma attacks, numbers of asthma-related emergency-room visits, numbers of asthma-related hospitalizations, and duration of hospitalization are higher in adult females than males in the United States.[46–49] Higher rates of asthma-related deaths among females than males span diverse ethnic groups, including among African Americans, Asians and whites in the United States.[86] In addition, use of hormone replacement therapy in postmenopausal women is associated with higher rates of asthma exacerbations, and use of oral contraceptives can reduce airway hyperresponsiveness suggesting a potential hormonal influence on asthma.[87–89] During the 2009 H1N1 pandemic, asthma was an underlying condition in 29% of children and 27% of adults hospitalized with critical illness in the United States.[45] Whether asthma differentially impacts the severity of disease caused by 2009 H1N1 between the sexes has not been investigated.

Male-female differences also are observed in chronic obstructive pulmonary disease (COPD). Several studies in both adults and adolescents in Denmark and the Netherlands have shown lower forced expiratory volume in one second (FEV1), a faster decline in FEV1, and increased smoking-related bronchial responsiveness in adult female smokers as compared to adult males.[90–93] These studies suggest that females may metabolize some constituents of tobacco smoke differently to males making them more susceptible to the toxic effects of tobacco, including development of COPD. Females with COPD report worse symptoms, lower exercise capacity, and more airway hyperresponsiveness than males.[91] Although morbidity from these conditions may be worse in females as compared to males, mortality both from all causes and from respiratory-related disease alone is still higher in males with COPD.[94] The exact impact of chronic respiratory conditions on influenza outcome and how this may vary between men and women is unclear; male-female differences, however, in the prevalence and morbidity/mortality associated with these chronic conditions should be evaluated in the context of the current pandemic.

Independent of a diagnosis of asthma or other chronic respiratory condition, tobacco use alone also is associated with increased rates and severity of influenza illness. Studies among otherwise healthy military recruits in Israel (both males and females) and in the United States (men only) have shown a 20–30% increase in the rate of influenza in smokers as compared to non-smokers.[11, 12] In addition, there was a dose-related increase in the severity of influenza with increased cough, dyspnoea and wheezing with increasing tobacco usage. Smoking is much more common in men than in women with global estimates of smoking behaviour being 48% of men and 12% of women (see Figure 2).[11, 12, 95] Tobacco use among females is rising, particularly among young women.[12, 95] These data further demonstrate that male-female differences in certain risk factors change due to cultural practices. Whether the interplay between sex, tobacco use and respiratory disease impacts the rate of or morbidity from influenza remains unclear.

Rates and severity of cardiovascular disease differ between elderly adult men and women, particularly in developed countries. Although data from developing countries are more limited, data from the Middle East, Spain, the United Kingdom and the United States suggest that although women develop cardiovascular disease approximately 10 years after men, they appear to have higher rates of post-myocardial infarction, congestive heart failure, and cardiovascular-related mortality than men, even after controlling for age.[96–99] Male-female differences are partly caused by differences in the presentation, symptoms and responses to treatments between males and females.[96–100] Further, the quality of care for cardiovascular disease often differs between males and females. The Framingham Heart Study in the United States as well as a study in 26 countries in Asia, Europe, Latin America, North America and the Middle East, and in Australia, Morocco and Turkey showed that elderly women receive different antihypertensive regimens than elderly men and that women had significantly worse blood pressure control than men of similar age.[101, 102]

Data on these comorbid conditions are much more limited in the developing world so generalization of these findings to other parts of the world is difficult. Also whether male-female differences in rates or severity of cardiovascular disease contribute to differences in the outcome of influenza virus infection should be considered.

5.4 Diabetes and obesity

Other comorbid conditions associated with poorer outcomes from seasonal influenza include diabetes and obesity. Diabetes mellitus and other metabolic disorders are a recognized risk factor for severe influenza[20], with a potential association between obesity, diabetes and increased 2009 H1N1 influenza morbidity. Rates of diabetes throughout the world, particularly in Africa, India and the Middle East are rising.[103] The lifetime risk of diabetes is higher in adult women than men (38.5% vs. 32.8%), at least in the United States where women account for approximately 55% of all diabetic-related deaths.[104] Globally, among individuals 65 years of age and older (i.e. the age group at highest risk for seasonal influenza-related morbidity and mortality) the prevalence of diabetes in women is slightly higher than in men (15% vs. 13%).[103]

Whether the increased risk of diabetes among adult women compared with adult men reflects the fact that women live longer must be considered through examination of male-female differences in age-adjusted rates. In the United States, gestational diabetes and rates of diabetes in obese adolescent girls have been increasing for the past decade, with this obesity epidemic now spreading to other areas of the world, including Asia.[105–108] Socioeconomic factors also affect rates of diabetes. In the United States, women, particularly those of lower socioeconomic status, receive less adequate diabetes care when compared with men of the same socioeconomic status, with variability in the number of services received as well as patient-associated factors (e.g. job benefits, child care and availability of transportation) contributing to differences between the sexes.[104, 109]

Females, particularly in developing countries, also tend to have higher rates of obesity as compared with males.[110–112] Although male-female differences in the rates of obesity vary from country to country, according to WHO, in 138 of 195 countries, females are over 50% more likely to be obese than males.[113] Data from China, North Africa, South Africa, South America, the United Kingdom and the United States indicate higher rates of obesity in women as compared to men, whereas Australia and western Europe report that obese men outnumber obese women.[110–112] The higher rates of obesity and diabetes in females may be significant factors contributing to higher 2009 H1N1-related morbidity in women. There are no data on the interactions among sex, obesity, diabetes and outcome of influenza infection. Because rates of obesity and diabetes are higher in women, this may predispose them to worse outcomes following influenza virus infection. Whether obesity is a risk factor for increased morbidity and mortality from 2009 H1N1 or simply represents the epidemic of obesity that is occurring in the United States requires consideration. There also are limited data evaluating the connection between obesity and influenza in countries outside of the United Kingdom and the United States. Future studies should continue to examine the relationship between obesity, diabetes and influenza in diverse cultures.

5.5 Immune responses

Another biological variable that differs between males and females and that may result in differential outcome of infection and development of disease is the response of the immune system. Sex differences in immune function are well established.[114–116] Innate detection of viruses by pattern recognition receptors, for example, differs between males and females.[117] Several genes (e.g. the *Tlr7* gene that encodes a receptor that recognizes single stranded RNA viruses, including influenza viruses) that encode for immunological proteins are on the X chromosome and may escape X inactivation, resulting in higher amounts of expression in females than males.[118] Studies in both humans and rodents illustrate that inflammatory immune responses are generally higher in females than males.[119] Clinical studies conducted in India, Italy, Sweden and the United States further reveal that men have lower CD3+ and CD4+ T cell counts, CD4+:CD8+ T cell ratios, and helper T cell type I (Th1) responses.[120–123] Cytokine responses, including production of interferons and interleukins, often differ between males and females during infection.[116, 124–126]

Both basal levels of immunoglobulin (Ig)[127] as well as antibody responses to viruses and vaccines are consis-

tently higher in females than males.[128, 129] The prevailing hypothesis for immunological differences between the sexes is that sex steroids, particularly androgens, estrogens and progesterone, influence the immune system[114]. Immune responses to viruses can vary with changes in hormone concentrations caused by natural fluctuations over the menstrual or estrous cycle, from contraception use, or during pregnancy. The extent to which immune responses differ between males and females during influenza virus infection requires assessment as this may contribute to differential severity of disease between the sexes. Disease associated with highly pathogenic influenza viruses and the clinical manifestations that ensue in humans, including fever, viral pneumonia, encephalitis, and acute respiratory distress syndrome, is hypothesized to be mediated by the profound proinflammatory cytokine and chemokine response (referred to as the 'cytokine storm') initiated by the host in response to infection.[130, 131] Humans, macaques and mice infected with highly pathogenic strains of influenza virus, including the 1918 H1N1 or avian H5N1, produce excessively high concentrations of proinflammatory cytokines and chemokines, which correlate with elevated mortality.[130–135]

Whether the duration and magnitude of the cytokine storm initiated during influenza virus infection differs between males and females has not been reported. Preliminary studies utilizing mouse-adapted pathogenic H1N1 influenza reveal that females mount higher inflammatory responses and are more likely to die following inoculation than are males.[136] Thus, elevated immunity in females against influenza A viruses represents a delicate balance between immune responses conferring protection through clearance of virus or causing pathology through increased production of proteins and an influx of immune cells into the lungs.

5.6 Occupation

In addition to biological differences between males and females, gender-specific societal roles and occupations may impact the risk of exposure to and acquisition of influenza. For example, there are significant differences between men and women in their patterns of contact with poultry that can impact transmission of H5N1 influenza.[137, 138] The size and structure of poultry farms and practices vary within and between Asian countries. On smaller farms, women are often responsible for caring for backyard fowl as well as for buying and selling live fowl at markets[139], whereas on larger farms and in commercialized systems men are more likely to be owners and employees.[140] A cross-sectional survey of 3600 backyard poultry owners in six provinces throughout Cambodia revealed that men, especially between the ages of 25–40, could have a higher risk of exposure to H5N1 than females because of increased contact with poultry.[137] Specifically, men are more likely than women to slaughter, remove internal organs and prepare poultry for consumption, and these tasks are each correlated with increased risk of exposure to H5N1.[137]

Similar studies of male/female differences in the occupational risk of exposure to H5N1 should be conducted in countries, such as Egypt, Indonesia and Viet Nam, where a majority of the cases have occurred. Additional consideration also must be given to the fact that male/female differences in contact with poultry vary with age as well as within and between countries. Increased mortality rates among men during the 1918 H1N1 pandemic may have been caused by participation in war and living in military camps in Europe and the United States, which increased the risk of acquiring influenza due to the close living quarters allowing for the rapid spread of the virus among troops.[141] The extent to which occupational differences between the sexes affect exposure to the 2009 H1N1 should be considered.

5.7 Caregiving

Influenza is primarily spread via respiratory droplets and contact with fomites; thus, close contact with influenza-infected individuals and their respiratory secretions results in higher risk of transmission.[142] As a result, health-care workers as well as those in frequent contact with young children are at a higher risk of exposure to influenza viruses, including seasonal outbreaks and pandemic strains, than are other individuals in the general public.[143–145] In most countries around the world, nurses, teachers and day-care workers are predominantly female[146, 147], potentially leading to a gender-specific occupational risk for influenza acquisition. Women represent more than 50% of the health-care workforce in many countries (see Figure 3).[28, 147–149]

Responsibility for caregiving for both children and ill family members within the home also has emerged as an important risk factor for exposure to influenza viruses. Women in the United States are more likely to develop viral respiratory illnesses than men, whether they work outside the home or not. Women who work outside the home have a lower risk of developing a viral illness as compared to women who do not work outside the home, suggesting that societal roles, such as child care, plays a role in acquisition of viral illness.[150, 151] Equally important is the fact that caregivers may themselves be unable to seek adequate treatment because of their responsibilities, potentially resulting in delayed treatment, especially among women.

5.8 Personal hygiene

Hygienic practices are instrumental in reducing the risk of exposure to and acquisition of influenza. The frequency of practice of hygienic behaviours differs between males and females. The primary preventative methods to reduce transmission of influenza include good hand hygiene, appropriate respiratory etiquette (i.e. covering a cough or sneeze), social distancing when ill (i.e. not working or going to school when ill), and, in health-care settings, appropriate use of personal protective equipment including gowns, gloves, masks and eye protections. Hand hygiene compliance, including use of gel sanitizers, which is thought to be the most effective way to prevent transmission of influenza, differs significantly between men and women. In community studies conducted during the severe acute respiratory syndrome (SARS) outbreak in Toronto as well as in health-care workers in the United States, women had significantly better hand-hygiene practices than men.[152, 153] Among health-care workers, self-reported rates of use and knowledge about appropriate personal protective equipment in response to influenza are similar between the sexes.[154]

5.9 Health-seeking behaviour and access to care

Differences in health-seeking behaviour or health-care access may impact both the acquisition and manifestation of seasonal, outbreak and pandemic strains of influenza. A World Health Survey in 59 countries from 2002–2004 revealed that adult women are more likely to seek out health care in both higher and lower income countries.[147, 155, 156] Access to basic health-care services, however, is often lacking in the developing world, especially for the poor.[157–159] Further, the quality of care for women in some parts of the developing world is not equivalent to that received by men, which may be due to several factors, including income, legal rights, socioeconomic status and educational differences between men and women in these countries.[157–159] In some countries, women also may be less likely to receive best practice-based care for comorbid conditions, such as cardiovascular disease, diabetes and HIV, which may put them at higher risk for complications from influenza.[97, 98, 102, 157, 159] Finally, access to information regarding health care and access to transportation to utilize medical care can, in some regions, also be lower for women than men.[160]

6 Male-female differences in response to influenza virus vaccines and antivirals

6.1 Rates of vaccination

Nurses immunize patients against influenza at Kenyatta National Hospital, Kenya.

