The Future of Pneumococcal Vaccination

James C Paton

Research Centre for Infectious Diseases, University of Adelaide, Australia

Pneumococcal disease

- *Streptococcus pneumoniae* remains the world's foremost bacterial pathogen.
  - Colonises human nasopharynx asymptomatically, but can invade tissues to cause of pneumonia, bacteraemia, meningitis and otitis media.
  - 1-2 million deaths per year.
  - Accounts for 20% of all deaths in children < 5 y.o. in developing countries.
  - Pneumococci exert lethal synergy with Flu.

Existing pneumococcal vaccines

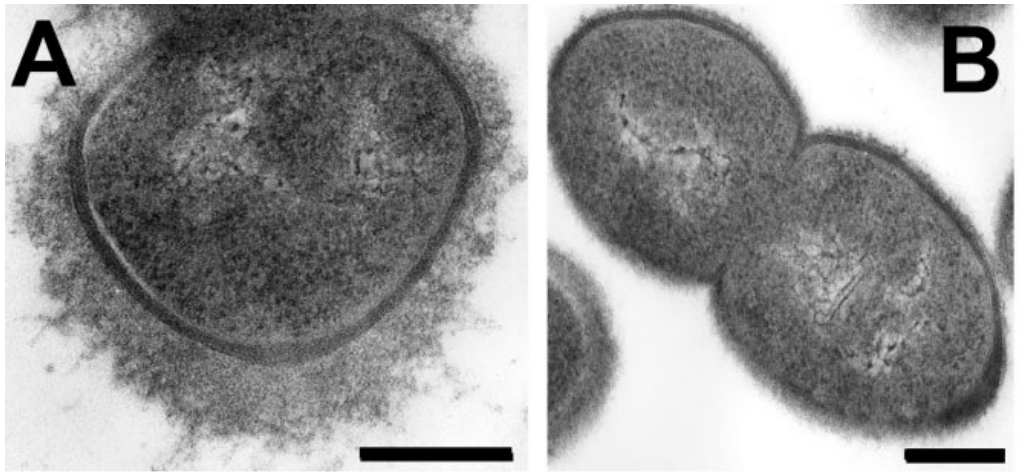
- Currently licensed vaccines target the capsular polysaccharide (CPS).
  - Major surface antigen and virulence factor (anti-phagocytic).
  - 98 structurally distinct serotypes.
  - Anti-CPS mediated protection is serotype specific.
- Polyvalent CPS vaccine (Pneumovax 23®) licensed in early 1980s.
  - Poor efficacy in children < 5 y.o.
- CPS-protein conjugate vaccines (PCVs) more immunogenic in children.
  - 7-valent PCV (Prevenar®) licensed in 2000;
  - 10- and 13-valent PCVs (Synflorix®, Prevenar 13®) introduced in 2013.
  - Massive reduction in IPD caused by included serotypes.
  - Being offset by increased carriage and disease caused by non-vaccine serotypes ("serotype replacement").
  - PCVs are expensive to manufacture.

New vaccines are needed to provide cheap, serotype-independent protection.

- Protein-based vaccines comprising virulence factors common to all serotypes:-
  - Pneumolysin shown to be a potential vaccine antigen (Paton *et al*., 1983); genetic pneumolysin toxoids developed (Paton *et al*., 1991).
  - Other protective proteins identified (PspA, CbpA, PcpA, PhtD, etc).
- Combination of proteins shown to provide enhanced protection (Ogunniyi *et al*., 2000).
- Protein combination vaccines at Phase II:
  - Sanofi Pasteur: Pneumolysoid/PhtD/PcpA.
  - GSK: Pneumolysoid/PhtD (with PCV).

