# Correlation of screening (S/N) and titer results to reduce analysis costs and increase delivery of patient immunogenicity data

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# Introduction

**Immunogenicity:**

The ability of a molecule or substance (drug) to provoke an immune response.

**Anti-Drug Antibody (ADA):**

The immune response in terms of antibody production directed against the drug.

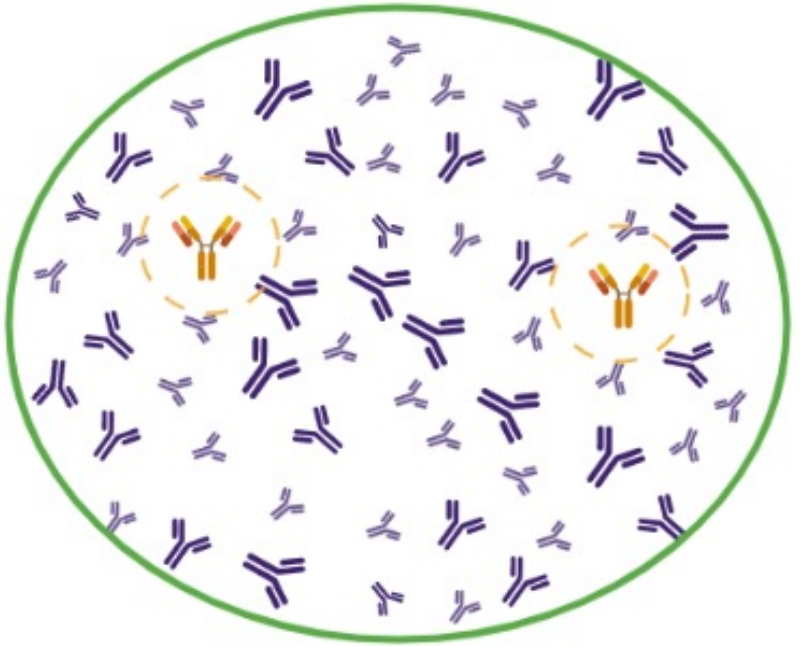
- Anti-Drug Antibodies
  - Binding Ab
  - Neutralising Ab

**A) Binding Antibodies (BAb):**

Includes all polyclonal isotypes capable of binding to the therapeutic.

**B) Neutralising (NAb):**

Sub-population of the total BAb that are specifically capable of inhibiting the functional activity of the therapeutic by binding to the active site.



# How we assess immunogenicity

Usually assessed with a multi-tiered approach:

