SPECIAL STATISTICAL AND PROGRAMMING CONSIDERATIONS IN VACCINE TRIALS

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Outline

- Vaccine Study in General
- Statistical and Programming Considerations in Vaccine Trials
- Programming Strategy for qHPV Vaccine Studies
- Summary

Vaccine Study in General

Introduction

- **A vaccine is a product that stimulates a person's immune system to produce immunity to a specific disease, protecting the person from that disease.**

  ---- US CDC

- A vaccine typically contains an agent that stimulates the body's immune system to recognize the agent as a threat, destroy it, and keep a record of it so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

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Clinical Development of Vaccine

Clinical development is built on rigorous ethical principles, with an emphasis on vaccine safety as well as efficacy.

- **Phase I (n ~ 10-100)**
  - ✓ Involve small groups of adults to receive the candidate vaccine
  - ✓ Assess the *safety and tolerability* of the candidate vaccine and to determine the type and extent of immune response that the vaccine provokes

- **Phase II (n ~ 100-500)**
  - ✓ Involve a larger group of individuals
  - ✓ Study the candidate vaccine's *safety, immunogenicity*, proposed doses, schedule of immunizations, and method of delivery.

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Clinical Development of Vaccine (Cont'd)

- **Phase III (n ~ 1,000–100,000)**
  - ✓ Involve thousand to tens of thousands of people
  - ✓ Are randomized and double blind; the candidate vaccine is tested against a placebo
  - ✓ Evaluate *efficacy* within the population of interest
  - ✓ Continue to assess safety and tolerability

  **** Multi-valent vaccine (against virus that has multiple strains) may require strain-specific analyses.***

- **Phase IV (Post-marketing Study)**
  - ✓ Happens after the vaccine has been licensed and introduced into use.
  - ✓ Aims to detect rare adverse effects as well as to assess long-term efficacy.

Comparisons between Vaccines and Drugs Development

- Vaccines are developed, tested, and regulated in a very similar manner to drugs.
- In general, vaccines are more thoroughly tested than drugs because the number of subjects in vaccine trials is usually greater.
- Compared to chemical drug development, vaccine trials are typically done on healthy subjects.
- The follow-up time for vaccine trials could be very long. Post-marketing vaccine studies focus on long-term efficacy and detecting safety signals.

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Statistical and Programming Considerations in Vaccine Trials

Using Gardasil® as a real example

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HPV and HPV Vaccine

- HPV is a sexually transmitted infection that causes cervical cancer and other HPV-related diseases.

- Merck's qHPV vaccine (GARDASIL®) is one of the top 10 medical advances. In US,
  - ✓ **GARDASIL®** helps protect girls and women ages 9 to 26 against cervical, vaginal, vulvar, and anal cancers and genital warts caused by 4 types of HPV (6, 11, 16, 18).
  - ✓ **GARDASIL®** helps protect boys and men ages 9 to 26 against anal cancer and genital warts caused by those same HPV types.