Rates of vaccination against seasonal influenza viruses vary worldwide, which probably reflect discrepancies in the availability of vaccines in developed when compared to developing countries. Many reports of vaccination rates as well as the safety, efficacy and effectiveness of vaccines around the world do not disaggregate data by sex and are limited to the developed world.[161–164] Among health-care workers, from 1985–2002, rates of vaccination were higher in the United States than in Canada or Europe, with considerable variation within each country.[162] Surveys of countries in the European Union reveal that individuals over 65 years of age, health-care workers, individuals with underlying medical conditions and children are most likely to receive seasonal influenza virus vaccines.[163, 164] In the United States, rates of vaccination in the general population (1997–2008) were also highest among individuals over 65 years of age (66.9%), followed by individuals 50–64 years of age (39.4%), two to 17 years of age (28.5%), and 18–49 years of age (19.9%)[165], which most likely reflect those groups targeted by governmental vaccine campaigns, at least in the United States.

The interaction between age and sex is apparent when looking at sex-specific rates of seasonal influenza vaccination. Data from national household surveys collected during the 2001–2008 annual influenza seasons in Europe reveal that several factors, including age, sex, socioeconomic status and occupation, contribute to the likelihood of receiving the seasonal influenza vaccine, which also varies significantly between countries.[166] In Europe, males of all ages are more likely to receive the seasonal influenza vaccine in the Czech Republic (OR: 1.34), France (OR: 1.26), Italy (OR: 1.43), Spain (OR: 1.37), the Netherlands (OR: 1.26), Poland (OR: 1.29) and Portugal (OR: 1.41).[166, 167]

Males and females are equally likely to be vaccinated in Austria, Finland, Germany and Ireland.[166] Analyses of vaccination data in the United States from 2005–2007 revealed that men 18–24 and over 70 years of age were more likely to receive the seasonal influenza vaccine,

whereas women 25–69 years of age were more likely to receive it.[168] In the United States, elderly female military veterans (75.5 + 6 years) were less likely than their male counterparts (73.9 + 5.6 years) to receive seasonal influenza virus vaccines.[169] Whether lower rates of vaccination among females in some European countries as well as among elderly people in the United States reflect greater negative beliefs about the risks associated with vaccination[170], differences in physicians' recommendations regarding vaccination, or occupational differences require additional examination. Among health-care workers in China, 73% (982/1399) of adult women reported their intention to decline both the H5N1 and 2009 H1N1 vaccines as compared to 64% (291/467) of men.[171] Data from developing countries are sparse.

6.2 Immune responses

Immunological responses to seasonal influenza virus vaccines differ between males and females (see Table 2). Numerous randomized, double-blind studies conducted in Australia, China, the United Kingdom and the United States reveal that hemagglutination inhibition (HAI) titers following influenza virus vaccination are consistently higher in adult as well as elderly women than men of comparable ages.[129, 172–179] In response to the TIV, for example, in the United States, adult women (18–64 years of age) generate a more robust antibody response following vaccination than men.[175] Importantly, the antibody response of adult women to a half dose of the TIV vaccine is equivalent to the antibody response of adult men to the full dose.[175] Whether antibody responses to other viral proteins, such as the neuraminidase protein, or production of mucosal IgA differ between males and females has not been reported. Furthermore, the extent to which cell-mediated immune responses to vaccines, which are important for broad recognition of conserved epitopes across strains of influenza viruses, differ between the sexes requires consideration. Whether development of stronger immune responses to seasonal influenza vaccines among females confers greater cross-protection against seasonal variants or pandemic strains of influenza viruses should be evaluated. Reports of responses to the H5N1 and 2009 H1N1 influenza A viruses have not included analyses of immune responses by the sex of the subject.[180, 181] As clinical trials of the 2009 H1N1 vaccines are initiated, the differences between the responses of males and females should be analyzed. Because HAI titers are a significant correlate of protection from influenza viruses, the data presented suggest that vaccine efficacy may be higher in females than males.[182]

6.3 Adverse side effects

In addition to having higher antibody responses, females consistently report more severe local and systemic reactions to influenza virus vaccines than males (see Table 2). Several prospective, randomized, double-blind studies conducted in Australia, Brazil, Finland, the Netherlands, Slovenia and the United States indicate that local reactions (e.g. redness, swelling, and tenderness), local inflammation, and injection site pain are consistently more severe and more frequent in adult and elderly women than men.[172, 175, 179, 183–188] In Brazil, for example, the independent variable that is most predictive of adverse reactions to the TIV vaccine in multi-regression logistic models is sex, with elderly women (over 60 years of age) being 5.89 times (95% CI: 2.08-16.68) more likely to report adverse reactions to the vaccine than elderly men.[188] In addition to the hypothesized increased pain sensitivity in females[185], investigators should consider that elevated inflammatory responses in females[4] may also contribute local adverse reactions to the seasonal influenza virus vaccines and could be reduced by administration of lower doses of vaccine.[182] Evaluation of the mechanisms mediating how males and females differ in adverse side effects following vaccination and how these reactions could be mitigated, especially in females should be incorporated into clinical trials. Further consideration also must be given to whether influenza vaccines are administered with or without a modified alum adjuvant which has been documented to cause greater side effects in females[189], perhaps due to stronger innate immune responses induced in females compared with males. The extent to which adverse reactions differ between males and females in response to vaccines against pandemic influenza viruses has not been reported, but should be considered, especially during the 2009 H1N1 pandemic. Unfortunately, most studies of safety, cross-reactivity and immunogenicity of seasonal and pandemic (e.g. H5N1 and 2009 H1N1) influenza virus vaccines in many countries, including Canada, China and the United States, do not decipher the responses of males and females in the analyses.[180, 181, 190–192]

6.4 Antiviral therapy

Antivirals are an effective treatment following infection with influenza viruses, including pandemic strains of influenza (see Table 2). Available data indicate that the rate of prescribing antivirals to influenza virus-infected individuals, ranging in age from infants to adults, is similar between males and females in the United States.[193–195] In contrast, inappropriate prescription of antibiotics for influenza in the United States (1995–2002) was greater for adult women than adult men (male OR: 0.6, 95% CI: 0.4-0.9).[194] Data from Israel reveal that adherence to oseltamivir treatment is similar between adult men (174/198) and women (2/3), but the low sample size of females in the study population makes it difficult to draw definitive conclusions.[196] A meta-analysis of data from randomized, double-blind clinical trials conducted in Argentina, Canada, China, Europe and the United States illustrates that following treatment with oseltamivir, adult males (n = 330) return to their baseline wellness, as measured by sleep (e.g. time to return to baseline sleep habits: median value eight hours for males and 28 hours for females) and daily activities (e.g. time to return to baseline daily activity rates: 24 hours for males and 40 hours for females), faster than females (n = 331), suggesting that antiviral treatment may be more effective in men than women.[197] Whether this observation reflects patient reporting biases, need for differential drug doses, or other confounding factors cannot be ruled out. These data do, however, indicate that sex and gender should be considered when evaluating the efficacy of antiviral treatments.

7 Influenza infection and pregnancy

Sex-based differences in the response to influenza infection and vaccination must take into account the uniquely female-specific state of pregnancy.[198–200] Because the risk of complications resulting from influenza infection increases during the second and third trimesters, the physiological changes associated with pregnancy, including the stress associated with increased demands on cardiovascular output, are often cited as primary reasons for increased disease severity.[201] Changes in immune function and hormone concentrations associated with pregnancy may play an equally important role in explaining the increased disease severity.[4] During pregnancy, the immune system shifts away from inflammatory responses associated with Th1-mediated immunity, while maintaining or augmenting the anti-inflammatory Th2 and regulatory T cell responses, which are modulated by hormones, including progesterone.[202] This immunological shift serves to prevent immune-mediated rejection of the fetus, but also reduces the capacity of the pregnant woman to mount a strong antiviral immune response which is needed to control a primary viral infection.[203, 204]

Two women prepare for childbirth at a hospital in Port-au-Prince, Haiti.

7.1 Risk to the fetus

Infection of a pregnant women can have direct and indirect effects on both the fetus and mother. While a limited number of case reports suggest influenza infection of the fetus can occur[205–207], there appears to be minimal risk to the fetus from maternal infection with influenza virus, as judged by preterm delivery rates, spontaneous abortion rates or the presence of fetal abnormalities.[198, 208] A notable exception was in the case of the 1918 pandemic, where the rate of spontaneous abortion in influenza-infected pregnant women was estimated to be 26%.[209] There appears to be very little risk of direct infection of the fetus with influenza[210] and the teratogenic effects of fever resulting from influenza infection do not appear to lead to additional cases of fetal abnormalities.[211, 212]

7.2 Morbidity

Influenza infection of pregnant women results in higher rates of severe disease and hospitalization in response to both seasonal and pandemic influenza viruses when compared to the general population (see Figure 4A) or to age-matched nonpregnant women. During seasonal influenza, rates of hospitalization have been demonstrated to be two to 18 times higher in pregnant women when compared to nonpregnant women, with a marked increase associated with the second and third trimesters of pregnancy.[213–218] Hospitalization rates were also significantly higher for pregnant women than for the general population during the 1918 and 1957 pandemics.[209, 219–221] There also is a strong association of severe disease and increased hospitalization rates in pregnant women infected with 2009 H1N1 (see Figure 4B), particularly during the second and third trimesters in Australia, Canada, Europe, New Zealand, South Africa and the United States, but not in Mexico or Singapore.[43–45, 61, 201, 222–227]

7.3 Mortality

Pregnant women have a higher rate of mortality after influenza infection during pandemics than nonpregnant women. The mortality rate of pregnant women in response to seasonal influenza infection is not consistently higher, though there are increased numbers of fatalities during years in which seasonal influenza is particularly severe.[198] During the 1918 pandemic, mortality rates in the United States among pregnant women were estimated to be as high as 25%.[209, 219] Mortality rates in pregnant women during the 1957 pandemic were three to four times higher than those seen in nonpregnant women in the United States.[220, 221] The mortality rate in pregnant women during the early stages of the 2009 H1N1 pandemic appears to be greater than those seen in the general population in Australia, Canada, Europe, New Zealand, South Africa and the United States, but not in Mexico or Singapore during the early stages of the pandemic.[43–45, 61, 201, 222–225, 227]

7.4 Comorbidities

Although pregnancy alone increases the likelihood of developing severe influenza, the presence of known comorbidities, such as asthma, diabetes, smoking, and heart or renal disease, is associated with an even higher rate of hospitalization with severe disease in both Canada and the United States.[228–230] In a study of pregnant women in the United States from 1974 to 1993, the presence of any comorbidity resulted in a greater than fivefold increase in the likelihood of hospitalization when compared to pregnant women with no known comorbidities.[216] Another study conducted in the United States demonstrated a threefold to sixfold increase in the risk of hospitalization due to respiratory illness in pregnant women with a known comorbidity, compared to healthy pregnant women.[229] A report from Canada (1994–2000) showed that nearly half of all pregnant women hospitalized with influenza-like illness had at least one defined comorbidity.[217] These data demonstrate that the risk of severe influenza in pregnant women is compounded by the presence of at least one of the known comorbidities associated with increased morbidity and mortality in nonpregnant women.

7.5 Biological basis for increased morbidity and mortality

Although the risk of influenza infection appears to be similar for pregnant and nonpregnant women[231, 232], severe disease and mortality rates can be significantly higher in pregnant women. The precise mechanisms responsible for this have yet to be elucidated. The presence of an underlying medical condition is associated with a portion of the cases of severe influenza in pregnant women. The contribution of pregnancy-related physiological changes on lung capacity and function combined with increased cardiopulmonary demands are often cited as important factors that may increase influenza disease severity.[201, 226] It is equally important, however, to consider the high levels of sex hormones present during and immediately after pregnancy and their effect on the immune response to infection. The general shift to a Th2-biased immune response in pregnant women serves to limit fetal rejection, but may also contribute to increased disease severity by altering the immune response to influenza infection. Severe 2009 H1N1 disease in pregnant women is associated with significantly lower levels of total IgG antibody and, in particular, IgG2 subclass antibodies as compared with pregnant women who are either healthy or suffering from only moderate H1N1 disease.[233]

A careful analysis of the immune response in influenza-infected pregnant women is needed in order to assess the

role of specific immune cells and proinflammatory cytokines and chemokines in the disease pathology. A majority of data evaluating the relationship between pregnancy and influenza virus infection and vaccination have been conducted in the United States; thus, considerably more research is required before these data can be extrapolated to other regions of the world.

