

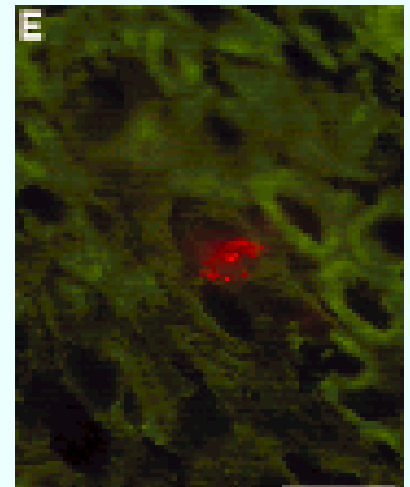
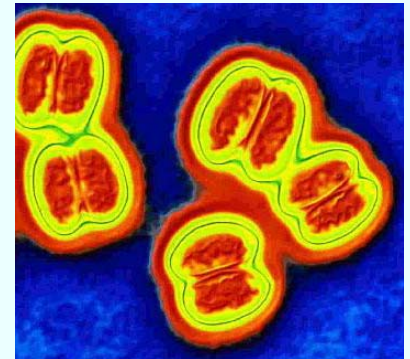
Mechanisms of mucosal immunity to systemic immunisation with a meningococcal serogroup B outer membrane vesicle vaccine

Neil A. Williams, Rob Heyderman, Sarah Glennie

Funded by Meningitis UK (2006 - 2009)

