Statistical Techniques for Immunogenicity Analysis in Vaccine Studies

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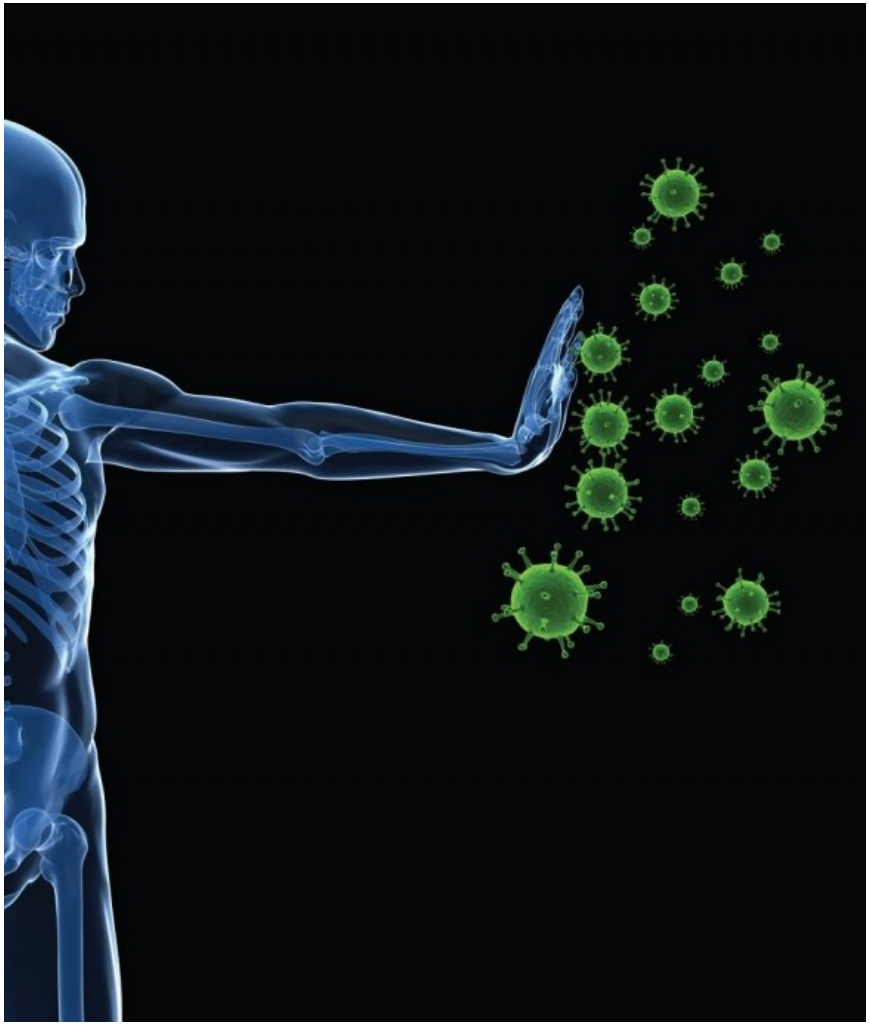
Immunogenicity of a Vaccine

Ability of a vaccine

to produce an

immune response

in the body



What is a Vaccine?