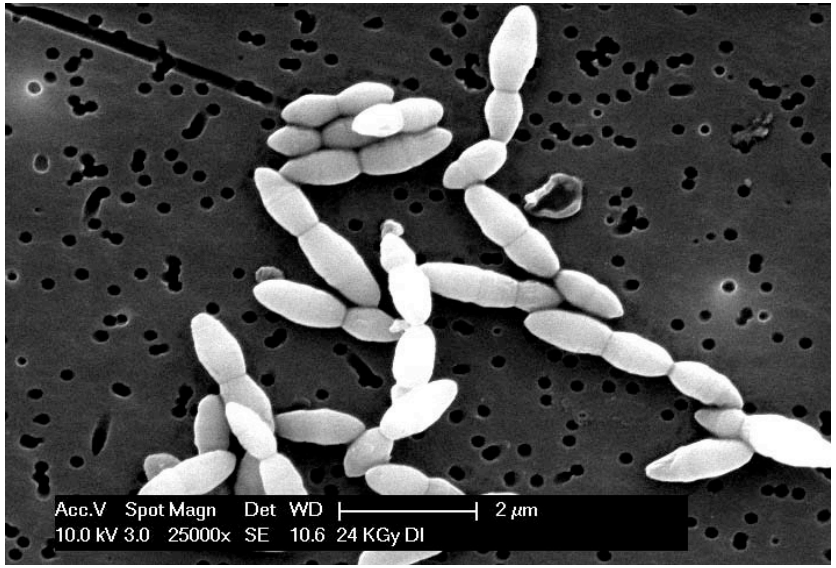
Pneumococcal whole cell vaccines (WCV)

- May provide cost effective serotype-independent protection.
- Uses killed non-encapsulated pneumococcal cells:
  - Maximises exposure of surface proteins.

