

# Progress in the Development of a Vi-CRM<sub>197</sub> Conjugate Vaccine

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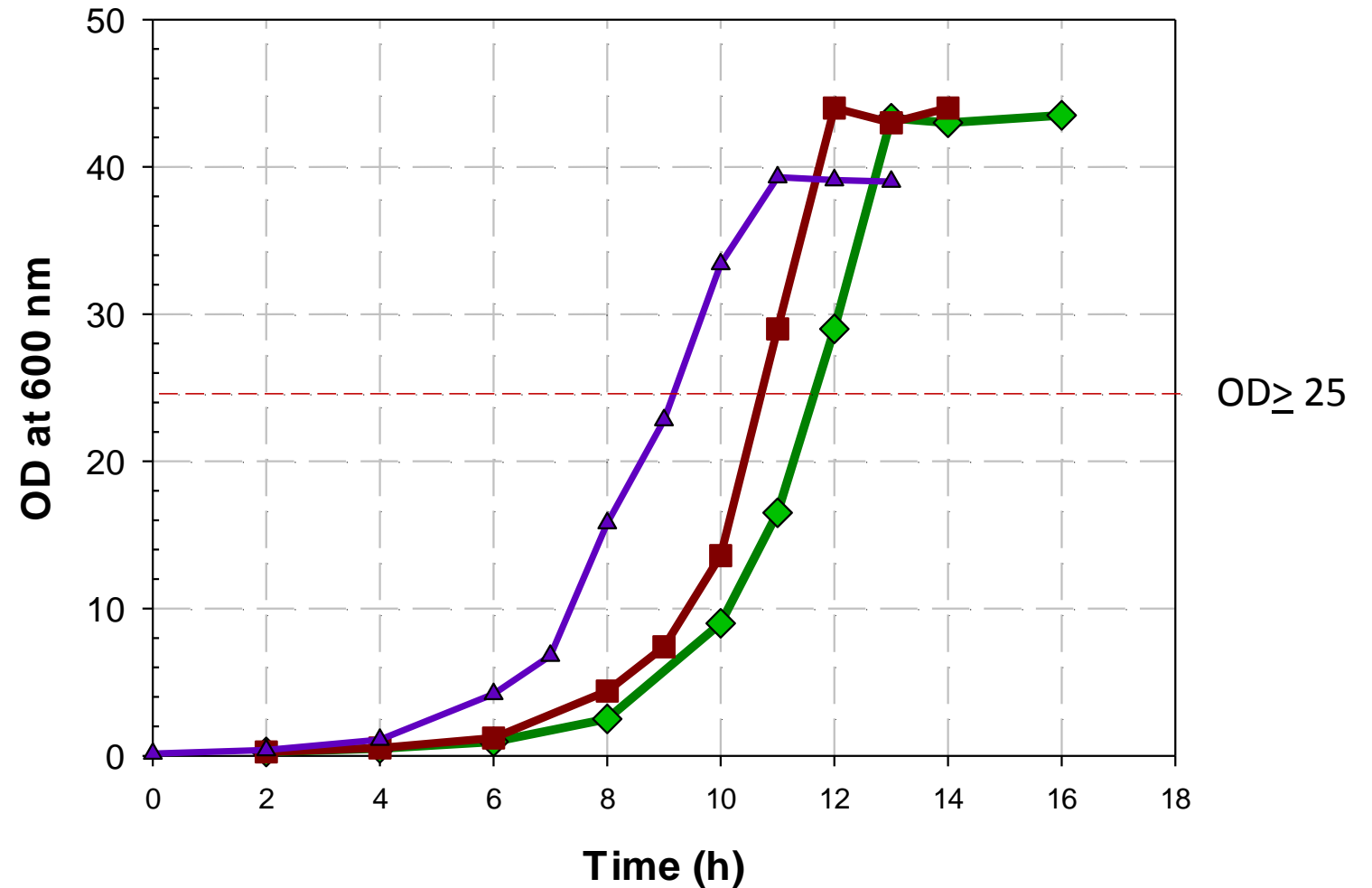
# BioE's TCV Monovalent Project