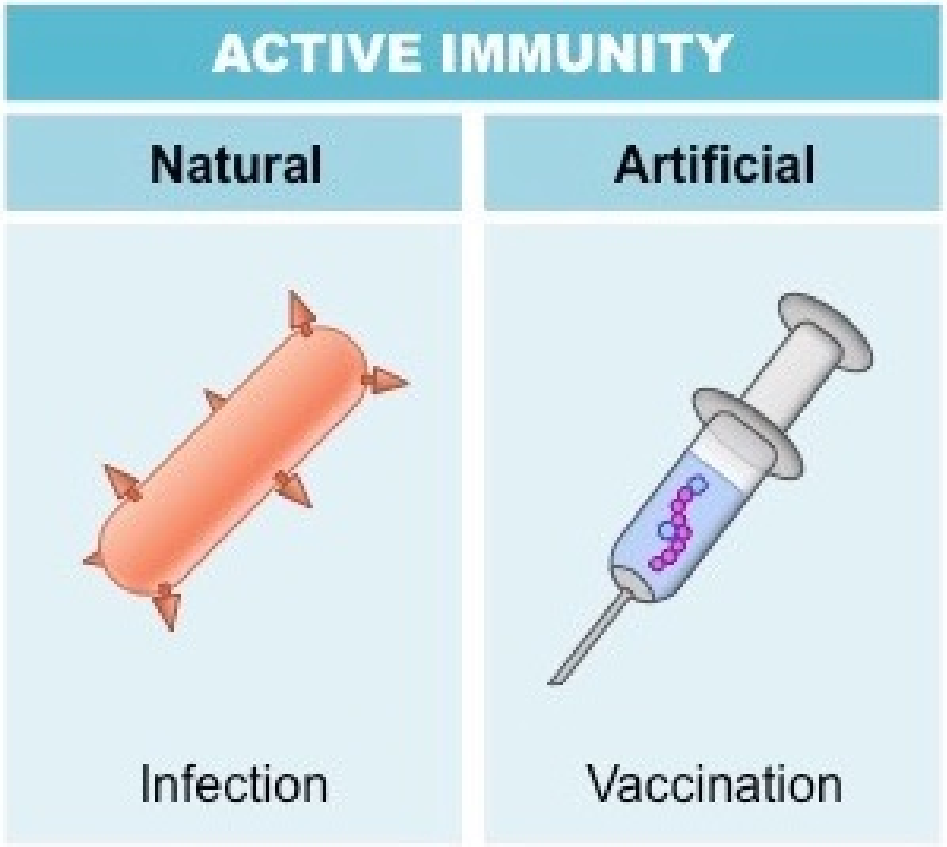
A biological preparation

that provides

active acquired immunity

to a particular disease

What is a Vaccine?



Vaccine Action

Vaccine (Contains Passive/Inactive form of Virus)

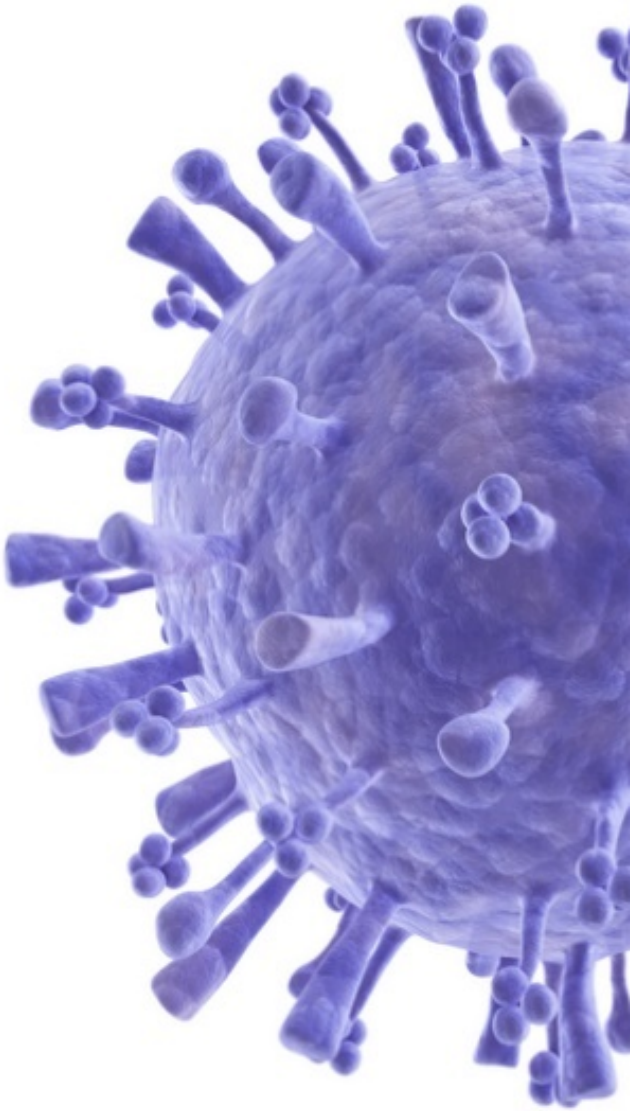
Actual Attack from Active Virus

Human Body

Vaccines are Specific to Strains

Viruses are characterized by **strains** (genetic variants) that are constantly mutating

