

Intranasal Live Attenuated Pneumococcus Vaccine to Protect Against Pneumonia & AOM and Potential Platform for Combination Vaccines

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Pneumococcus Vaccines: Success and Limitations



Problem: Pneumococcus causes serious diseases (e.g., acute otitis media, sinusitis, pneumonia, bacteremia, sepsis, meningitis, etc) that cause high morbidity and mortality in children and elderly

Success

- ✓ Introduction of the highly efficacious polysaccharide-conjugate vaccines (e.g., Prevnar series, Synflorix, etc.) reduced pneumococcus infections dramatically

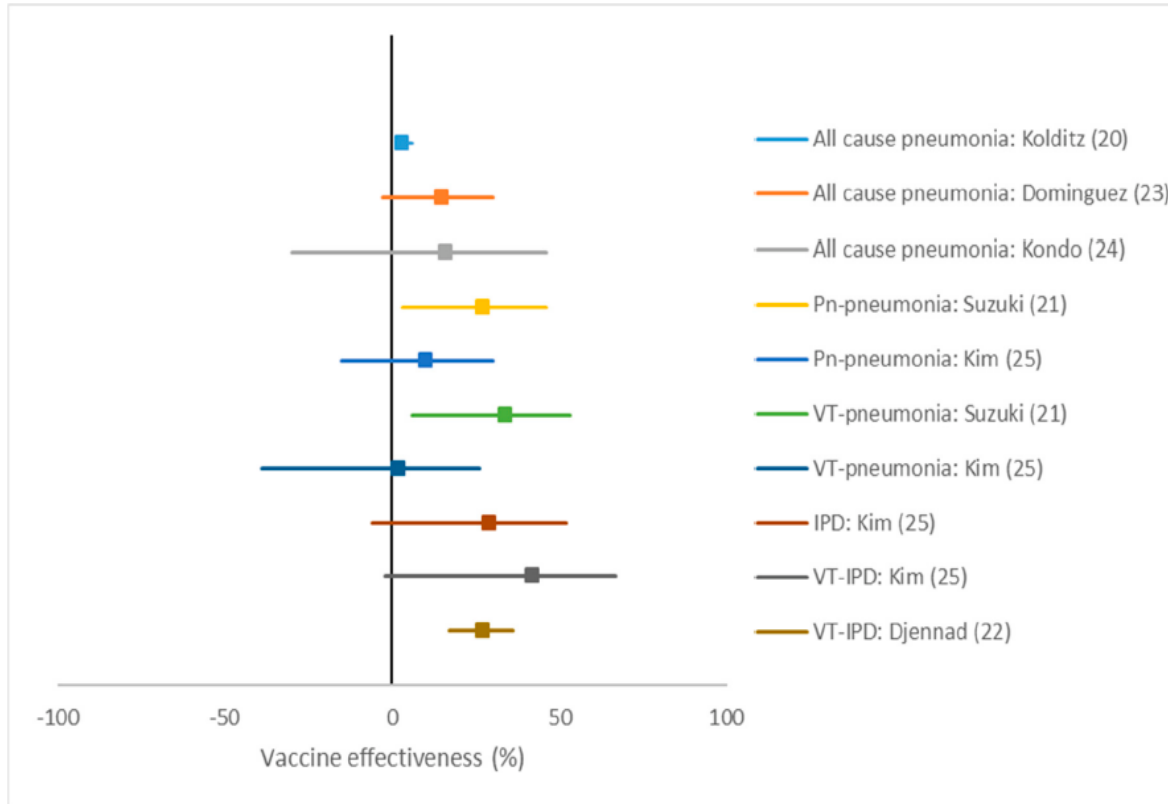
Limitations

- × Protection is serotype specific
- × Efficacy was almost exclusive to invasive diseases; Bacteremia, sepsis, and meningitis
- × Emergence of non-vaccine type in the community
- × Cost and availability in LMIC
- × Poor protection against major infections: Pneumonia, AOM, and nasopharyngeal colonization