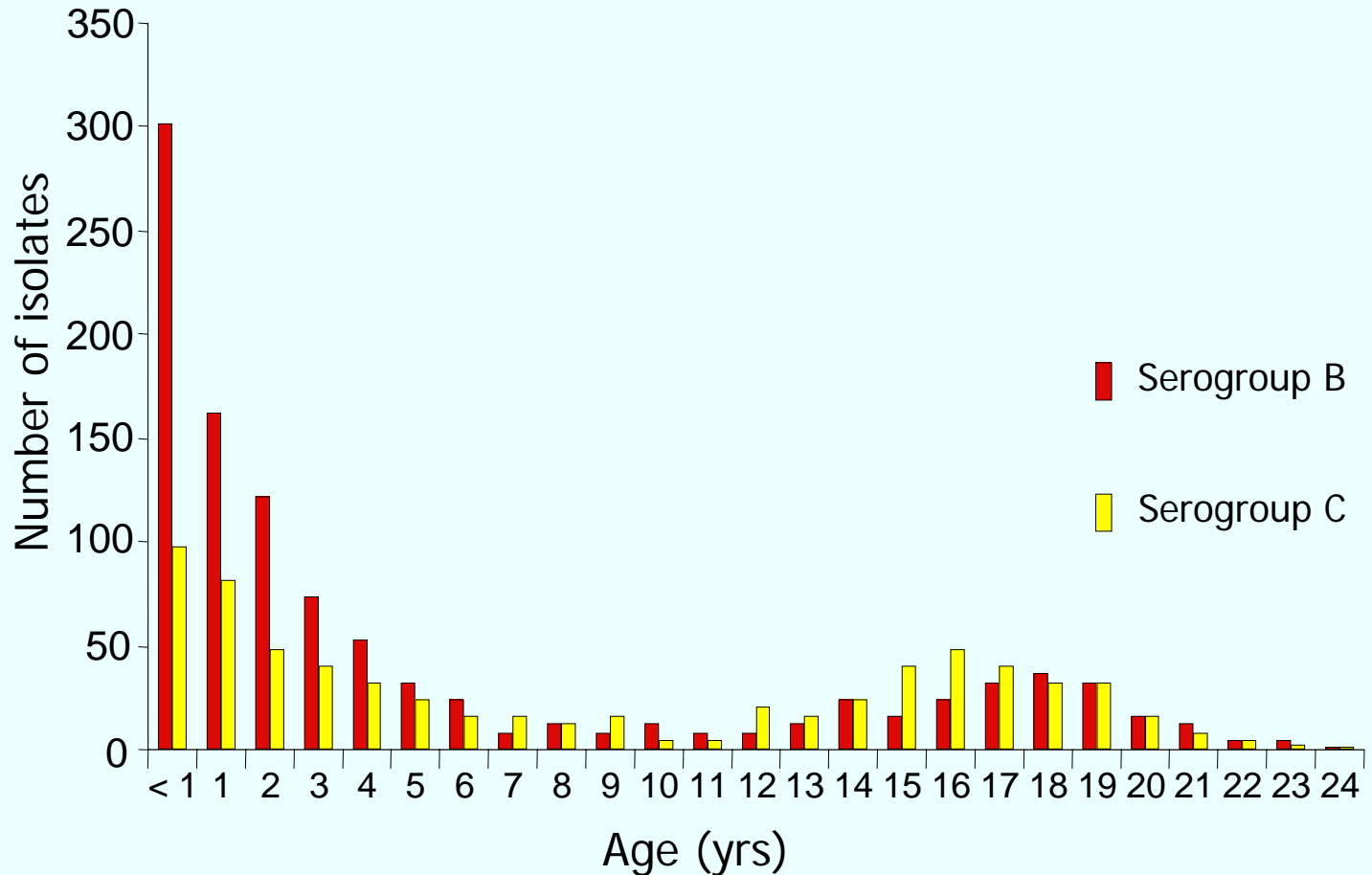
Neisseria meningitidis

- Diplococcus encapsulated bacteria
- Meningococcal naturally colonizes the nasopharynx of 10-40% of the population
- Disease incidence is 1-3:100,000 - mainly affecting children and adolescents



From: Sim, et al The Lancet 356 (2000)

Incidence of *N. meningitidis* by age



Meningococcal disease by age

(PHLS data 1998/9)

The effects of the introduction of the meningococcus group C vaccine in the UK

QuickTime™ and a
decompressor
are needed to see this picture.

So what about Men B?

Vaccinating against Meningococcus group B

- Capsular polysaccharide (it works for the Group A and others!)
- Outer membrane vesicles (OMV)

NIPH (Norway), Finlay Institute (Cuba)

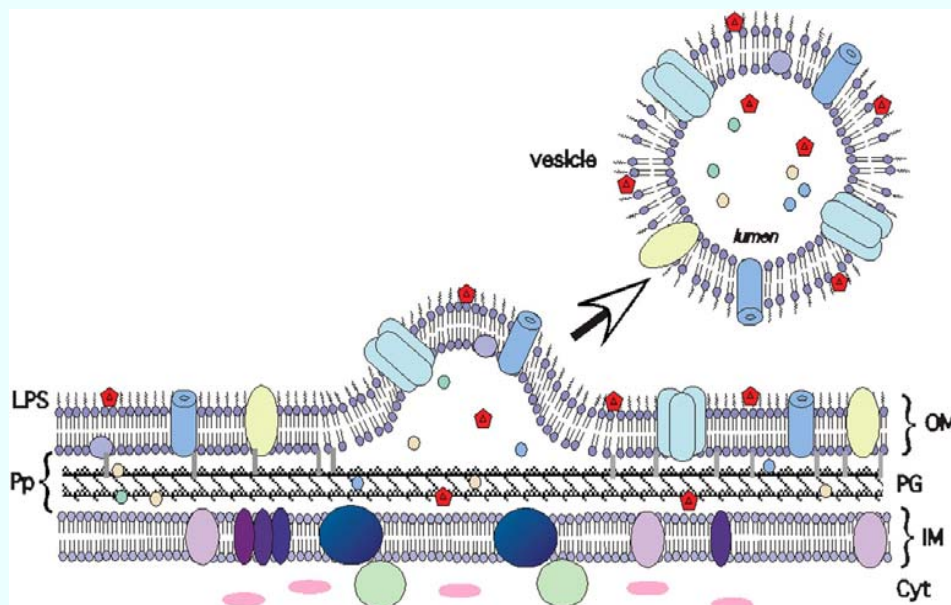
- Short-lived immunity
- Not very cross-reactive (esp in children)

