VACCINE DEVELOPMENT AND IMMUNOBRIDGING

WHAT IS IT, WHY WE DO IT

….AND WHY IT MAKES US NERVOUS

Introduction

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DEFINITIONS (PART 1) - FUNDAMENTALS

- Biomarkers for vaccine development
  - Measurement that can substitute for the outcome of most importance (e.g., disease / death)
- Immunologic correlates of protection (CoP)
  - Mechanistic CoP ---- immunogenicity readout that is directly responsible for protection
  - Non-mechanistic CoP ---- immunogenicity readout that substitutes with reasonable fidelity to true CoP

NIH/FDA glossary, a **biomarker** is:

> "*A defined characteristic that is measured as an **indicator** of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.*"

Plotkin & Gilbert. CID 2012

DEFINITIONS: PART 2 --- CONTEXT OF USE

HOW WE THINK ABOUT CORRELATES OF PROTECTION DEPENDS WHERE YOU SIT IN THE PUBLIC HEALTH RESPONSE

	What problem need to be solved?	Who uses it to solve the problem?	What solutions can emerge?
1	Understanding of disease immunology	Immunologist	Understand target immune profile to provide protection
2	Enable selection of appropriate immunogen / adjuvant	Translational research	Optimized vaccine dossier to advance
3	Where efficacy not an option, enable licensure, improvement, target age-, dose- or dose-regimen changes	Clinical developer	Accelerated and expanded access to higher impact vaccine
4	Guide assessment of quality of manufacturing process	Manufacturer / CMC	Early identification of product problem, support manufacturing changes
5	Determine susceptibility of individual or population	Epidemiologist / policy-maker	Guide public health recommendations

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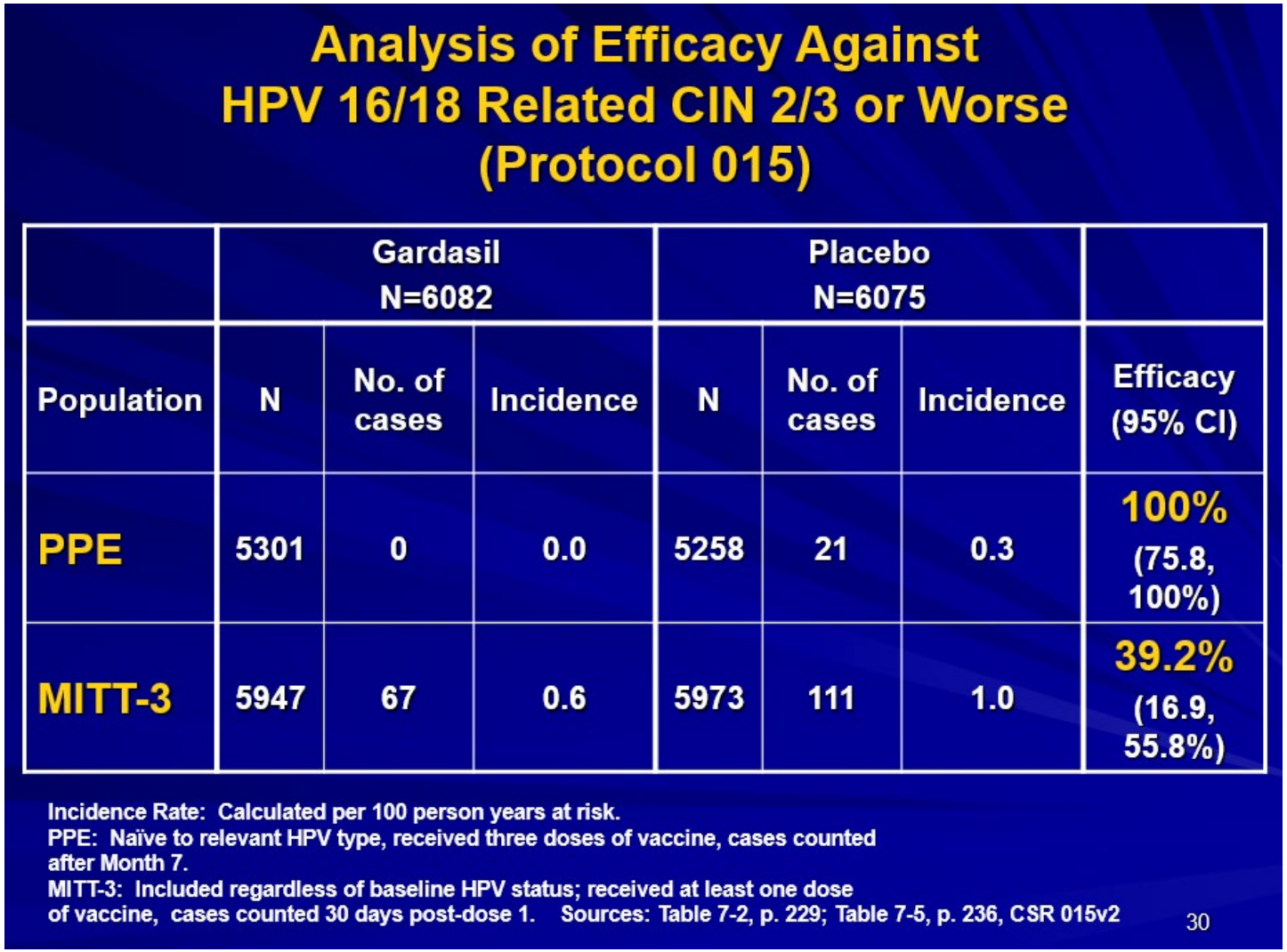
IMMUNOBRIDGING USE CASES – WHERE EFFICACY STUDIES NOT FEASIBLE