Vaccines are meant to protect against specific strains of a virus



Immunogenicity of a Vaccine

Ability of a vaccine

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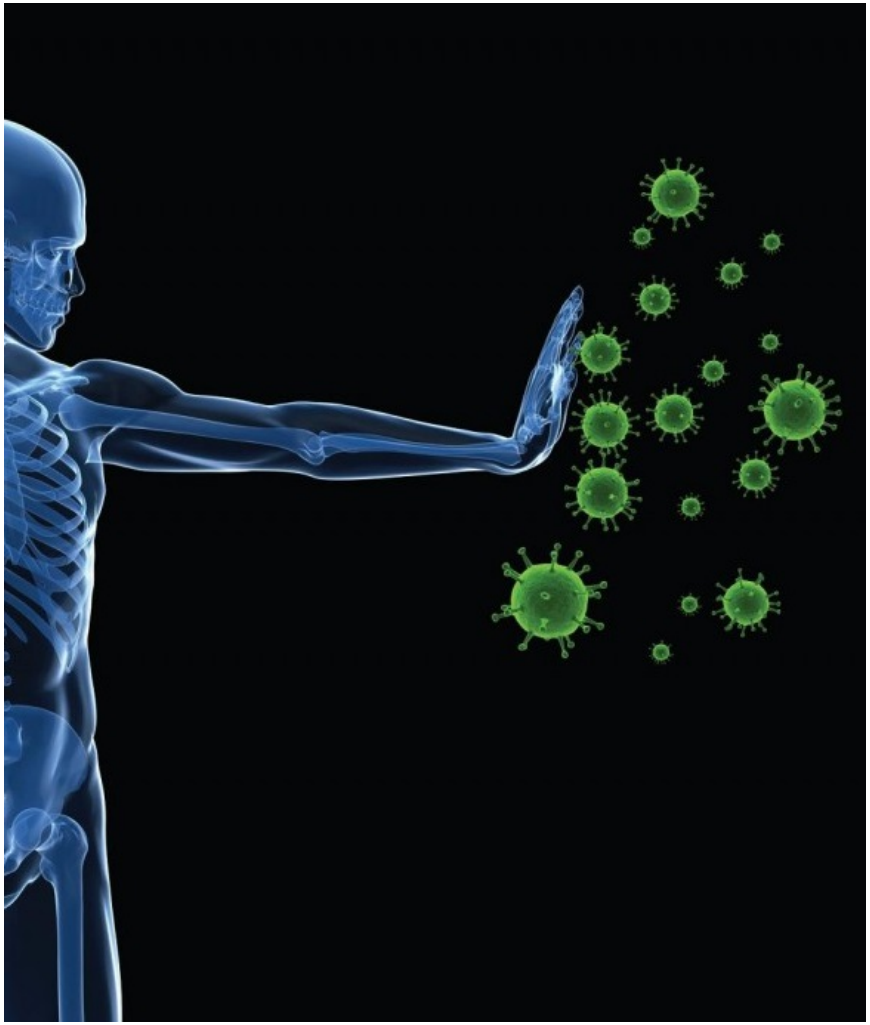