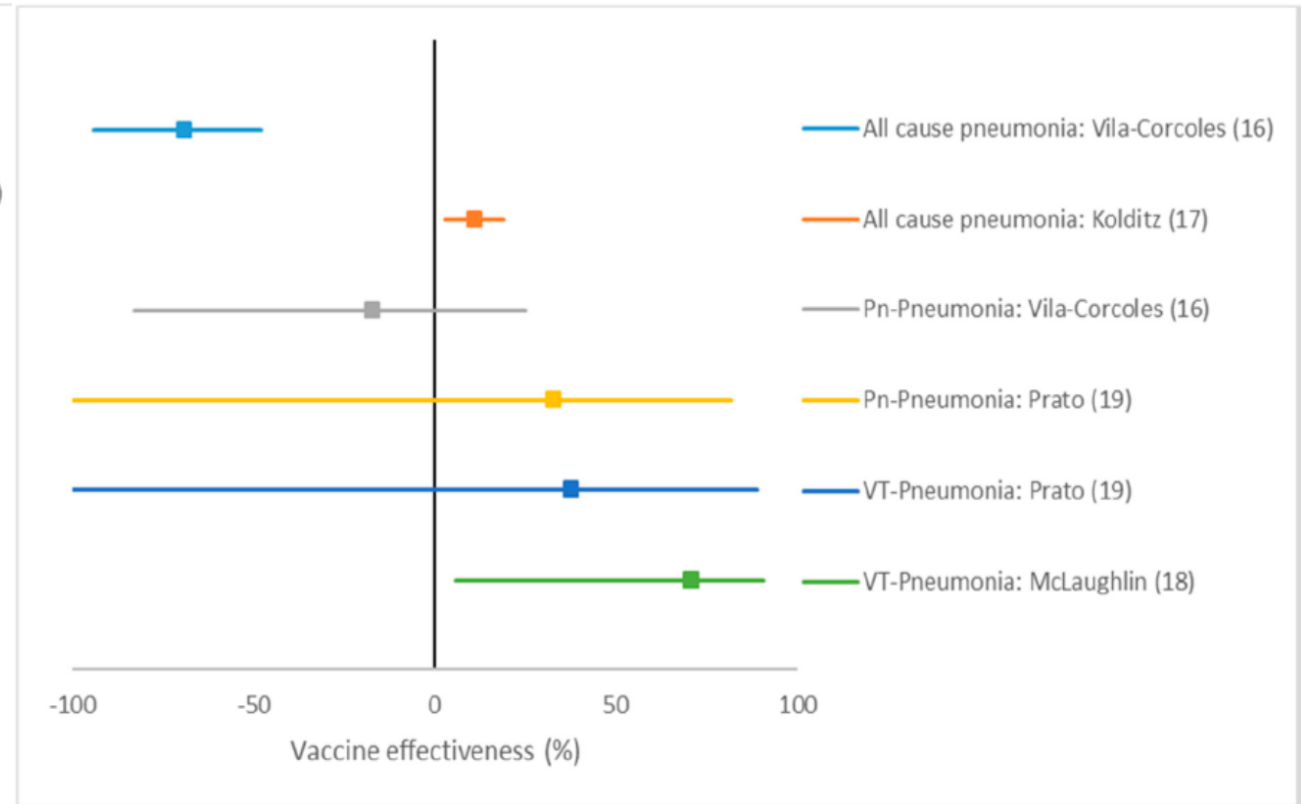
Moffitt & Malley, 2016

PPV23 and PCV13 Vaccines Effectiveness Against *S. pneumoniae* in Elderly

PPV23 Pneumococcal Pneumonia Efficacy Rates



PCV13 Pneumococcal Pneumonia Efficacy Rates



Characteristics of an Ideal, Safe, & Effective Vaccine

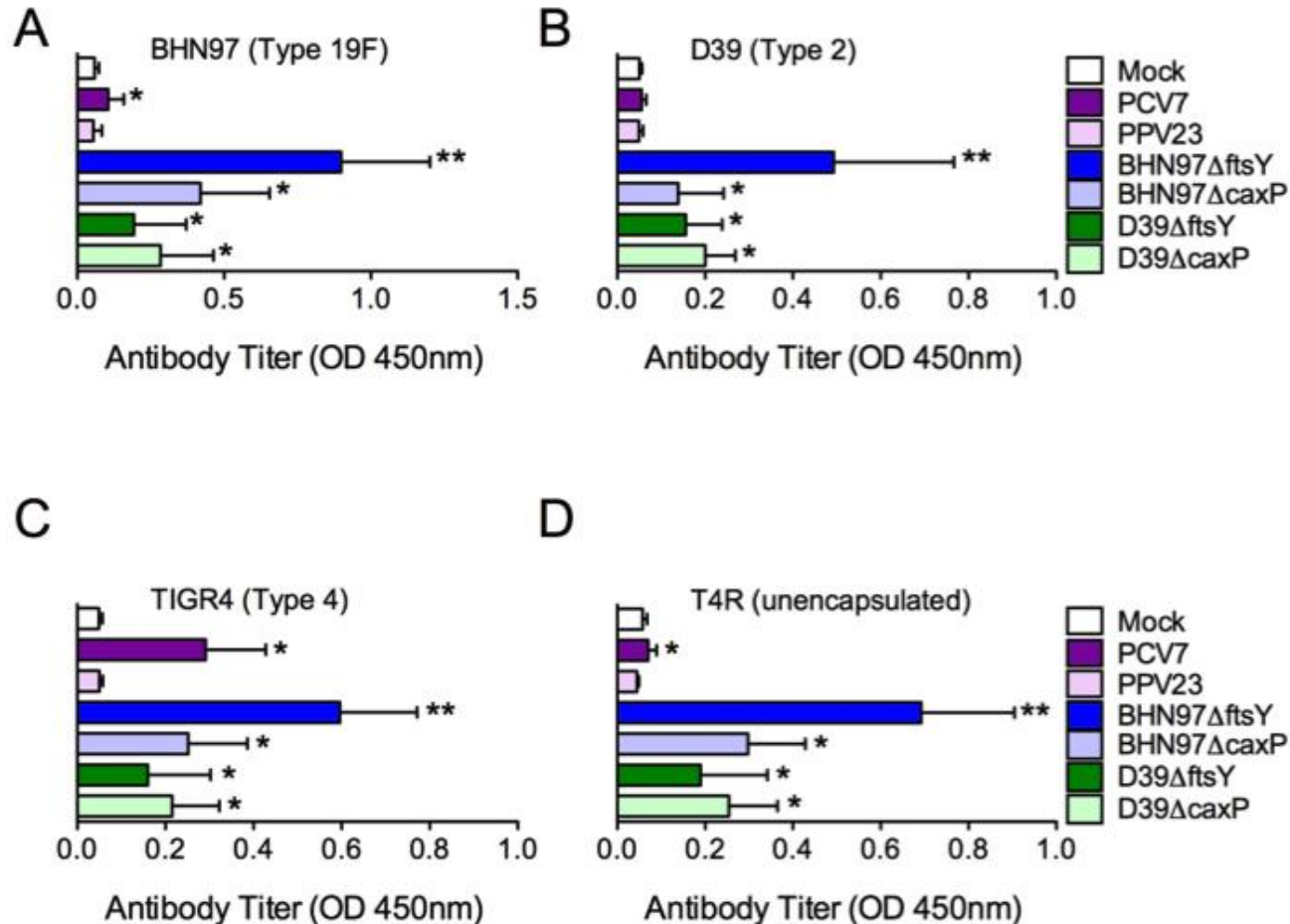
- ✓ Highly cross-reactive and serotype independent (Conserved surface proteins)
- ✓ Highly immunogenic and elicits:
 - ✓ Mucosal Immunity: IgA, Th17, Homed B and T-cells
 - ✓ Systemic Immunity: Opsonic IgG, balanced Th1/Th2
- ✓ Efficacious against nasopharyngeal colonization, AOM, and pneumonia
- ✓ Low cost (e.g., to ensure utilization in LMICs)
- ✓ Easily delivered
- ✓ Longevity of immune response
- ✓ Localized long-term memory