RIVM (Netherlands)

- Hexavalent OMV (i.e. 6 different strains)
- responses to individual types variable

NIPH/Novartis

- New Zealand group B strain



Vaccinating against Meningococcus group B

- Capsular polysaccharide (it works for the Group A and others!)
- Outer membrane vesicles (OMV)
 - Other proteins of interest



Identification of Vaccine Candidates
Against Serogroup B Meningococcus by
Whole-Genome Sequencing Identification
of Vaccine Candidates Against Serogroup
B Meningococcus by Whole-Genome
Sequencing

Mariagrazia Pizza, Vincenzo Scarlato, Vega Masignani, Marzia Monica Giuliani, Beatrice Aricò, Maurizio Comanducci, Gary T. Jennings, Lucia Baldi, Erika Bartolini, Barbara Capecchi, Cesira L. Galeotti, Enrico Luzzi, Roberto Manetti, Elisa Marchetti, Marirosa Mora, Sandra Nuti, Giulio Ratti, Laura Santini, Silvana Savino, Maria Scarselli, Elisa Storni, Peijun Zuo, Michael Broecker, Erika Hundt, Bernard Knapp, Eric Blair, Tanya Mason, Hervé Tettelin, Derek W. Hood, Alex C. Jeffries, Nigel J. Saunders, Dan M. Granoff, J. Craig Venter, E. Richard Moxon, Guido Grandi, Rino Rappuoli

Novartis (Chiron)

- 5 novel proteins plus NZ OMV
- Early stages encouraging

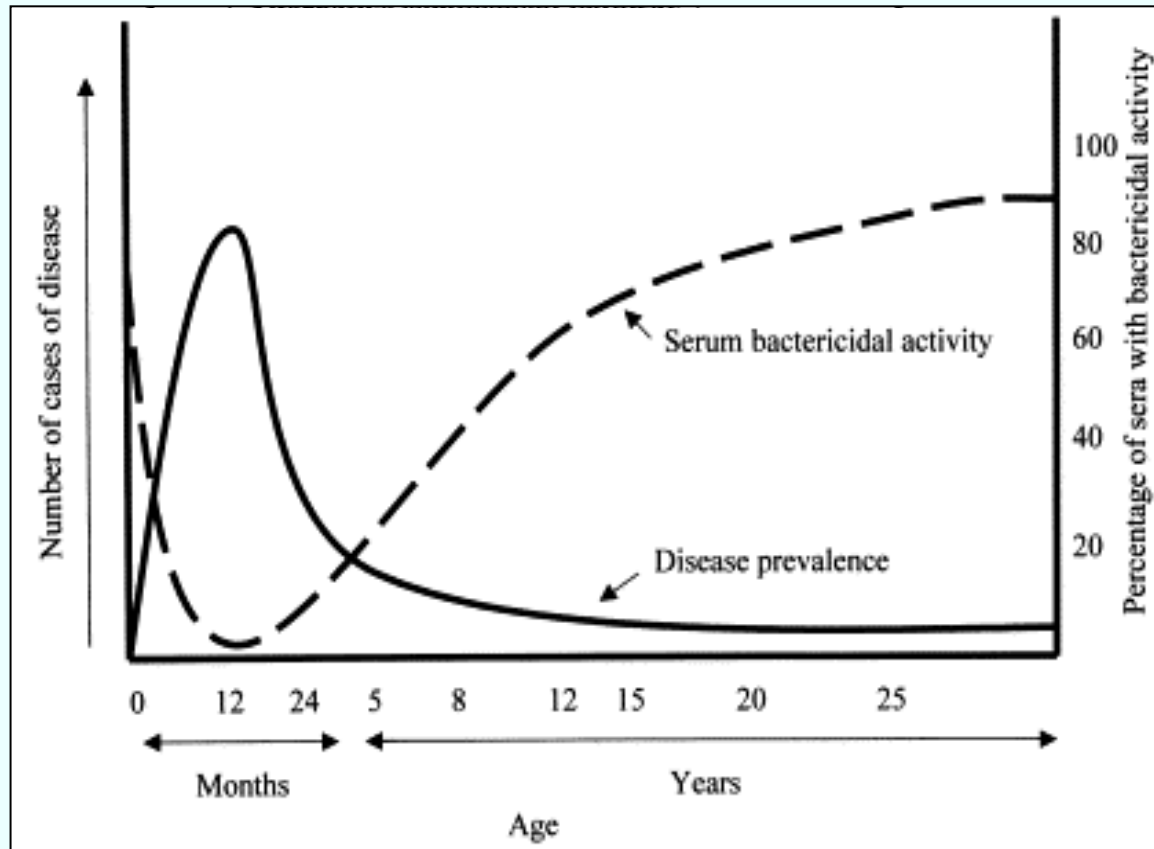
QuickTime™ and a
decompressor
are needed to see this picture.