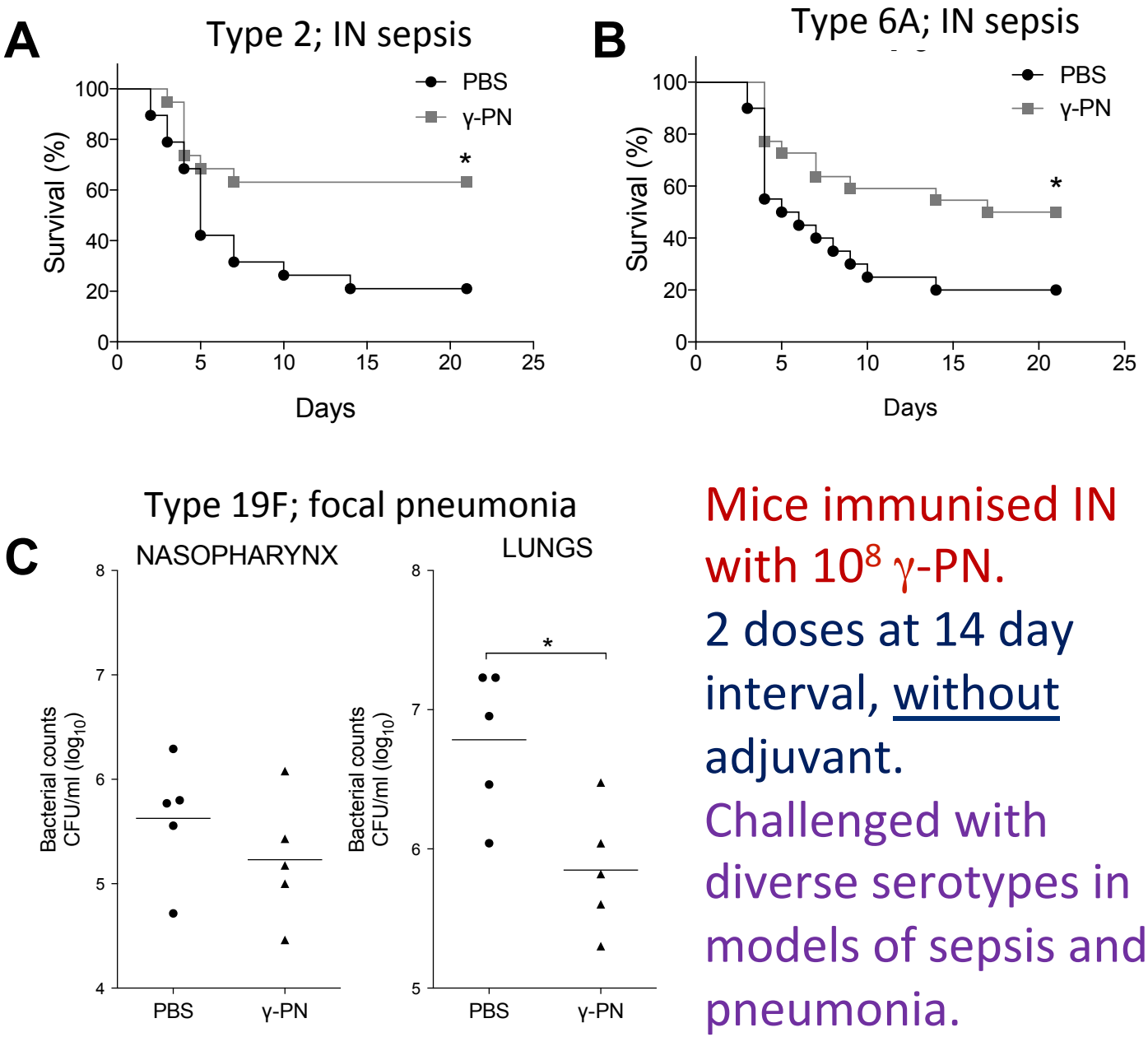


- Chemically killed WCV currently at Phase II (PATH/Boston CH).
  - SC injection with Alum adjuvant elicits Th17-dependent protection from nasopharyngeal carriage in mice.
  - Intranasal administration mandates strong mucosal adjuvant (e.g. cholera toxin).

Gamma-irradiated WCV (γ-PN)



- Gamma-irradiation preserves antigenic structure of WCV surface.
- Based on *S. pneumoniae* Rx1 Δ*lytA/*PdT (non-encapsulated, doesn't autolyse, expresses non-toxic pneumolysin).
  - Killed by exposure to 18 kGy (^{60}Co source; ANSTO).

