Improving the Efficacy of Vaccinations for Women, Children, and Men

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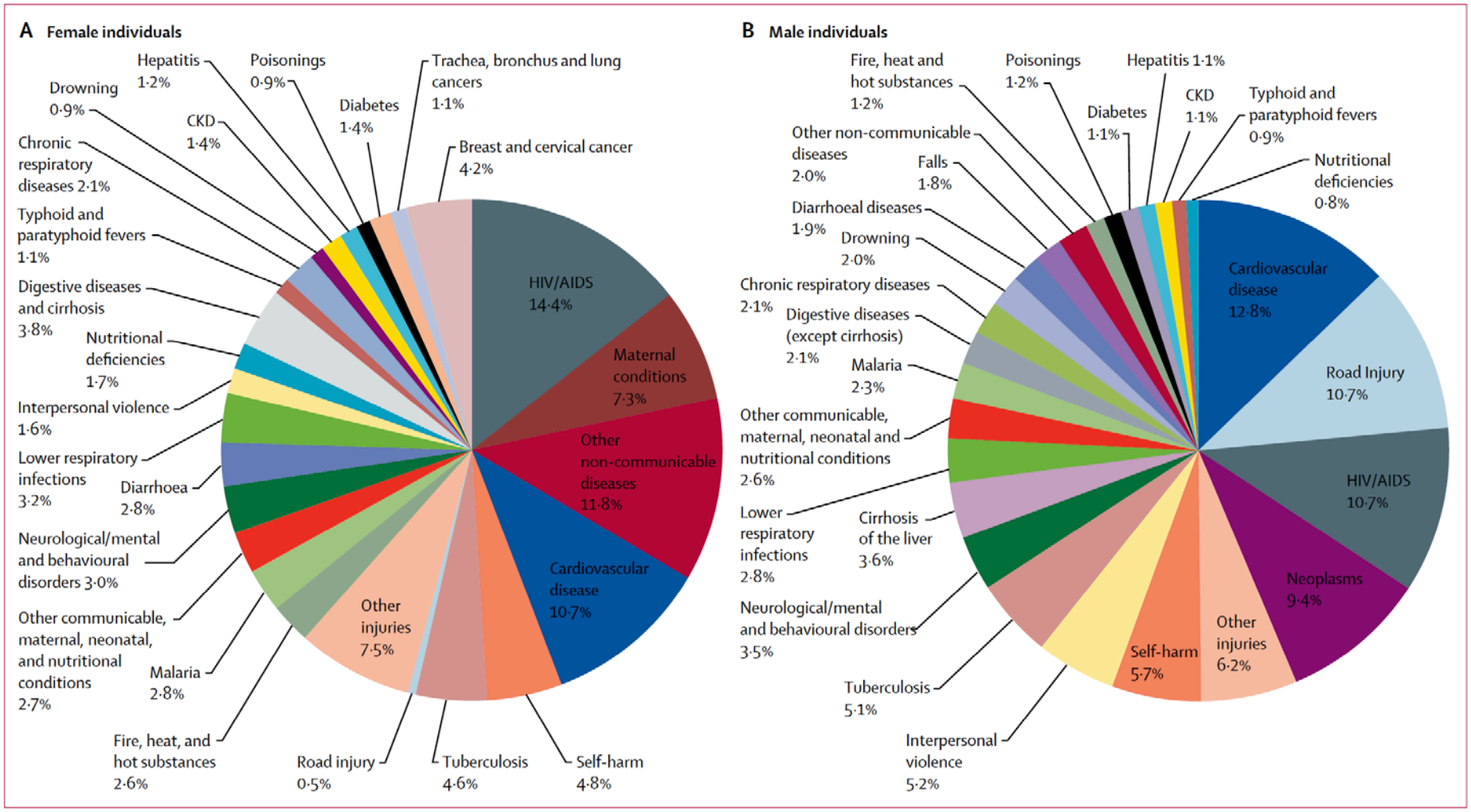
Causes of global deaths differ between males and females (15-49 years)



3,496,480 total deaths

5,741,344 total deaths

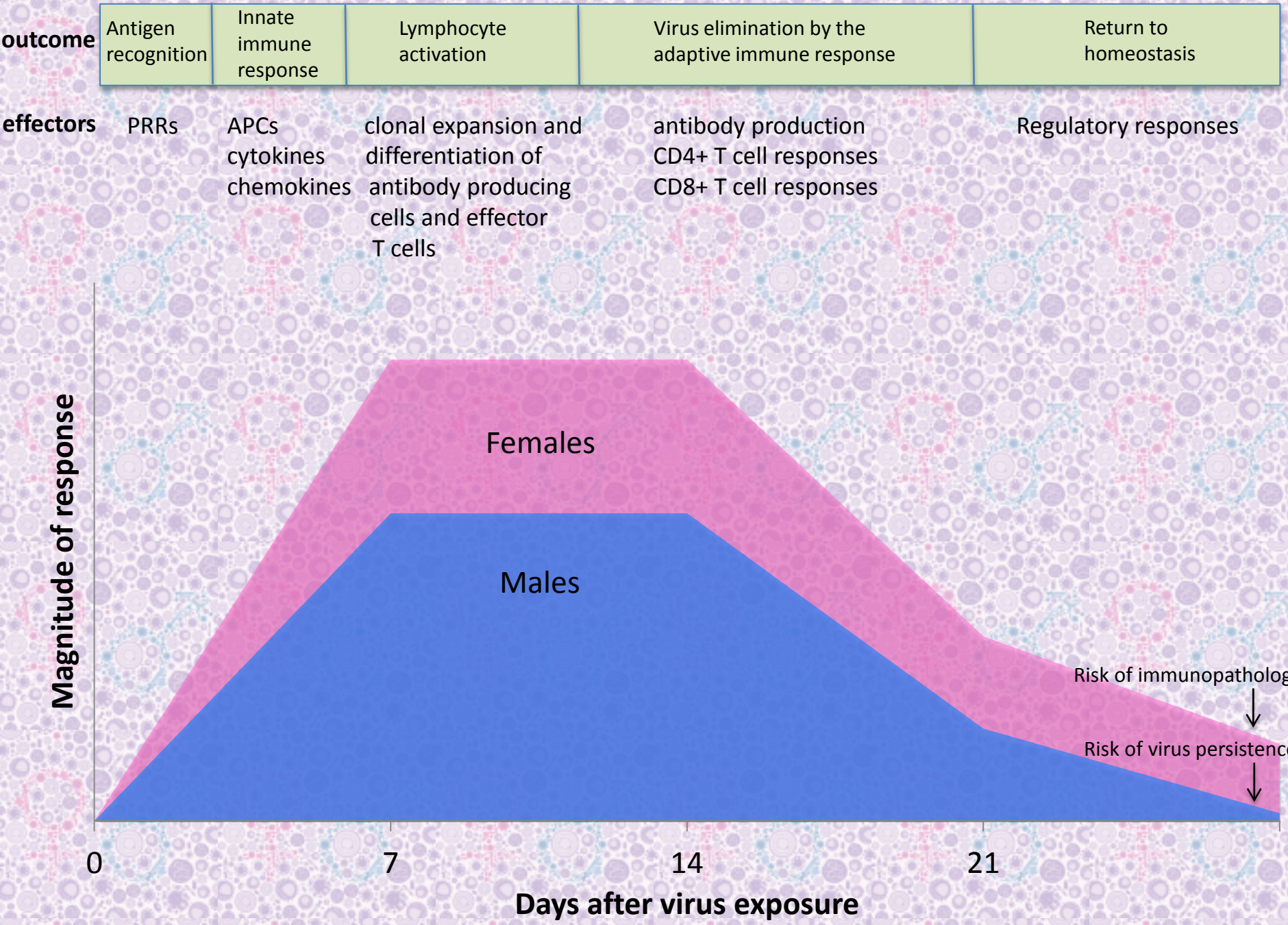
Lozano et al. 2012 *Lancet* 380:2095

The outcome of viral infections differ between males and females

Virus	Dependent measure	Sex-specific difference	Reference
Cytomegalovirus	P	M < F	[14]
Dengue virus	P	M > F	[106]
Epstein Barr virus	D	M > F	[107]
Hantaviruses (multiple species)	P M	M > F M < F	[108]
Hepatitis B virus	I, P, D	M > F	[61, 64, 65, 67]
Hepatitis C virus	P, I	M > F	[70, 71]
Herpes simplex virus type 2	I, P	M < F	[48, 109]
Human immunodeficiency virus (HIV)	I D	M > F M < F	[32, 33, 37]
Human T-cell leukemia virus Type 1	P	M < F	[110]
Influenza A viruses	D, M	M < F	[86, 88, 89]
Measles	M	M < F	[111]
West Nile virus	I	M > F	[112]