BWV-201: A Live Attenuated Vaccine Candidate

- Noninvasive serotype 19F strain BHN97 which normally causes sinusitis/purulent rhinitis and AOM
- Deleted *ftsY*, a component of the signal recognition particle pathway (SRP) pathway (*responsible for delivering membrane and secretory proteins to proper cellular destination*)
- Vaccine strain BHN97 Δ ftsY
 - Attenuated for invasive disease
 - Deficient for competence/recombination
 - Surface protein content is similar to the WT
 - Colonizes murine nasal passages for 3-7 days
 - Induced serotype-independent immune response

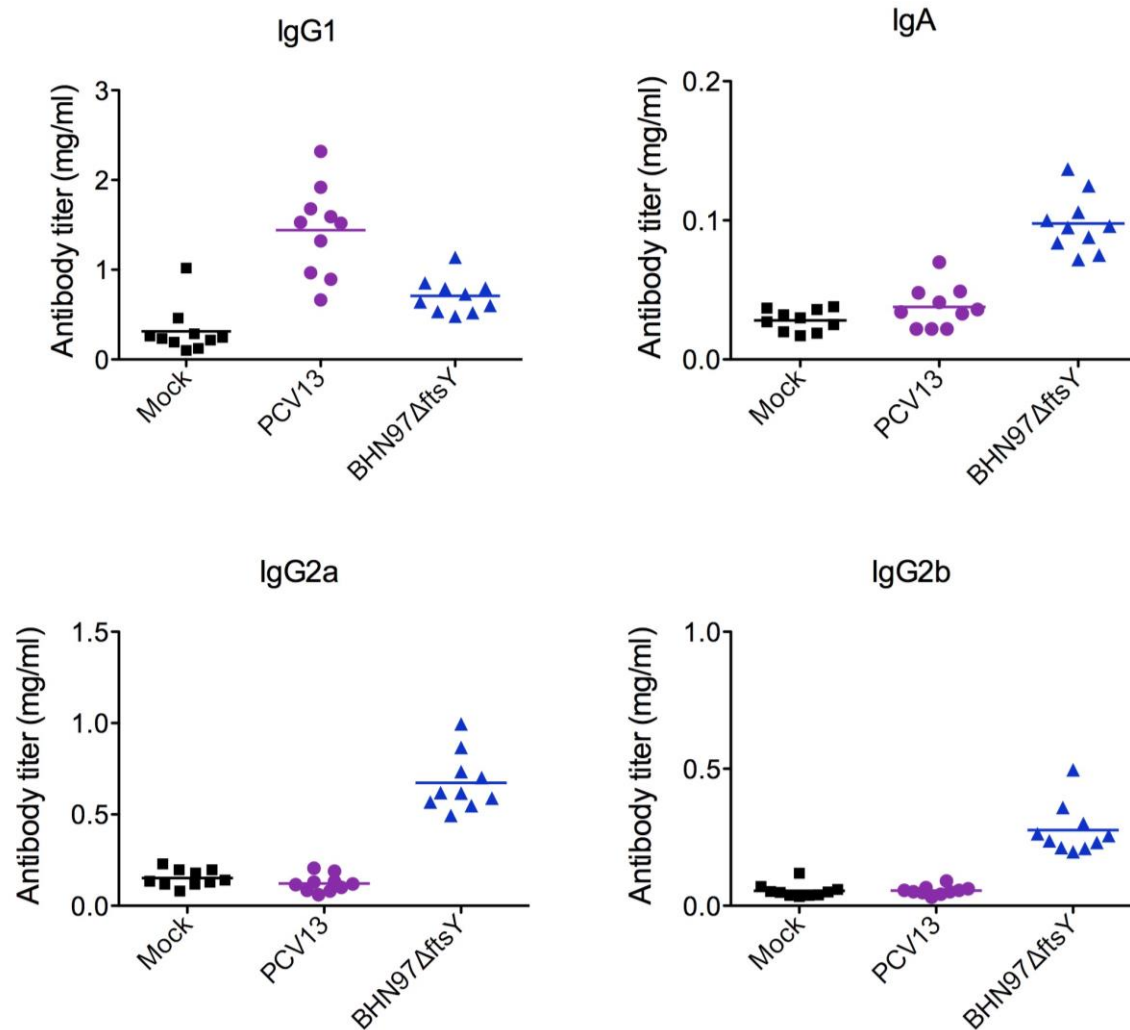
BWV-201: Highly Immunogenic against Homologous and Heterologous Serotypes