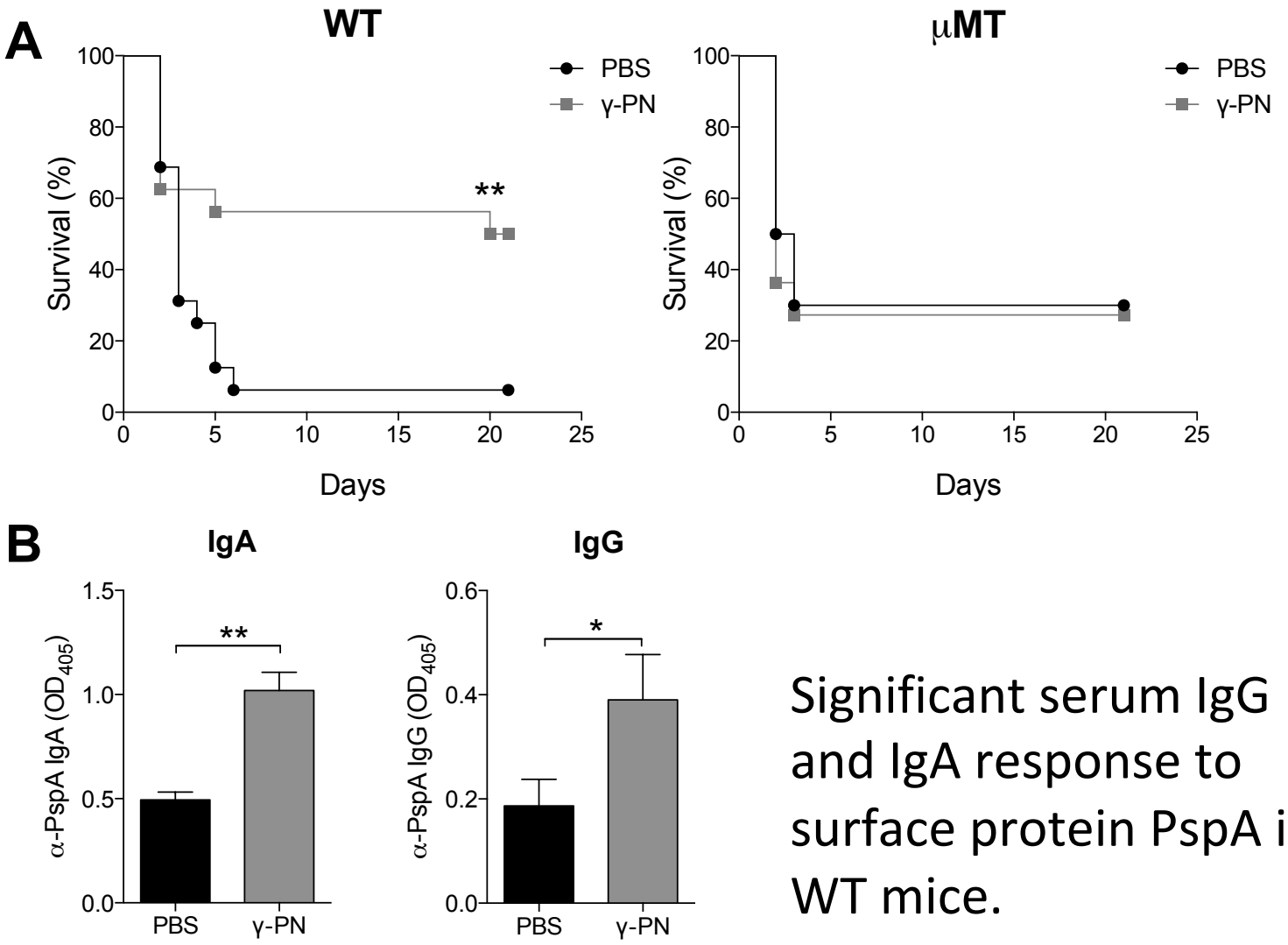


Mice immunised IN with 10^8 γ-PN.

2 doses at 14 day interval, without adjuvant.

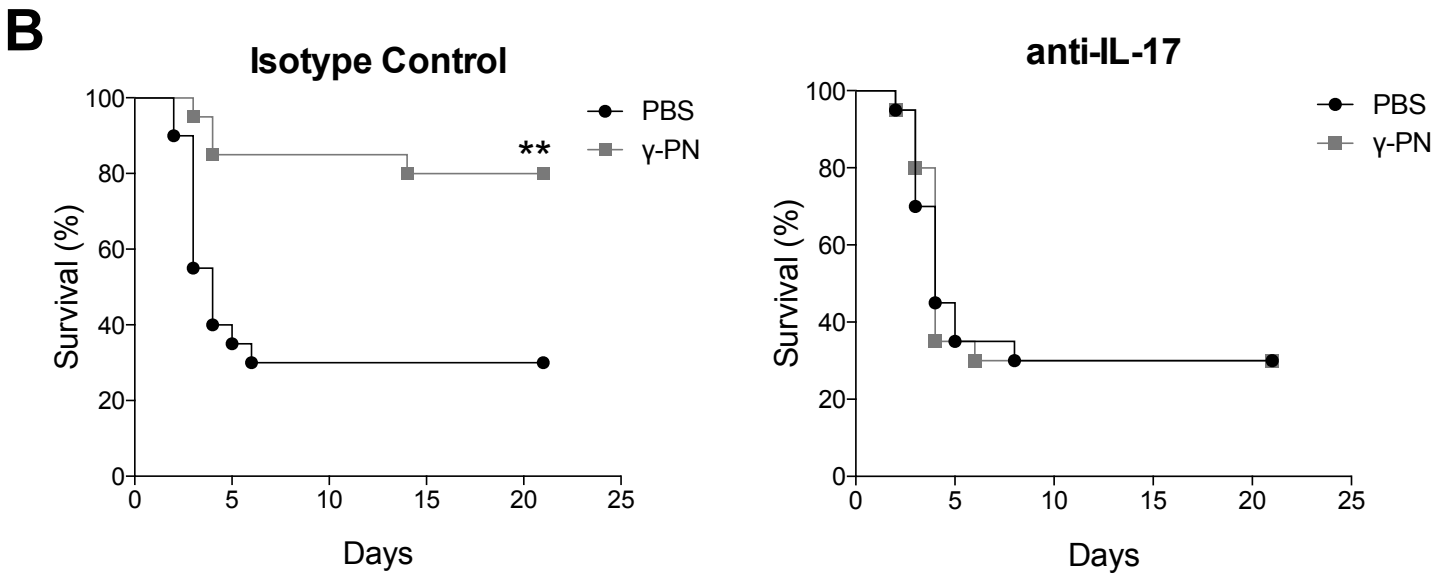
Challenged with diverse serotypes in models of sepsis and pneumonia.