Klein 2012 *Bioessays* 34:1050

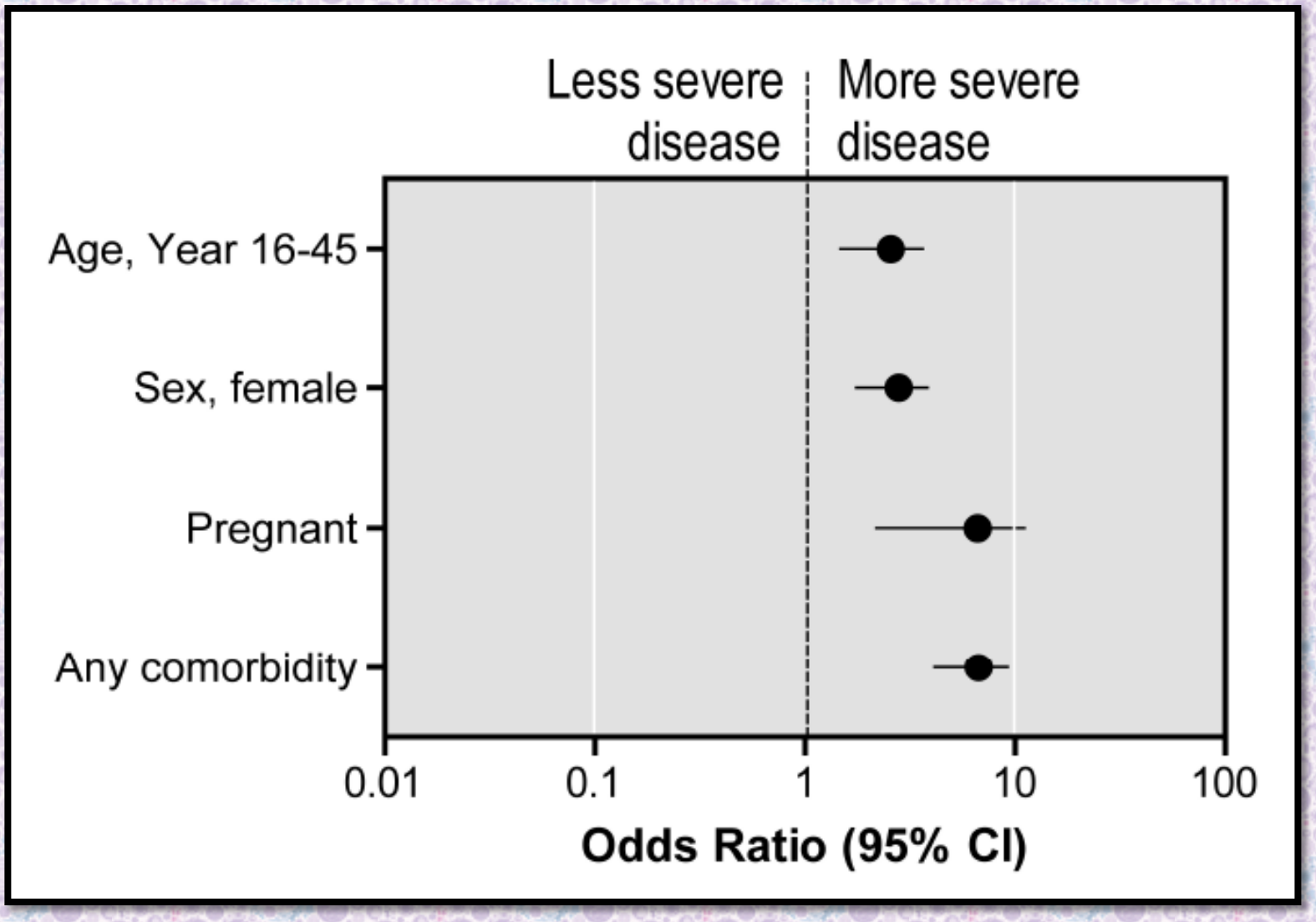
P = prevalence; I = intensity; D = disease; M = mortality