QuickTime™ and a
decompressor
are needed to see this picture.

- Wyeth, GSK....

Why are they so confident?

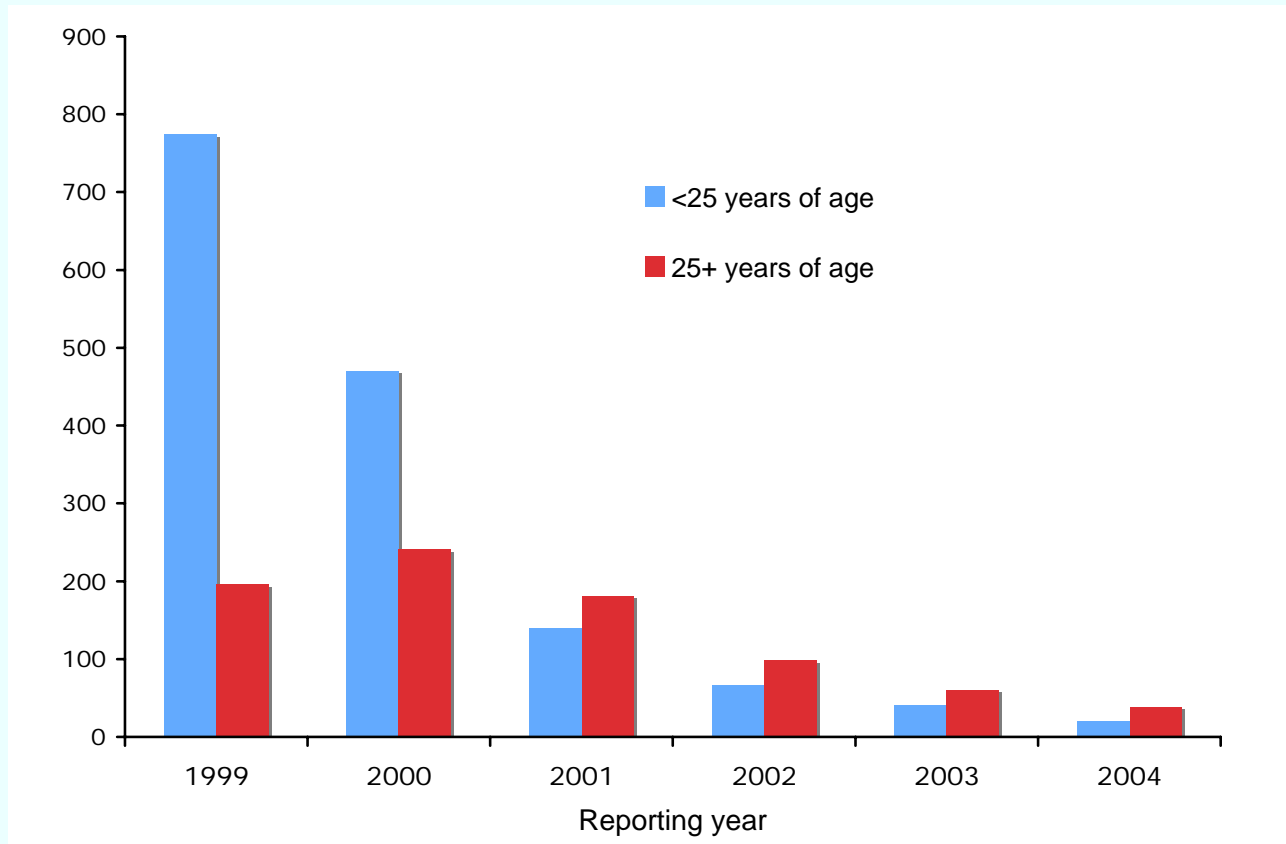
- 2 phase 2 trials completed and the reports suggest that the vaccine induces SBA which are cross-reactive