- Immunobridging trials:
  - Infer efficacy by comparing immune response marker(s) induced in new setting against comparator where efficacy has been demonstrated
  - New settings of use may include ----
    - Different target age or demographic group
    - Different dose, dose-regimen or formulation
    - Inclusion/exclusion adjuvant(?)
    - New vaccine (same or different platform (with justification))
  - Presumes disease pathogenesis, mechanism of protection are sufficiently similar across settings

IMMUNOBRIDGING USE CASES – IMMUNE MARKER CHOICE AND SUCCESS CRITERIA

- Method should be sensitive/specific with validated assay, typically target relevant virulence factor
- If immune marker robust and scientifically established to predict protection, seroresponse comparison may be sufficient
  - e.g., HepB ELISA >10 mIU/ml, Tetanus tox neut 0.1 IU/ml, JE PRNT ab 1:10
- Scientific consensus not clear but evidence strong for clinical relevance
  - More than one endpoint of same immune marker (GMT/C, seroresponse) augmented by RCDF descriptive curves to understand full population response
- Typical statistical success criteria (based on appropriate confidence interval of point estimate):
  - 1.5- or 2.0- fold non-inferiority margin (ratio of geometric means)
  - 10% or 5% non-inferiority margin (difference in seroresponse rates)

EXAMPLES OF IMMUNOBRIDGING(1): HPV VACCINES



Analysis of Efficacy Against HPV 16/18 Related CIN 2/3 or Worse (Protocol 015)

	Gardasil N=6082			Placebo N=6075			
Population	N	No. of cases	Incidence	N	No. of cases	Incidence	Efficacy (95% CI)
PPE	5301	0	0.0	5258	21	0.3	100% (75.8, 100%)
MITT-3	5947	67	0.6	5973	111	1.0	39.2% (16.9, 55.8%)

Incidence Rate: Calculated per 100 person years at risk.
PPE: Naïve to relevant HPV type, received three doses of vaccine, cases counted after Month 7.
MITT-3: Included regardless of baseline HPV status; received at least one dose of vaccine, cases counted 30 days post-dose 1. Sources: Table 7-2, p. 229; Table 7-5, p. 236, CSR 015v2

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- Efficacy study among women females aged 16 – 26 years
- "Global" study included subject in North and South America, Europe and parts of Asia
- Per protocol population included all doses and no evidence of prior infection

- Target age for use is 9 – 14 yo girls? How to demonstrate efficacy?