Klein 2012 *Bioessays* doi:10.1002/bies.201200099

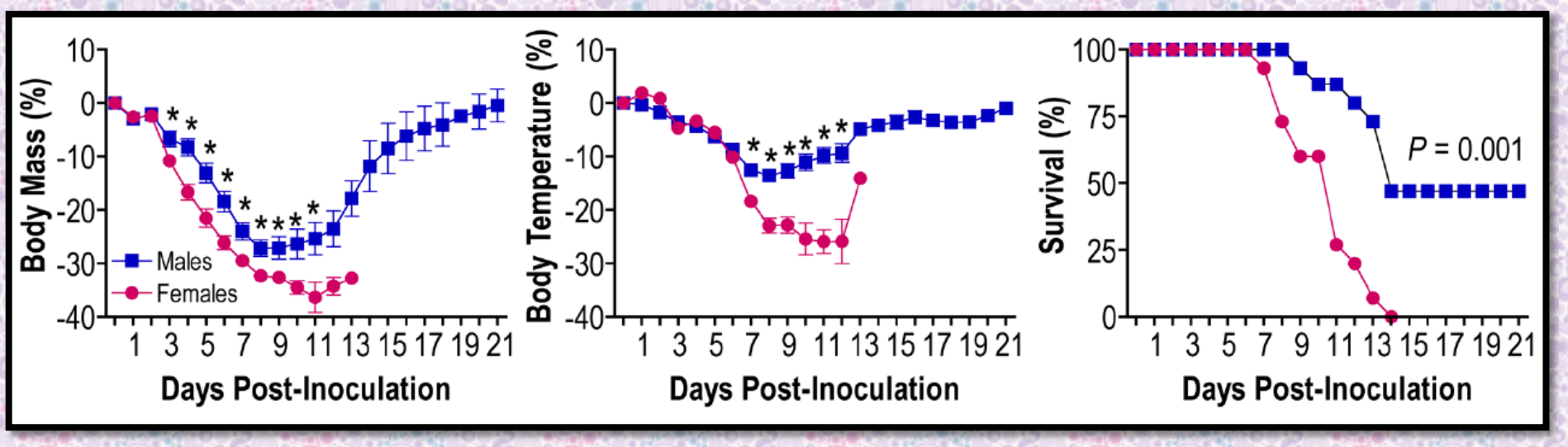
SEX DIFFERENCES IN IMMUNE RESPONSES AND THE OUTCOME OF INFECTION

Correlates of severe 2009 H1N1 disease in young adults



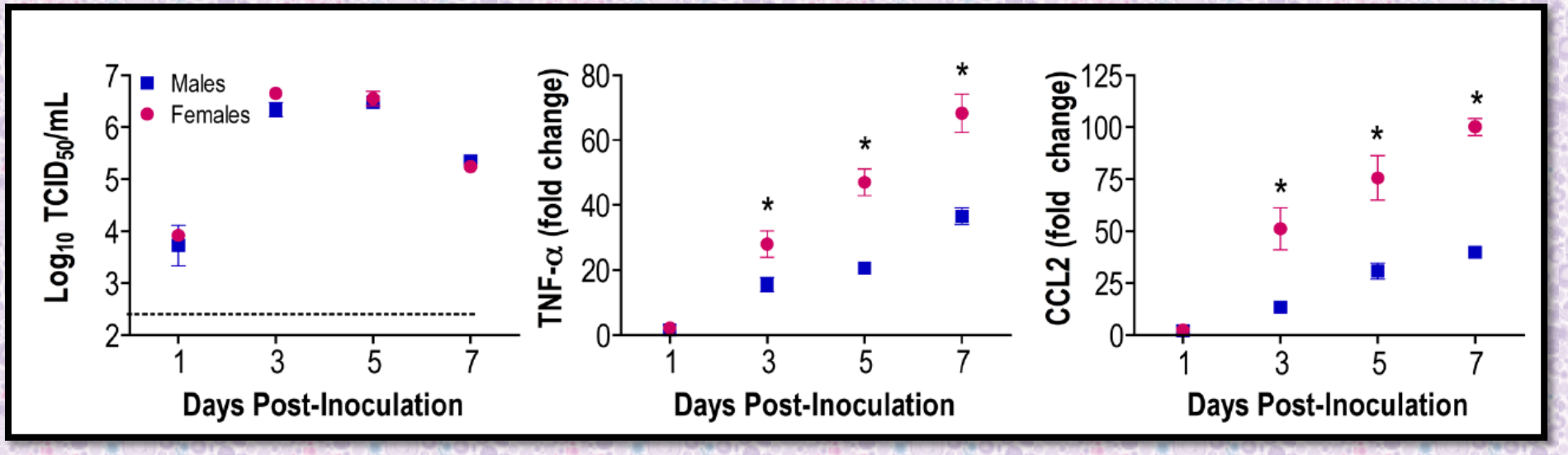
Zarychanski et al. 2010 *CMAJ* 182:257

Morbidity and mortality from influenza A virus infection is greater in females



Robinson, Lorenzo, Jian, & Klein 2011, *PLoS Pathogens*, 7:e1002149

Females have a greater induction of cytokines and chemokines in their lungs than males



Robinson, Lorenzo, Jian, & Klein 2011, *PLoS Pathogens*, 7:e1002149

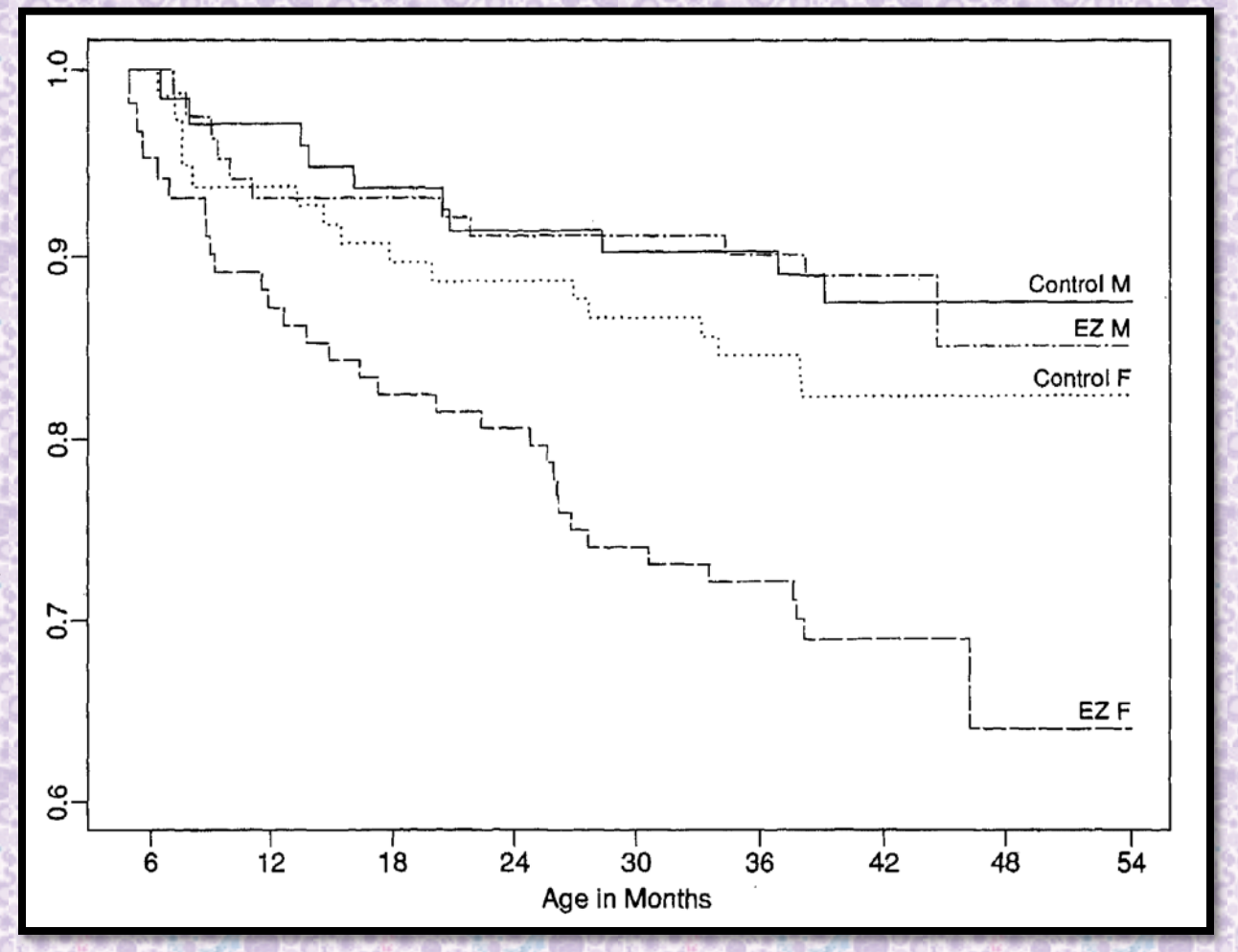
The responses to viral vaccines differ between males and females

Vaccine	Humoral response	Adverse reactions	Age (years)
TIV	F > M	F > M	18-65+
MMR	F >/= M	F > M	< 3
HBV	F > M	?	> 18
HSV-2	F > M	?	> 18
YFV	F > M	F > M	> 18
HPV	F > M	F > M	5-17
HIV	?	F > M	> 18
Rabies	F > M	?	> 18
Smallpox	F > M	?	> 18
Dengue	F > M	?	> 18

Klein et al. 2010 *Lancet ID* 10:338

CHILD MORTALITY FOLLOWING VACCINATION IN DEVELOPING COUNTRIES IS HIGHER AMONG GIRLS

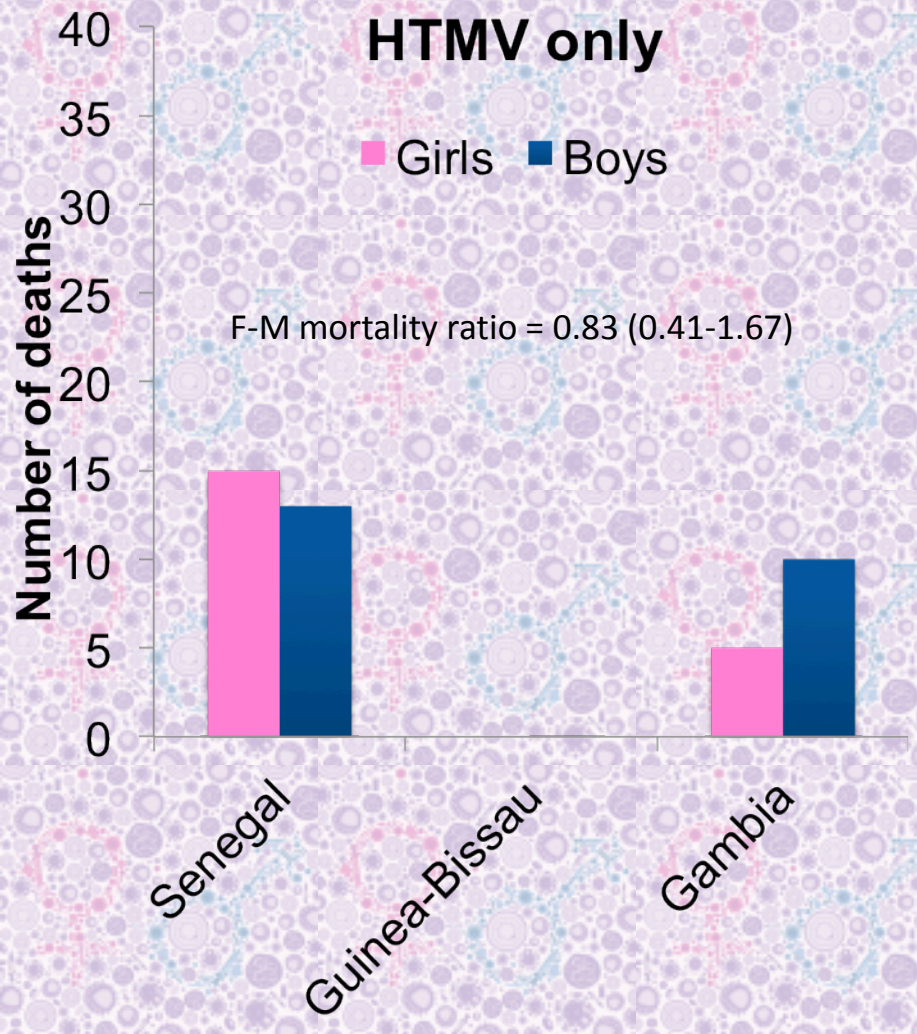
Mortality Following the High-Titer Measles Vaccine was Higher Among Girls, Bissau 1986-1990