So, should we give up now and wait for Novartis to solve the problem?

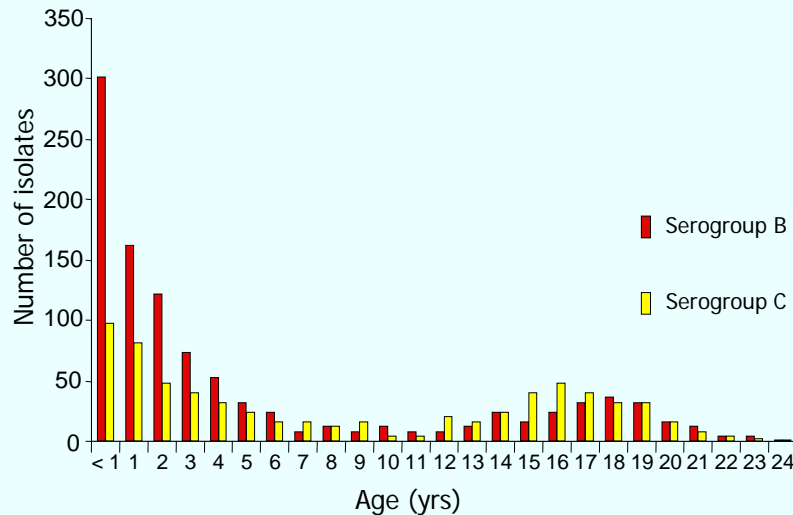
- Wyeth, GSK... are not
- Growing understanding that immunity to MenB is not just about SBA
- Will protein-based vaccines work in all age groups?
- Will protein-based vaccines induce herd immunity?

Herd immunity induced by vaccination



What are we doing and why?

1. Trying to understand the basis of natural immunity so that we know what we need from an effective vaccine



- What is going on in the mucosa (herd immunity)?
- What is the nature of the T cell response to men B (the cells that control the nature and effectiveness of the immune response)?