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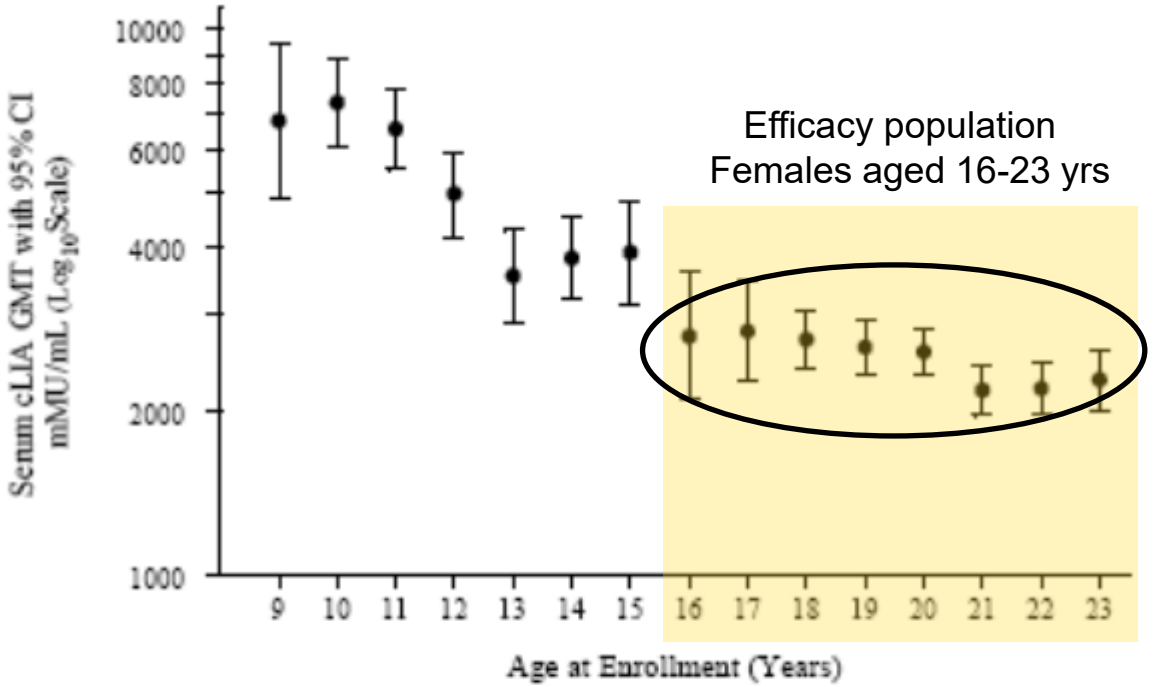

Number of Subjects Evaluable (n)															
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	67	131	165	142	165	150	109	80	135	423	506	594	550	527	375

HPV = Human papillomavirus; cLIA = Competitive Luminex immunoassay; GMT = Geometric mean titer; mMU = Milli Merck units.