Live vaccines induce a potent serotype independent antibody responses



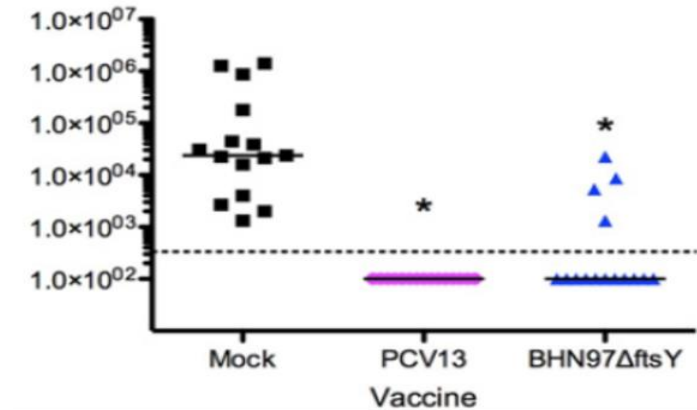
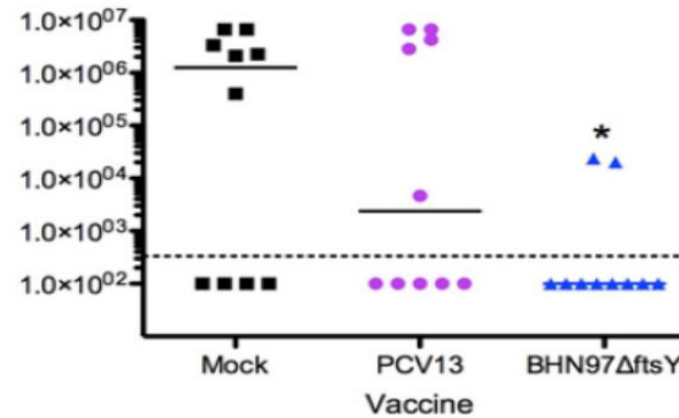
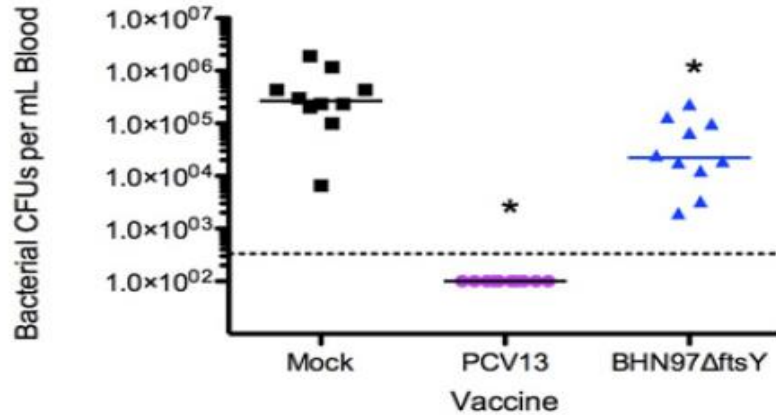
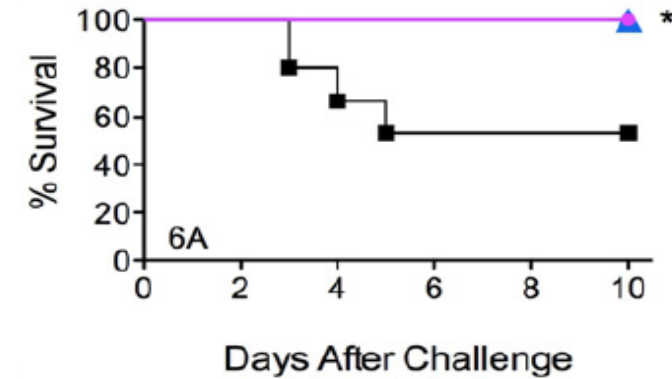
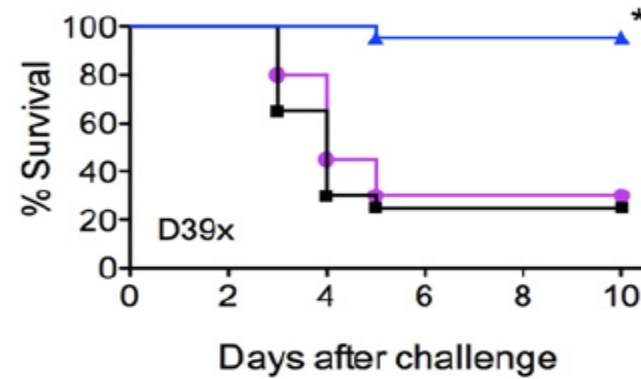
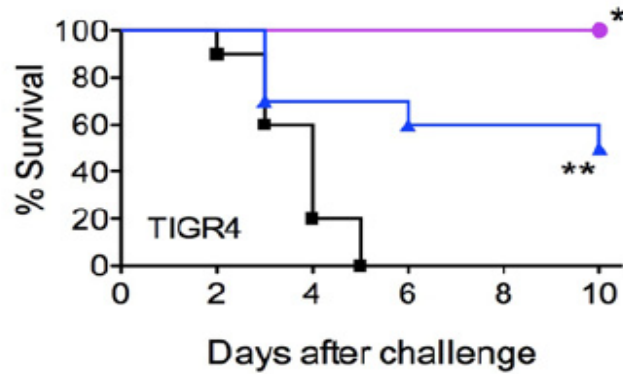
- ELISA against whole bacterial lysates following standard vaccination schedules in mice
- BHN97 Δ ftsY consistently gave the strongest serotype independent responses in a strain and serotype independent manner