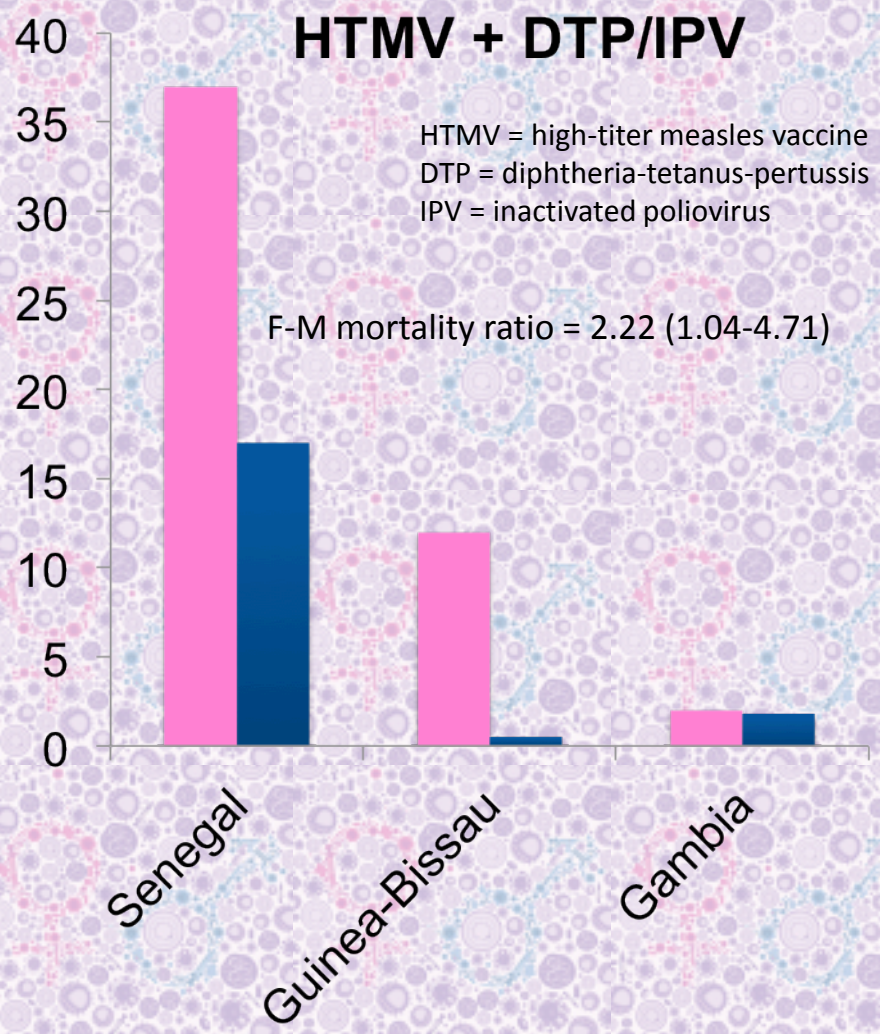


EZ = Edmonston-Zagreb high-titer measles vaccination

Aaby et al. 1993 *J Pediatr* 122:904

Should Vaccine Schedules Differ for Boys and Girls?





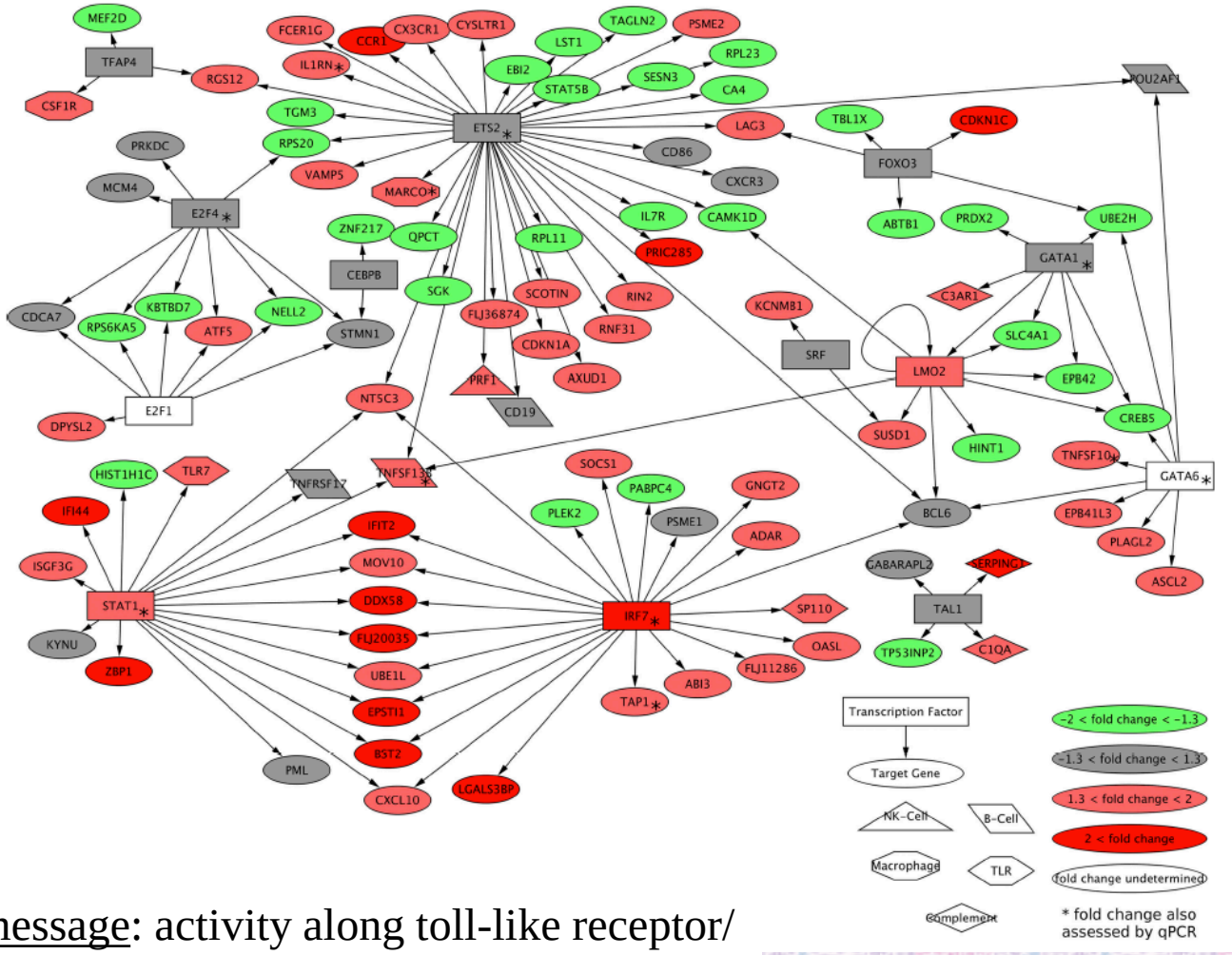
(Aaby et al. 1993 *Lancet* 361:2183)

INFLAMMATORY RESPONSES TO VACCINES ARE HIGHER IN WOMEN

Yellow fever vaccine induces integrated multilineage and polyfunctional immune responses