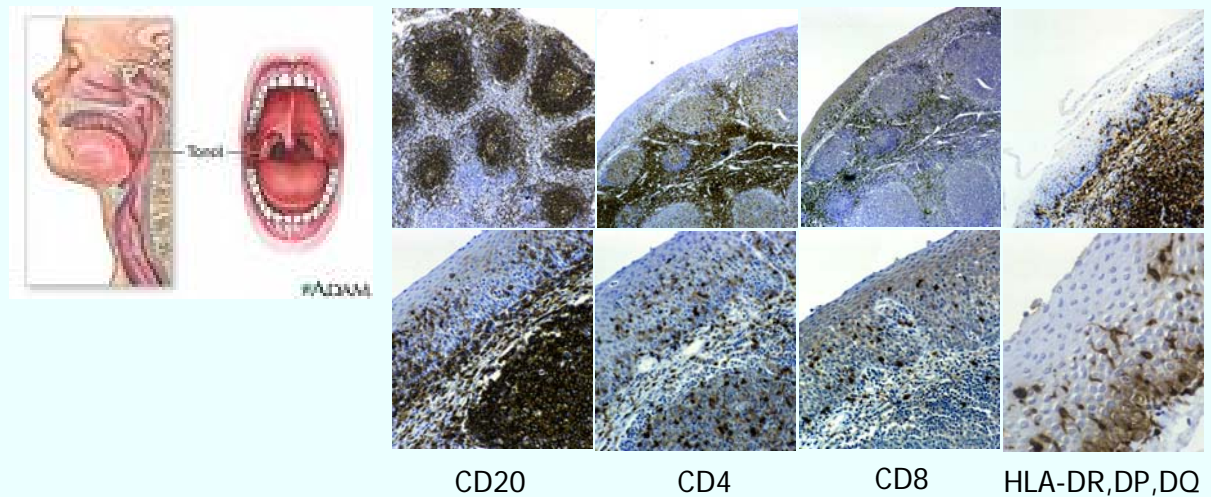
2. Determine whether protein-based vaccines are going to give us what we need in these respects.

Studying natural immunity

- Saliva samples
- Blood samples

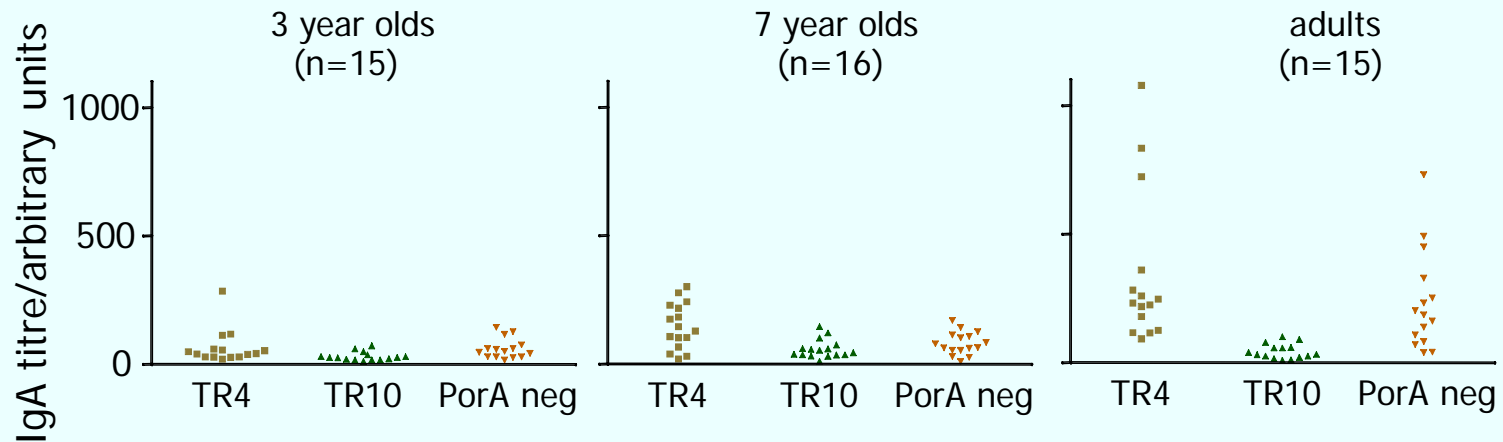
QuickTime™ and a decompressor are needed to see this picture.

