Homework due at the start of class on July 1

Read "A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants" (*New England Journal of Medicine* **367**: 2284-95, 2012; PubMed ID 23136909) and do the assignment below, consulting any additional sources as needed. You may be able to access the full text of the article by going to http://pubmed.gov, doing a search for the PubMed ID, and following a link from the article's abstract page to the publisher's website. Alternatively, you can access the article online from the E-Journals section of the UW Libraries website (http://www.lib.washington.edu/types/ejournals/), as follows:

- If you are working off-campus, log in by clicking on the box at the upper right of the web page.
- Under "Find e-journals by title," select N.
- Among the listings of journals beginning with the letter N, find *New England Journal of Medicine*. Follow the link to the publisher's website, then find the article in the journal's archives by using the citation information (title, author, volume, page numbers, and year) listed above.

General background

With this article we begin a two-part series addressing the question of "Why do we need new malaria drugs?" The simplistic answer is (1) malaria vaccines are not very effective (the topic of today's paper) and (2) the *Plasmodium* parasite is good at evolving resistance to current drugs (the topic of the following paper).

The assigned article presents a bit of a challenge because it concerns a clinical trial of a vaccine, but we have not yet covered any basic immunology, nor have we learned anything about the malaria parasite! Therefore this homework will help you acquire relevant background information, whereas we will focus mostly on the article itself during class time.

To start with, let's note that the malaria parasites belong to genus *Plasmodium* (which is a member of phylum Apicomplexa, which also includes the protists that cause toxoplasmosis, cryptosporidiosis, and babesiosis). The species causing most severe cases of malaria in humans is *Plasmodium falciparum*; other species that can infect humans and other primates include *P. vivax*, *P. ovale*, *P. malariae*, *P. cynomolgi*, *P. knowlesi*, and others. For research purposes, the rodent-infecting species *P. berghei*, *P. chabaudi*, and *P. yoelii* are also of significant interest.

Worksheet to hand in

1. name, date, and assigned article

Greg Crowther, June 30, PubMed ID 23136909

2. In general, how do vaccines work? Consult any reliable online source or textbook. (2-3 sentences)

Vaccines consist of some sort of pathogen antigens (e.g., bacterial surface proteins) against which the body will make antibodies, which serve to neutralize the pathogens. Wikipedia: "Antibodies contribute to immunity in three ways: they prevent pathogens from entering or damaging cells by binding to them; they stimulate removal of pathogens by macrophages and other cells by coating the pathogen; and they trigger destruction of pathogens by stimulating other immune responses such as the complement pathway."

3. In the context of vaccines, what is an adjuvant? Consult any reliable online source or textbook. (1-2 sentences)

An adjuvant enhances the immune system's response to an antigen, so that less antigen needs to be provided in a vaccine and a given supply of a vaccine can cover more people.

4. Make a simple diagram of the life cycle of *Plasmodium falciparum*, covering both the human and mosquito stages. (You can follow an existing diagram from another source, but don't just download and paste the image! And remember to cite your source.)

Representations may vary, of course.

In humans: …sporozoites from mosquito saliva go through skin and invade liver cells => invasion of red blood cells => cycle of multiplication inside and destruction of red blood cells => some parasites peel off into gametocyte differentiation

In mosquitos: uptake of gametocytes from blood => gamete formation in gut; fertilization and creation of ookinetes; exit from the gut and formation of oocysts, which divide into sporozoites => sporozoites colonize the salivary glands => mosquito bites human….

5. What is the circumsporozoite protein (CSP)? Consult any reliable online source or textbook. (1-2 sentences)

CSP is a ~400-amino-acid-long protein that is abundant on the surface of sporozoites in the mosquito salivery glands and in the liver.

6. What is the RTS,S/AS01 vaccine? Consult "Development of the RTS,S/AS malaria candidate vaccine" (PubMed ID 20006143) by J. Vekemans et al. (2 sentences)

RTS,S/AS01 is a malaria vaccine containing a large portion of the CSP (amino acids 207-395), plus a proprietary antigen known as AS01. It represents at least the 2nd-generation of CSP-based vaccines; earlier versions, which included a much smaller piece of CSP, were ineffective.

7. In brief, nontechnical terms, what does Cox regression allow you to do with the data? Consult "Statistical methodology for the evaluation of vaccine efficacy in a phase III multi-centre trial of the RTS, S/AS01 malaria vaccine in African children" (PubMed ID 21816030) by M. Lievens et al. (1-2 sentences)

Cox regression seems to let you correct for different levels of infection risk at different study sites and during different seasons. The Cox proportional hazards method allows you to determine whether a vaccine's effect is constant or changing over time following administration of it.