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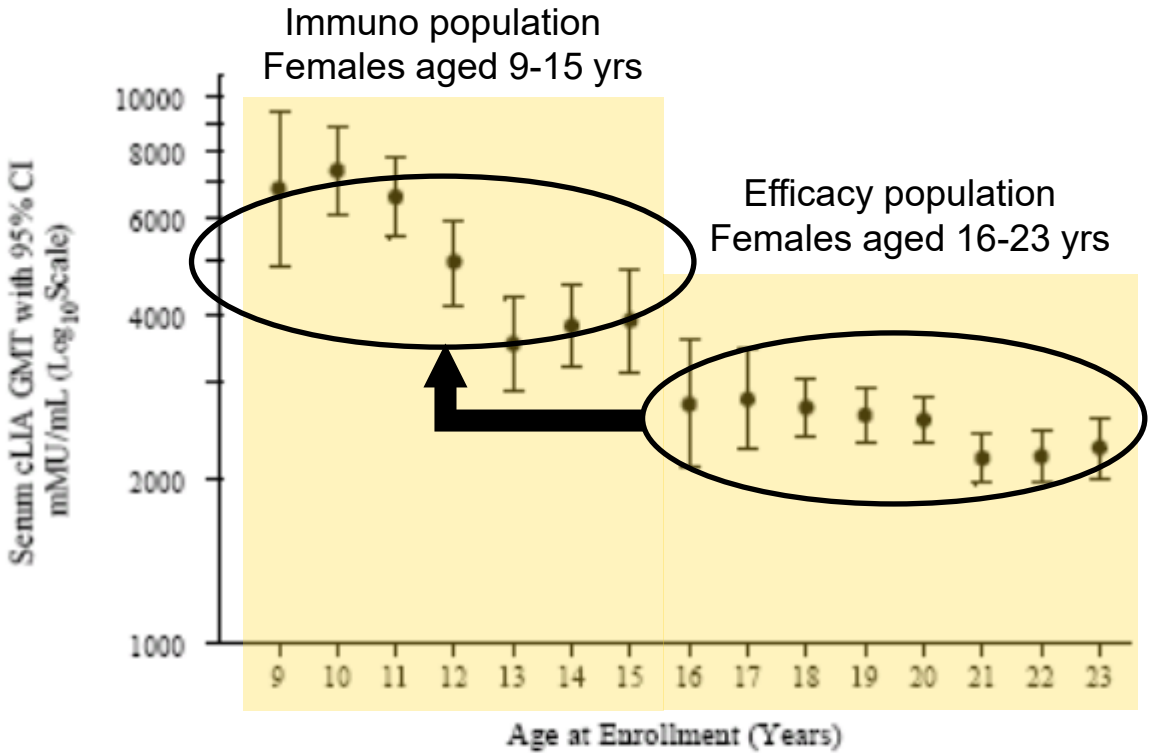

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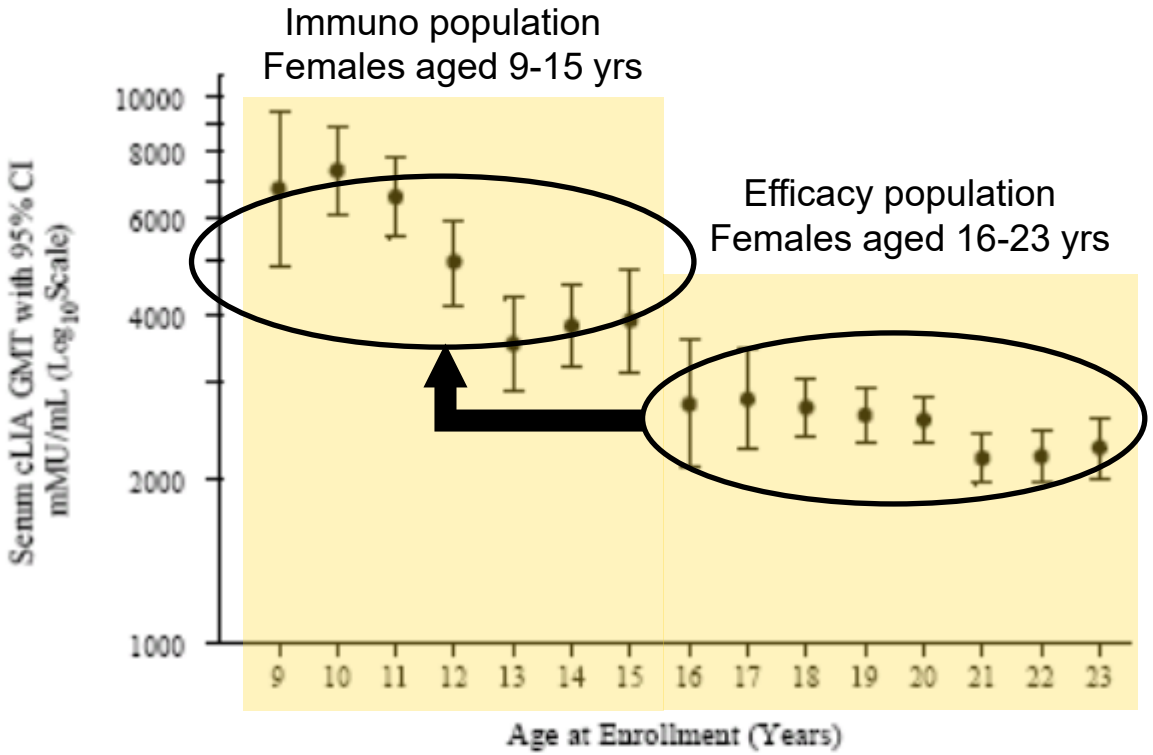