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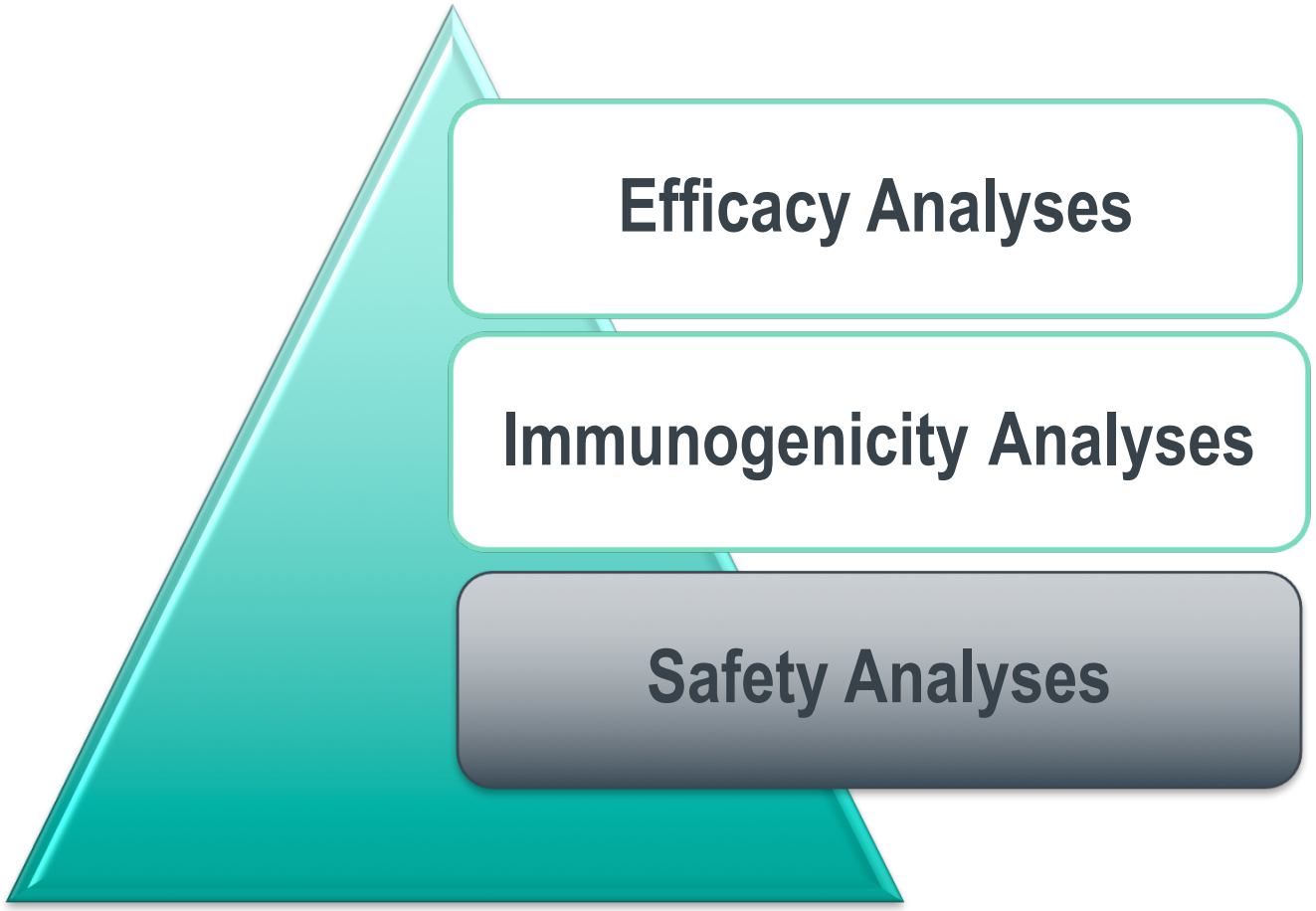
Statistical Analyses in Vaccine Trials



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Statistical Analyses in Vaccine Trials

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Efficacy Endpoint

The definition of trial endpoints with respect to efficacy depends on characteristics of the disease and the candidate vaccine.

- **Disease** as the primary endpoint
  - ✓ In general, the goal of vaccination is to prevent or ameliorate disease, and not necessarily to prevent infection.
- **Infection** as the primary endpoint
  - ✓ For diseases with long incubation time such as HPV, HIV and tuberculosis, the traditional endpoint of clinical disease morbidity or mortality may not be feasible due to the required duration of follow-up. Thus the more proximal endpoint of infection may be designated primary.

Case-Driven Design

In many vaccine efficacy studies where the endpoint is a rare infection/disease event, an event-driven design is commonly used for testing the hypothesis that study vaccine lowers the risk of the event.