Published December 1, 2008

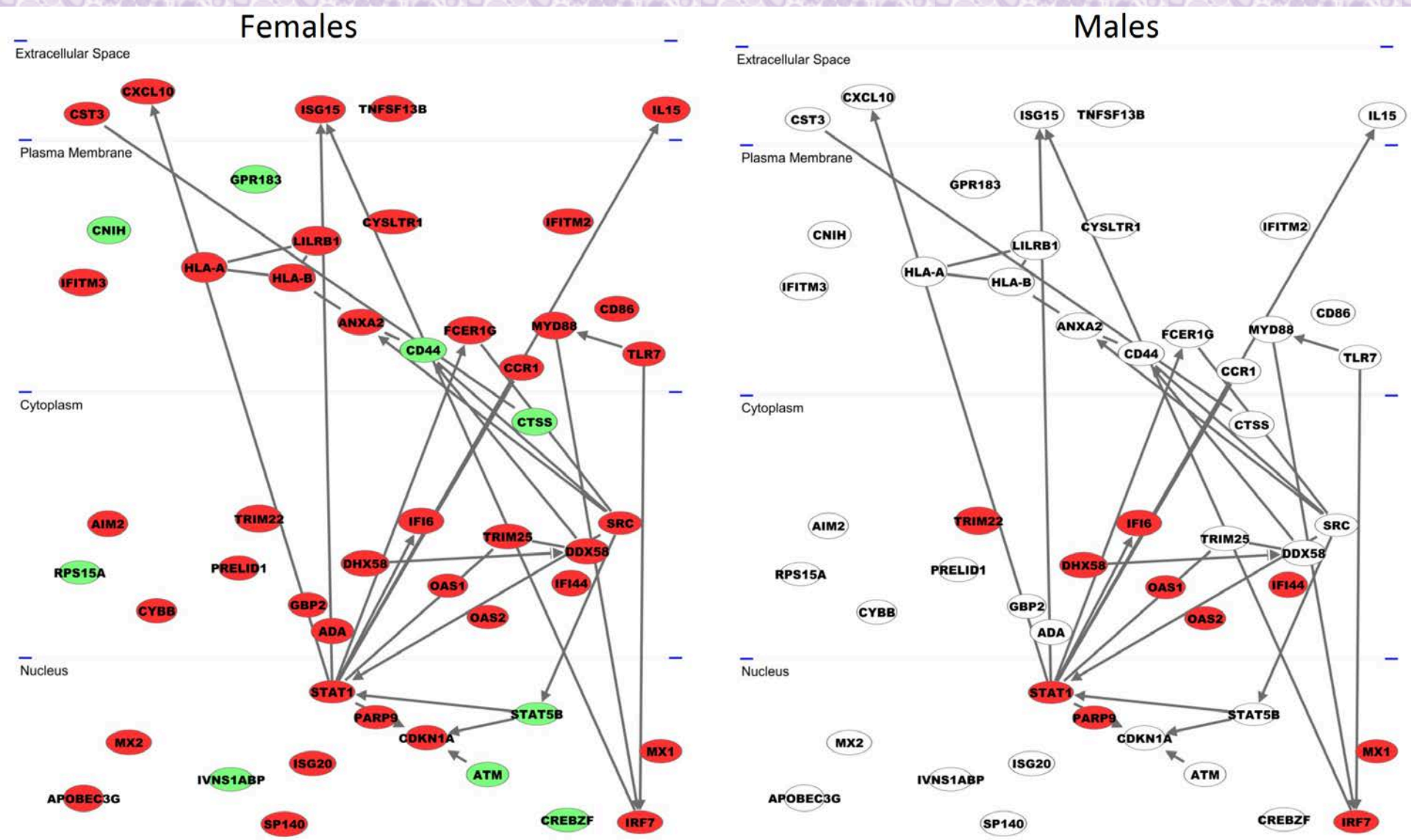
JEM



<u>Take home message</u>: activity along toll-like receptor/ inflammatory pathways predicts long-term protection

Gaucher et al. 2008 *J Exp Med* 205:543

Females develop higher inflammatory responses to the yellow fever vaccine



Klein et al. 2010 *Lancet ID* 10:338

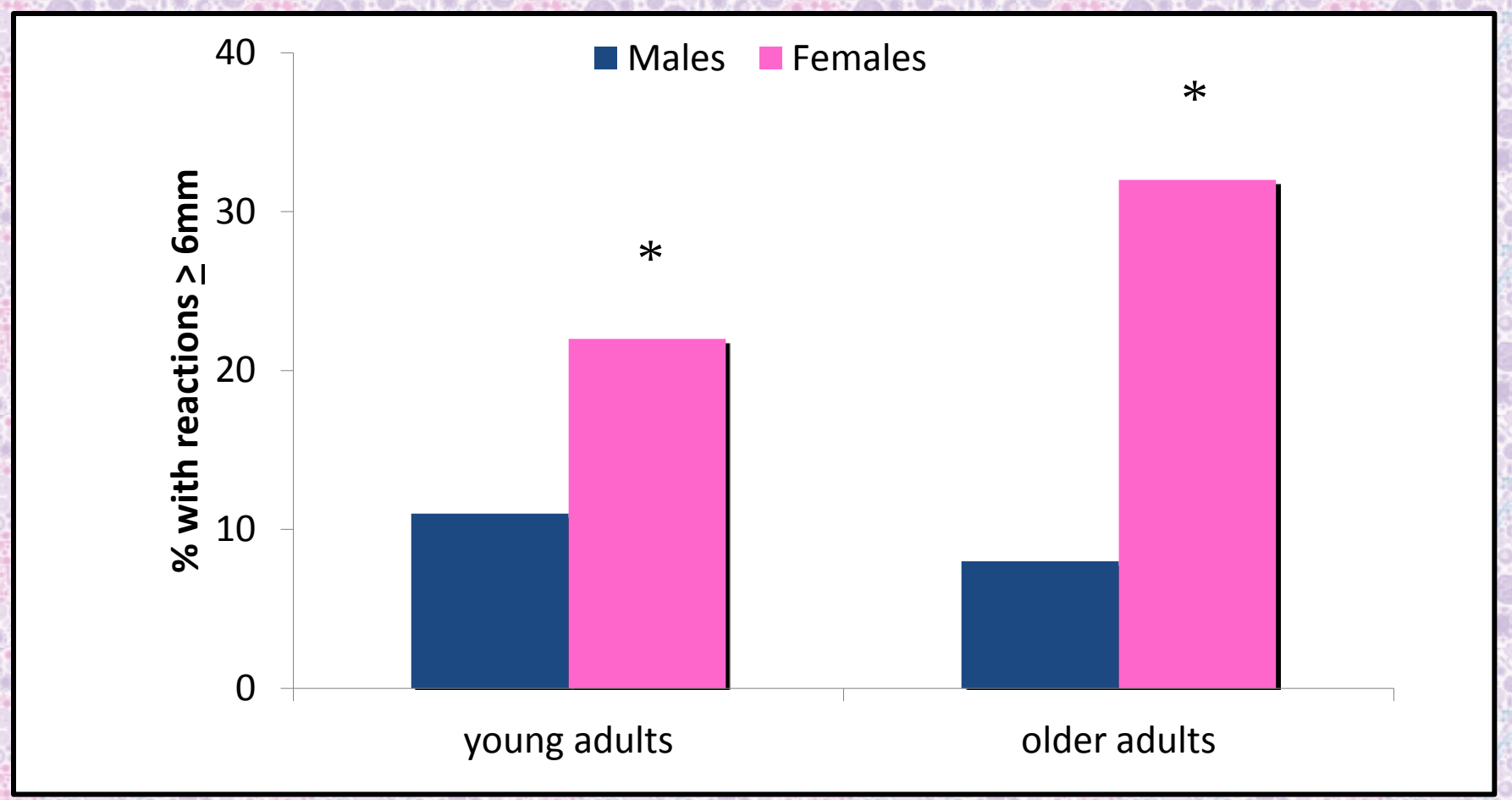
ANTIBODY RESPONSES AND CROSS PROTECTION ARE HIGHER IN WOMEN FOLLOWING VACCINATION

Current Influenza Vaccines

- **Trivalent inactivated vaccine (TIV):** Killed virus vaccine, given as an intramuscular injection, and typically recommended for children 6 months to 2 years of age and older adult over 65 years of age.
- **High dose TIV:** recommended for older adults over 65 years of age.
- **Live attenuated influenza vaccine (LAIV):** contains weakened live virus that is administered into the nostrils and induces greater immunity than TIV to influenza.