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- HPV GMT ratio for all 4 HPV types non-inferior among girls aged 9-15 years versus women aged 16-23 years
- HPV vaccine immunobridging considerations
  - Bridging “within” a vaccine platform across age groups
  - Mechanism of protection expected to be similar across populations
  - Neutralizing antibodies correlate well with binding antibodies
  - Virus “stable” over time
- HPV vaccine available to target population 5-7 years earlier

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EXAMPLES OF IMMUNOBRIDGING (2): TYPHOID CONJUGATE VACCINES

- Vi capsular polysaccharide (PS) vaccine licensed (aged 2 and above) – based on efficacy studies in Nepal and South Africa
- Similar to other PS-based vaccines, poorly immunogenic under 2 years of age
- IgG antibodies against capsule (Vi) thought to be basis of protection
- Vi-rEPA conjugate vaccine first typhoid conjugate vaccine developed
  - Demonstrated high efficacy (89%) among 2-5 yo and immunogenic in infants from 2 months of age -- Not advanced to commercial development

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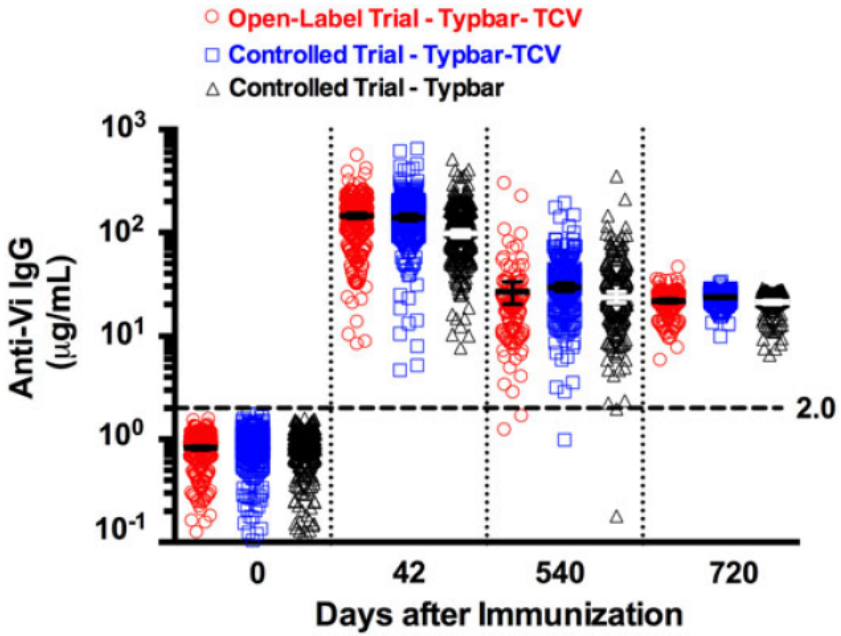

Figure 2. Serum anti Vi immunoglobulin G (IgG) antibodies in a subset of samples, estimated by the enzyme-linked immunosorbent assay method of Szu et al [23]. Dotted line represents protective level of anti-Vi antibodies. Geometric mean titers and 95% confidence intervals are shown for each time-point. Day 0, 42, 540, and 720 sample sizes were as follows: open-label trial, Typbar-TCV (302, 302, 122, and 198, respectively); controlled trial, Typbar-TCV (305, 305, 220, and 179, respectively); and controlled trial, Typbar (283, 283, 194, and 164, respectively).