BWV-201: Induction of a Balanced Th1/Th2 and Mucosal Immunity



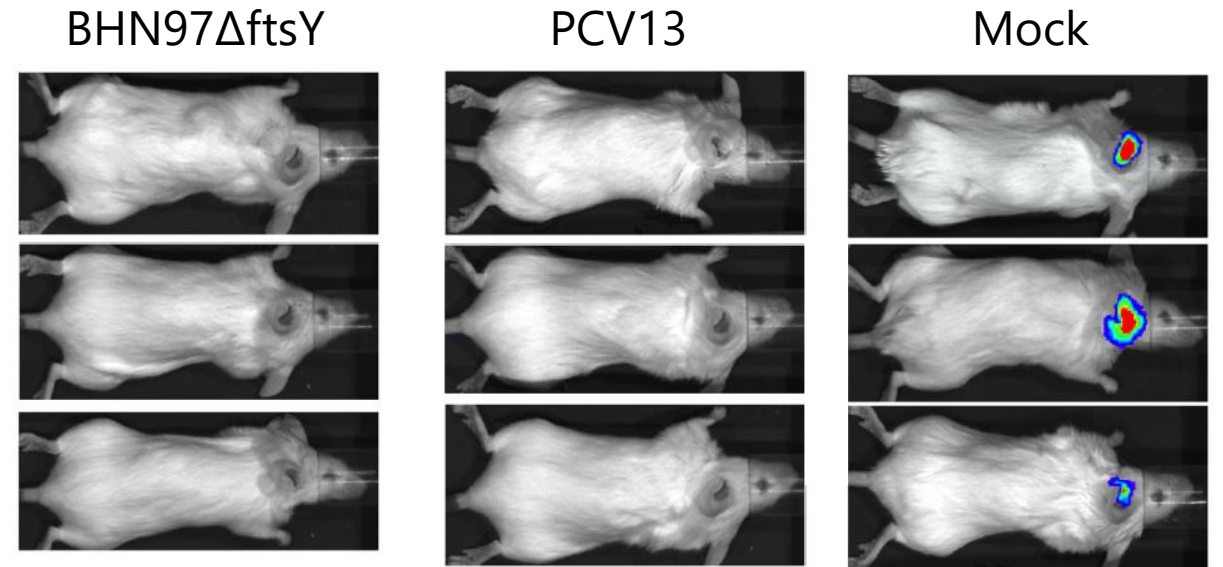
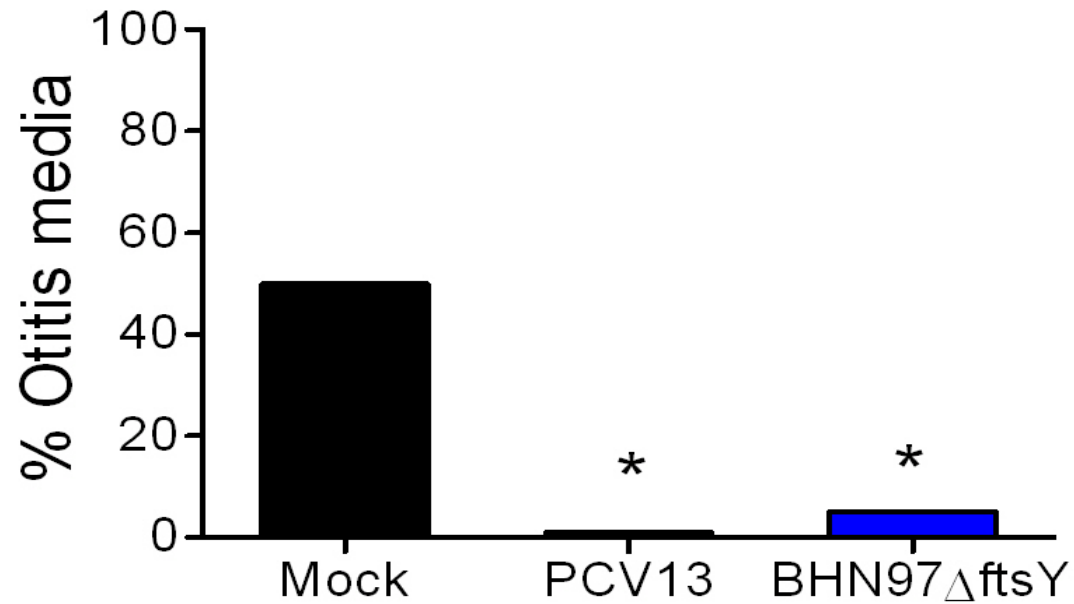
BWV-201: Protected Against IP Challenge (Sepsis/Bacteremia*) with Heterologous Serotypes - 4, 2, and 6A