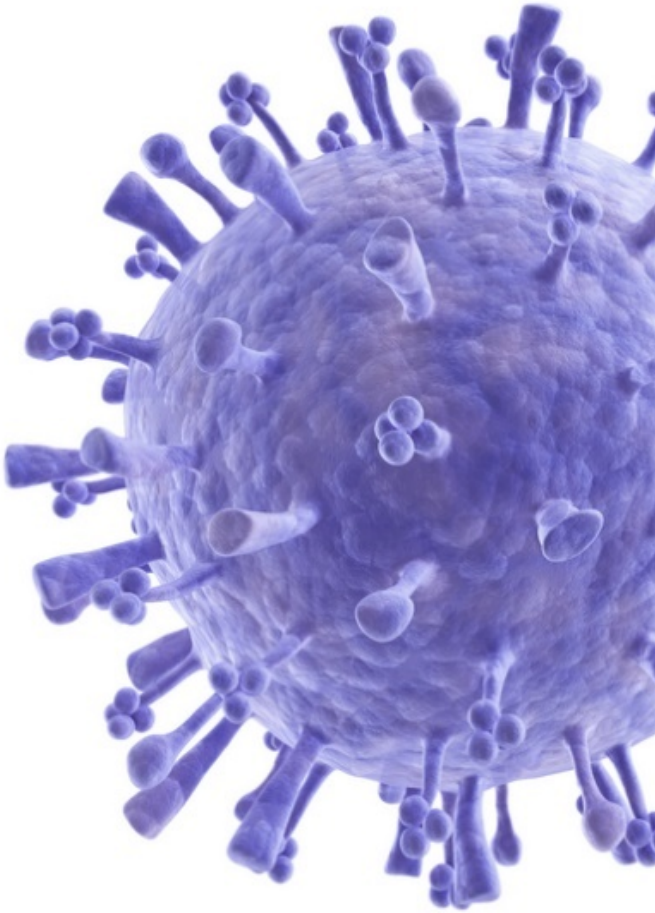
Measuring Immune Response

Using Assays

- Assays are tests that assess antibody count in the blood
- Immune response of the body is measured as increased antibody count
- Assays are specific to virus strains

Sample Vaccine - Influenza (Flu) Vaccine

Seasonal Flu vaccine updated every flu season because the virus is constantly changing



Immunogenicity for Influenza Vaccine

The HI Assay

FDA Guidelines* recommend:

HI (Hemagglutination Inhibition) assay for each strain

The HI assay is a lab test that quantifies the

relative concentration of viruses / antibodies

in the blood

*Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

Immunogenicity for Influenza Vaccine

The HI Assay

Result of the HI assay is a titer value

Sample titer values are 1:10, 1:20, 1:40 etc.

For analysis purpose, the values 10, 20, 40 are used

The higher the titer value, higher is the antibody concentration

Hence higher is the immunity

Immunogenicity Endpoints

For Influenza Vaccine

FDA Guidelines* recommend:

Comparison of **geometric mean** (GMT) HI titer value

Comparison of percentage of subjects achieving a specific HI titer value (1:40)

Comparison of **seroconversion** rates

*Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

Example Influenza Vaccine Study

Phase III randomized, blinded study to evaluate safety and immunogenicity of **Influenza virus vaccine**