Protection dependent on B cells (no protection in μMT mice)



Significant serum IgG and IgA response to surface protein PspA in WT mice.

D39 intranasal challenge; anti-IL-17 administered IP, 24 h pre- and 6 & 24 h post-challenge.

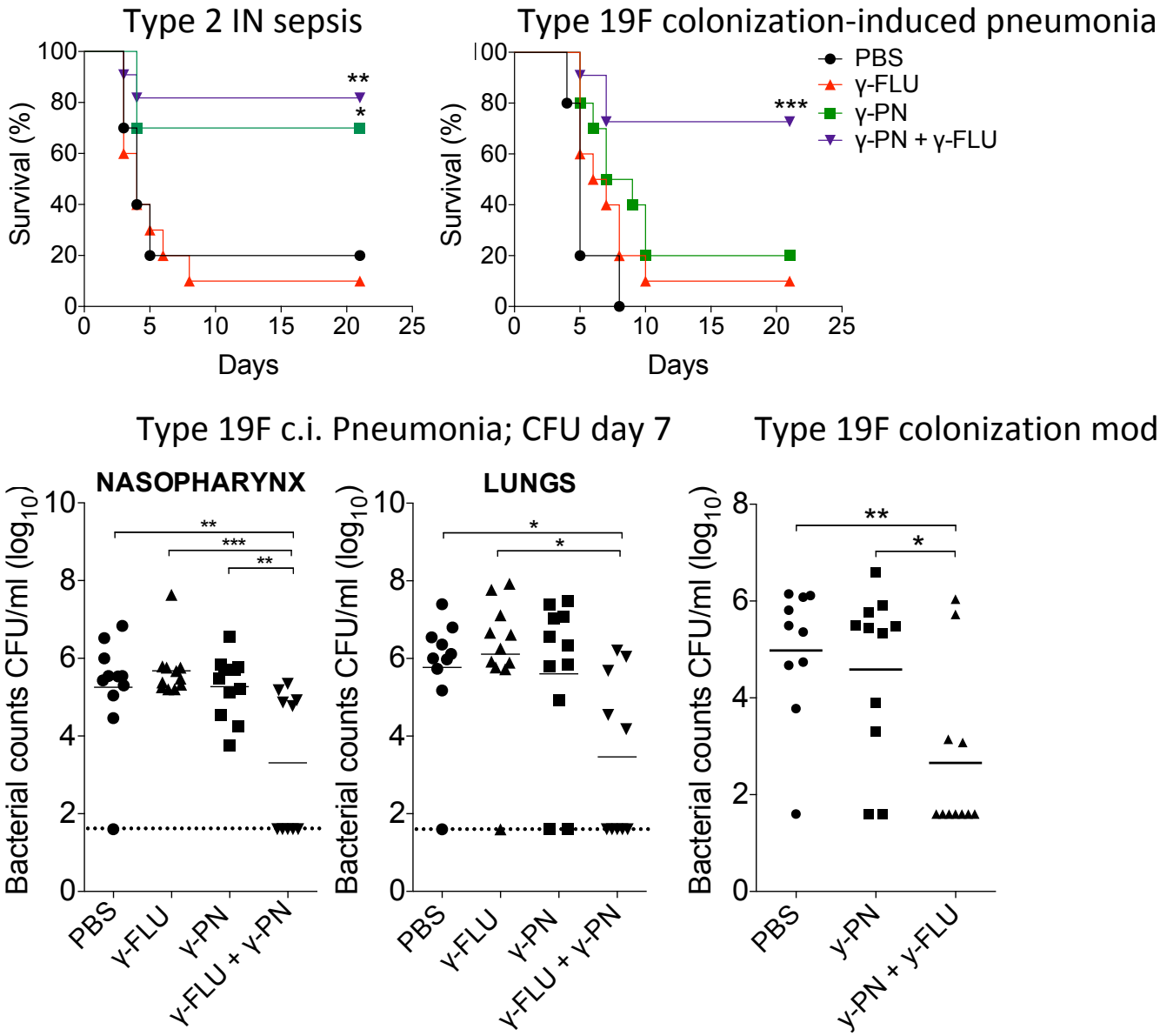


Protection also dependent on IL-17:

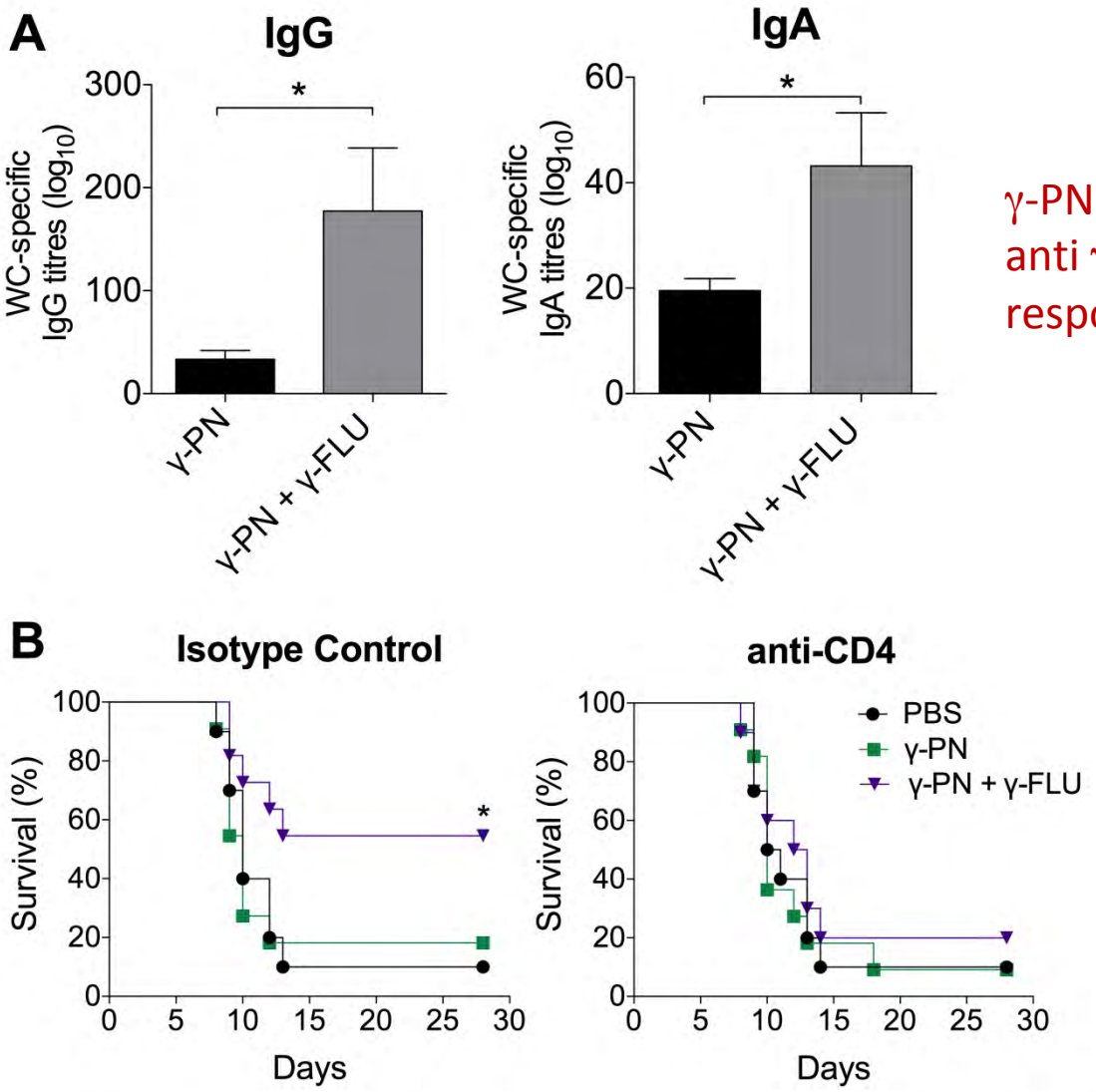
- γ-PN did not induce Th17 cells or TRM IL-17+ cells;
- Rather, γ-PN enhanced γδT17 cells in lungs.

Co-immunization with γ-PN and γ-FLU

- Pneumococcus and Flu virus exert lethal synergy.
- Heterotypic protection elicited by γ-FLU (J Virol 2010; 84:4212-21) raises possibility of combined influenza/ pneumococcal immunization.
- Tested efficacy of γ-PN ± γ-FLU (2 doses IN without adjuvant).