■ Mock ● PCV13 ▲ BHN97ΔftsY



* Blood obtained at 24hrs Post IN challenge

BWV-201: Protected against AOM Caused by Serotype 7F Challenge

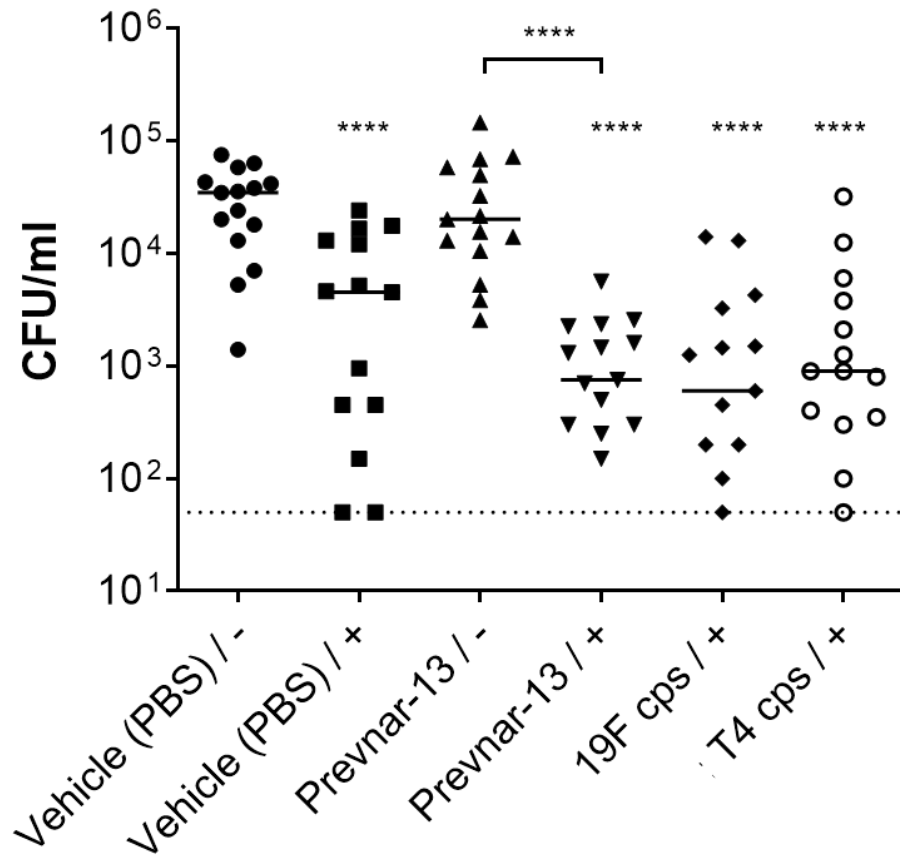


Rosch J, 2013



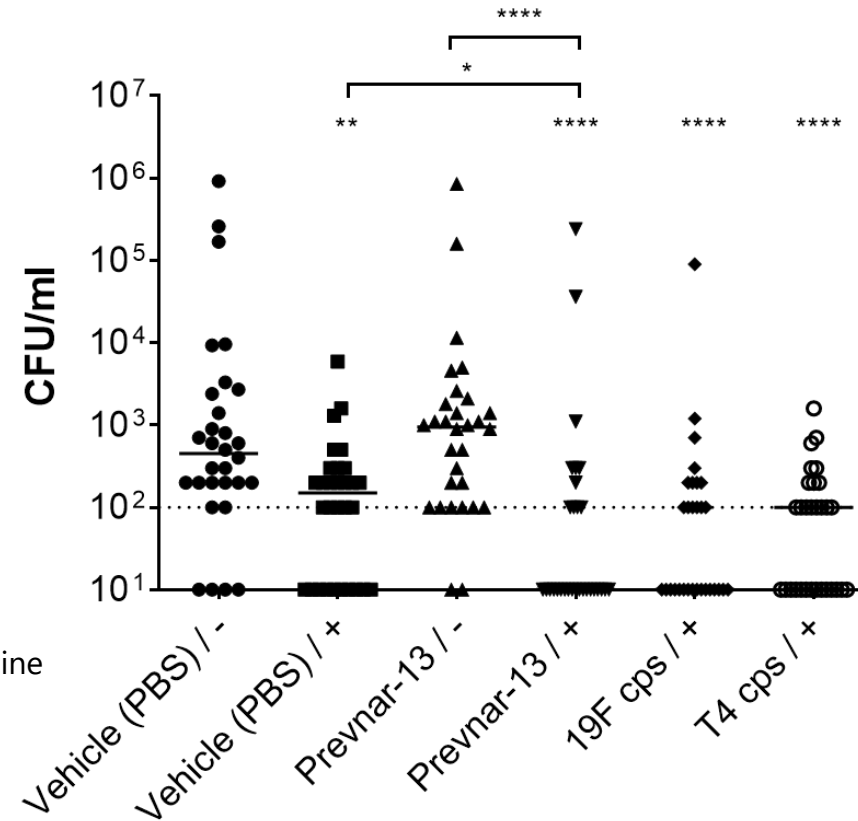
BWV-201: Previous Exposure to Heterologous Infections or PCV Vaccination Enhanced Efficacy (Lungs and Ears)