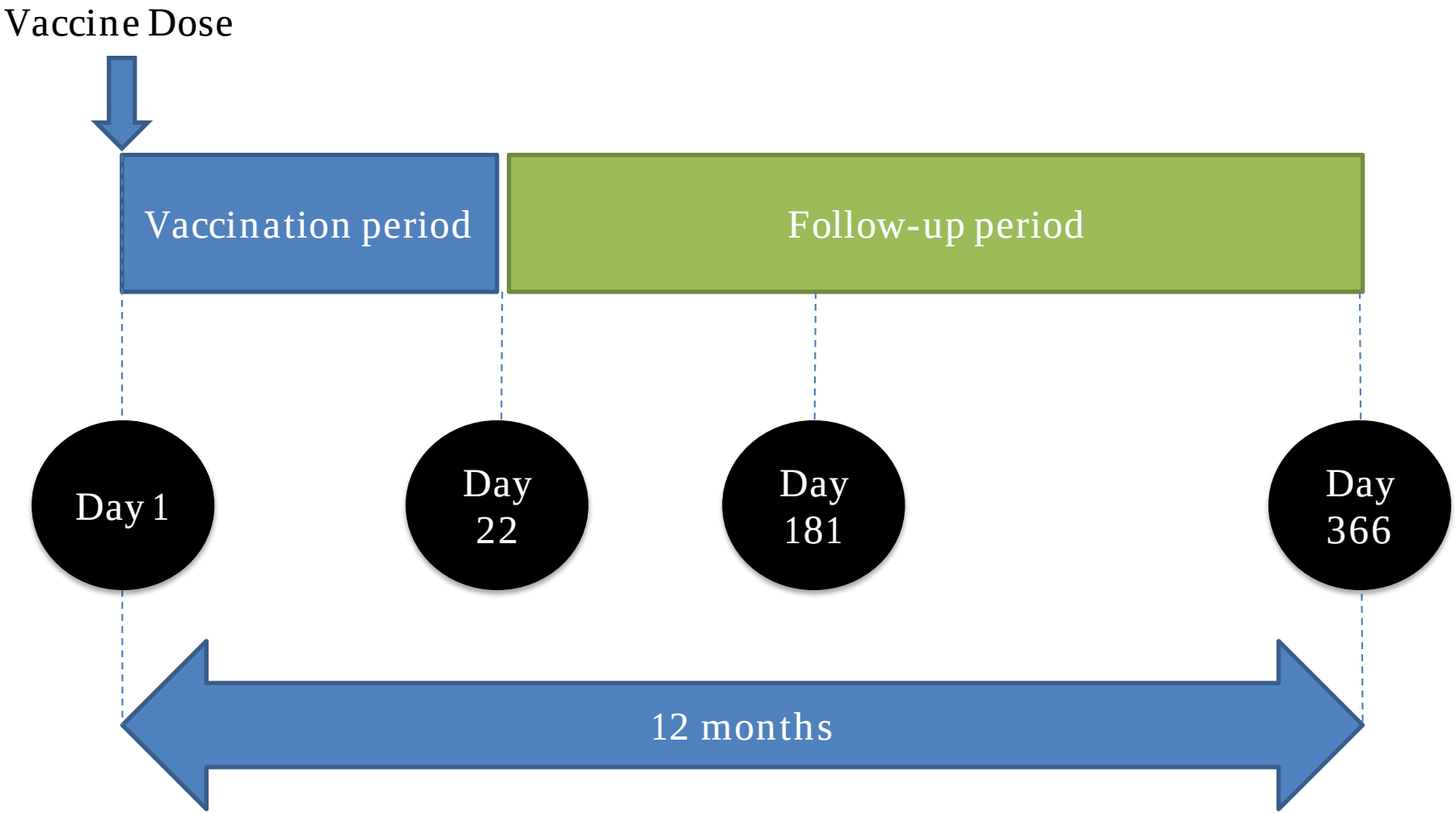
Age group

12 months - 7 years (Healthy volunteers)

2 Treatment arms:

Study vaccine vs. Comparator

Example Study: Visit Schedule



Example Study: Safety Endpoints

Safety - Adverse events:

Solicited AEs

Unsolicited AEs

Example Study: Immunogenicity Endpoints

Endpoint 1:

Treatment comparison of percentage of subjects achieving threshold antibody count (Titer of 1:40)

Endpoint 2:

Treatment comparison of geometric mean Titers (GMTs) and geometric mean ratios (GMRs)

Endpoint 3:

Treatment comparison of seroconversion rates

Immunogenicity Endpoints

Endpoint 1:

Treatment comparison of percentage of subjects achieving threshold HI Titer (1:40) on Day 22 and Day 181

Analysis uses PROC CATMOD for getting adjusted difference in percentage for post-baseline Titer value

Percentage of Subjects with HI Titers >= 40 and Vaccine Group Differences at Day 22