γ-PN+γ-FLU protects against sepsis, pneumonia AND nasopharyngeal colonization



γ-PN+γ-FLU increases anti γ-PN antibody responses.

- γ-PN+γ-FLU-mediated protection is dependent on CD4+ T cells.
- Co-immunization induces Th17 and CD4+ TRM cells following live D39 challenge.

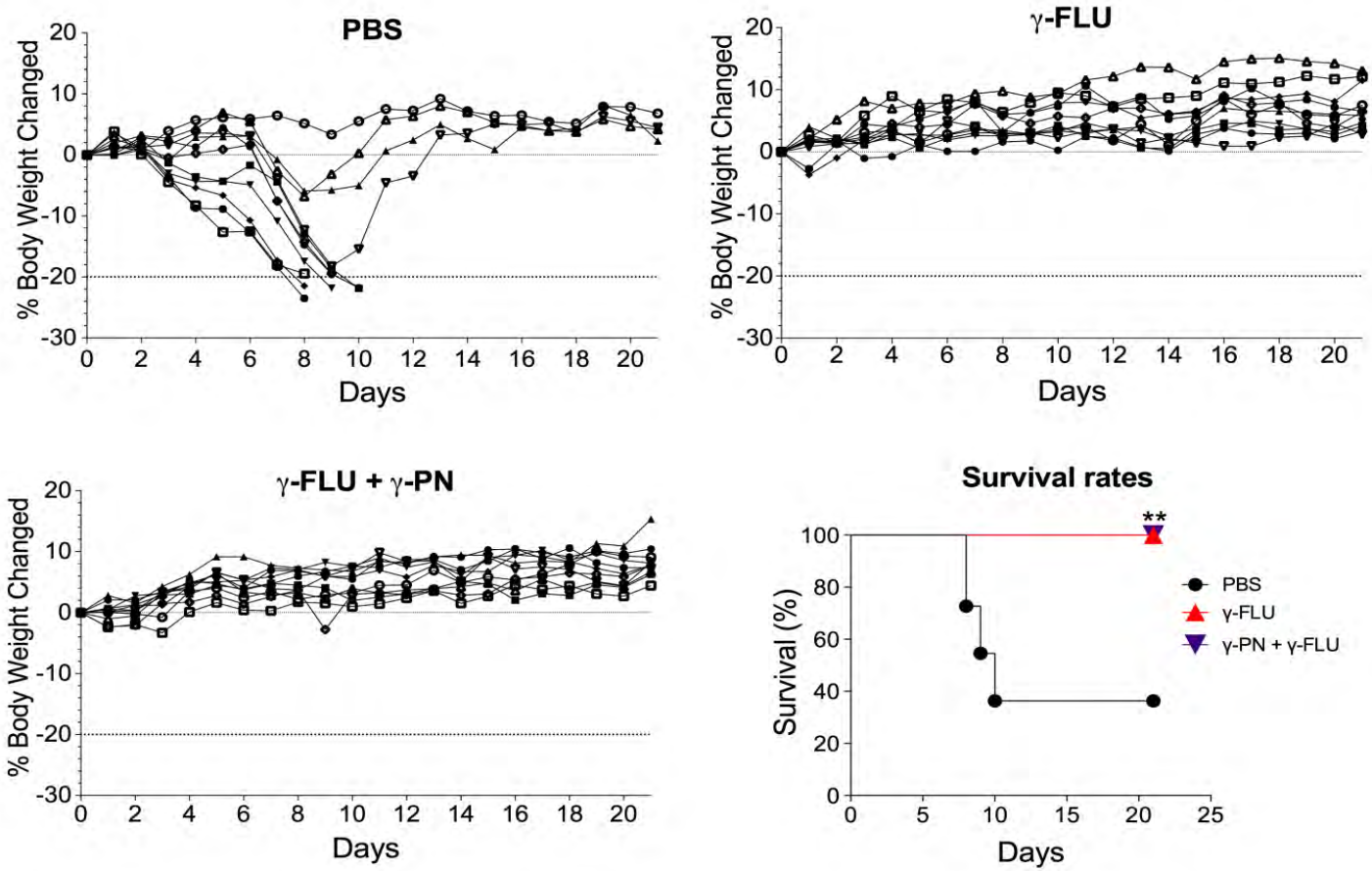
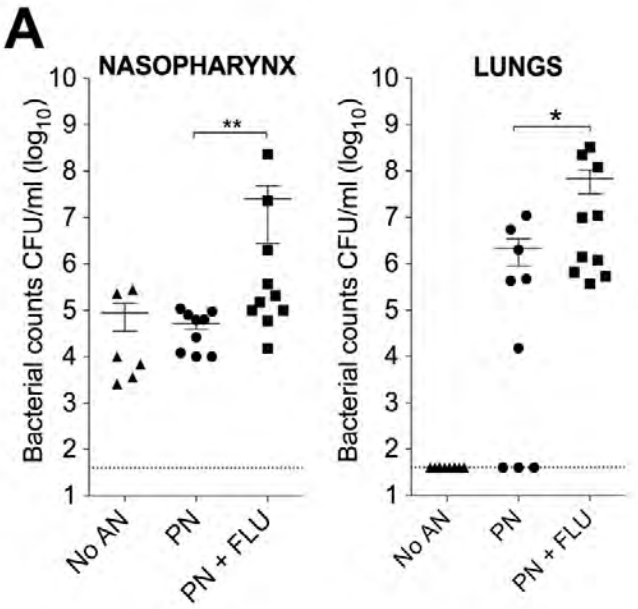