7.6 Effectiveness of antiviral therapy

Clinical trials of influenza antiviral safety in pregnant women are lacking. Amantadine use during pregnancy is contraindicated due to conflicting results from animal studies on teratogenicity and adverse side effects[234, 235] combined with data on adverse side effects (e.g. nervousness, anxiety, difficulty concentrating and nausea) in normal, healthy adult humans.[20, 236] Data on the safety of neuraminidase inhibitors in pregnant women is limited to several studies of relatively small groups of pregnant women but no adverse effects were reported.[237, 238] Studies of oseltamivir in populations at high risk for severe disease after infection with influenza (excluding pregnant women) indicate no significant safety concerns when compared to the general population.[239, 240] Pharmacological and teratogenic studies of oseltamivir in laboratory animals have indicated no significant risks associated with either the mother or fetus.[239, 241] Data from the 2009 H1N1 pandemic indicate that treatment with oseltamivir within 48 hours of symptom onset can significantly improve the outcome of influenza infection of pregnant women.[43, 201, 222, 242]

The World Health Organization and a number of governments recommend early treatment of any pregnant woman suspected of being infected with 2009 H1N1 because early treatment has been associated with better outcomes after infection.[243] Oseltamivir is, however, still considered a pregnancy category C drug, indicating that additional data from clinical and animal studies are needed to assess its safety in pregnant women.[20] Taken together, the data on safety and efficacy of influenza antivirals in pregnant women is very limited but supports the use of oseltamivir to prevent severe influenza in pregnant women.

8 Influenza vaccination and pregnancy

8.1 Recommendations for vaccination

In Canada and the United States, pregnant women are considered one of the high risk groups for developing severe influenza and, therefore, vaccination against seasonal influenza is recommended irrespective of trimester.[20] This policy, however, varies among other nations with vaccination recommendations in the second and third trimesters in Australia[244], but only in pregnant women with comorbidities in the United Kingdom.[245] A WHO position paper on influenza vaccination recommends vaccination of all pregnant women during the influenza season[246], and that policy was extended to include vaccination against 2009 H1N1.[247]

The TIV vaccine is recommended during pregnancy as LAIV is contraindicated due to concerns over potential adverse effects to the fetus and the pregnant woman's ability to control the replication of the attenuated vaccine strains. Despite the clear increase in morbidity stemming from influenza infection of pregnant women, for the most part, vaccine coverage rates tend to lag behind those seen in the general population.[168, 248, 249] In a United States study of influenza vaccination rates from 1997 to 2005, the coverage rate for pregnant women ranged from 9.3 to 14.4%, which was lower than that observed with other high-risk populations, such as those 65 and older (60.2–70%), 18–49 year olds with high risk conditions (17.6–27.2%), or 50–64 year olds with high risk conditions (33–50.5%).[250]

A number of reasons are cited for the lack of influenza vaccine coverage in pregnant women. A Canadian study found that nearly 90% of pregnant women were unaware of the increased risks associated with influenza infection during pregnancy.[251] In surveys of health-care providers in the United States, nearly half would not recommend or encourage vaccination with a pandemic influenza vaccine due to concerns over administering vaccines to pregnant women.[252] In a survey of obstetrician-gynaecologists from the United States, only 52% would recommend influenza vaccination to pregnant women in their first trimester, while 95% would recommend it to women in their second or third trimesters. Only 36–38% of those physicians, however, actually offered the vaccine to their patients.[253] Increased awareness of the benefits of vaccination as well as a recommendation for vaccination from a health-care provider were important factors associated with the acceptance of seasonal influenza vaccination by pregnant women.[254] These data suggest that making health-care providers and pregnant women more aware of the United States' Advisory Committee on Immunization Practices (ACIP)[20] and WHO recommendations for vaccination[246] in addition to the data on the safety of TIV in pregnant women could increase vaccine coverage rates worldwide.

8.2 Adverse side effects and safety

There is a good record of vaccine safety in pregnant women, particularly with regard to immunization during the second and third trimester. A long term study of over 50 000 immunized women and their children in the United States, of whom over 2000 received TIV, demonstrated no significant increased risk of adverse side effects to TIV.[255, 256] Another study of 252 TIV-immunized pregnant women in the United States showed no adverse side effects in mothers or children born to the immunized mothers when compared with unimmunized pregnant women.[257] Passive surveillance for adverse side effects to influenza vaccination has been conducted through the Vaccine Adverse Event Reporting System in the United States and no significant increases in adverse effect reporting have been noted in the over two million pregnant women who have received TIV.[258] There appears to be no adverse effect of the MF59-adjuvanted influenza vaccines on pregnancy outcomes, a preliminary but important finding given the use of MF59-adjuvant in pandemic influenza vaccines used in Canada, Europe and elsewhere.[259] Taken together, the data on TIV immunization of pregnant women indicate that there are no major adverse side effects to mother, fetus or child from TIV immunization.

8.3 Vaccine efficacy

Studies demonstrating the efficacy of influenza vaccination in either inducing antibody correlates of protection or protection from confirmed influenza infection are not as extensive as the TIV safety studies in pregnant women. Studies carried out during several influenza seasons in the early 1960s in the United States indicated that influenza vaccination was equivalent in pregnant and nonpregnant women with respect to adverse side effects and antibody responses.[260] Immunization of pregnant women in the United States with the 1976 'swine' influenza vaccine was determined to be as safe and immunogenic as vaccination of nonpregnant women.[261–263] These studies formed at least part of the basis for the assumption that pregnant and nonpregnant women respond to TIV vaccine in a similar manner. In a 2008 study from Bangladesh, 340 pregnant women randomly assigned either TIV or pneumococcal vaccine showed a vaccine efficacy rate of 63% against laboratory confirmed influenza, which represents the first prospective study of confirmed protection from influenza by TIV in pregnant women.[264]

8.4 Pregnancy and the immune response to vaccines

Clinical or animal studies designed to investigate the optimum dosing and range of immune responses to influenza vaccine in pregnant females could provide important information as to how to effectively vaccinate this population. These studies also would serve to further alleviate fears over vaccine safety and efficacy by providing data to support the assertion that influenza vaccination is not only safe but also effective in pregnant woman. Based on data describing the Th2 polarization of the antibody response in pregnant women, it is surprising that pregnant and nonpregnant women respond equivalently to a uniform TIV dose.[260–263] Because influenza vaccines are designed to induce a strong protective immune response across both sexes and a wide spectrum of age groups[182], it may be that the administered TIV doses are high enough to mask pregnancy-associated differences in the immune response of women.

9 Conclusions and recommendations

- Conclusions about the precise impact of sex and gender on influenza infection and vaccination are difficult to determine because most published studies do not disaggregate data by both age and sex.
- Sex hormones have a documented effect on immune responses and because hormone levels vary significantly over the life-course, an effect of sex hormones on responses to influenza may not be apparent unless responses are further disaggregated by age, as outlined in the WHO Gender Strategy.[7]
- Societal and behavioural differences between males and females contribute to differences in exposure to and outcome of influenza virus infection.
- Sex-specific effects of a number of influenza risk factors vary considerably around the world which may further contribute to the differences in the outcome to infection seen across geographical regions.
- With regard to morbidity and mortality from seasonal, outbreak and pandemic influenza viruses, there is evidence that the outcome of infection is worse for females, but the magnitude of this difference varies across countries and it is likely that the differential contribution of gender and sex varies in different regions of the world.
- In response to vaccines, females consistently mount higher antibody responses and experience more frequent and severe side effects, which should be considered in the drafting of guidelines for vaccination worldwide.
- Recommendations for vaccination and the use of antivirals against influenza in pregnant women are based on limited clinical and animal model data. Improving the scientific data supporting these recommendations would greatly improve the public health argument for vaccination and administration of antiviral treatments in pregnant women.
- Improved awareness of the risks of influenza to pregnant women could increase vaccination rates, particularly if health-care providers of pregnant women were targeted with this information.
- Future research should consider the physiological differences between males and females, including differences in hormone concentrations and immune responses to infection and vaccination, in greater detail as there may also be biological mechanisms mediating sex-specific development of disease and outcome of infection.
- Although the increased risk of seasonal and pandemic influenza to pregnant women has been well documented, the biological basis of this risk has yet to be defined or studied comprehensively. A better understanding of how pregnancy alters susceptibility to severe influenza would provide important data that could augment the treatment of influenza-infected pregnant women.
- The economic and societal impact of male-female differences in the outcome of influenza virus infection among individuals of reproductive age should be considered.

10 Statistical data

Table 1

Male-female differences in response to influenza A virus infection

Dependent measure	Influenza	Virus	Sex difference[1]	Study population[2]	Study country	Reference nos.
Incidence/ exposure	Seasonal	H3N2/ H1N1	M > F	All ages	Spain	*24*, *265*
			M > F	Infants/ toddlers	USA	*25*
	Outbreak	H5N1	F > M	After puberty	China, Egypt	*26*, *139*
			M > F	Adults	Cambodia	*137*
			F > M	All ages	Indonesia	*26*
	Pandemic	2009 H1N1	M > F F > M M = F	10–19 20–39 40+	Canada	*266*
			F > M M > F	20–39 40–59	Argentina	*28*
			F > M	0–19	France	*29*
			F > M	15–49	Brazil	*30*
			M = F	All ages	Belgium, Italy, Peru	*31–33*
Rate of hospitalization	Seasonal	H3N2/ H1N1	M > F	All ages	Canada	*38*
			M > F	Before puberty	Denmark	*41*
			M > F	Infants	Canada	*39*
			F > M	After puberty	Denmark	*41*
	Pandemic	2009 H1N1	F > M	Adults	Canada	*43*
			F > M	After puberty	Australia, Brazil	*30*, *51*
			M = F	All ages	Australia, Mexico, New Zealand, USA	*44, 225, 267*

Table 1 continued

Dependent measure	Influenza	Virus	Sex difference[1]	Study population[2]	Study country	Reference nos.
Morbidity/ mortality	Seasonal	H3N2/ H1N1	F > M	Elderly	Portugal	*53*
			M > F	Elderly	Switzerland	*54*
	Pandemic	H2N2	F > M M > F	1–44 45+	USA	*55*
	Epidemic	H2N2	F > M M > F	1–44 45+	USA	*55*
	Outbreak	H5N1	F > M	After puberty to adults	Egypt, Indonesia	*57, 268*
			M = F	Adults	China, Viet Nam	*269, 270*
	Pandemic	1918 H1N1	M > F	After puberty	Australia, Denmark, Finland, France, Italy, the Netherlands, New Zealand, Norway, Spain, Sweden, Switzerland, the United Kingdom, USA	*58–60*
		2009 H1N1	F > M	Adults	South Africa	*61*
			M > F	Adults	Australia	*51*
			M = F	Adults	Brazil, Peru	*30, 33*

[1] For all reported differences between males (M) and females (F), only differences that were determined to be statistically significant are reported.

[2] Infants/toddlers = 6–59 months of age; before puberty = < 10 years of age; after puberty = > 10 years of age; adults = > 18 years of age; elderly = > 65 years of age.

Table 2
Male-female differences in response to influenza virus vaccination and antivirals

Dependent measure	Type of treatment	Sex difference[1]	Study population[2]	Study country	Reference nos.
VACCINES					
Likelihood of getting vaccinated	LAIV/TIV	M = F	All ages	Spain	*271*
		M > F	All ages	Czech Republic, France, Italy, Spain, Poland, Portugal	*166*
		M = F	All ages	Austria, Finland, Germany, Ireland	*166*
		F > M	Adults	The United Kingdom	*272*
		M > F	Adults	The Netherlands	*167*
		F > M	Adults	USA	*165*
		M = F	Elderly adults	USA	*165*
		M > F	Elderly adults	USA	*169*
	LAIV	M > F	Adults	USA	*168*
Negative beliefs about vaccination	TIV	F > M	Elderly adults	USA	*170*
Intentions to decline vaccine	H5N1 and H1N1 vaccines	F > M	Adult health-care workers	China	*171*
Humoral/antibody response	TIV	F > M	Adults	The United Kingdom, USA	*174, 175, 177, 179*
		F > M	Elderly adults	Australia, China, USA	*172, 173, 176, 178*
Adverse reactions	TIV	F > M	Adults	The Netherlands, USA	*175, 179, 183, 184, 186*
		F > M	Elderly adults	Australia, the Netherlands, Slovenia	*172, 176, 183, 187, 188, 273, 274*
		M = F	Adult health-care workers	Turkey	*275*
ANTIVIRALS					
Prescription of antivirals	Oseltamivir	M = F	Infants-adults	USA	*193*
	Rimantadine, Zanamivir	M = F	Adults	USA	*194, 195*
Effectiveness of antivirals	Oseltamivir	M > F	Adults	Argentina, Canada, China, Europe, USA	*197*
Adherence to antiviral treatment	Oseltamivir	M = F	Adults	Israel	*196*
Inappropriate prescription of antibiotics	Any	F > M	Adults	USA	*194*

[1] For all reported differences between males (M) and females (F), only differences that were determined to be statistically significant are reported.