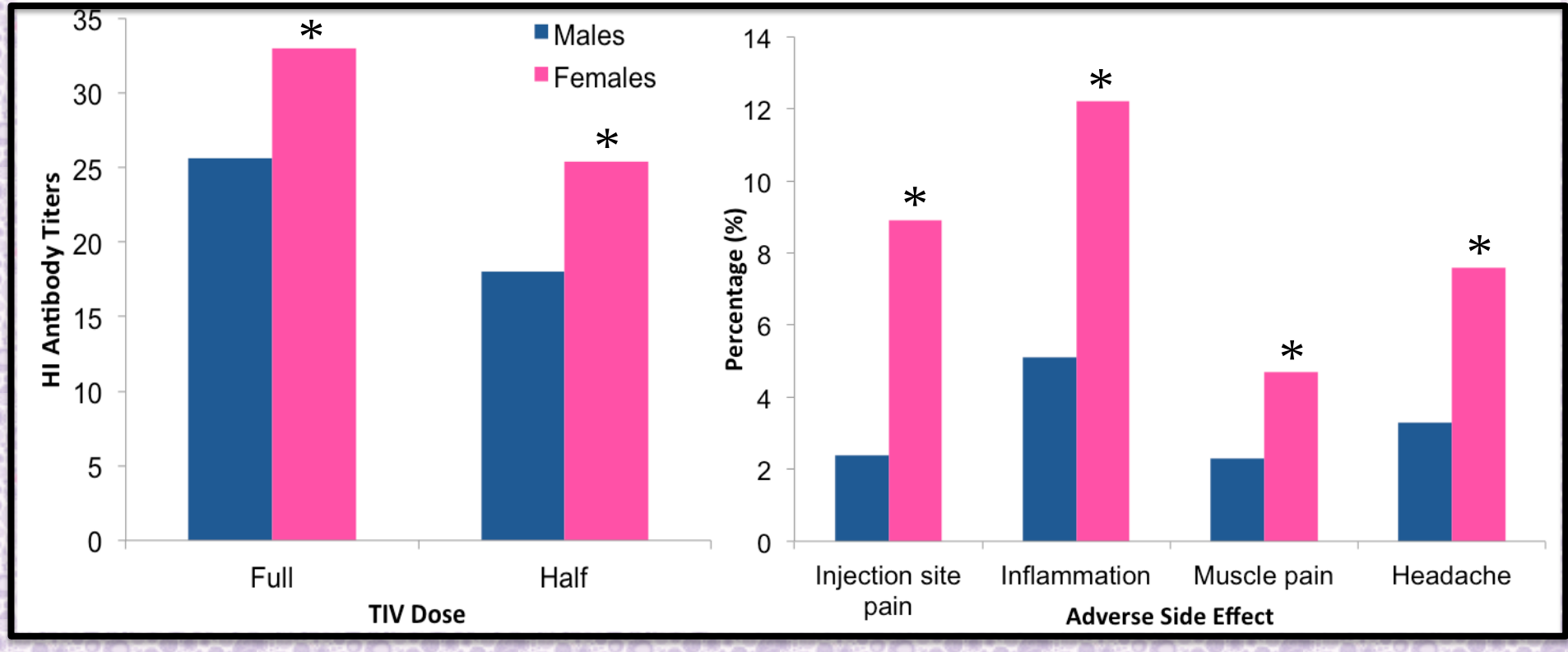
Reference: Centers for Disease Control and Prevention. Seasonal influenza. http://www.cdc.gov/flu/about/qa/disease.htm.

Local Erythema/Induration following TIV is Greater in Females



Cate et al. 1983 Rev Infect Dis 5:737

Sex differences in response to the seasonal influenza vaccine



(Engler et al. 2008 *Arch Intern Med* 168:2405)

Sex differences in response to TIV among older adults

- Women > 65 also develop higher antibody responses to high-dose and standard-dose TIV in Phase I and III clinical trials;
- Women > 65 report two times more side effects than males to the standard dose TIV;
- Women > 65 also are significantly more likely to report adverse events (e.g., myalgias and pain) following TIV.

References: Engler RJM et al. Arch Intern Med 2008; 168(22):2405-2414; Falsey AR, et al. *J Infect Dis.* 2009;200(2):172-180; Keitel W, et al. *Arch Intern Med.* 2006;166(10):1121-1127

The New York Times

October 28, 2009

OP-ED CONTRIBUTORS

Do Women Need Such Big Flu Shots?

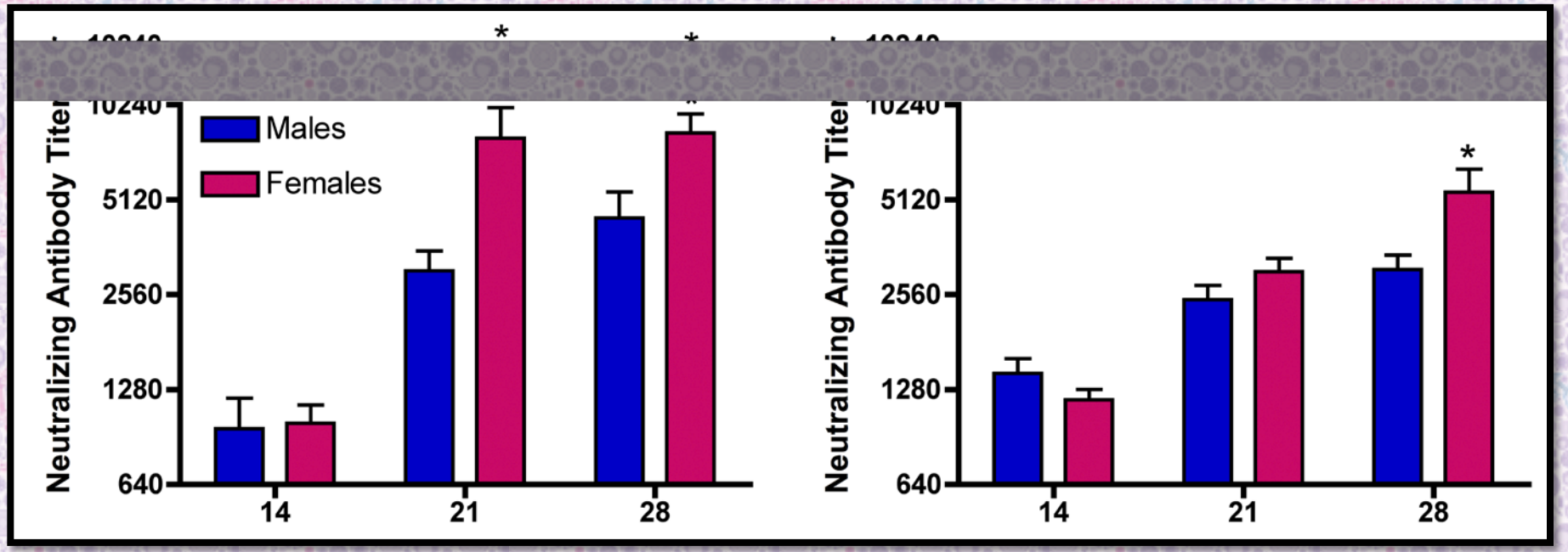
By SABRA L. KLEIN and PHYLLIS GREENBERGER

THE emergence of the H1N1 swine flu has added urgency to what has become an annual ritual for millions of Americans: getting a flu shot. The good news is that scientists have developed a vaccine against the H1N1 virus. But it is taking much longer than expected to produce the hundreds of millions of doses the government had planned to distribute. And it is still too soon to know how effective the vaccine will be in preventing swine flu.

In all likelihood, we'd have a better H1N1 vaccine — and more of it — if in our preparations we had accounted for the biological differences between men and women.