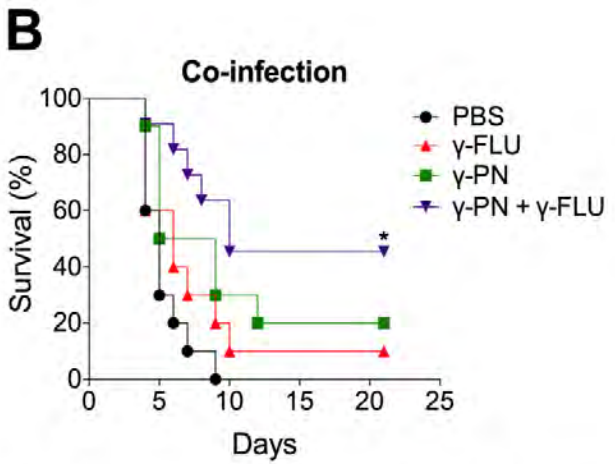
Fig. 5. Co-immunisation with γ-PN + γ-FLU does not compromise vaccine-induced anti-influenza immunity. Mice (n = 10) were immunized IN with 2 doses of, γ-FLU or co-immunized with γ-PN + γ-FLU. 2 weeks after the second immunisation, mice were challenged IN under anaesthesia with A/PR8. Survival rates and percentage weight loss are shown for a period of 21 days. The dotted line represents 20% weight loss (trigger for euthanasia). Data were analyzed using a Fisher exact test (*, $P < 0.05$; ** $P < 0.01$).

Co-infection model: mice colonized with type 19F pneumococcus and then challenged at day 4 with Flu (A/PR8). Bacterial loads measured 7 days later.

Naïve mice:
Flu infection increases bacterial loads in nasopharynx and lungs.



Immunized mice challenged with flu + S. pn



Conclusions

- Intranasal γ-PN WCV without adjuvant elicits serotype-independent protection against sepsis and pneumonia.
  - Currently assessing IM injection with Alum.
- Intranasal γ-PN + γ-FLU combination vaccine enhances protection against pneumococcal sepsis and pneumonia:
  - Protects against nasopharyngeal colonization (transmission);
  - Anti-Flu protection undiminished;
  - Protects against Flu/pneumococcal co-infection.

THE UNIVERSITY of ADELAIDE

DECLARATION

JCP is a director and shareholder of GPN Vaccines Pty Ltd

ACKNOWLEDGEMENTS

Research Centre for Infectious Diseases, University of Adelaide

Rachelle Babb
Austen Chen
Shannon David
Mohammed Alsharifi
David Ogunniyi
Shaun McColl

GPN Vaccines Pty Ltd

Tim Hirst

Funding:

Australian Research Council
National Health and Medical Research Council