[2] Infants/toddlers = 6–59 months of age; before puberty = < 10 years of age; after puberty = > 10 years of age; adults = > 18 years of age; elderly = > 65 years of age.

Figure 1

Individuals with immunodeficiencies, including HIV, are at an increased risk for severe outcome of influenza. HIV prevalence is higher in women than men in several countries[147], which may increase the risk of severe outcome of influenza in women.

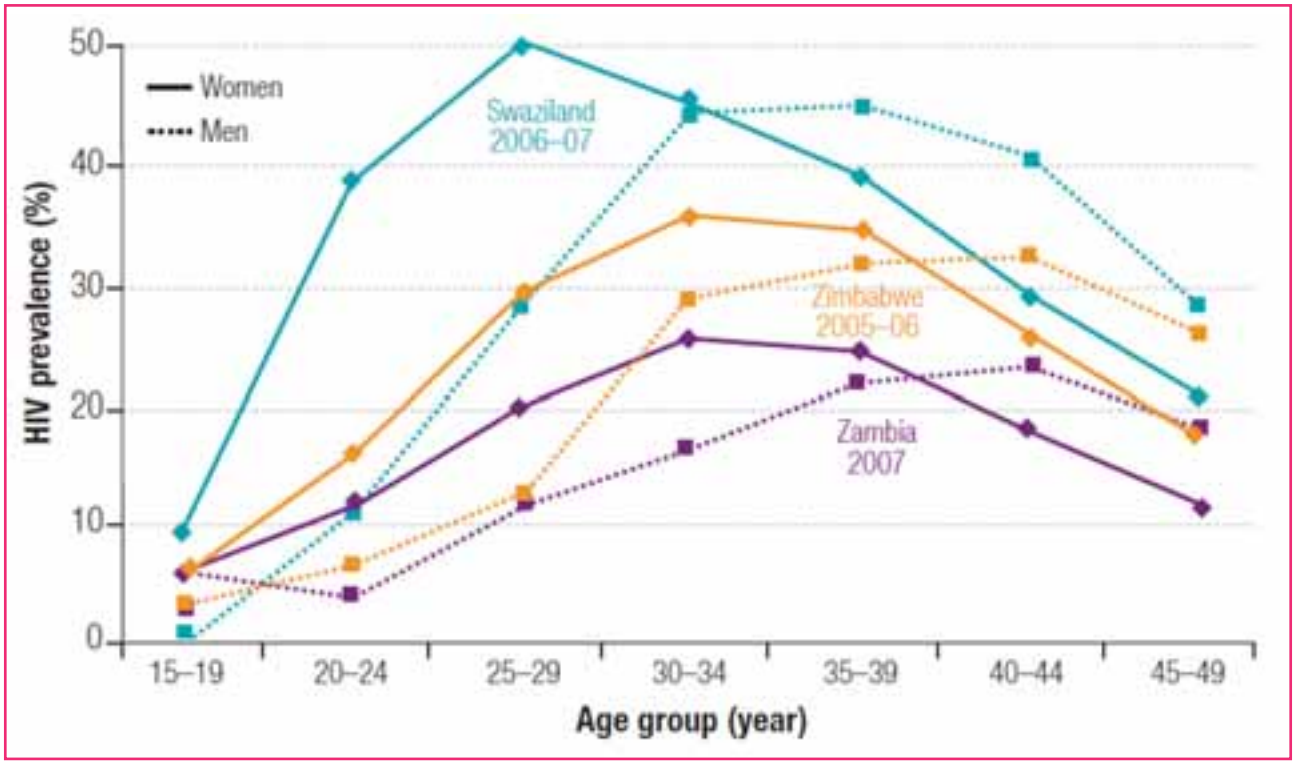


Figure 2

Tobacco use is associated with increased severity of influenza illness. Smoking is much more common among adult and adolescent males than females in most WHO regions examined 2002–2008[276].

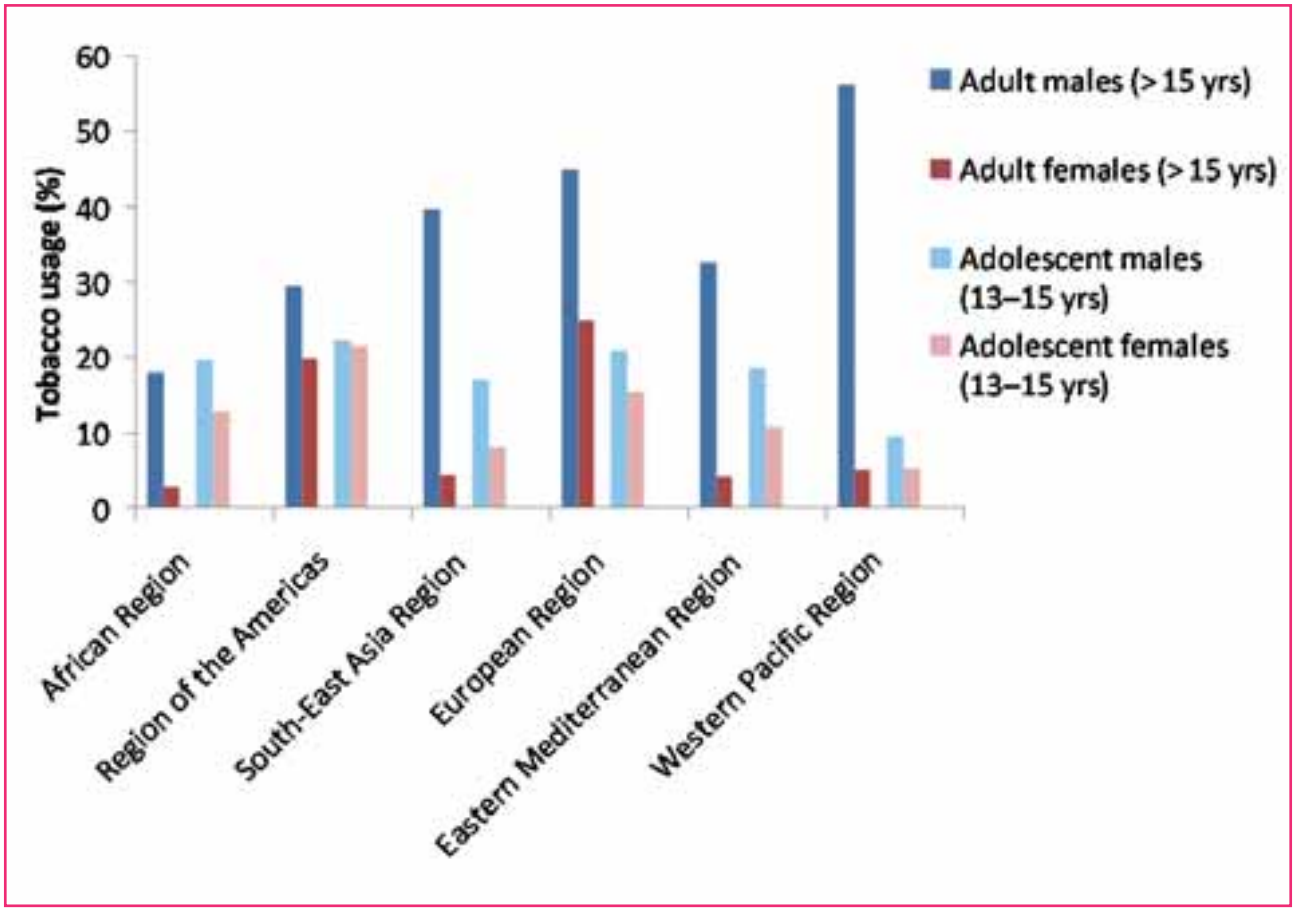


Figure 3

Health-care workers are at an increased risk of exposure to influenza viruses. Women constitute a majority of the formal health workforce in many countries, based on analyses of the health workforce 1989–1997[149, 277], which may increase the likelihood of exposure to influenza among women compared with men.

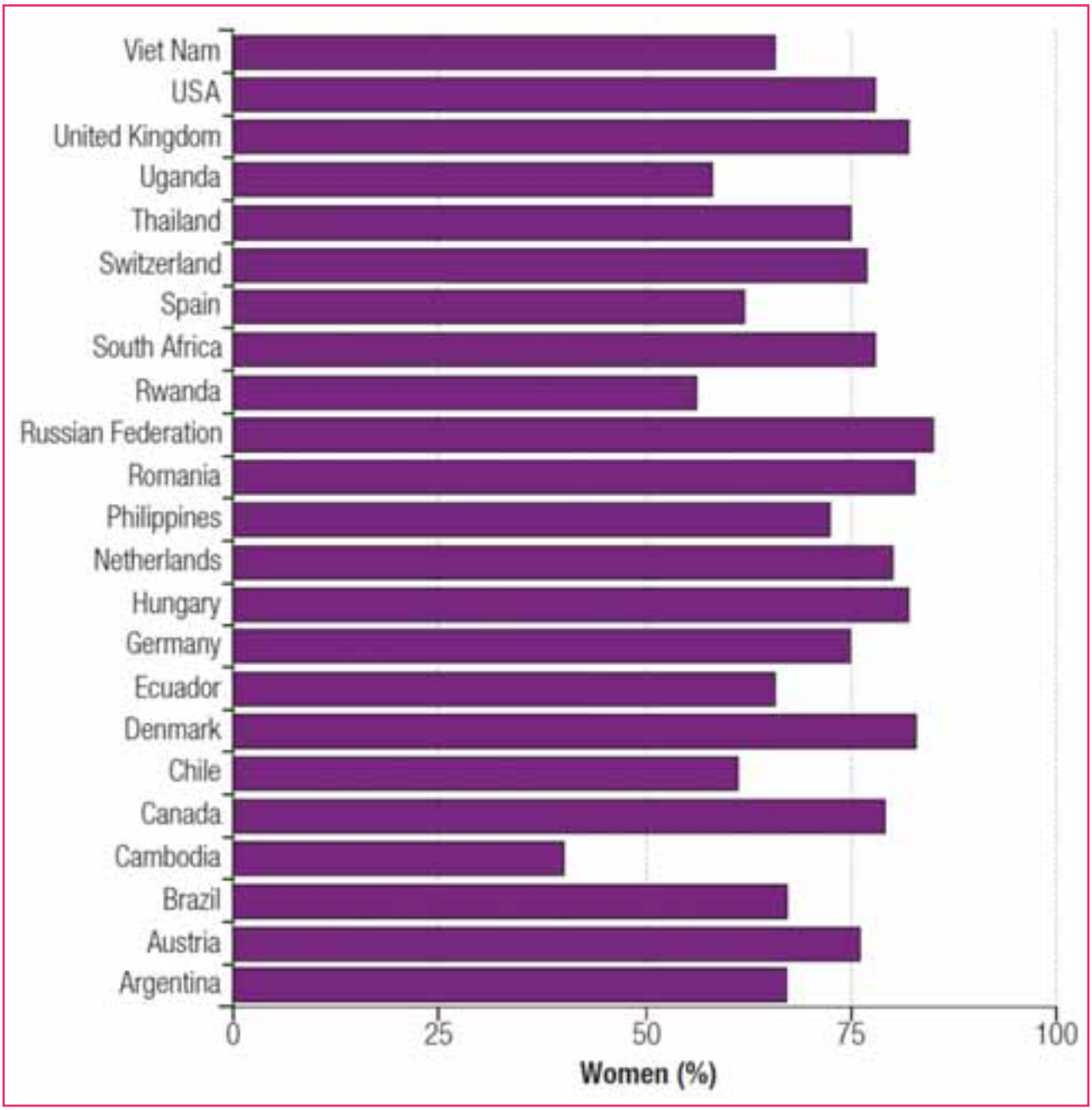
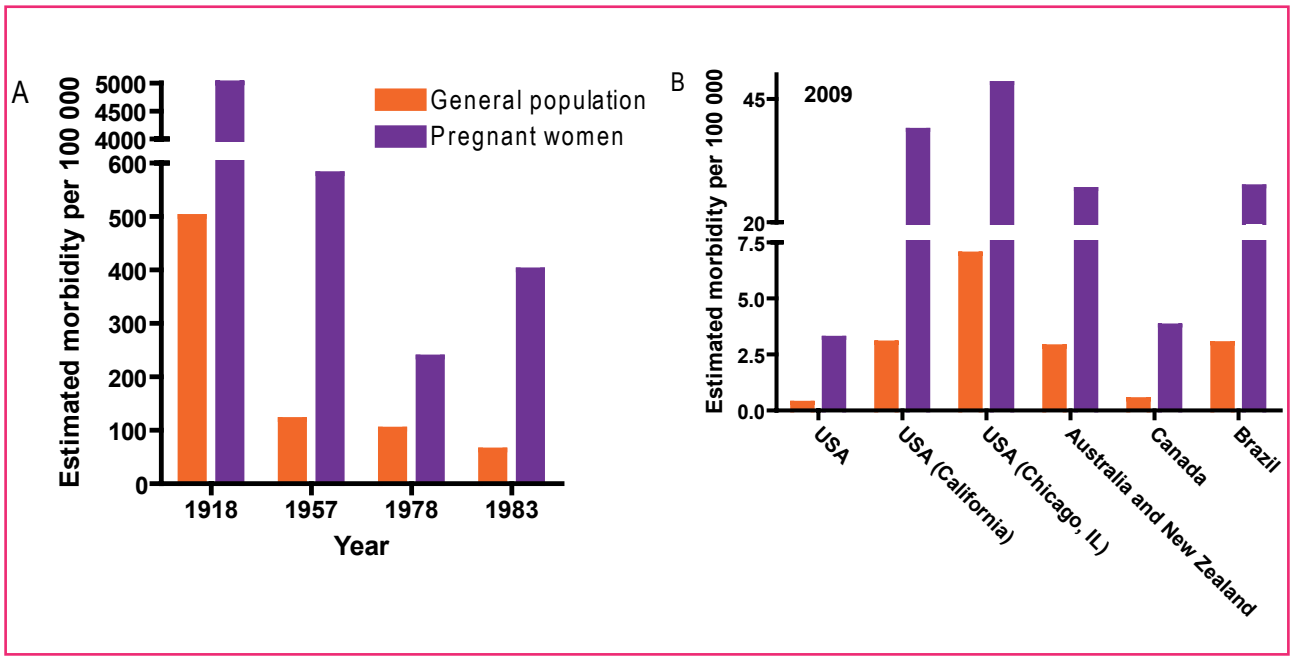