- When there is good knowledge about the disease's natural history and incidence rate of the endpoint, the study sample size and duration can be accurately determined based on design parameters.
- Uncertainty of the incidence rate in disease natural history poses a great challenge in study planning as to how many subjects are required in the trial, how many study sites are needed, how long the study will last, and how much the trial may cost.

Vaccine Efficacy

- The typical formula is:

  VE = (1 - RR) x 100% = (1- $\frac{R_V}{R_P}$) x 100%

  where

  RR = rate ratio (incidence rate of disease/infection in vaccine group divided by that of placebo group);

  RR is a ratio of incidence rate.

  R_V = incidence rate in vaccine group;

  R_P = incidence rate in placebo group.

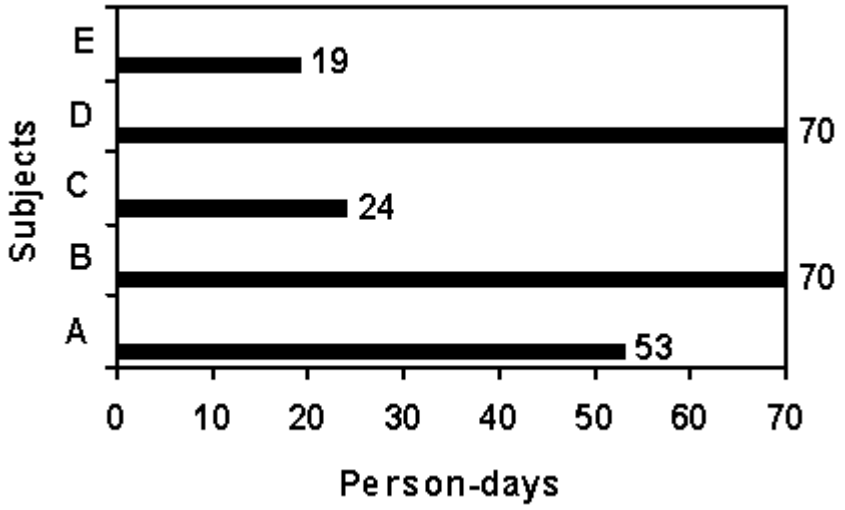
- Given that risk ratio is non-negative, $VE \epsilon\ (-\infty, 1]$.
- VE = 1 indicates complete protection, VE = 0 indicates no effect.

Special Terms Used in Vaccine Trials

- **Person-time**
  - ✓ Person-time is an estimate of the actual time-at-risk in years, months, or days that all persons contributed to a study.
  - ✓ If Person-time is multiplied by 1000, then it becomes 1000 Person-time.
- **Incidence rate**
  - ✓ The incidence rate is the number of new cases of disease during a period of time divided by the person-time-at-risk throughout the observation period.

Special Terms Used in Vaccine Trials (Example)

- 3 cases are observed from 5 subjects.
- Time contributed by each subject:
  - ✓ Subject A: 53 days; Subject B: 70 days; Subject C: 24 days; Subject D: 70 days; Subject E: 19 days
  - ✓ Total person-days in the study: 53+70+24+70+19=236 person-days
  - ✓ Therefore the incidence rate of case is 3÷(236 p-d), which is .0127 cases per person-day.
  - ✓ If person-day is multiplied by 1000, the incidence rate becomes 12.7 cases per 1000 person-days.



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Confidence Intervals for VE

- An exact conditional procedure will be used under the assumption that within each age stratum, C_v (number of cases observed in vaccine group) and C_p (number of cases observed in placebo group) are independent Poisson variables.
- The exact confidence interval for the common vaccine efficacy will be computed from the exact confidence interval for RR= r_v/r_p, the common rate ratio for the age strata.
- This confidence interval for each age group will be constructed based on the methodology for stratified Poisson samples