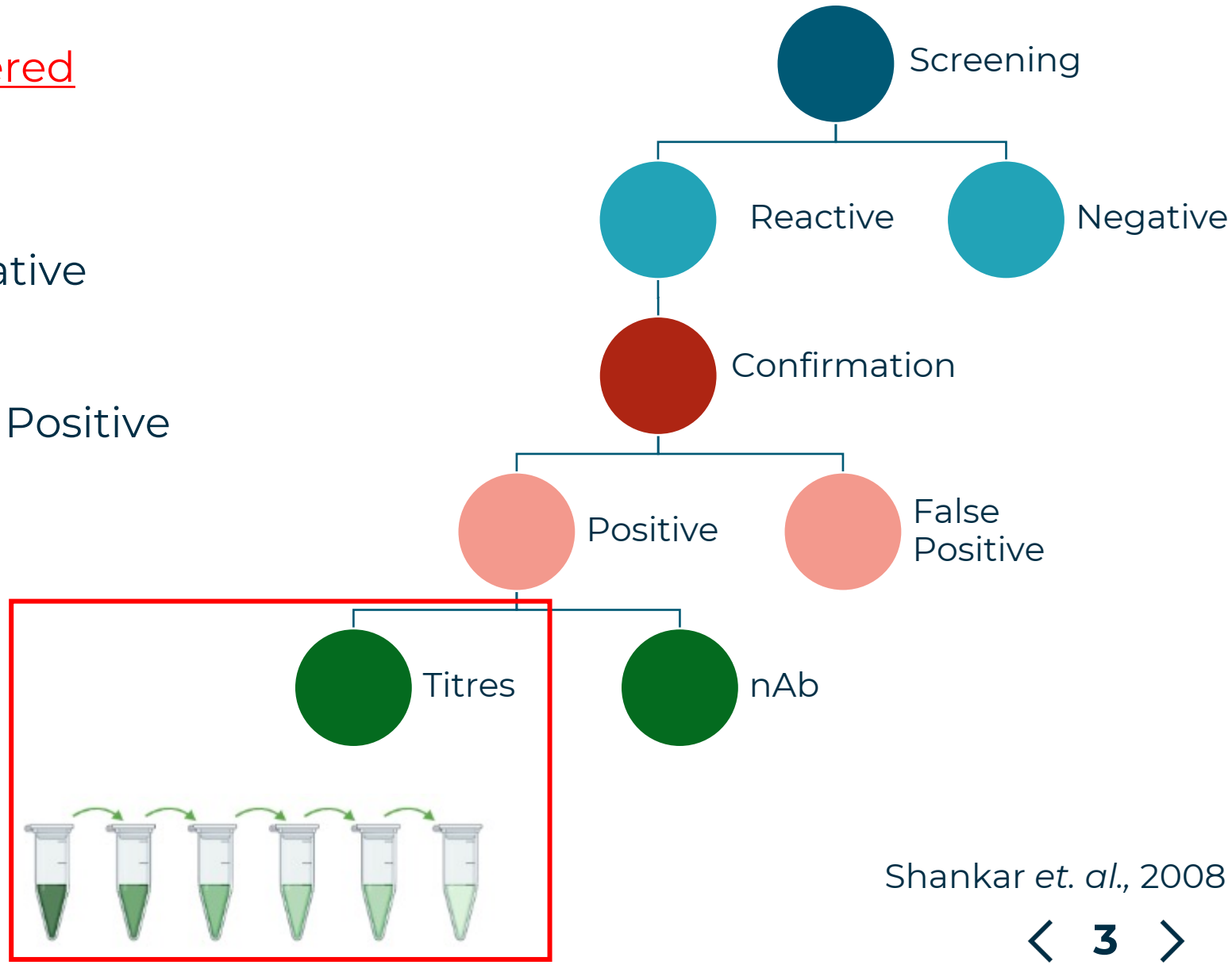
- **Screening**

  Use SCP : Reactive / Negative

- **Confirmation**

  Use CCP : Positive / False Positive

- **Characterizing**
  - **Titre**
  - Neutralizing




Shankar *et. al.*, 2008

# Titre assessment:

Characterization of the ADA response is an important component of immunogenicity as it provides pharmaceutical companies a semi-quantitative measure of the ADA response

However titre assessment has limitations:

- Extensive sample handling
- Increased sample volume requirements
- Poor precision in the lower assay range
- Increased analysis costs
- Serial dilutions do not provide “discrete” data (i.e. there is a big difference between each fold-change)

# Titre assessment: New Approach

An alternative approach gaining popularity:

- ✓ Involves no extra dilution steps
- ✓ Reduces reagent and sample consumption and requirements
- ✓ Saves analyst time
- ✓ Provides quasi-quantitative titre magnitude data = can be more accurately correlated with PK and PD data

Screening Signal-to-Noise Ratio (S/N) ~ ADA magnitude

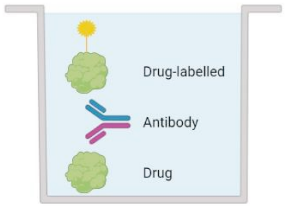
Ratner, 2009; Manning *et. al.*, 2022

# Aim

To determine whether **S/N ratio** could be used as a **suitable alternative to traditional titer assessment**, by determining the **correlation** between the S/N ratios obtained during Screening analysis, and their respective titres, for samples confirmed ADA positive.

# Method and Materials

- Data from various projects, obtained using a single method were combined
- Method was validated according to applicable white papers and regulatory agency guidance available at the time of validation*

| Assay Platform | Assay Format | Modality | Immunogenicity Risk | Study Population | Immunogenicity Rate | Cut Point |
|---|---|---|---|---|---|---|
| MSD (ECL) | Bridging   | mAb | Low | Autoimmune Disease | ~6% | Floating* |

**Shankar et. al., 2008; FDA guideline (2018); FDA guideline (2019); EMA guideline(2011)*

# Statistical Analysis

- A selected portion of ADA-positive samples underwent traditional titre analysis
  - Samples chosen, represented the full range of dosing time points and subject demographics
  - Titre results were generated for 105 samples
- The strength of the relationship between S/N and titer was assessed using log-transformed S/N and titer data and Spearman's and Pearson's' rank correlation coefficient (r).
- A correlation coefficient **≥0.7** was considered a **strong positive correlation** between ADA S/N and titre.