Figure 4

Rates of severe influenza disease are increased among pregnant women.

(A) Estimated morbidity in pregnant women when compared to the general population during two pandemics (1918, 1957) and two seasonal years. Morbidity estimates are calculated based on datasets for 1918[209, 278, 279], 1957[220, 221], 1978[215], and 1983.[216] (B) Estimated morbidity rates during the first wave (April–June) of the 2009 H1N1 pandemic in select countries or geographical regions. Morbidity estimates for 2009 are calculated based on datasets for Australia and New Zealand[44], Brazil[30], Canada[43], and the United States.[45, 267, 280] Estimates of the general and pregnant women populations are based on data from the United States Census Bureau or WHO.



References

1. Morens DM, Folkers GK, Fauci AS. *The challenge of emerging and re-emerging infectious diseases. Nature,* 2004, 430:242–249.

2. Gender and tuberculosis. In: *Gender and health.* Geneva, World Health Organization: 2002.

3. Gender and HIV/AIDS. In: *Gender and health.* Geneva, World Health Organization, 2002.

4. Fish EN. The X-files in immunity: sex-based differences predispose immune responses. *Nature Reviews Immunology*, 2008, 8:737–8744.

5. Klein SL, Roberts CW, eds. *Sex hormones and immunity to infection.* Berlin, Springer-Verlag, 2010.

6. Anker M. *Addressing sex and gender in epidemic-prone infectious diseases.* Geneva, World Health Organization, 2007 (http://www.who.int/csr/resources/publications/sexandgenderinfectiousdiseases/en, accessed 6 April 2010).

7. *Strategy for integrating gender analysis and actions into the work of WHO.* Geneva, World Health Organization, 2007.

8. Wizemann TM, Pardue M, eds. *Exploring the biological contributions to human health: does sex matter?* Washington DC, National Academy Press, 2001.

9. Migeon BR. *Females are mosaics: X inactivation and sex differences in disease.* New York NY, Oxford University Press, 2007.

10. Brabin L. Interactions of the female hormonal environment, susceptibility to viral infections, and disease progression. *AIDS Patient Care STDS*, 2002, 16:211–221.

11. Thun MJ et al. Age and the exposure-response relationships between cigarette smoking and premature death in Cancer Prevention Study II. In: Shopland DR et al, eds. *Changes in cigarette-related disease risks and their implications for prevention and control*, Rockville MD, National Cancer Institute, 1997:383–475.

12. Samet JM, Yoon S-Y. *Women and the tobacco epidemic: challenges for the 21st century. The World Health Organization in collaboration with the Institute for Global Tobacco Control Johns Hopkins School of Public Health.* Geneva, World Health Organization, 2001.

13. *State of the world's children 2009.* New York NY, United Nations Children's Fund, 2009.

14. Hausman RL, Tyson LD, Zahidi S. *The global gender gap report.* Geneva, World Economic Forum. 2008.

15. *Gender equality and the millennium development goals.* Washington DC, The World Bank, 2003.

16. *Gender mainstreaming in health: a practical guide.* New York NY, Pan American Health Organization, 2009 (http://new.paho.org/hq/index.php?option=com_content&task=view&id=1594&Itemid=1, accessed 6 April 2010).

17. Cox NJ, Subbarao K. Global epidemiology of influenza: past and present. *Annual Review of Medicine*, 2000, 51:407–421.

18. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *Journal of Infectious Diseases*, 2006, 194:S82–S91.

19. Viboud C et al. Influenza in tropical regions. *PLoS Medicine*, 2006, 3:e89.

20. Fiore AE et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), *2009. MMWR Recommendations and Reports*, 2009, 58:1–52.

21. Monto AS. The role of antivirals in the control of influenza. *Vaccine*, 2003, 21:1796–1800.

22. Monto AS. Editorial commentary: implications of antiviral resistance of influenza viruses. *Clinical Infectious Diseases*, 2009, 48:397–399.

23. Chiaramonte GR, Friend R. Medical students' and residents' gender bias in the diagnosis, treatment, and interpretation of coronary heart disease symptoms. *Health Psychology*, 2006, 25:255–266.

24. Larrauri A, de Mateo S. Characterisation of swabbing for virological analysis in the Spanish Influenza Sentinel Surveillance System during four influenza seasons in the period 2002-2006. *Eurosurveillance*, 2007, 12 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=706, accessed 6 April 2010).

25. Szilagyi PG et al. Influenza vaccine effectiveness among children 6 to 59 months of age during 2 influenza seasons: a case-cohort study. *Archives of Pediatrics & Adolescent Medicine*, 2008, 162:943–951.

26. World Health Organization. Update: WHO-confirmed human cases of avian influenza A (H5N1) infection, November 2003–May 2008. *Weekly Epidemiological Record*, 2008, 83:415–420.

27. *Ontario Novel H1N1 Influenza A Virus epidemiologic summary, May 13,* 2009. Ottawa, Public Health Agency of Canada. 2009.

28. *Influenza pandémica (H1N1) 2009 [Influenza pandemic (H1N1) 2009]*. Buenos Aires, Ministry of Health, Republic of Argentina, 2009 (Epidemiological Weekly Report No. 39) (http://www.msal.gov.ar/archivos/Informe_SE_39-ARG_COM%5B1%5D.pdf, accessed 27 June 2010).

29. Levy-Bruhl D, Vaux S. Modified surveillance of influenza A(H1N1)v virus infections in France. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19276, accessed 6 April 2010).

30. Oliveira W et al. Pandemic H1N1 influenza in Brazil: analysis of the first 34,506 notified cases of influenza-like illness with severe acute respiratory infection (SARI). *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19362, accessed 6 April 2010).

31. Belgian working group on influenza A(H1N1)v. Influenza A(H1N1)v virus infections in Belgium, May-June 2009. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19270, accessed 6 April 2010).

32. Surveillance Group for New Influenza A(H1N1) Virus Investigation in Italy. Virological surveillance of human cases of influenza A(H1N1)v virus in Italy: preliminary results. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19247, accessed 6 April 2010).

33. Gomez J et al. Pandemic influenza in a southern hemisphere setting: the experience in Peru from May to September, 2009. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/images/dynamic/EE/V14N42/art19371.pdf, accessed 6 April 2010).

34. Surveillance Group for New Influenza A(H1N1) Virus Investigation and Control in Spain. New influenza A(H1N1) virus infections in Spain, April-May 2009. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19209, accessed 6 April 2010).

35. Hahné S et al. Epidemiology and control of influenza A(H1N1)v in the Netherlands: the first 115 cases. Eurosurveillance, 2009, 14 (http://www.eurosurveillance.org/images/dynamic/EE/V14N27/V14N27.pdf, accessed 6 April 2010).

36. de Silva UC et al. A preliminary analysis of the epidemiology of influenza A(H1N1)v virus infection in Thailand from early outbreak data, June-July 2009. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19292, accessed 6 Apzil 2010).

37. European Centre for Disease Prevention and Control. Preliminary analysis of influenza A(H1N1) v individual and aggregated case reports from EU and EFTA countries. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19238, accessed 6 April 2010).

38. Crighton EJ et al. An exploratory spatial analysis of pneumonia and influenza hospitalizations in Ontario by age and gender. *Epidemiology and Infection*, 2007, 135: 253–261.

39. Quach C et al. Risk factors associated with severe influenza infections in childhood: implication for vaccine strategy. *Pediatrics*, 2003, 112:e197–e201.

40. Crighton EJ et al. Influenza and pneumonia hospitalizations in Ontario: a time-series analysis. *Epidemiology and Infection*, 2004, 132:1167–1174.

41. Jensen-Fangel S et al. Gender differences in hospitalization rates for respiratory tract infections in Danish youth. *Scandanavian Journal of Infectious Diseases*, 2004, 36:31–36.

42. Chen KF, Gaydos C, Rothman RE. Update on emerging infections: news from the Centers for Disease Control and Prevention. Hospitalized patients with novel influenza A (H1N1) virus

infection--California, April-May, 2009. *Annals of Emergency Medicine*, 2009, 54:732–736.

43. Kumar A et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. J*AMA*, 2009, 302:1872–1879.

44. The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 Influenza in Australia and New Zealand. *New England Journal of Medicine*, 2009, 361:1925–1934.

45. Jain S et al. Hospitalized patients with 2009 H1N1 Influenza in the United States, April-June 2009. *New England Journal of Medicine*, 2009, 361:1935–1944.

46. Singh AK et al. Sex differences among adults presenting to the emergency department with acute asthma. Multicenter Asthma Research Collaboration Investigators. *Archives of Internal Medicine*, 1999, 159:1237–1243.

47. Schatz M, Camargo Jr. CA. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Annals of Allergy, Asthma and Immunology,* 2003, 91:553–558.

48. Schatz M, Clark S, Camargo Jr. CA. Sex differences in the presentation and course of asthma hospitalizations. *Chest*, 2006, 129:50–55.

49. Moorman JE et al. National surveillance for asthma--United States, 1980-2004. *Morbidity and Mortality Weekly Report: Surveillance Summaries*, 2007, 56:1–54.

50. Fielding J et al. Pandemic H1N1 influenza surveillance in Victoria, Australia, April - September, 2009. *Eurosurveillance*, 2009. 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19368, accessed 8 April 2010).

51. Cretikos MA et al. Progression and impact of the first winter wave of the 2009 pandemic H1N1 influenza in New South Wales, Australia. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19365, accessed 8 April 2010).

52. Ahmed R, Oldstone MB, Palese P. Protective immunity and susceptibility to infectious diseases: lessons from the 1918 influenza pandemic. *Nature Immunology*, 2007, 8:1188–1193.