## *Vi source*

- Source of Vi is *Citrobacter freundii*
- Citrobacter generates Vi PS which is structurally identical to the Vi PS
- High yields, BSL1 provides significant advantages
- Purified Vi PS meets WHO TRS requirements

# Vi Fermentation Lots Summary: GMP Campaign

- GMP MCB & WCB
- All regulatory approvals (DCGI) in place for Clin Mfg
- Fermentation carried out at Pilot Scale in GMP Pilot Plant
- Three consecutive GMP lots completed, lots met acceptance criteria



# BioE's TCV Monovalent Project

## *Carrier Protein used for Conjugation*

- CRM<sub>197</sub> used as a carrier protein
- BioE has developed two technology platforms for CRM<sub>197</sub>
  - Recombinant C7 based technology platform
  - Recombinant *E.coli* based technology platform
- Both technologies result in purified CRM<sub>197</sub> which meets predetermined quality attributes
- Both CRM<sub>197</sub> technologies have been presented to Indian Regulatory Agency RCGM (Review Committee on Genetic Manipulation)
- BioE is proceeding with the recombinant C7 derived CRM<sub>197</sub> for the TCV program

# BioE's TCV Monovalent Project

## *Acceleration Strategy*

- BBIL has recently introduced Typbar-TCV<sup>®</sup> in the market
- Typbar-TCV<sup>®</sup> contains 25 µg Vi antigen conjugated to TT
- Typbar-TCV<sup>®</sup> is licensed children  $\geq$  6 months of age and adults as a single dose administered intramuscularly
- WHO TRS defines an immunological threshold value:
  - Seroconversion (4-fold)
  - 4.3 µg/ml anti-Vi antibody measured by ELISA appears to be associated with a high level of sustained protection

BioE's TCV is targeted as a single dose with 25 µg Vi conjugated to CRM<sub>197</sub>. It is targeted to be licensed in children > 6 months of age and adults.

# Vi-CRM<sub>197</sub> Conjugates: Critical to Quality

## Bulk Conjugate

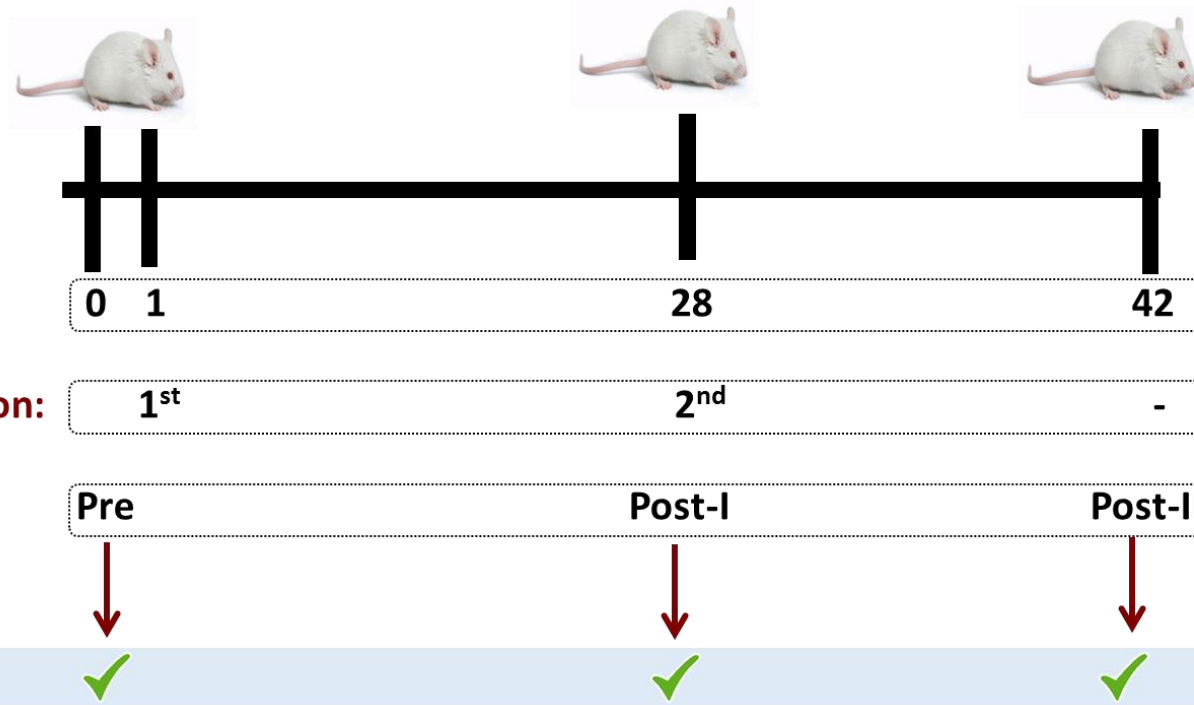
- Identity
- Vi Concentration
- Vi:CRM<sub>197</sub> ratio
- Size
- % Free PS
- O-Acetylation level
- Residual reagents
- Endotoxin
- Stability