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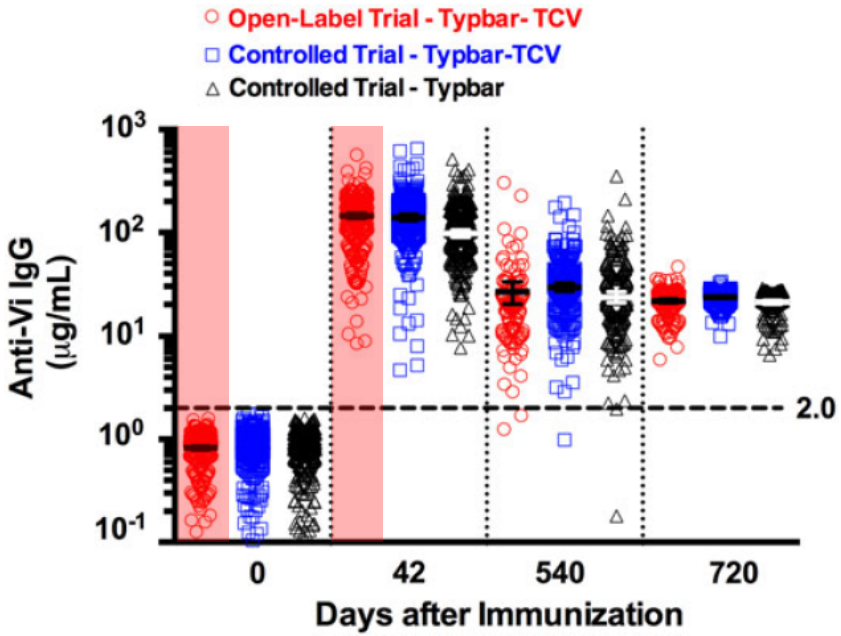

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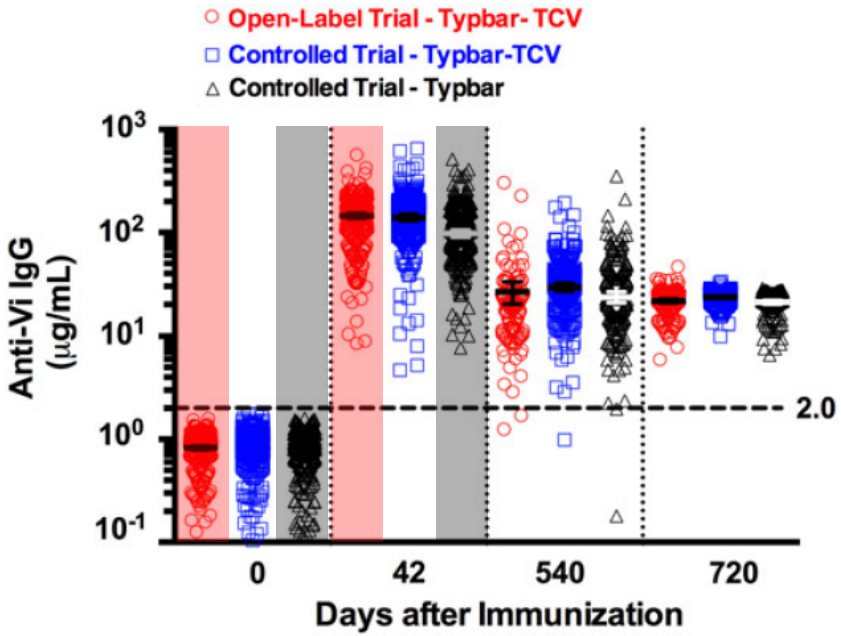
  - Immunobridge to older subjects receiving PS vaccines



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IMMUNOBRIDGING FOR VACCINE DEVELOPMENT

- Immunobridging approaches are an essential tool to advance product development --- can allow for:
  - Expanded access to broader populations to improve impact
  - Improved products to capture learnings and advance from first generation products
  - Optimization around dose, dose regimen/intervals and formulations
- Requires thoughtful science and understanding of immunologic basis of protection
- General pathways established although customization to new and changing pathogens and “immune landscape” requires attention
- Risks / benefits should be weighed including attention to “biocreep” or serial bridging