Strain: A/Texas/2001	Study Drug	Comparator
Day 1		
Number	xxx	xxx
Percentage	xx.x%	xx.x%
95% CI	(xx.x% – xx.x%)	(xx.x% – xx.x%)
N	xxx	xxx
Day 22		
Number	xxx	xxx
Percentage	xx.x%	xx.x%
95% CI	(xx.x% – xx.x%)	(xx.x% – xx.x%)
N	xxx	xxx
Vaccine Comparison at Day 22		
Adjusted Difference		xx.x%
Adjusted 95% CI		(xx.x% – xx.x%)
Unadjusted Difference		xx.x%
Unadjusted 95% CI		(xx.x% – xx.x%)

PROC UNIVARIATE

PROC UNIVARIATE

PROC CATMOD

PROC FREQ

Percentage of Subjects with HI Titers >= 40 and Vaccine Group Differences at Day 181

Strain: A/Texas/2001	Study Drug	Comparator
Day 1		
Number	xxx	xxx
Percentage	xx.x%	xx.x%
95% CI	(xx.x% – xx.x%)	(xx.x% – xx.x%)
N	xxx	xxx
Day 181		
Number	xxx	xxx
Percentage	xx.x%	xx.x%
95% CI	(xx.x% – xx.x%)	(xx.x% – xx.x%)
N	xxx	xxx
Vaccine Comparison at Day 181		
Adjusted Difference		xx.x%
Adjusted 95% CI		(xx.x% – xx.x%)
Unadjusted Difference		xx.x%
Unadjusted 95% CI		(xx.x% – xx.x%)

Immunogenicity Endpoint 1

The CATMOD procedure

```
PROC CATMOD DATA=HI_DATA;
    BY STRAIN VISITN;
    RESPONSE 0 1;
    MODEL RESP=TRT RISK AGEGRP BASE;
    CONTRAST "STUDY vs. COMP." TRT 2/EST=PARM;
RUN;
```

Input dataset has post-baseline data only (Day 22 & 181)

RESP is Y for HI titer >= 1:40
N otherwise

Treatment

Risk Status

Age Group

Baseline (Day 1) HI Titer value

Percentage of Subjects with HI Titers >= 40 and Vaccine Group Differences at Day 22

Strain: A/Texas/2001	Study Drug	Comparator
Day 1		
Number	xxx	xxx
Percentage	xx.x%	xx.x%
95% CI	(xx.x% – xx.x%)	(xx.x% – xx.x%)
N	xxx	xxx
Day 22		
Number	xxx	xxx
Percentage	xx.x%	xx.x%
95% CI	(xx.x% – xx.x%)	(xx.x% – xx.x%)
N	xxx	xxx
Vaccine Comparison at Day 22		
Adjusted Difference		xx.x%
Adjusted 95% CI		(xx.x% – xx.x%)
Unadjusted Difference		xx.x%
Unadjusted 95% CI		(xx.x% – xx.x%)

PROC UNIVARIATE

PROC UNIVARIATE

PROC CATMOD

PROC FREQ

Immunogenicity Endpoint 1

Unadjusted difference using Miettinen-Nurminen CIs

```
PROC FREQ DATA=HI_DATA;
   BY STRAIN VISITN;
   TABLES TRT*RESP / RISKDIFF (CORRECT CL=(MN));
RUN;
```

Input dataset has post-baseline data only (Day 22 & 181)

RESP is Y for HI titer >= 1:40
N otherwise

Immunogenicity Endpoint 1

CATMOD provides adjusted difference in percentage and CIs

Adjustment for variation due to the co-variates

Risk Status (Healthy/At High Risk)

Age Group (< 36 months, >= 36 months)

Baseline value

Estimate using PROC FREQ does not allow for adjustment

Immunogenicity Endpoint 1

For an accelerated approval,

FDA Guidelines* recommend:

For adults < 65 years of age and for the pediatric population:

The lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%.

*Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

Sample Table

Percentage of Subjects with HI Titers >= 40 and Vaccine Group Differences at Day 22

Strain: A/Texas/2001	Study Drug	Comparator
Day 1		
Number	194	69
Percentage	62.8%	25.3%
95% CI	(57.1%, 68.2%)	(20.2%, 30.9%)
N	309	273
Day 22		
Number	296	185
Percentage	98.0%	72.0%
95% CI	(95.7%, 99.3%)	(66.1%, 77.4%)
N	302	257
Vaccine Comparison at Day 22		
Adjusted Difference		2.2%
Adjusted 95% CI		(1.8%, 2.5%)
Unadjusted Difference		26.0%
Unadjusted 95% CI		(20.6%, 32.0%)

Immunogenicity Endpoints

Endpoint 2:

Treatment comparison of geometric mean Titers (GMTs) and geometric mean ratios (GMRs)

Geometric means more suitable for comparison of actual titer values

Since titer values are in multiples of 2: 10, 20, 40, 80 and so on.

Geometric Mean Titers and Vaccine Group Ratios at Day 22
(Page 1)

Strain: A/Texas/2001	Study Drug	Comparator
Day 1		
Adjusted GMT	xxx.x	xxx.x
Adjusted 95% CI	(xxx.x – xxx.x)	(xxx.x – xxx.x)
Median	xxx	Xxx
Min, Max	xx, xxx	xx, xx
N	xxx	Xxx
Day 22		
Adjusted GMT	xxx.x	xxx.x
Adjusted 95% CI	(xxx.x – xxx.x)	(xxx.x – xxx.x)
Median	xxx	Xxx
Min, Max	xx, xxx	xx, xx
N	xxx	Xxx

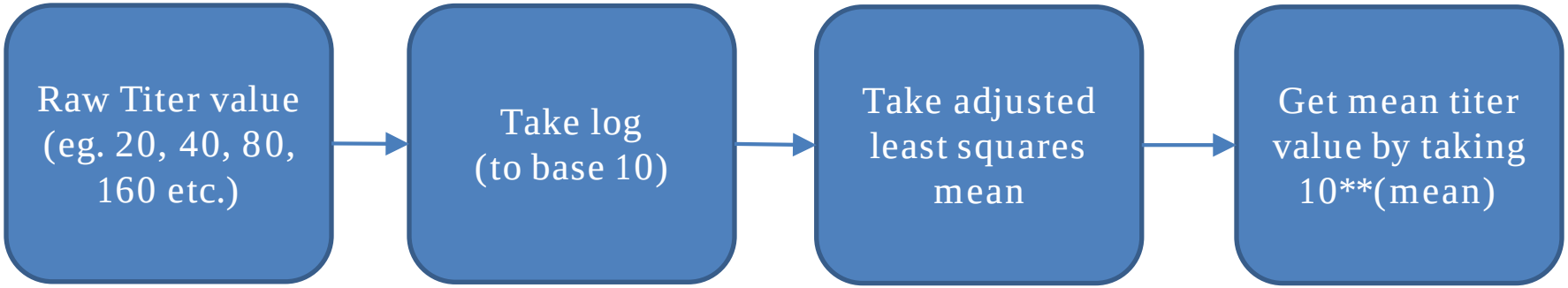
PROC GLM

PROC UNIVARIATE

PROC GLM

PROC UNIVARIATE

Geometric Mean Titers (Adjusted GMTs)



Geometric Mean Titers (Adjusted GMTs)

The GLM procedure

```
PROC GLM DATA=HI_LOG;
   CLASS TRT AGEGRP RISK;
   MODEL AVAL=TRT AGEGRP RISK BASE;
   LSMEANS TRT / CL ALPHA=0.05;
   ODS OUTPUT LSMEANCL=LSM;
RUN;
```

Input data contains only log Titer values for each visit (Day 1 or 22)

Log Titer value

Age Group

Risk Status

Log of Baseline (Day 1) HI Titer value

Geometric Mean Titers and Vaccine Group Ratios at Day 22

(Page 2)

	Study Drug	Comparator
Day 22/Day 1		
Adjusted GMR	xxx.x	xxx.X
Adjusted 95% CI	(xxx.x – xxx.x)	(xxx.x – xxx.x)
Median	xxx	xxx
Min, Max	xxx, xxx	xxx, xxx
N	xxx	xxx
Vaccine Comparison at Day 22		
Adjusted Ratio of GMTs		xxx.x
Adjusted 95% CI (GMTs)		(xxx.x – xxx.x)
Adjusted Ratio of GMRs		xxx.x
Adjusted 95% CI (GMRs)		(xxx.x – xxx.x)