Females have higher neutralizing antibody titers against influenza A viruses

H1N1 (PR8) **H3N2 (HK68)**



Lorenzo et al. 2011 *Vaccine* 29:9246

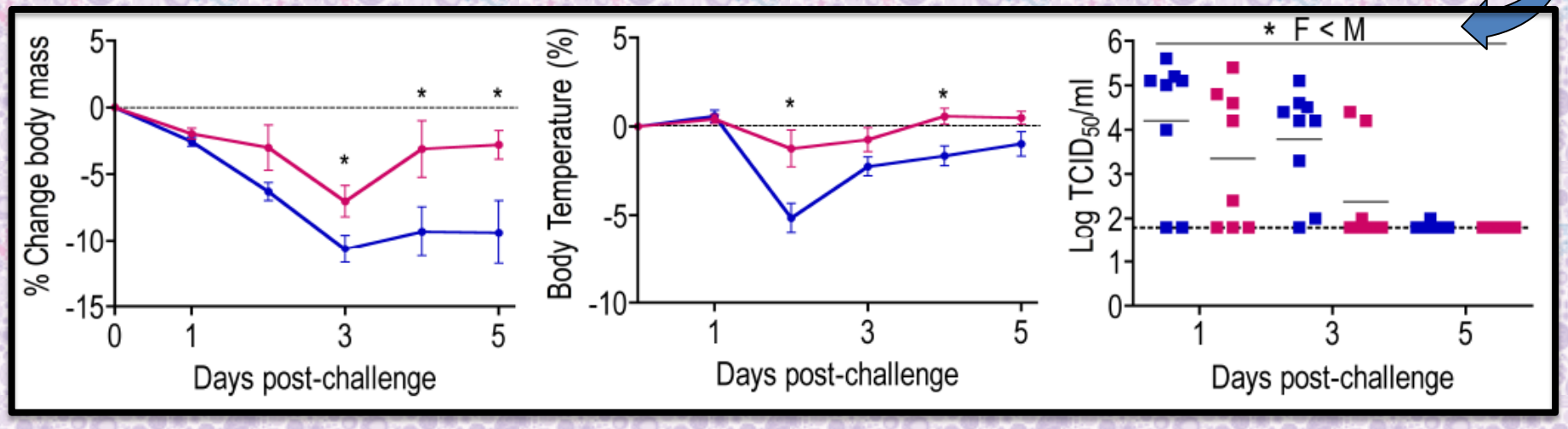
Females are better protected against lethal influenza challenge

Immunize with sublethal H3N2 (day 0)

Measure antibody (day 14-28)

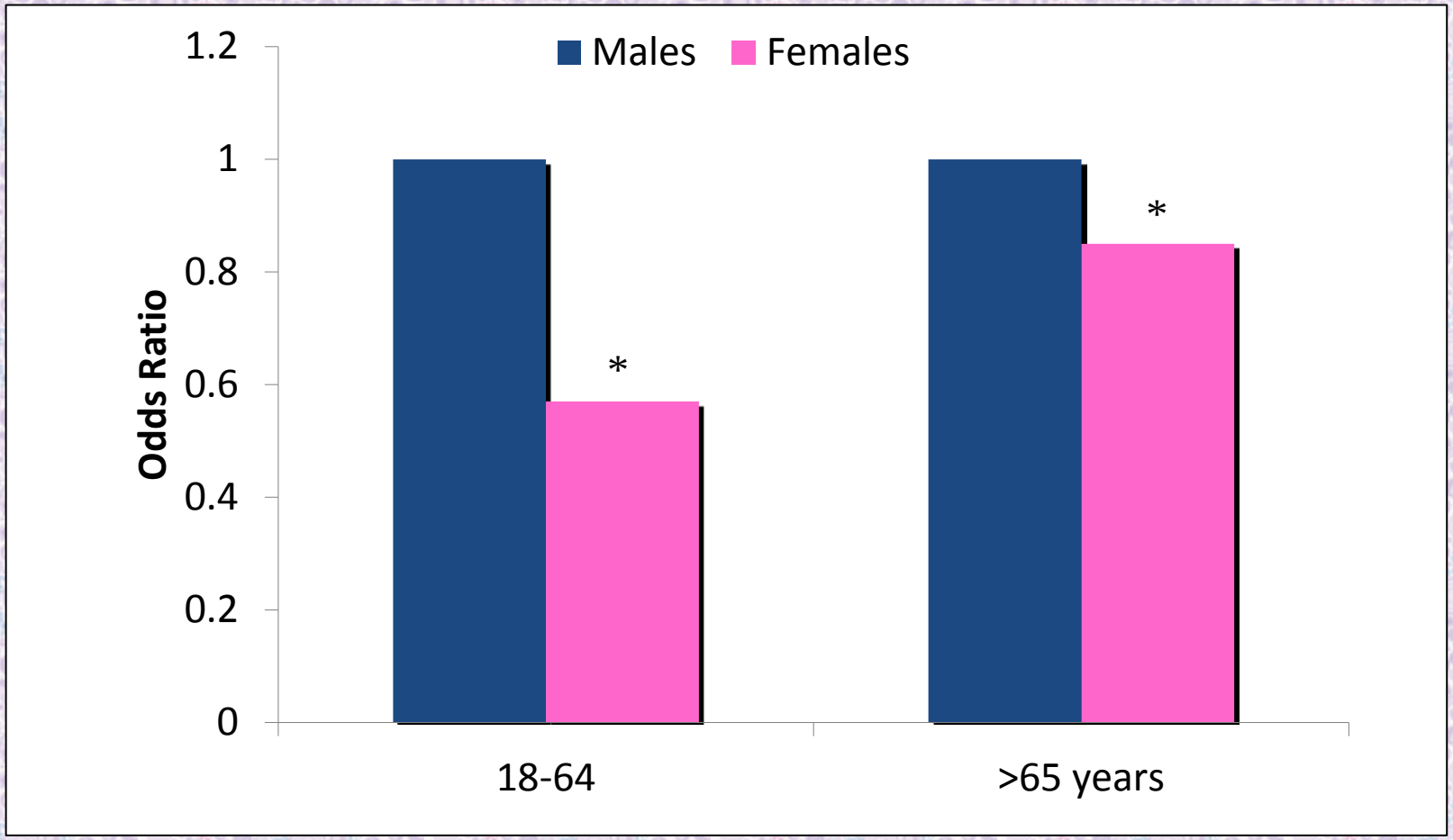
Infect with lethal H1N1 (day 49)

Measure morbidity and virus titers (day 49-56)



Lorenzo et al. 2011 *Vaccine* 29:9246

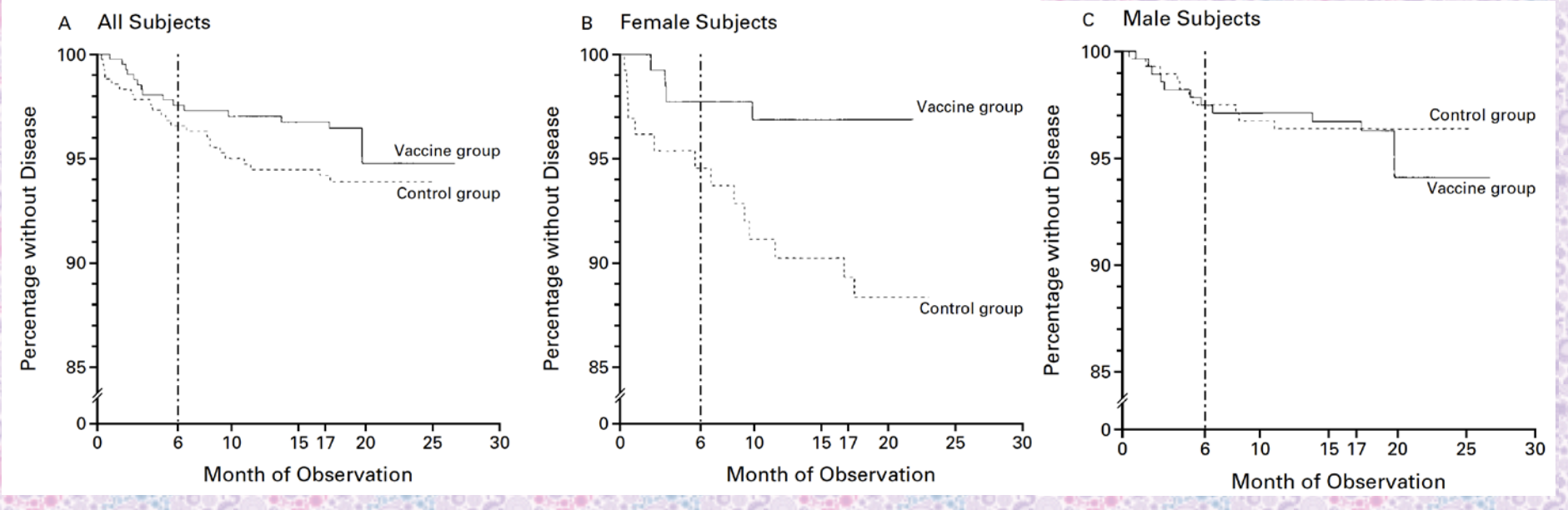
Women are less likely to accept influenza vaccines



Schwarzing M, et al. *PLoS One* 2010; 5(4): e10199;
Bean-Mayberry, B, et al. *J Am Geriatr Soc* 2009; 57:1427

VACCINE EFFICACY IS HIGHER IN WOMEN

Glycoprotein D-Adjuvant Vaccine Prevents Genital Herpes in Women, but not Men



Phase III trials showed no overall efficacy, but noted substantial differences in the efficacy between women and men.