Program Based on the Methodology for Stratified Poisson Samples

```
 proc sql noprint;
    create table input as
    select AGEL35FN, hpv, sum(casefn) as cases, sum(persnyr) as prys
    from eff
    group by 1, 2
    order by  1, 2 desc;
quit;

proc poisson data=input out=out1_ od=0.95;
pr/ex;
event cases;
ftime prys;
gr hpv;
st AGEL35FN;
run;
```

```
data _final;
    retain ds_anal cv cp kv kp;

    ** set vaccine group statistics **;
        nv=&nv;                * subjects evaluable     *;
        cv=&cv. + &add_vac.;   * number of cases        *;
        kv=&kv;                * person years follow-up *;
        rate_v=(cv/kv)*100;    * incidence rate         *;

    ** set placebo group statistics **;
        np=&np;                * subjects evaluable     *;
        cp=&cp. + &add_pbo.;   * number of cases        *;
        kp=&kp;                * person years follow-up *;
        rate_p=(cp/kp)*100;    * incidence rate         *;

    set out1_;

      VE    = (1 - rr_hat)*100;
      VEL   = (1-uci_p)*100;
      VEU   = (1-lci_p)*100;
      VE_ci ="(" || compress(_VEl) || ", " || compress(_VEu) || ")";
 run;
```


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Sample Output

Analysis of Efficacy Against HPV 6/11/16/18-Related CIN 2/3 or AIS
(Per-Protocol Efficacy Population)

Endpoint	qHPV Vaccine (N=1,910)				Placebo (N=1,907)				Observed Efficacy (%)	95% CI
	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk		
HPV 6/11/16/18-Related CIN 2/3 or AIS (All Ages)	1,581	1	5,049.9	0.0	1,584	6	5,056.9	0.1	83.3	(-37.6, 99.6)
24 to 34 year-olds	772	0	2,407.8	0.0	785	3	2,475.4	0.1	100	(-148.8, 100)
35 to 45 year-olds	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
HPV 6/11-Related CIN 2/3 or AIS (All Ages)	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
24 to 34 year-olds	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
35 to 45 year-olds	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
HPV 16/18-Related CIN 2/3 or AIS (All Ages)	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
24 to 34 year-olds	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
35 to 45 year-olds	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
By HPV Type (All Ages)										
HPV 6-Related CIN 2/3 or AIS	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
HPV 11-Related CIN 2/3 or AIS	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
HPV 16-Related CIN 2/3 or AIS	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)
HPV 18-Related CIN 2/3 or AIS	xxx	xx	xxx.x	x.x	xxx	xx	xxx.x	x.x	xx	(xx, xx)

Vaccine Efficacy vs. Vaccine Effectiveness

- **Vaccine Efficacy**

  Percentage reduction in disease incidence in a vaccinated group compared to an unvaccinated group under the most favorable conditions.

- **Vaccine Effectiveness**

  Ability of vaccine to prevent outcomes of interest in the “real world”.

Vaccine Effectiveness Calculation

- In the absence of a control group in the Long-term Follow-up study, it is not possible to formally test the effectiveness hypotheses.
- Instead, effectiveness will be measured in terms of incidence rates of disease, with analyses performed periodically until the end of the follow-up.
- Assume an incidence rate in unvaccinated subjects of **2.87**/1,000 person-years

Programs Using Historical Data in the Denominator in the Absence of Control Group

```
rate  = 100*(c/k);                                  * incidence rate         *;
ratel = 100*(0.5*CINV((1-&ci_level)/2,2*c)/k);        * lower ci for incidence rate ;
rateu = 100*(0.5*CINV((1+&ci_level)/2,(2*c + 2))/k);  * upper ci for incidence rate ;

_rate   = compress(put(round(rate,0.1), comma5.1));
_ratel  = compress(put(round(ratel,0.1), comma5.1));
_rateu  = compress(put(round(rateu,0.1), comma5.1));
rate_ci ="(" || compress(_ratel) || ", " || compress(_rateu) || ")";

%if %length(&n_cutoff) ^=0 %then %do;
  if c < &n_cutoff then rate_ci ="NA";
%end;

%if %length(&baseline) ^=0 %then %do;
  ve  = 100*(1-(rate/&baseline.));       * vaccine effectiveness ;
  vel = 100*(1-(rateu/&baseline.)); * lower ci for vaccine effectiveness ;
  veu = 100*(1-(ratel/&baseline.)); * upper ci for vaccine effectiveness ;
```