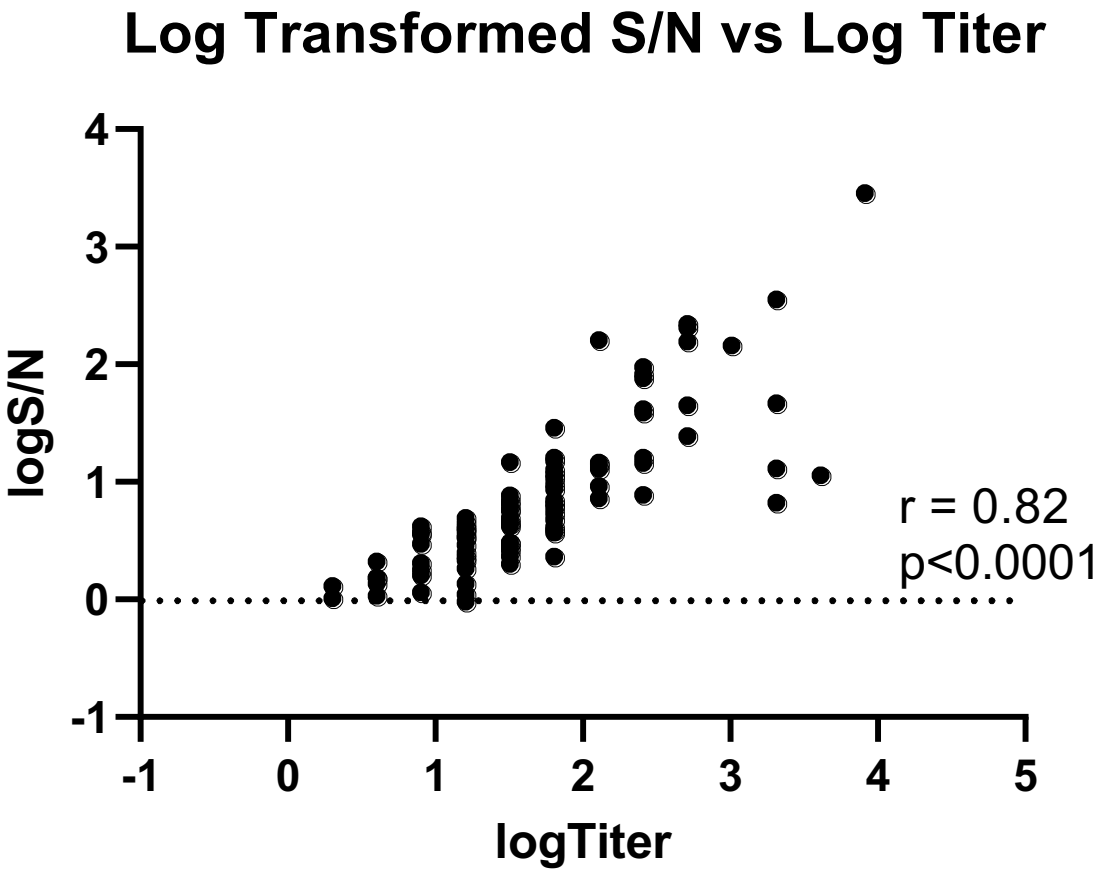




Ratner, 2009; Manning *et. al.*, 2022

# Results and Discussion

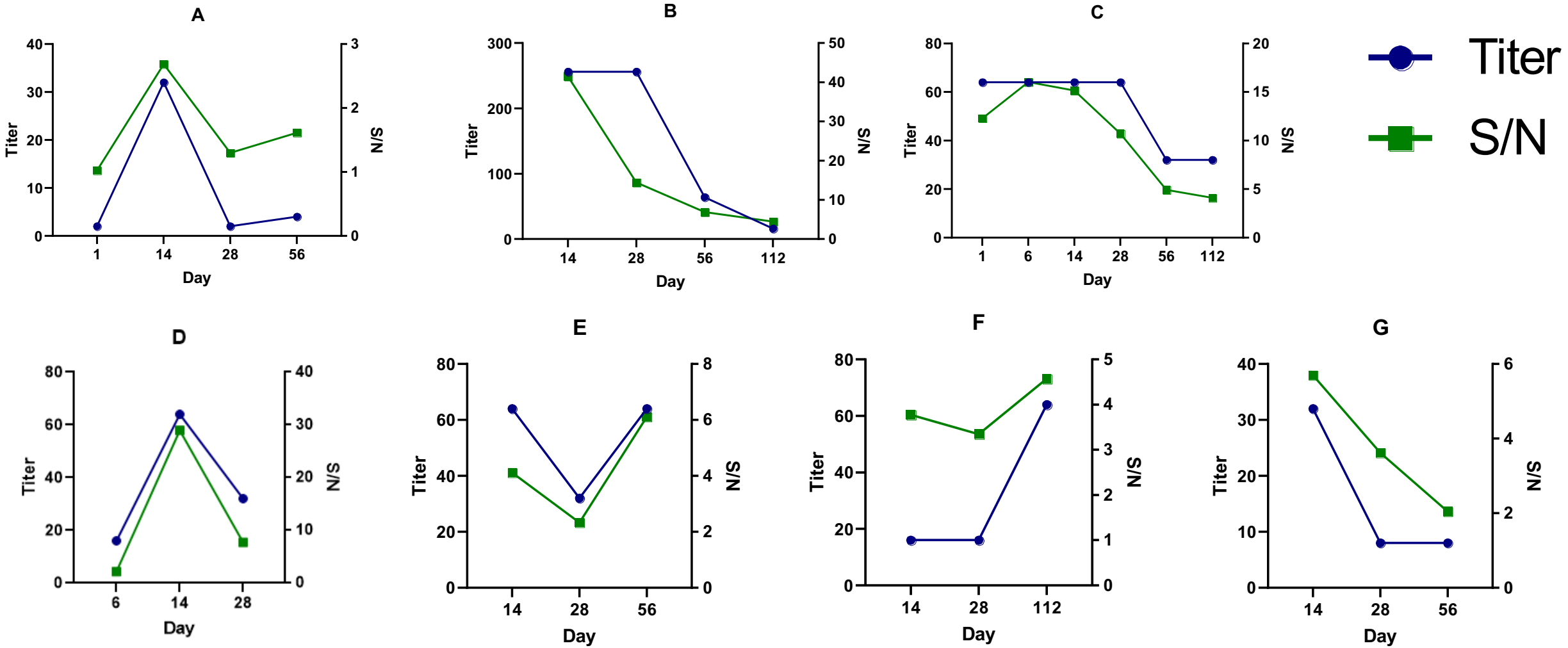
A strong **positive correlation** was established between the titre value (i.e. ADA magnitude) and ADA S/N




| Log S/N vs. Log Titre | |
|---|---|
| **Pearson** | |
| r | 0.821 |
| 95% confidence interval | 0.747 to 0.875 |
| R squared | 0.674 |
| P (two-tailed) | <0.0001 |
| P value summary | **** |
| Significant? (alpha = 0.05) | Yes |
| Number of XY Pairs | 105 |

# Results and Discussion

## S/N and Titre portray similar trends in **individual subjects**



# Summary & Conclusions

- Our analysis contributes to available literature supporting the use of S/N as a quasi-quantitative alternative to traditional titre determination
- This approach positively impacts the delivery of clinical data (meeting DBL deadlines) and the reduction of assay costs by up to 90%
- Retrospective analysis of other studies could provide further support to implement this approach as the new “titre assessment” technique (where permitting) – we urge all companies with data available to perform this analysis and publish where possible
- **Considerations:**
    - **Dilution linearity**
    - **Broad dynamic range – Prozone (Hook effect), ELISA more susceptible**
    - **Drug tolerance**
- With good supporting data, regulators are open to accepting this data as an alternative

# References


1. Shankar *et al.*, (2008). Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products.

2. Ratner (2009). The correlation coefficient: Its values range between +1/-1, or do they?

3. Manning *et al.*, (2017). Assay signal as an alternative to titer for assessment of magnitude of an antidrug antibody response.

4. Manning *et al.*, (2022). Comparison of Titer and Signal to Noise (S/N) for Determination of Anti-drug Antibody Magnitude Using Clinical Data from an Industry Consortium.