PROC GLM

1

PROC GLM

2

Adjusted Geometric Mean Ratios (GMRs) 1

The GLM procedure

```
PROC GLM DATA=LOG_DATA;
   CLASS TRT AGEGRP RISK;
   MODEL LR2B=TRT LOGBASE AGEGRP RISK;
   LSMEANS TRT / CL ALPHA=0.05;
   ODS OUTPUT LSMEANCL=LSM;
RUN;
```

Input data contains log (AVAL/BASE) values for Day 22

Log of (AVAL/BASE)

Log of BASE Titer value (Day 1)

Geometric Mean Titers and Vaccine Group Ratios at Day 22

(Page 2)

	Study Drug	Comparator
Day 22/Day 1		
Adjusted GMR	xxx.x	xxx.X
Adjusted 95% CI	(xxx.x – xxx.x)	(xxx.x – xxx.x)
Median	xxx	xxx
Min, Max	xxx, xxx	xxx, xxx
N	xxx	xxx
Vaccine Comparison at Day 22		
Adjusted Ratio of GMTs		xxx.x
Adjusted 95% CI (GMTs)		(xxx.x – xxx.x)
Adjusted Ratio of GMRs		xxx.x
Adjusted 95% CI (GMRs)		(xxx.x – xxx.x)

PROC GLM

2

Geometric Mean Titers (Adjusted GMTs)

2

The GLM procedure

```
PROC GLM DATA=HI_LOG;
   CLASS TRT (REF='Comp') AGEGRP RISK;
   MODEL AVAL=TRT AGEGRP RISK;
   LSMEANS TRT / CL ALPHA=0.05;
   ODS OUTPUT LSMEANDIFFCL=LSMDIFF;
RUN;
```

Input data contains only log Titer values for each visit (Day 22)

Log Titer value

Sample Table

Geometric Mean Titers and Vaccine Group Ratios at Day 22

(Page 1)

Strain: A/Texas/2001	Study Drug	Comparator
Day 1		
Adjusted GMT	227.71	114.24
Adjusted 95% CI	(185.0, 280.3)	(92.2, 141.5)
Median	280.0	140.0
Min, Max	5.0, 2560.0	5.0, 2560.0
N	309	273
Day 22		
Adjusted GMT	1119.63	753.12
Adjusted 95% CI	(998.7, 1255.2)	(669.0, 847.8)
Median	1280.0	640.0
Min, Max	302	257
N		

Sample Table
Geometric Mean Titers and Vaccine Group Ratios at Day 22
(Page 2)

	Study Drug	Comparator
Day 22/Day 1		
Adjusted GMR	6.28	4.23
Adjusted 95% CI	(5.6, 7.0)	(3.8, 4.8)
Median	4.5	4.6
Min, Max	0.1, 512.0	0.5, 256.0
N	302	257
Vaccine Comparison at Day 22		
Adjusted Ratio of GMTs		1.49
Adjusted 95% CI (GMTs)		(1.3, 1.7)
Adjusted Ratio of GMRs		1.49
Adjusted 95% CI (GMRs)		(1.3, 1.7)

Immunogenicity Endpoint 2

For an accelerated approval,

FDA Guidelines* recommend:

The upper bound of the two-sided 95% CI on the ratio of the GMTs

($GMT_{comparator}$/$GMT_{study\ vaccine}$) should not exceed 1.5.

*Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines

Statistical Techniques for Immunogenicity Analysis in Vaccine Studies

Summary

- What is a Vaccine and Immunogenicity
- Sample Study (Flu vaccine)
  - Visit Schedule
  - End points
- Immunogenicity Endpoints
- FDA Guidelines for Immunogenicity endpoints
- Adjusted vs. Unadjusted percentage difference (CATMOD & FREQ)
- Adjusted GMTs and GMRs (PROC GLM)

Questions

THANK YOU