(Stanberry et al. 2002 *N Engl J Med* 347:1652)

How to overcome sex-based differences in subunit HSV vaccines

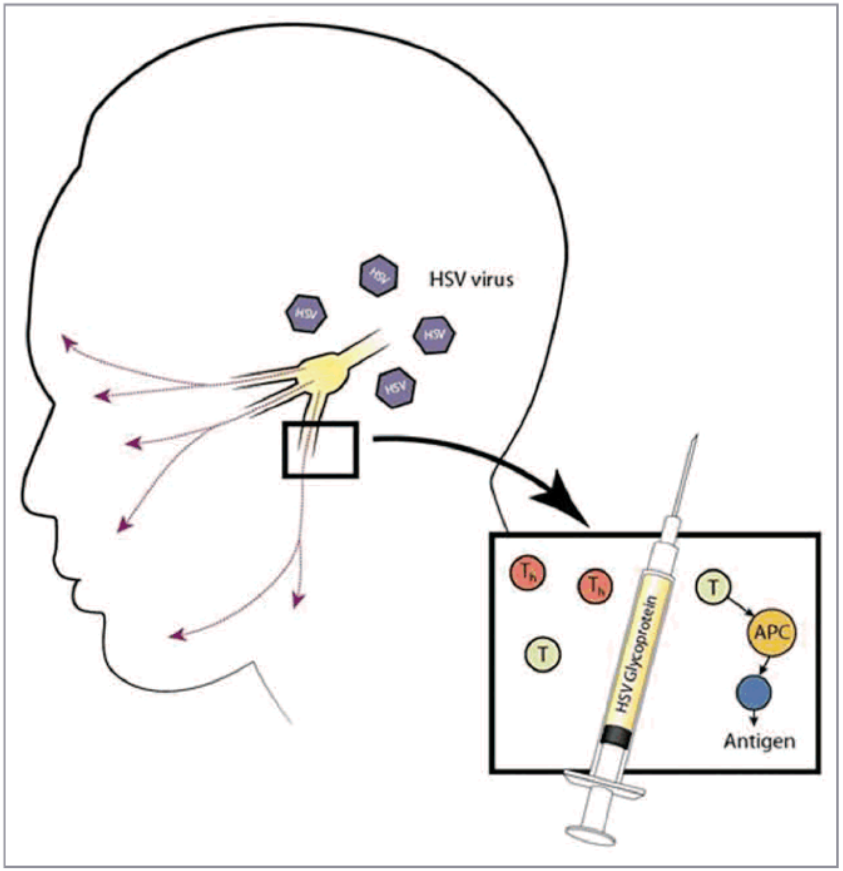
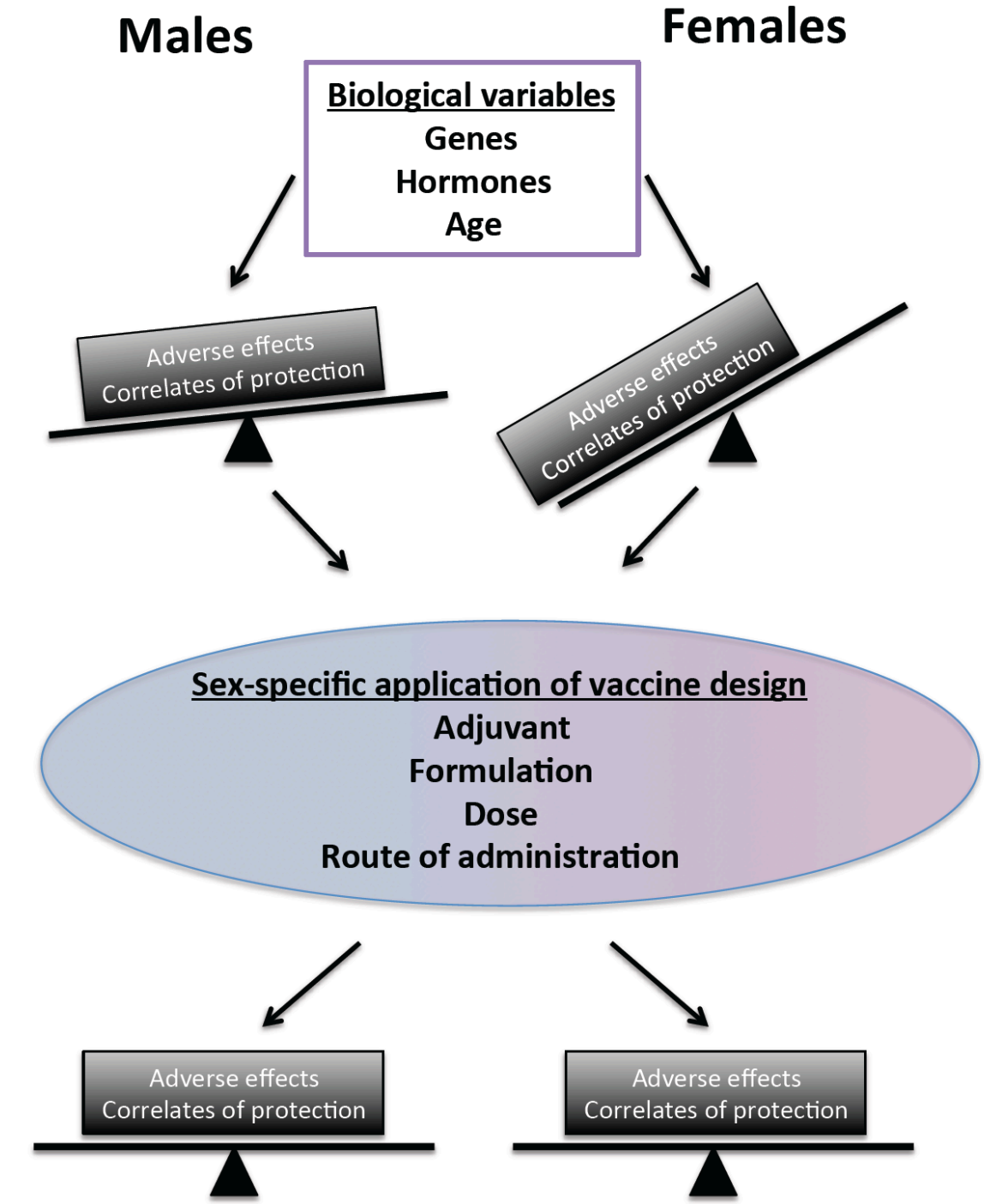


Figure 1. Subunit vaccine. This illustration shows a glycoprotein subunit vaccine administered through a syringe into the oro-facial pathway inducing an accessory cell to elicit a T cell response. The antigen presentation will cause these cells to become either CD4+ cells or CD8+ cells. These will then act against HSV, which has established latency in the trigeminal or cervical ganglia.

- Focus on viral immune evasion strategies
- Neutralizing antibody, complement, and T-cell responses
- HSV seropositive women have more T cells and stronger IFN-γproduction by T cells to gD peptides

Coleman & Shukla 2013 Hum Vaccin Immunother 9:1

Sex-specific rational design of vaccines



Klein & Pekosz JID in press