The tonsil



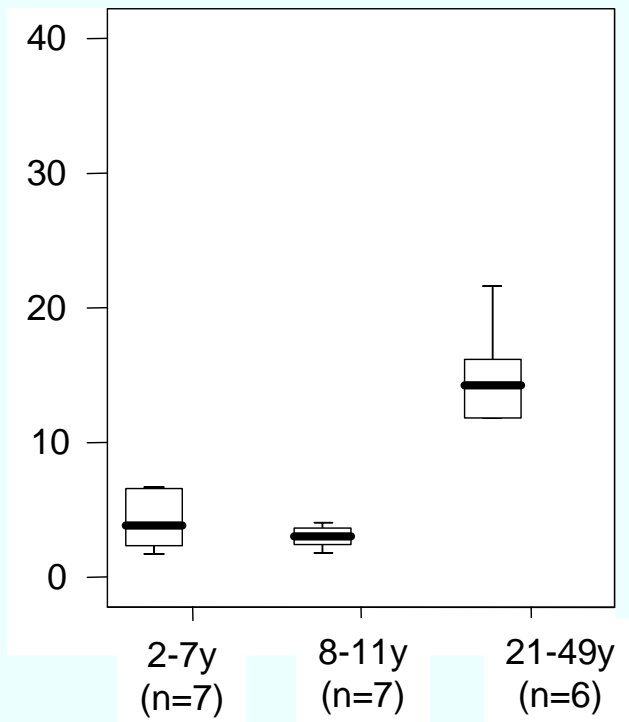
What have we found?

1. Mucosal antibody responses increase with age



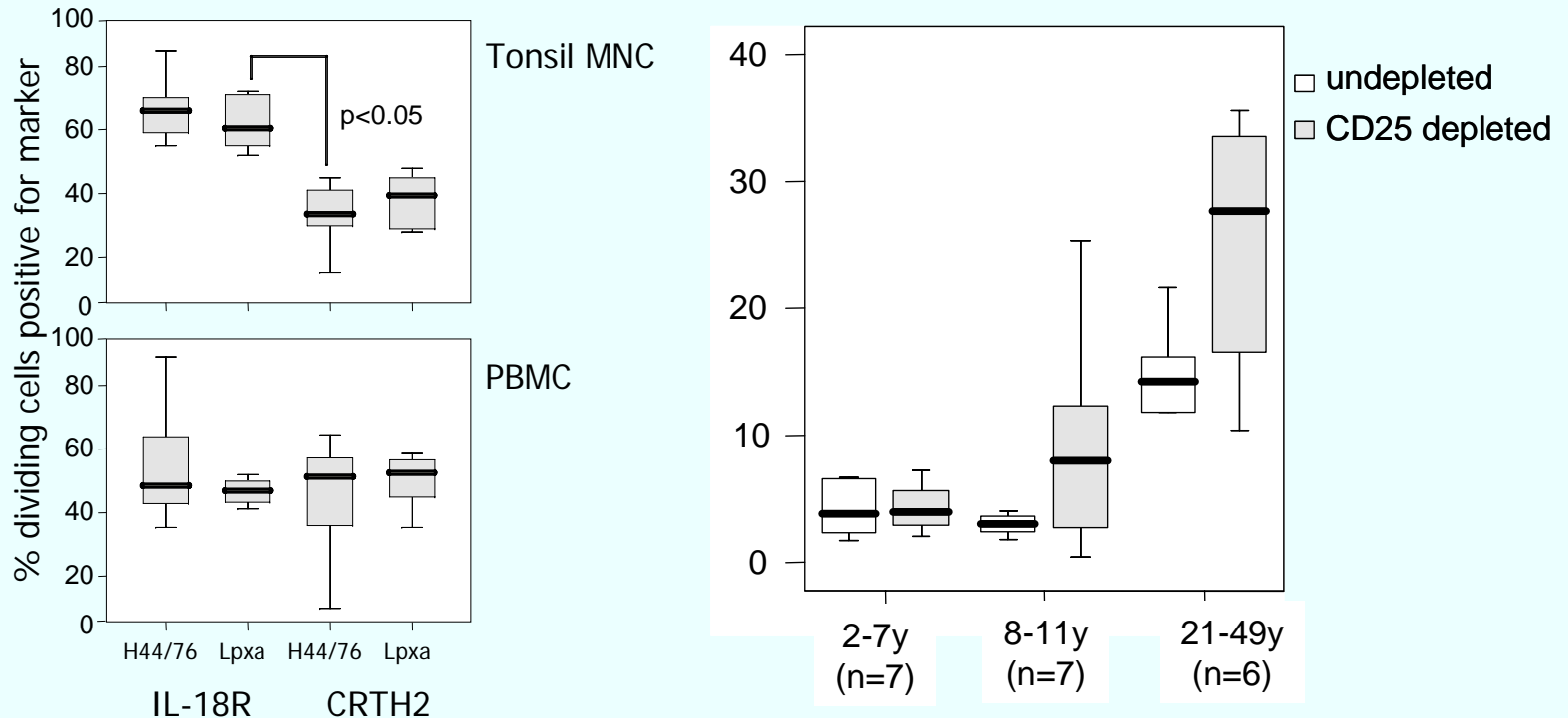
What have we found?

