



Immunobridging to Evaluate Vaccines

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Purpose of Immunobridging

- **Regulatory and scientific approach to infer vaccine effectiveness through comparison of immune response marker(s) elicited by a vaccine under different sets of conditions**
- **Following demonstration of vaccine effectiveness in a clinical endpoint efficacy trial conducted under one set of conditions, immunobridging has been used to infer vaccine effectiveness under another set of conditions:**
 - Different age group or other demographic group than enrolled in the efficacy trial
 - Different dose level or dosing regimen than evaluated in the efficacy trial
 - Different formulation of the same vaccine (including addition or modification of antigens)
 - Concomitant administration with other vaccines (to evaluate for immune interference)
 - Different vaccine platform (in select circumstances)
- **When scientifically justified, can obviate the need to conduct another clinical endpoint efficacy trial under the new set of conditions**

Immunobridging Schematic

Reference group of study subjects

- Study population in whom clinical endpoint efficacy was demonstrated
- Authorized/approved vaccine formulation, dose level, and regimen

Test group of study subjects

- New study population, vaccine formulation, dose level, or regimen

(ideally, limit the number of variables that differ from the reference group)

Immune response marker(s)

Immune response marker(s)

Comparison via statistical hypothesis testing
(non-inferiority or superiority of test group to reference group)

Selection of Immune Marker(s)

- **Typically, an antibody response measured using a validated assay**
- **In situations when an immune response marker has been scientifically established to predict protection against disease, immunobridging analyses can evaluate seroresponse rate (= seroprotection rate)**
 - Has been required for immunobridging across vaccine platforms to infer effectiveness of new vaccines (e.g., Hepatitis B vaccines, based on anti-HBsAg ≥ 10 mIU/mL)
- **Immunobridging may be acceptable with use of immune response markers that are clinically relevant but not scientifically established to predict protection**
 - Depends on strength of evidence to support clinical relevance of the immune marker, and potentially additional measures to mitigate against uncertain or erroneous conclusions
 - More than one endpoint on the same immune marker may be evaluated to compare the range of responses between study groups (e.g., geometric mean titer to evaluate upper end of the range and seroresponse rate to evaluate lower end of the range)

Immunobridging Success Criteria

- **Should be sufficiently stringent to mitigate against erroneously concluding vaccine effectiveness**
- **Statistical success criteria most commonly used for regulatory purposes (evaluated on confidence interval around point estimate):**
 - 1.5-fold non-inferiority margin for ratio of geometric mean titers
 - 10% non-inferiority margin for difference in seroresponse (or seroprotection) rates
- **Less stringent (or more stringent) success criteria may be appropriate in certain situations**
- **Serial immunobridging, even with stringent success criteria, is best avoided due to the potential for biocreep**

Immunobridging Examples (COVID)

- **Emergency use authorization of Pfizer-BioNTech COVID-19 Vaccine for use in pediatric age groups (12-15 years, 5-11 years):**
 - Effectiveness inferred by immunobridging vs. 16–25 years reference group, using neutralizing antibody GMTs (1.5-fold margin) and seroresponse rates (10% margin)
 - For reduced dose level in ages 5-11 years, additional success criterion was a GMT ratio point estimate of at least 1
- **Emergency use authorization of booster doses for Pfizer-BioNTech and Moderna COVID-19 Vaccines:**
 - Effectiveness inferred by immunobridging vs. respective primary series reference group, using neutralizing antibody GMTs (1.5-fold margin) and seroresponse rates (10% margin)
 - For reduced dose level of Moderna booster dose, additional success criterion was a GMT ratio point estimate of at least 1

Immunobridging Examples (COVID)

- **FDA Guidance: Emergency Use Authorization for Vaccines to Prevent COVID-19**
 - Appendix 2 of the Guidance covers evaluation of modified vaccines to address emerging SARS-CoV-2 variants
 - Outlines use of neutralizing antibody GMT and seroresponse rate endpoints, and associated immunobridging success criteria vs. prototype (reference) vaccine, to infer effectiveness of modified vaccine primary series or booster dose
 - Immunobridging can be conducted in a single age group (e.g., younger adults 18-55 years of age), and effectiveness extrapolated to other age groups for which the prototype vaccine has been authorized/approved



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