Lung Titers

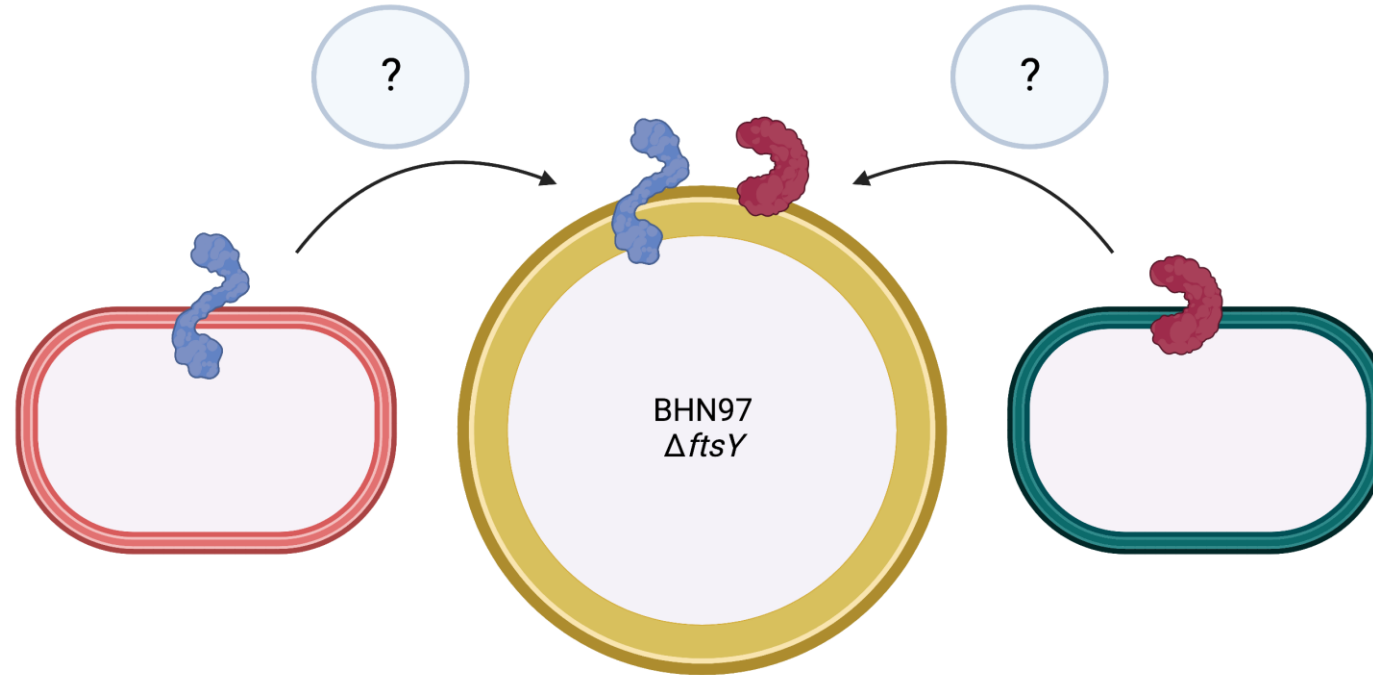


+ indicates LAV vaccine
- No LAV vaccine

Ear Titers



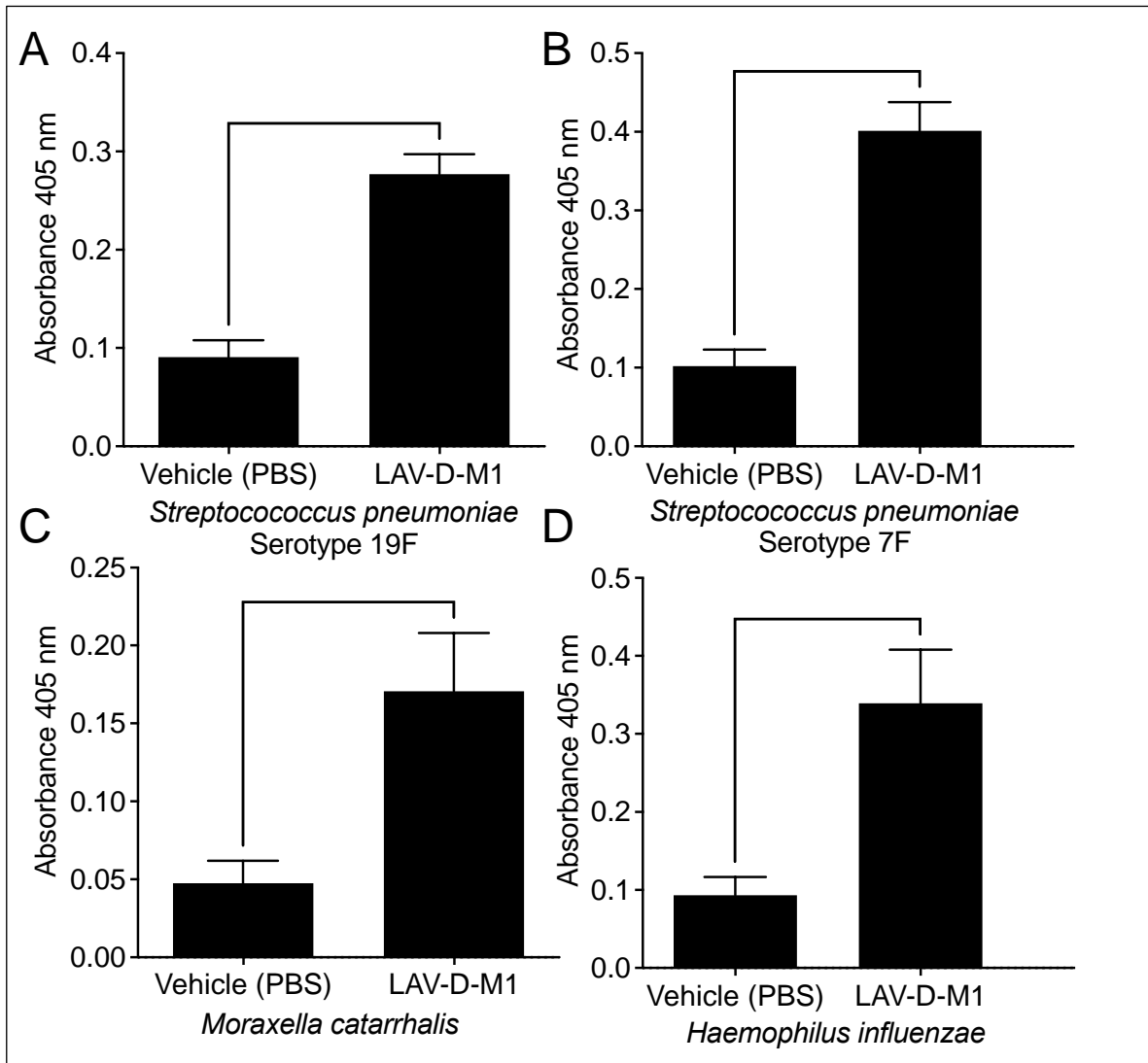
BHN97 Δ *ftsY*: A Potential Platform for Combination Vaccines



