This year, the United States Food and Drug Administration (FDA) recommended using lower doses of insomnia drugs in women than men [1]. Drugs containing zolpidem, in particular, remain in circulation longer, take longer to metabolize, and result in a longer duration of impairment of mental alertness in women. The FDA cut the recommended dose of sleep medications that contain zolpidem in half for women [1]. Media outlets extensively reported this story as novel and newsworthy—primarily on the basis that drugs may need to be administered with sex-specific dosage recommendations. This is the very basis of personalized medicine. While personalized medicine has begun to be applied to drugs, more novel has been its application to biologics such as vaccines.

1. History of women in clinical trials

In an effort to protect vulnerable populations from adverse drug and treatment effects, in 1977 the FDA published guidelines advising that women of childbearing potential be excluded from drug development studies [2], which was interpreted to mean that women should be excluded from most clinical trials, including those for vaccines. Over time, this resulted in inadequate representation of women in many clinical trials and in the 1990s both the FDA and the National Institutes of Health (NIH) began recommending that clinical trials include women as subjects [3,4]. Although women are now included in clinical trials for drugs and vaccines, there is still inadequate analysis of outcome data by sex [5]. It is often not considered whether adverse reactions, dosages, or the efficacy of drugs or vaccines are different between the sexes. Yet in an analysis of drugs withdrawn from the US market in 2005, it was reported that 8 out of every 10 drugs were taken off the market because of greater adverse side effects in women [6]. One of us (SLK) has published a comprehensive review demonstrating consistent and strong evidence that both the reactogenicity and immunogenicity of vaccines are higher for females than males [7], How can we translate information about an individual’s sex into personalized vaccinomics [8,9]? One of our laboratories (GAP) has pioneered the concept of vaccinomics and personalized vaccinology whereby understanding host factors impacting the immune response to vaccines can be used to predict immune response, dose, and adverse events; this can be useful in reverse engineering novel vaccine candidates based on such factors [8,9].

2. Responses to vaccines are higher in women

A consistent finding across studies has been that females develop higher antibody immune responses to vaccines than males. After vaccination against influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex (HSV) 2, rabies, smallpox, and dengue viruses, protective antibody responses are often at least twice as high in females than males [10–20]. Measures of cell-mediated immunity following vaccination are also higher in females than males for some vaccines [21,22]. To illustrate the functional significance of these immunological differences between the sexes, consider the failed HSV-2 vaccine clinical trials. Following immunization with a recombinant HSV-2 vaccine, no overall protection from infection was observed in phase 1 or 2 trials [16]. When data were analyzed by sex, the efficacy of the vaccine was 73% in females and only 11% in males, indicating that the vaccine was able to provide protection against development of symptoms associated with genital herpes in women, but not in men. This could be interpreted to mean that the sex of an individual impacts, and may even predict, protective immune responses to vaccines.

On the other hand, females develop more frequent and severe adverse reactions, including fever, pain, and inflammation, to vaccines [7,11,23]. Because information about adverse events is often acquired through passive reporting, it is assumed that this reflects that females might be more likely to report adverse side effects than their male counterparts. Alternatively, inflammatory responses to vaccines might be higher in females and result in increased adverse biological reactions to vaccines in females compared with males. The diameter of inflammation at the site of anthrax vaccination, for example, is significantly greater in females than males [24].

We contend that greater consideration should be given to how sex contributes to heterogeneity in the unintended reactions to biologics, particularly vaccines. For drugs, the increased rate of adverse reactions in females presumably contributes to the fact that females are more likely than males to modify or terminate drug treatments for infectious diseases, including those for HIV [25]. Could the same be true for vaccines? Are women more likely to request modified doses of vaccines? Could increased adverse side effects contribute to the observed reduced acceptance of some vaccines in females compared with males [26,27]?

3. Abandon a ‘one size and dose fits all’ vaccine approach

Research in the 21st century should move past the “one size fits all” public health paradigm to individualized vaccinology and rigorously assess the host factors that result in population-level and inter-individual level variations in vaccine efficacy [8]. We believe that the sex of an individual is an important host biologic variable relevant to the study of vaccine-induced immune
responses, adverse events, number and size of doses, and delivery of vaccines [8]. Understanding the genetic and other mechanisms mediating sex differences in the outcome of vaccination seems critical to advancing the science. Sex-based differences in antibody responses to vaccines are observed prior to puberty, during the reproductive years, and after reproductive senescence [10–20], suggesting that sex hormones are not necessary mediators of sex differences in humoral immune responses to vaccines [7]. Alternatively, genetic differences might underlie sex-based differences in adaptive immune responses to viral vaccines. To date, there are no data identifying the genetic correlates of differential adaptive immune responses to vaccines between the sexes. There also have been no attempts to evaluate whether higher adaptive antibody immune responses to vaccines necessarily lead to greater protection or efficacy in females. This lack of knowledge is a critical barrier preventing optimization of vaccine design, dosage, and usage. We are reaching a tipping point where the public health implications of sex-based differences in responses to vaccines cannot be ignored, as a growing number of studies illustrate the robustness of these sex-based differences across diverse vaccine antigens, dosages, schedules, and age groups.

At the current time, we are in the midst of an early peak in the influenza A/H3N2 season in the US and concerns have been raised about shortages of the seasonal influenza vaccine. Much like the 2009 H1N1 pandemic when fears of vaccine shortages circulated, we could be asking whether females could receive smaller doses of seasonal influenza vaccines and be as equally protected as their male counterparts, while experiencing fewer adverse reactions. Personalizing vaccine administration based on the sex of an individual might be one public health answer for increased acceptance, distribution, and coverage of vaccines worldwide. Other research opportunities and knowledge gaps are also apparent. Might vaccine adjuvants be used differentially based in part on sex? Should vaccine safety surveillance systems be specifically powered to detect differential safety signals between the sexes? Might vaccination doses and schedules be different in males versus females, and possibly based on sex-specific clinical trials? These and other such questions reveal the relative paucity of information on sex-based immune responses to vaccines currently available. As we progress into the second decade of the 21st century, we can no longer ignore sex-based differences in vaccinology, just as we can no longer ignore such differences in the use of drugs. We hope that a much richer research agenda that advances the science in sex-based vaccine research can be accomplished, with the goal of improving vaccine safety, efficacy, and discovery.

References