53. Nogueira PJ et al. Early estimates of the excess mortality associated with the 2008-9 influenza season in Portugal. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/images/dynamic/EE/V14N18/art19194.pdf, accessed 8 April 2010).

54. Brinkhof MW et al. Influenza-attributable mortality among the elderly in Switzerland. *Swiss Medical Weekly*, 2006, 136:302–309.

55. Serfling RE, Sherman IL, Houseworth WJ. Excess pneumonia-influenza mortality by age and sex in three major influenza A2 epidemics, United States, 1957-58, 1960 and 1963. *American Journal of Epidemiology*, 1967, 86:433–441.

56. Sedyaningsih ER et al. Epidemiology of cases of H5N1 virus infection in Indonesia, July 2005-June 2006. *Journal of Infectious Diseases*, 2007, 196:522–527.

57. Dudley JP. Age-specific infection and death rates for human A(H5N1) avian influenza in Egypt. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19198, accessed 8 April 2010).

58. Noymer A, Garenne M. The 1918 influenza epidemic's effects on sex differentials in mortality in the United States. *Population and Development Review*, 2000, 26:565–581.

59. Curson P, McCracken K. An Australian perspective of the 1918-1919 influenza pandemic. *New South Wales Public Health Bulletin*, 2006, 17:103–107.

60. Murray CJ et al. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-20 pandemic: a quantitative analysis. *Lancet*, 2006, 368:2211–2218.

61. Archer B et al. Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: epidemiology and factors associated with fatal cases. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19369, accessed 8 April 2010).

62. Thompson WW et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*, 2003, 289:179–186.

63. Housworth WJ, Spoon MM. The age distribution of excess mortality during A2 Hong Kong influenza epidemics compared with earlier A2 outbreaks. *American Journal of Epidemiology*, 1971, 94:348–350.

64. OwensIP. Ecology and evolution. Sex differences in mortality rate. *Science*, 2002, 297:2008–2009.

65. Population, demographic population of the older population. In: *World population ageing 1950-2050*. New York NY, Dept. of Economic and Social Affairs, United Nations. 2001.

66. Thomas MR et al. Respiratory function of very prematurely born infants at follow up: influence of sex. *Archives of Disease in Childhood, Fetal and Neonatal Edition*, 2006, 91:F197–F201.

67. Murray CS et al. Lung function at one month of age as a risk factor for infant respiratory symptoms in a high risk population. *Thorax*, 2002, 57:388–392.

68. Klein MI et al. Differential gender response to respiratory infections and to the protective effect of breast milk in preterm infants. *Pediatrics*, 2008, 121:e1510–e1516.

69. Libster R et al. Breastfeeding prevents severe disease in full term female infants with acute respiratory infection. *Pediatric Infectious Disease Journal*, 2009, 28:131–134.

70. Morales A, Heaton JP, Carson CC 3rd. Andropause: a misnomer for a true clinical entity. *Journal of Urology*, 2000, 163:705-712.

71. Luk J, Gross P, Thompson WW. Observations on mortality during the 1918 influenza pandemic. *Clinical infectious diseases*, 2001, 33:1375–1378.

72. Richard SA et al. A comparative study of the 1918-1920 influenza pandemic in Japan, USA and UK: mortality impact and implications for pandemic planning. *Epidemiology and Infection*, 2009, 137:1062–1072.

73. Borgdorff MW et al. Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:123–132.

74. Sawchuk LA. Brief communication: rethinking the impact of the 1918 influenza pandemic on sex differentials in mortality. *American Journal of Physical Anthropology*, 2009, 139:584–90.

75. Noymer A. The 1918-19 influenza pandemic affected tuberculosis in the United States: reconsidering Bradshaw, Smith, and Blanchard. *Biodemography and Social Biology*, 2008, 54:125–133 (discussion 134–40).

76. Noymer A. Testing the influenza-tuberculosis selective mortality hypothesis with Union Army data. *Social Science and Medicine*, 2009, 68:1599-608.

77. Bradshaw BS, Smith DW, Blanchard S. A cohort study of tuberculosis and influenza mortality in the twentieth century. *Biodemography and Social Biology*, 2008, 54:74–94.

78. Quinn TC, Overbaugh J. HIV/AIDS in women: an expanding epidemic. *Science*, 2005, 308:1582–1583.

79. Farzadegan H et al. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet*, 1998, 352:1510–1514.

80. Remien RH et al. Gender and care: access to HIV testing, care, and treatment. *Journal of Acquired Immune Deficiency Syndromes*, 2009, 51:S106-S1010.

81. Sohler NL, Li X, Cunningham CO. Gender disparities in HIV health care utilization among the severely disadvantaged: can we determine the reasons? *AIDS Patient Care and STDs*, 2009, 23:775–783.

82. Andersen M et al. HIV health care access issues for women living with HIV, mental illness, and substance abuse. *AIDS Patient Care and STDs*, 2005, 19:449–459.

83. Chakrapani V et al. Barriers to free antiretroviral treatment access for female sex workers in Chennai, India. *AIDS Patient Care and STDs*, 2009, 23:973–980.

84. Jones N, Walsh C, Buse K. *Gender in GAVI: a knowledge stocktaking exercise*. London, Overseas Development Institute, 2008.

85. Sears MR. Epidemiology of asthma exacerbations. *The Journal of Allergy and Clinical Immunology*, 2008. 122:662–668; quiz 669–70.

86. McCoy L et al. A multiple cause-of-death analysis of asthma mortality in the United States, 1990-2001. *Journal of Asthma*, 2005, 42:757–763.

87. Barr RG, Camargo Jr. CA. Hormone replacement therapy and obstructive airway diseases. *Treatments in Respiratory Medicine*, 2004, 3:1–7.

88. Dimitropoulou C et al. Estrogen replacement therapy prevents airway dysfunction in a murine

model of allergen-induced asthma. *Lung*, 2009, 187:116–127.

89. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. *American Journal of Respiratory and Critical Care Medicine*, 1997, 155:1273–1277.

90. Holmen TL et al. Gender differences in the impact of adolescent smoking on lung function and respiratory symptoms. The Nord-Trondelag Health Study, Norway, 1995-1997. *Respiratory Medicine*, 2002, 96:796–804.

91. Langhammer A et al. Sex differences in lung vulnerability to tobacco smoking. *European Respiratory Journal*, 2003, 21:1017–1023.

92. Langhammer A et al. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trondelag Health Study (HUNT). *Journal of Epidemiology and Community Health*, 2000, 54:917–922.

93. Chen Y, Horne SL, Dosman JA. Increased susceptibility to lung dysfunction in female smokers. *American Review of Respiratory Disease*, 1991, 143:1224–1230.

94. de Torres JP et al. Sex differences in mortality in patients with COPD. *The European Respiratory Journal*, 2009, 33:528–535.

95. Greaves L. *Sifting the evidence: gender and tobacco control*. Geneva, World Health Organization, 2007.

96. El-Menyar A et al. Comparison of men and women with acute coronary syndrome in six Middle Eastern countries. *American Journal of Cardiology*, 2009, 104:1018–1022.

97. Meier P, Duvernoy CS. Influence of gender of physicians and patients on guideline-recommended treatment of chronic heart failure in a cross-sectional study. *European Journal of Heart Failure*, 2009, 11:631–632.

98. Adams A et al. The influence of patient and doctor gender on diagnosing coronary heart disease. *Sociology of Health and Illness*, 2008, 30:1–18.

99. Hochman JS et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. *New England Journal of Medicine*, 1999, 341:226–232.

100. Arain FA et al. Sex/gender medicine. The biological basis for personalized care in cardiovascular medicine. *Circulation Journal*, 2009, 73:1774–1782.

101. Thoenes M et al. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. *Journal of Human Hypertension*, 2009, 11:23–28,

102. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. *JAMA*, 2005, 294:466–472.

103. Wild S et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*, 2004, 27:1047–1053.

104. Narayan KM et al. Lifetime risk for diabetes mellitus in the United States. *JAMA*, 2003, 290:1884–1890.

105. Zeitler P. Update on nonautoimmune diabetes in children. *Journal of Clinical Endocrinology and Metabolism*, 2009, 94:2215–2220.

106. Jovanovic L, Pettitt DJ. Gestational diabetes mellitus. *JAMA*, 2001, 286:2516–2518.

107. Chan JC et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*, 2009, 301:2129–2140.

108. Landon MB et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *New England Journal of Medicine*, 2009, 361:1339–1348.

109. Correa-de-Araujo R, McDermott K, Moy E. Gender differences across racial and ethnic groups in the quality of care for diabetes. *Women's Health Issues*, 2006, 16:56–65.

110. *Obesity: preventing and managing the global epidemic. Report of a WHO consultation*. Geneva, World Health Organization, 2000 (WHO Technical Report Series, No. 894).

111. Eckel RH et al. Prevention Conference VII: Obesity, a worldwide epidemic related to heart disease and stroke: executive summary. *Circulation*, 2004, 110:2968–2975.

112. Low S, Chin MC, Deurenberg-Yap M. Review on epidemic of obesity. *Annals of the Academy of Medicine*, 2009, 38:57–59.

113. Case A, Menendez A. Sex differences in obesity rates in poor countries: Evidence from South Africa. *Economics and Human Biology*, 2009, 7:271–282.

114. Klein SL. The effects of hormones on sex differences in infection: from genes to behavior. *Neuroscience and Biobehavioral Reviews*, 2000, 24:627–638.

115. Schuurs AH, Verheul HA. Effects of gender and sex steroids on the immune response. *Journal of Steroid Biochemistry*, 1990, 35:157–172.

116. Roberts CW, Walker W, Alexander J. Sex-associated hormones and immunity to protozoan parasites. *Clinical Microbiology Reviews*, 2001, 14:476–488.

117. Meier A et al. Sex differences in the Toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. *Nature Medicine*, 2009, 15:955–959.

118. Pisitkun P et al. Autoreactive B cell responses to RNA-related antigens due to TLR7 gene duplication. *Science*, 2006, 312:1669–1672.

119. Da Silva JA. Sex hormones, glucocorticoids and autoimmunity: facts and hypotheses. *Annals of the Rheumatic Diseases*, 1995, 54:6–16.

120. Wikby A et al. The immune risk profile is associated with age and gender: findings from three Swedish population studies of individuals 20-100 years of age. *Biogerontology,* 2008, 9:299–308.

121. Villacres MC et al. Predominant type 1 CMV-specific memory T-helper response in humans: evidence for gender differences in cytokine secretion. *Human Immunology*, 2004, 65:476–485.

122. Amadori A et al. Genetic control of the CD4/CD8 T-cell ratio in humans. *Nature Medicine*, 1995, 1:1279–1283.

123. Das BR et al. Reference ranges for lymphocyte subsets in adults from western India: influence of sex, age and method of enumeration. Indian *Journal of Medical Sciences*, 2008, 62:397–406.

124. Bijlsma JW et al. The neuroendocrine immune basis of rheumatic diseases. *Immunology Today*, 1999, 20:298–301.

125. Araneo BA et al. Dihydrotestosterone exerts a depressive influence on the production of interleukin-4 (IL-4), IL-5, and gamma-interferon, but not IL-2 by activated murine T cells. *Blood*, 1991, 78:688–699.

126. Barrat F et al. Sex and parity modulate cytokine production during murine ageing. *Clinical and Experimental Immunology*, 1997, 109:562–568.

127. Butterworth M, McClellan B, Allansmith M. Influence of sex in immunoglobulin levels. *Nature*, 1967, 214:1224–1225.

128. Klein SL, Huber S. Sex differences in susceptibility to viral infection. In: Klein SL, Roberts CW, eds. *Sex hormones and immunity to infection.* Berlin, Springer-Verlag, 2009.

129. Cook IF. Sexual dimorphism of humoral immunity with human vaccines. *Vaccine*, 2008, 26:3551–3555.

130. Guan Y et al. H5N1 influenza: a protean pandemic threat. *Proceedings of the National Academy of Sciences, USA*, 2004, 101:8156–8161.

131. de Jong MD et al. Fatal outcome of human influenza A (H5N1) is associated with high viral load and hypercytokinemia. *Nature Medicine*, 2006, 12:1203–1207.

132. Cook DN et al. Requirement of MIP-1 alpha for an inflammatory response to viral infection. *Science*, 1995, 269:1583–1585.

133. Szretter KJ et al. Role of host cytokine responses in the pathogenesis of avian H5N1 influenza viruses in mice. *Journal of Virology*, 2007, 81:2736–2744.

134. Kobasa D et al. Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. *Nature*, 2007, 445:319–323.

135. Kash JC et al. Genomic analysis of increased host immune and cell death responses induced by 1918 influenza virus. *Nature,* 2006, 443:578–581.