1. Mucosal antibody responses increase with age
2. Mucosal T cell responses increase with age



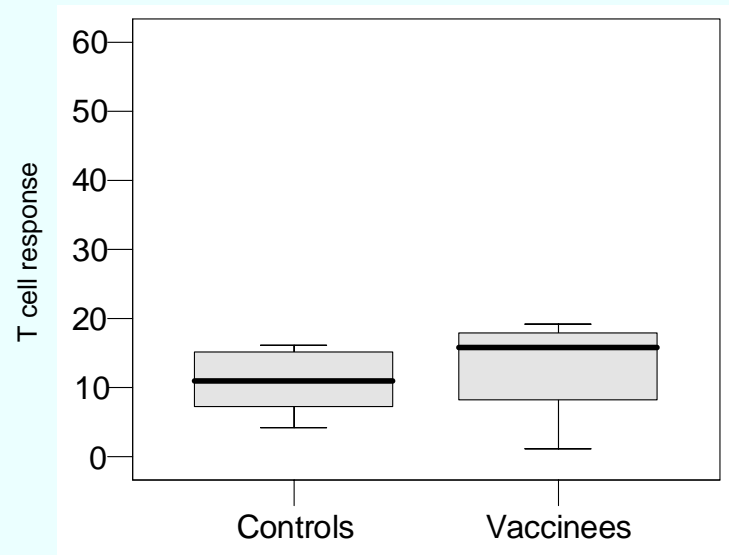
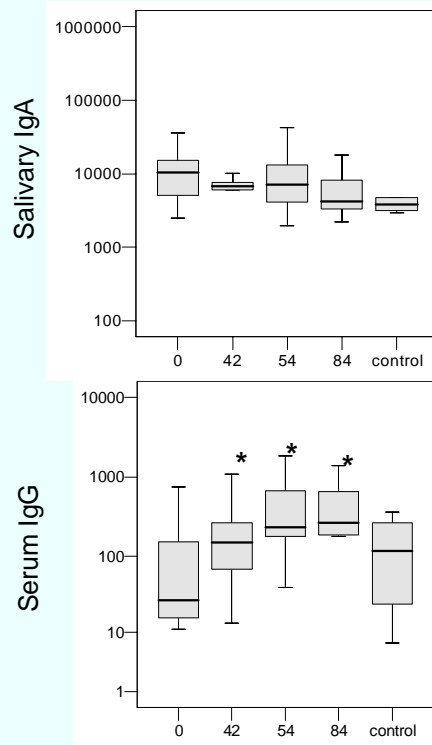
What have we found?

3. Importantly, the naturally induced T cell response in the mucosa is of a very different type to that seen in the blood
4. This T cell response has a much greater potential to cause inflammation, but it is held in check by very tight regulation



Does protein-based vaccination mimic these responses in young children, and/or boost them in young adults?

1. The NZ OMV vaccine does not stimulate increases in salivary IgA responses in adults
2. The NZ OMV vaccine does not enhance mucosal T cell responses in adults



Only part of the story

1. What about young children?
2. Is the failure of the vaccine to stimulate mucosal immunity in adults a consequence of the regulation that we see at this site?
3. What is controlling that regulation and are there ways of modulating it?