## Formulated Bulk

- Identity
- Vi Concentration (25 µg/0.5 mL)
- Vi:CRM<sub>197</sub> ratio
- Size
- % Free PS
- Sterility
- Osmolarity, pH
- Stability

TCV DS and DP meets Indian Pharmacopoeia (IP) and WHO TRS recommendations

# Balb/c Mice Immunization Plan for TCV



Day:

Immunization:

Sera:

Post-III

ELISA:

## Study Plan:

- Mice:
  - Inbred Balb/C Female SPF Mice
  - ≤ 6weeks old
  - 20 mice/per group
- Route: Subcutaneous
- Dose: 1/10 SHD
- Sera collected by terminal bleeding

## Samples Evaluated:

- PBS
- Vi PS
- Vi-CRM
- Typbar-TCV<sup>®</sup>

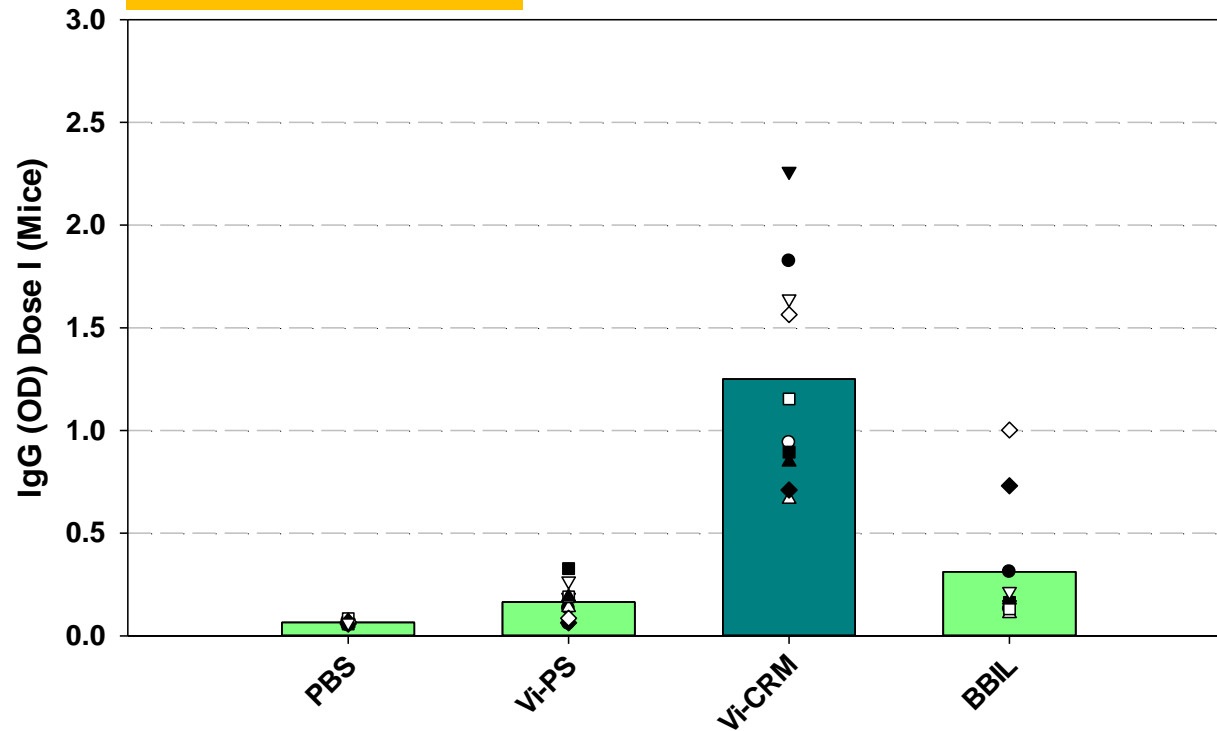
## Responses Evaluated:

- Anti-Vi IgG (Fold increase over Placebo and over PS only)
- Secondary antibody response

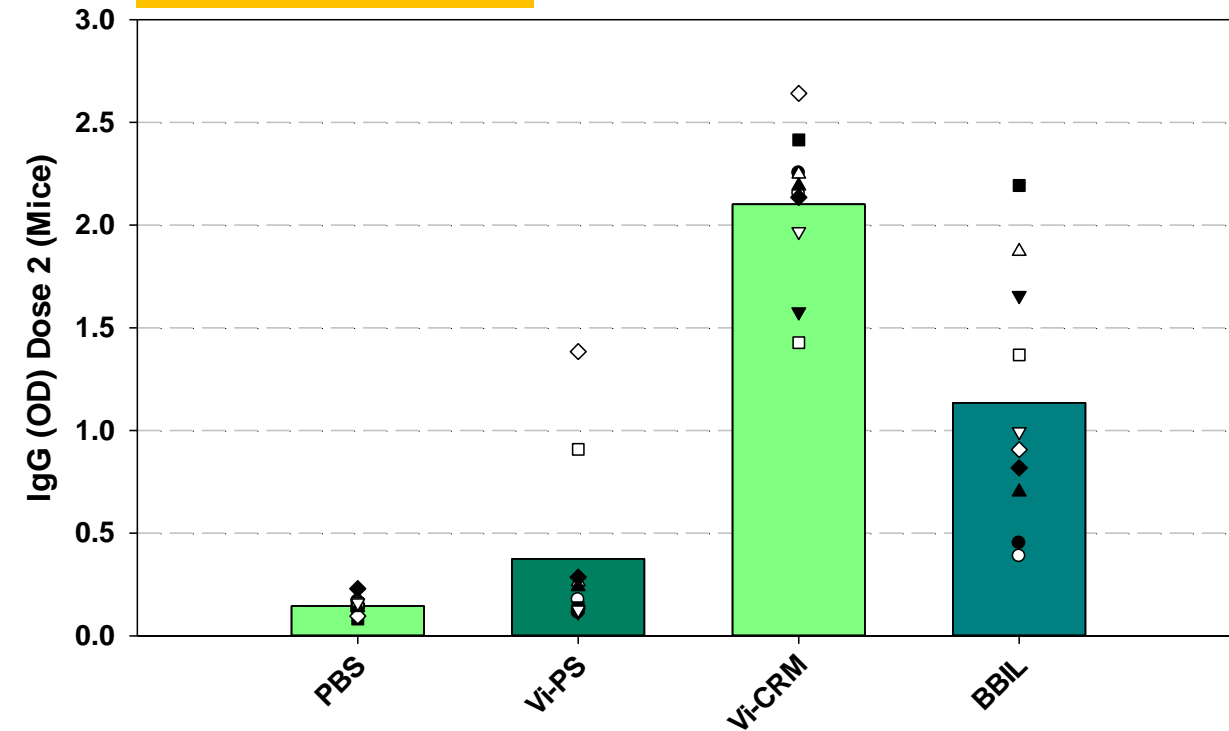
# Dose 1 and Dose 2 – Anti Vi IgG, Mice

## Experiment Set 1

Post dose 1



Post dose 2

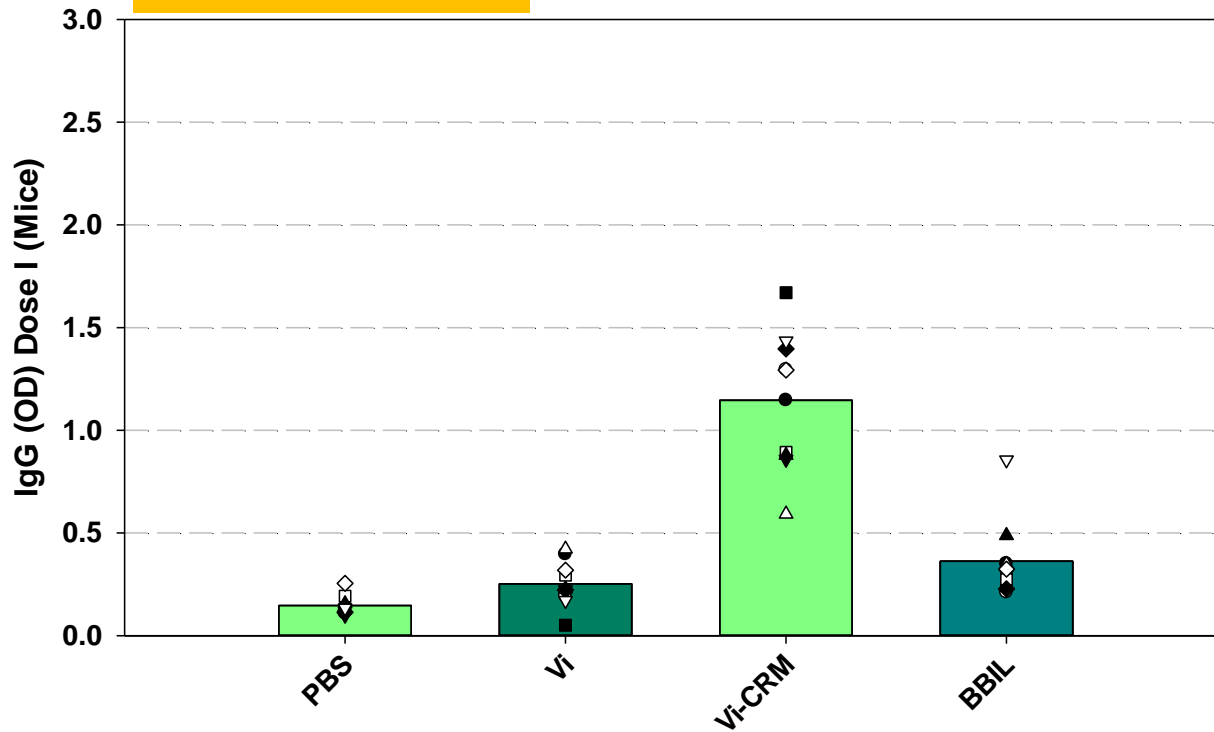




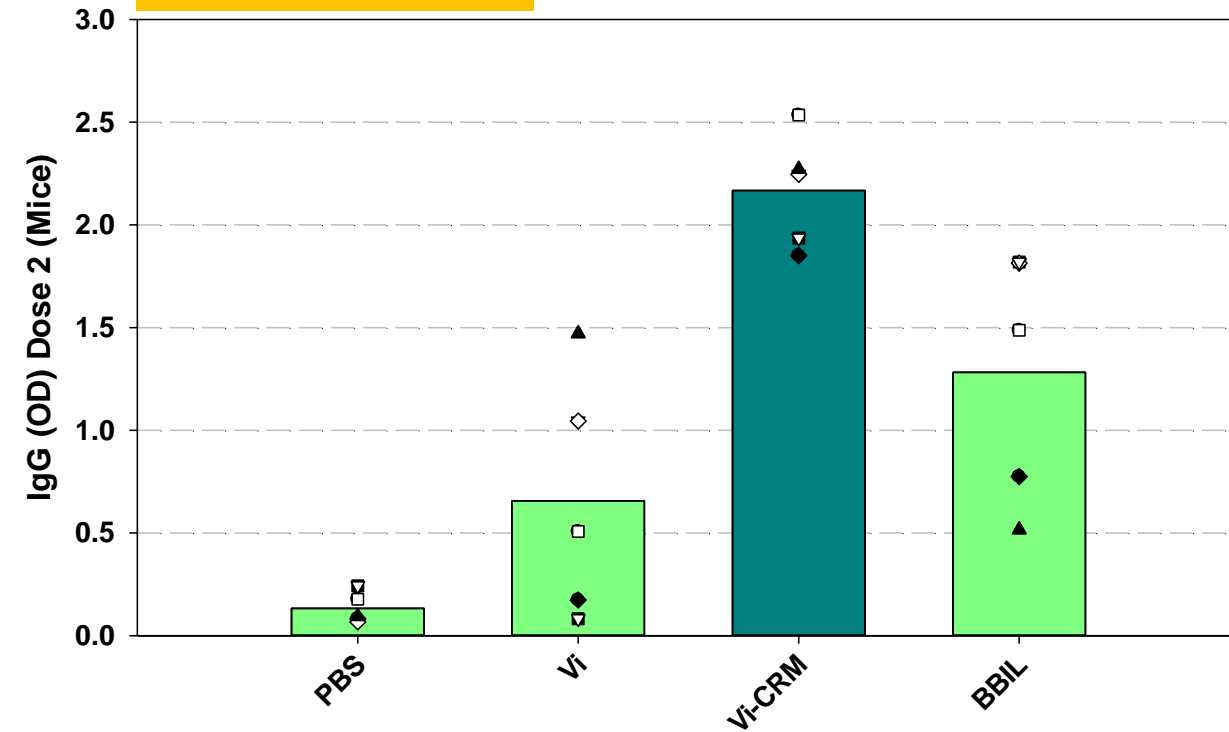
# Dose 1 and Dose 2 – Anti Vi IgG, Mice

## Experiment Set 2

Post dose 1



Post dose 2



# Initial Immunogenicity Evaluation

## Vi-CRM<sub>197</sub>: Conclusions

- BE Vi-CRM<sub>197</sub> is highly immunogenic in mice. BE Vi-CRM<sub>197</sub> preclinical immunogenicity results meet WHO TRS requirements.
- BE Vi-CRM<sub>197</sub> elicits a secondary antibody response in mice.
- Similar immunogenicity patterns observed in Rabbits
- BE Vi-CRM conjugate has similar characteristics to other reported conjugates
  - Vi-TT by BBIL
  - Vi-rEPA by Szu et al
  - Vi-CRM by Eubiologics
  - Vi-DT by IVI

# TCV Monovalent Project: Current Status

- RCGM approval for use of recombinant CRM<sub>197</sub>
- PCT completed, submitted to NRA
- Process development and pilot-plant scaleup complete
- GMP clinical material made and on stability (both DS & DP)
- Phase I dossier submitted to DCGI. Expect clinical studies to start 2Q17
- Large scale clinical manufacturing in 3Q-4Q'17
- Target NRA licensure 2018
- Target WHO PQ 2019

# THANK YOU