136. Robinson DP, Klein SL. *Female-biased susceptibility to influenza A virus in mice. Paper for the third annual scientific meeting of the Organization for the Study of Sex Differences, 4–6 June 2009*, Toronto ON, Canada.

137. Van Kerkhove MD et al. Frequency and patterns of contact with domestic poultry and potential risk of H5N1 transmission to humans living in rural Cambodia. *Influenza and Other Respiratory Viruses*, 2008, 2:155–163.

138. Rabinowitz P, Perdue M, Mumford E. Contact variables for exposure to avian influenza H5N1 virus at the human-animal interface. *Zoonoses and Public Health*, 2010, 57:227–238.

139. Chen JM et al. *A survey of human cases of H5N1 avian influenza reported by the WHO before June 2006 for infection control. American Journal of Infection Control*, 2007, 35:467–469.

140. Edan D et al. *Review of free-range duck farming system in Northern Vietnam and assessment of their implication in the spreading of the Highly Pathogenic (H5N1) strain of Avian Influenza (HPAI), final report.* Rome, Agronomes et Vétérinaires sans Frontières for the Food and Agriculture Organization of the United Nations, 2006 (http://www.fao.org/docs/eims/upload/213829/agal_duckfarming_vientnam_mar06.pdf, accessed 4 April 2010).

141. Barry JM, Viboud C, Simonsen L. Cross-protection between successive waves of the 1918-1919 influenza pandemic: epidemiological evidence from US Army camps and from Britain. *Journal of Infectious Diseases*, 2008, 198:1427–1434.

142. Brankston G et al. Transmission of influenza A in human beings. *Lancet Infectious Diseases*, 2007, 7:257–265.

143. Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. *Clinical Infectious Diseases*, 2003, 37:1094–1101.

144. Apisarnthanarak A, Mundy LM. Influenza outbreak among health care workers in an avian influenza (H5N1)-endemic setting. *Clinical Infectious Diseases*, 2006, 43:1493–1494.

145. Apisarnthanarak A et al. Outbreaks of influenza A among nonvaccinated healthcare workers: implications for resource-limited settings. *Infection Control and Hospital Epidemiology*, 2008, 29:777–780.

146. Anker R, *Gender and jobs: sex segregation of occupations in the world.* Geneva, International Labour Office, 1998.

147. *Women and health: today's evidence tomorrow's agenda.* Geneva, World Health Organization, 2009.

148. Carrasco-Garrido P et al. Predictive factors of self-medicated drug use among the Spanish adult population. *Pharmacoepidemiology and Drug Safety*, 2008, 17:193–199.

149. Gupta N et al. *Assessing human resources for health: what can be learned from labour force surveys?* Human resources for health, 2003, 1:5.

150. Monto AS. Epidemiology of viral respiratory infections. *American Journal of Medicine*, 2002, 112(Suppl 6A):4S–12S.

151. Monto AS, Sullivan KM. Acute respiratory illness in the community. Frequency of illness and the agents involved. *Epidemiology and Infection*, 1993, 110:145–160.

152. Fung IC, Cairncross S. How often do you wash your hands? A review of studies of hand-washing practices in the community during and after the SARS outbreak in 2003. *International Journal of Environmental Health Research*, 2007, 17:161–183.

153. Sax H et al. Determinants of good adherence to hand hygiene among healthcare workers who have extensive exposure to hand hygiene campaigns. *Infection Control and Hospital Epidemiology*, 2007, 28:1267–1274.

154. Daugherty EL et al. The use of personal protective equipment for control of influenza among critical care clinicians: A survey study. *Critical Care Medicine*, 2009, 37:1210–1216.

155. Briscoe ME. Why do people go to the doctor? Sex differences in the correlates of GP consultation. *Social Science and Medicine*, 1987, 25:507–513.

156. Koopmans GT, Lamers LM. Gender and health care utilization: the role of mental distress and help-seeking propensity. *Social Science and Medicine*, 2007, 64:1216–1230.

157. Puentes-Markides C. *Women and access to health care. Social Science and Medicine*, 1992, 35:619–626.

158. Ahsan G et al. Gender difference in treatment seeking behaviors of tuberculosis cases in rural communities of Bangladesh. *Southeast Asian Journal of Tropical Medicine and Public Health*, 2004, 35:126–135.

159. Ojanuga DN, Gilbert C. Women's access to health care in developing countries. *Social Science and Medicine*, 1992, 35:613–617.

160. Eastwood SV, Hill PC. A gender-focused qualitative study of barriers to accessing tuberculosis treatment in The Gambia, West Africa. *International Journal of Tuberculosis and Lung Disease*, 2004, 8:70–75.

161. Belshe RB et al. Safety, efficacy, and effectiveness of live, attenuated, cold-adapted influenza vaccine in an indicated population aged 5-49 years. *Clinical Infectious Diseases*, 2004, 39:920–927.

162. Hofmann F et al. Influenza vaccination of healthcare workers: a literature review of attitudes and beliefs. *Infection*, 2006, 34:142–147.

163. Mereckiene J et al. National seasonal influenza vaccination survey in Europe, 2008. *Eurosurveillance*, 2008, 13 (http://www.eurosurveillance.org/images/dynamic/EE/V13N43/V13N43.pdf, accessed 11 April 2010).

164. Blank PR, Schwenkglenks M, Szucs TD. Disparities in influenza vaccination coverage rates by target group in five European countries: trends over seven consecutive seasons. *Infection*, 2009, 37:390–400.

165. Centers for Disease Control and Prevention. *Receipt of influenza vaccination*, in *early release of selected estimates based on data from the 2008 National Health Interview Survey*. Atlanta GA, 2009.

166. Endrich MM, Blank PR, Szucs TD. Influenza vaccination uptake and socioeconomic determinants in 11 European countries. *Vaccine*, 2009, 27:4018–4024.

167. Opstelten W et al. Influenza immunization of Dutch general practitioners: vaccination rate and attitudes towards vaccination. *Vaccine*, 2008, 26:5918–5921.

168. Merrill RM, Beard JD. Influenza vaccination in the United States, 2005-2007. *Medical Science Monitor*, 2009, 15:PH92–PH100.

169. Bean-Mayberry B et al. Does sex influence immunization status for influenza and pneumonia in older veterans? *Journal of the American Geriatrics Society*, 2009, 57:1427–1432.

170. Santibanez TA et al. Behavior and beliefs about influenza vaccine among adults aged 50-64 years. *American Journal of Health Behavior*, 2010, 34:77–89.

171. Chor JS et al. Willingness of Hong Kong healthcare workers to accept pre-pandemic influenza vaccination at different WHO alert levels: two questionnaire surveys. *BMJ*, 2009, 339:b3391.

172. Keitel WA et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Archives of Internal Medicine*, 2006, 166:1121–1127.

173. Hui SL et al. Immune response to influenza vaccination in community-dwelling Chinese elderly persons. *Vaccine*, 2006, 24:5371–5380.

174. Edwards KM et al. Eccentric exercise as an adjuvant to influenza vaccination in humans. *Brain, Behavior, and Immunity,* 2007, 21:209–217.

175. Engler RJ et al. Half- vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses. *Archives of Internal Medicine*, 2008, 168:2405–2414.

176. Cook IF et al. Reactogenicity and immunogenicity of an inactivated influenza vaccine administered by intramuscular or subcutaneous injection in elderly adults. *Vaccine*, 2006, 24:2395–23402.

177. Edwards KM et al. Acute stress exposure prior to influenza vaccination enhances antibody response in women. *Brain, Behavor, and Immunity*, 2006, 20:159–168.

178. Couch RB et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine*, 2007, 25:7656–7663.

179. Jackson LA et al. Safety and immunogenicity of varying dosages of trivalent inactivated influenza vaccine administered by needle-free jet injectors. *Vaccine*, 2001, 19:4703-9.

180. Greenberg ME et al. Response after one dose of a monovalent influenza A (H1N1) 2009 vaccine-preliminary report. *New England Journal of Medicine*, September 2009 (10.1056/NEJMoa907413).

181. Clark TW et al. Trial of Influenza A (H1N1) 2009 Monovalent MF59-adjuvanted vaccine-preliminary report. *New England Journal of Medicine*, September 2009 (10.1056/NEJMoa907650).

182. Klein SL, Greenberger P. Do women need such big flu shots? *New York Times,* October 28, 2009.

183. Beyer WE et al. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. *European Journal of Clinical Microbiology and Infectious Diseases*, 1996, 15:65–70.

184. Nichol K, et al. Side effects associated with influenza vaccination in healthy working adults. A randomized, placebo-controlled trial. *Archives of Internal Medicine*, 1996, 156:1546–1550.

185. Cook IF. Sex differences in injection site reactions with human vaccines. *Human Vaccines*, 2009, 5:441–449.

186. Robb H et al. Side effects from influenza vaccination: differences between returned and random surveys. *Military Medicine*, 1996, 161:29–32.

187. Honkanen PO, Keistinen T, Kivela SL. Reactions following administration of influenza vaccine alone or with pneumococcal vaccine to the elderly. *Archives of Internal Medicine*, 1996, 156:205–208.

188. Donalisio MR, Ramalheira RM, Cordeiro R. Eventos Adversos após vacinação contra influenza em idosos, Distrito de Campinas, SP, 2000Adverse reactions to influenza vaccine in the elderly, Campinas District, SP, 2000. *Revista da Sociedade Brasileira de Medicina Tropical*, 2003, 36:467–471.

189. Pittman PR. Aluminum-containing vaccine associated adverse events: role of route of administration and gender. *Vaccine*, 2002, 20(Suppl. 3):S48-50.

190. Dharan NJ et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA*, 2009, 301:1034–1041.

191. Wu J et al. Immunogenicity, safety, and cross-reactivity of an inactivated, adjuvanted, prototype pandemic influenza (H5N1) vaccine: a phase II, double-blind, randomized trial. *Clinical Infectious Diseases*, 2009, 48:1087–1095.

192. Kwong JC et al. The effect of universal influenza immunization on mortality and health care use. *PLoS Medicine*, 2008, 5:e211.

193. Casscells SW et al. The association between oseltamivir use and adverse neuropsychiatric outcomes among TRICARE beneficiaries, ages 1 through 21 years diagnosed with influenza. *International Journal of Adolescent Medicine and Health*, 2009, 21:79–89.

194. Linder JA, Bates DW, Platt R. Antivirals and antibiotics for influenza in the United States, 1995–2002. *Pharmacoepidemiology and Drug Safety*, 2005, 14:531–536.

195. Leon K et al. Disparities in Influenza Treatment Among Disabled Medicaid Patients in Georgia. *American Journal of Public Health*, 2009.

196. Belmaker I et al. Adherence with oseltamivir chemoprophylaxis among workers exposed to poultry during avian influenza outbreaks in southern Israel. *International Journal of Infectious Diseases*, 2009, 13:261–265.

197. Bettis R et al. Impact of influenza treatment with oseltamivir on health, sleep and daily activities of otherwise healthy adults and adolescents. *Clinical Drug Investigation*, 2006, 26:329–340.

198. Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? *Vaccine*, 2009, 27:4754–4770.

199. Rasmussen SA, Jamieson DJ, Bresee JS. Pandemic influenza and pregnant women. *Emerging Infectious Diseases*, 2008, 14:95–100.

200. Rasmussen SA et al. Pandemic influenza and pregnant women: summary of a meeting of experts. *American Journal of Public Health*, 2009.

201. Jamieson DJ et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet*, 2009, 374:451–458.

202. Szekeres-Bartho J et al. The immunological pregnancy protective effect of progesterone is manifested via controlling cytokine production. *American Journal of Reproductive Immunology*, 1996, 35:348–351.

203. Gaunt G, Ramin K. Immunological tolerance of the human fetus. *American Journal of Perinatology*, 2001, 18:299–312.

204. Szekeres-Bartho J. Immunological relationship between the mother and the fetus. *International Reviews of Immunology*, 2002, 21:471–495.

205. McGregor JA et al. Transplacental passage of influenza A/Bangkok (H3N2) mimicking amniotic fluid infection syndrome. *American Journal of Obstetrics and Gynecology*, 1984, 149:856–859.

206. Gu J et al. H5N1 infection of the respiratory tract and beyond: a molecular pathology study. *Lancet*, 2007, 370:1137–1145.

207. Yawn DH et al. Transplacental transfer of influenza virus. *JAMA*, 1971, 216:1022–1023.

208. Hartert TV et al. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. *American Journal of Obstetrics and Gynecology*, 2003, 189:1705–1712.