Assume an incidence rate in unvaccinated subjects of **2.87**/1,000 person-years

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Sample Output

Analysis of Effectiveness Against HPV 16/18-Related CIN 2 or Worse by Time Since qHPV Vaccination Dose 1, HPV Type, and Lesion Type
(Cohort 1 Per-Protocol Efficacy Population)

Endpoint	Cohort 1 (N=2,650) n	Number of Cases	Person-Years at Risk	Incidence Rate per 100 Person-Years at Risk	Incidence Rate 95% CI	Vaccine Effectiveness† (%)	Vaccine Effectiveness 95% CI
HPV 16/18-Related CIN 2 or Worse	2,084	0	13,794.9	0.0	(0.0, 0.0)	100	NA
By Time Since qHPV Vaccination Dose 1							
4 Years or Less	1,930	0	803.5	0.0	(0.0, 0.5)		
>4 to 6 Years	xxx	xx	xxx.x	x.x	(xx.x, xx.x)		
>6 to 8 Years	xxx	xx	xxx.x	x.x	(xx.x, xx.x)		
>8 to 10 Years	xxx	xx	xxx.x	x.x	(xx.x, xx.x)		
>10 to 12 Years	xxx	xx	xxx.x	x.x	(xx.x, xx.x)		
>12 to 14 Years	xxx	xx	xxx.x	x.x	(xx.x, xx.x)		
By HPV Type							
HPV 16-Related CIN 2 or Worse	xxx	xx	xxx.x	x.x	(xx.x, xx.x)		
HPV 18-Related CIN 2 or Worse	xxx	xx	xxx.x	x.x	(xx.x, xx.x)		