Multiple Challenges:

- 1) Codon optimization and regulation strategies vary dramatically between species
- 2) Different strategies and mechanisms for protein sorting and localization between different bacterial species, particularly Gram-positive and Gram-negatives

Can this platform be used to deliver multiple antigens from different species to the mucosal surface?

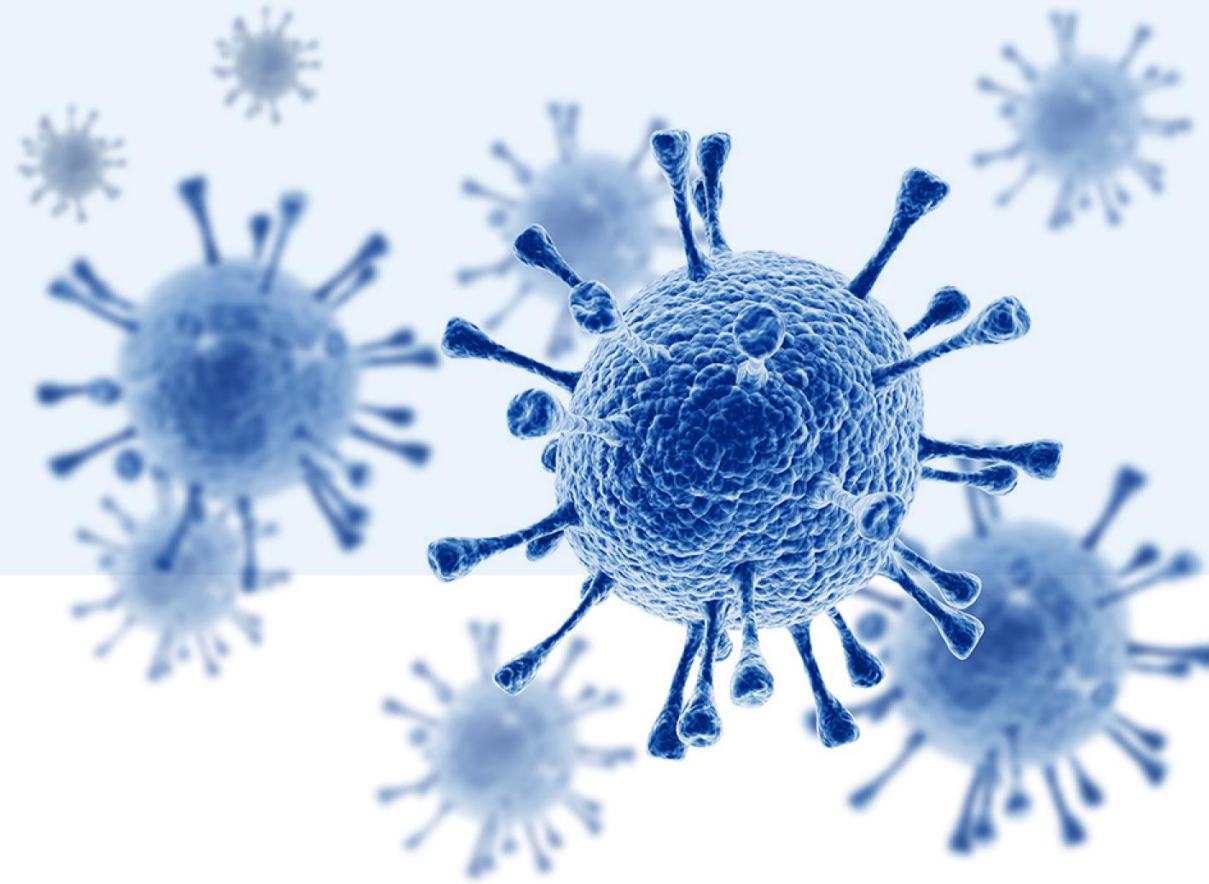


Multiple foreign epitopes can be expressed & are immunogenic *in vivo*

- Engineered live vaccine to express protective epitopes of *Haemophilus influenzae* and *Moraxella catarrhalis* on the cell surface of the live vaccines strain of pneumococcus
- Vaccine construct raised antibodies following intranasal vaccination against all three pathogens by ELISA

Conclusions

- ✓ Live attenuated pneumococcal vaccines elicited **robust protection** against both **invasive** (sepsis/bacteremia) and **not invasive** infections (AOM/pneumonia) media
- ✓ Protection across **heterologous serotypes**
- ✓ **Existing immunity** (vaccination or colonization) is **synergistic** and enhanced protection
- ✓ BWV-201 may serve as a **platform** to include other proteins from multiple bacterial species
- ✓ Potential for **combination vaccine** with disease-specific indication AOM or Pneumonia caused by different pathogens



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