209. Harris J. Influenza occurring in pregnant women. *JAMA*, 1919, 72:978–980.

210. Irving WL et al. Influenza virus infection in the second and third trimesters of pregnancy: a clinical

and seroepidemiological study. *BJOG*, 2000, 107:1282–1289.

211. Acs N et al. Pregnancy complications and delivery outcomes of pregnant women with influenza. *Journal of Maternal-Fetal and Neonatal Medicine*, 2006, 19:135–140.

212. Acs N et al. Maternal influenza during pregnancy and risk of congenital abnormalities in offspring. *Birth Defects Research and Clinical Molecular Teratology*, 2005, 73:989–996.

213. Eickhoff TC, Sherman IL, Serfling RE. Observations on excess mortality associated with epidemic influenza. *JAMA*, 1961, 176:776–782.

214. Jewett JF. Influenza pneumonia at term. *New England Journal of Medicine*, 1974, 291:256–257.

215. Mullooly JP, Barker WH, Nolan Jr. TF. Risk of acute respiratory disease among pregnant women during influenza A epidemics. *Public Health Reports*, 1986, 101:205–211.

216. Neuzil KM et al. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *American Journal of Epidemiology*, 1998, 148:1094–1102.

217. Schanzer DL, Langley JM, Tam TW. Influenza-attributed hospitalization rates among pregnant women in Canada 1994-2000. *Journal of Obstetrics and Gynaecology Canada*, 2007, 29:622–629.

218. Schanzer DL et al. Influenza-attributable deaths, Canada 1990-1999. *Epidemiology and Infection*, 2007, 135:1109–1116.

219. Bland P. Influenza and its relation to pregnancy and labor. *American Journal of Obstetrics*, 1919, 79:184–197.

220. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. *American Journal of Obstetrics and Gynecology*, 1959, 78:1172–1175.

221. Greenberg M et al. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. *American Journal of Obstetrics and Gynecology*, 1958, 76:897–902.

222. Lim ML et al. Influenza A/H1N1 (2009) infection in pregnancy-an Asian perspective. *BJOG*, 2010.

223. Hewagama S et al. 2009 H1N1 influenza A and pregnancy outcomes in Victoria, Australia. *Clinical Infectious Diseases*, 2010, 50:686–690.

224. Vaillant L et al. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. *Eurosurveillance*, 2009, 14 (http://www.eurosurveillance.org/viewarticle.aspx?articleid=19309, accessed 11 April 2010).

225. Dominguez-Cherit G et al. Critically ill patients with 2009 Influenza A(H1N1) in Mexico. *JAMA*, 2009, 302:1880–1887.

226. Louie JK et al. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *New England Journal of Medicine*, 2010, 362:27–35.

227. Langenegger E et al. Severe acute respiratory infection with influenza A (H1N1) during pregnancy. *South African Medical Journal*, 2009, 99:713–716.

228. Cox S et al. Influenza and pregnant women: hospitalization burden, United States, 1998-2002. *Journal of Women's Health (Larchmont)*, 2006, 15:891–893.

229. Cox S et al. Hospitalizations with respiratory illness among pregnant women during influenza season. *Obstetrics and Gynecology*, 2006, 107:1315–1322.

230. Dodds L et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *Canadian Medical Assocjation Journal*, 2007, 176:463–468.

231. Lindsay L et al. Community influenza activity and risk of acute influenza-like illness episodes among healthy unvaccinated pregnant and postpartum women. *American Journal of Epidemiology*, 2006, 163:838–848.

232. Laibl VR, Sheffield JS. Influenza and pneumonia in pregnancy. *Clinical Perinatology*, 2005, 32:727–738.

233. Gordon CL et al. Association between severe pandemic 2009 influenza A (H1N1) virus infection and immunoglobulin G(2) subclass deficiency. *Clinical Infectious Diseases*, 2010, 50:672–678.

234. Lamar J, Calhoun F, Darr A. Effects of amantadine hydrochloride on cleavage and embryonic development in the rat and rabbit. *Toxicology and Applied Pharmacology*, 1970, 17:272.

235. Vernier VG et al. The toxicologic and pharmacologic properties of amantadine hydrochloride. *Toxicology and Applied Pharmacology*, 1969, 15:642–665.

236. Harper SA et al. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report. Recommendations and Reports*, 2005, 54:1–40.

237. Tanaka T et al. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. *Canadian Medical Association Journal*, 2009, 181:55–58.

238. Ward P et al. Oseltamivir (Tamiflu(R)) and its potential for use in the event of an influenza pandemic. *Journal of Antimicrobial Chemotherapy*, 2005, 55(Suppl. 1):5–21.

239. Freund B et al. Zanamivir: a review of clinical safety. *Drug Safety*, 1999. 21:267–281.

240. Gravenstein S et al. Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Safety*, 2001, 24:1113–1125.

241. Dutkowski R et al. Safety and pharmacology of oseltamivir in clinical use. *Drug Safety*, 2003, 26:787–801.

242. Joyce HY et al. Extracorporeal membrane oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *JAMA*, 2009, 302:1888–1895.

243. *Global Alert and Response (GAR)*. Geneva, World Health Organization, 2010 (http://www.who.int/csr/disease/swineflu/guidance/clincal/en/index.html, accessed 8 April 2010).

244. Australia. Department of Health and Ageing. *The Australian immunisation handbook, 9th ed.* Canberra, 2008.

245. Mak T.K et al. Influenza vaccination in pregnancy: current evidence and selected national policies. *Lancet Infectious Diseases*, 2008, 8:44–52.

246. World Health Organization. Influenza vaccines: WHO position paper. *Weekly Epidemiological Record*, 2005, 80:277–288.

247. World Health Organization. Strategic Advisory Group of Experts on Immunization - report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic, 7 July 2009. *Weekly Epidemiological Record*, 2009, 84:301–304.

248. Ahluwalia I et al. Receipt of influenza vaccine during pregnancy among women with live births--Georgia and Rhode Island, 2004-2007. *Morbidity and Mortallity Weekly Report*, 2009, 58:972–975.

249. Shah SI, Turcotte F, Meng HD. Influenza vaccination rates of expectant parents with neonatal intensive care admission. *Journal of Maternal-Fetal and Neonatal Medicine*, 2008, 21:752–757.

250. Lu P et al. Influenza vaccination of recommended adult populations, U.S., 1989-2005. *Vaccine*, 2008, 26:1786–1793.

251. Yudin MH, Salaripour M, Sgro MD. Pregnant women's knowledge of influenza and the use and safety of the influenza vaccine during pregnancy. *Journal of Obstetrics and Gynaecology Canada*, 2009, 31:120–125.

252. Beigi RH, Switzer GE, Meyn LA. Acceptance of a pandemic avian influenza vaccine in pregnancy. *Journal of Reproductive Medicine*, 2009, 54:341–346.

253. Centers for Disease Control. Influenza vaccination in pregnancy: practices among obstetrician-gynecologists–United States, 2003-04 influenza season. *Morbidity and Mortality Weekly Report*, 2005, 54:1050–1052.

254. Tong A et al. A cross-sectional study of maternity care providers' and women's knowledge, attitudes, and behaviours towards influenza vaccination during pregnancy. *Journal of Obstetrics and Gynaecology Canada*, 2008, 30:404–410.

255. Heinonen OP, Shapiro S, Monson RR. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *International Journal of Epidemiology*, 1973, 2:229–235.

256. Heinonen OP, Slone D, Shapiro S. The Collaborative Perinatal Project. In: Kaufman DW, ed. *Birth defects and drugs in pregnancy*, Boston MA, Littleton Publishing Sciences Group, 1977. pp. 8–14, 314–321.

257. Munoz FM et al. Safety of influenza vaccination during pregnancy. *American Journal of Obstetrics and Gynecology*, 2005, 192:1098–1106.

258. Pool V, Iskander J. Safety of influenza vaccination during pregnancy. *American Journal of Obstetrics and Gynecology*, 2006, 194:1200.

259. Tsai T et al. Exposure to MF59-adjuvanted influenza vaccines during pregnancy--a retrospective analysis. *Vaccine*, 2010, 28:1877–1880.

260. Hulka JF. Effectiveness of polyvalent influenza vaccine in pregnancy: report of a controlled study during an outbreak of Asian influenza. *Obstetrics and Gynaecology,* 1964, 23:830–837.

261. Deinard AS, Ogburn Jr. P. A/NJ/8/76 influenza vaccination program: Effects on maternal health and pregnancy outcome. *American Journal of Obstetrics and Gynecology*, 1981, 140:240–245.

262. Murray DL et al. Antibody response to monovalent A/New Jersey/8/76 influenza vaccine in pregnant women. *Journal of Clinical Microbiology*, 1979, 10:184–187.

263. Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. *Journal of Infectious Diseases*, 1979, 140:141–146.

264. Zaman K et al. Effectiveness of maternal influenza immunization in mothers and infants. *New England Journal of Medicine*, 2008, 359:1555–1564.

265. Gutierrez F et al. The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. *Journal of Infection*, 2006, 53:166–174.

266. Ontario. Ministry of Health. *Ontario Novel H1N1 Influenza A Virus Epidemiological Summary*. Toronto, 2009.

267. Centers for Disease Control. 2009 pandemic influenza A (H1N1) virus infections - Chicago, Illinois, April-July 2009. *Morbidity and Mortality Weekly Report*, 2009, 58:913–918.

268. Kandun IN et al. Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. *Lancet*, 2008, 372:744–749.

269. Liem NT et al. Clinical features of human influenza A (H5N1) infection in Vietnam: 2004-2006. *Clinical Infectious Diseases*, 2009, 48:1639–1646.

270. Yu H et al. Clinical characteristics of 26 human cases of highly pathogenic avian influenza A (H5N1) virus infection in China. *PLoS One*, 2008, 3:e2985.

271. Jimenez-Garcia R et al. Influenza vaccination coverages among children, adults, health care workers and immigrants in Spain: related factors and trends, 2003-2006. *Journal of Infection*, 2008, 57:472–480.

272. Qureshi AM et al. Factors influencing uptake of influenza vaccination among hospital-based health care workers. *Occupational Medicine (London)*, 2004, 54:197–201.

273. Govaert TM et al. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. *British Medical Journal*, 1993, 307:988–990.

274. Socan M et al. Reactions after pneumococcal vaccine alone or in combination with influenza vaccine. *Vaccine*, 2004, 22:3087–3091.

275. Naz H, Cevik F, Aykin N. Influenza vaccination in healthcare workers. *Journal of Infection in Developing Countries*, 2009, 3:50–54.

276. *World Health Statistics 2009*. Geneva, World Health Organization, 2009 (http://www.who.int/whosis/whostat/2009/en/, accessed 6 April 2010).

277. Lavallee RP, Hanvoravongchai P, Gupta N. The use of population census data for gender analysis of the health workforce. In: Dal Poz MR, Quain E, Soucat ALB, eds. *Handbook on monitoring and evaluation of human resources for health*. Geneva, World Health Organization and the United States Agency for International Development, 2009.

278. Hatchett RJ, Mecher CE, Lipsitch M. Public health interventions and epidemic intensity during the 1918 influenza pandemic. *Proceedings of the National Academy of Sciences, USA*, 2007, 104:7582–7587.

279. Andreasen V, Viboud C, Simonsen L. Epidemiologic characterization of the 1918 influenza pandemic summer wave in Copenhagen: implications for pandemic control strategies. *Journal of Infectious Diseases*, 2008, 197:270–278.

280. Louie JK et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA*, 2009, 302:1896–18902.

Whilst sex and gender are known to have an impact on the vulnerability of people to a number of infectious diseases, the impact of sex and gender on exposure, susceptibility and immune responses to acute infections has not yet been explored comprehensively.

This publication, *Sex, gender and influenza*, draws on information from seasonal epidemics, pandemics and localized outbreaks of influenza, and focuses on the different effects of such infections on males and females, including pregnant women. The results suggest that the outcome of infection is generally worse for females, but that the magnitude of this difference varies across geographical regions. Although the increased risk of seasonal and pandemic influenza to pregnant women has been documented, the biological basis of this risk has yet to be defined. Furthermore, while pregnancy is one factor contributing to a worse outcome in women, several additional risk factors may influence male-female differences.

The paper concludes that significantly more research is required to gain a more complete understanding of the complex and varied effects of sex and gender on influenza infection and vaccination, and underscores the need to consider their interplay with any infectious disease of global concern.

ISBN 978 92 4 150011 1

9 789241 500111