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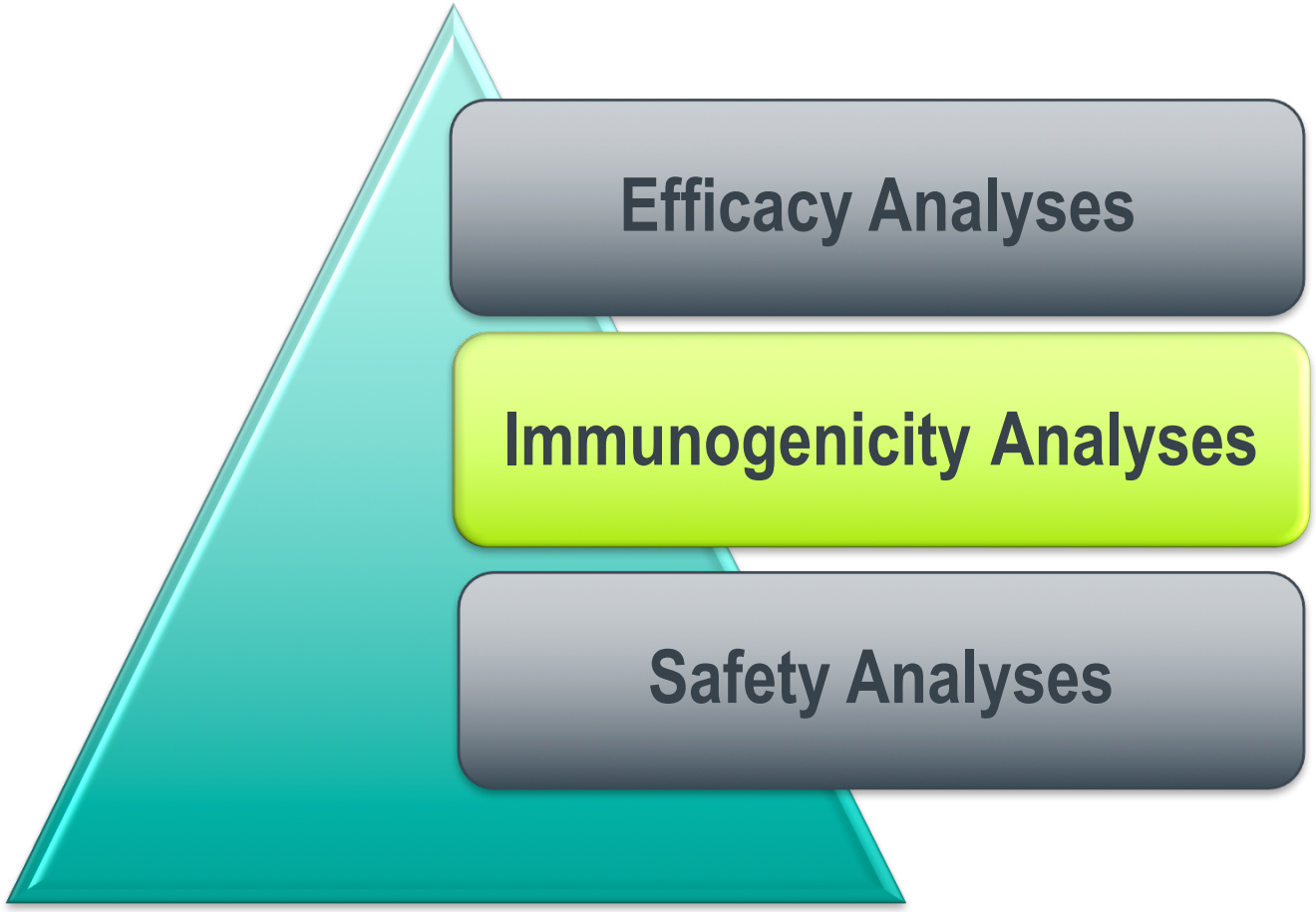
Statistical Analyses in Vaccine Trials



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Statistical Methods for Immunogenicity Data

- There are 4 standard statistics to summarize humoral and cellular immunity data:
  1) the geometric mean response
  2) the geometric mean fold increase
  3) the seroprotection rate
  4) the seroconversion rate
- Two of these statistics, the geometric mean response and the seroprotection rate, quantify absolute immunogenicity values.
- The other two, the geometric mean fold increase and the seroconversion rate, quantify intra-individual increases in values.

Immunogenicity Analysis in Gardasil®

- **Geometric Mean Titre (GMT)**
  - ✓ Distribution of post-vaccination humoral and cellular immunogenicity values tend to be skewed to the right.
  - ✓ Log-transformed immunogenicity values, are usually approximately Normally distributed.
  - ✓ The geometric mean is defined as:

$$GM = (v_1 \times \cdots \times v_n)^{1/n} = \exp \sum_{i=1}^{n} (log_e v_i / n)$$

- **Seropositivity Rate**

Programs Used for GMT Modeling

```
data _imm_dt;
   set imm_data;
   if upcase(compress(assay))="LIA 6";
   if examval > 0 then lexamval=log(examval);
   if lexamval = . then delete;
   keep an examval lexamval agel35fn;
run;
```

```
/*Get summary statistics for GMT output from fitting model*/
proc sort data=_imm_dt;
    by agel35fn;
run;
```

```
proc means data=_imm_dt noprint;
   by agel35fn;
   var lexamval;
   output out=cngmt n=n;
run;
```

```
/*Fit the model to get estimate and CI*/
proc mixed data=_imm_dt order=internal;
    class agel35fn;
    model lexamval = agel35fn;
    lsmeans agel35fn / cl alpha=&alpha;
    ods output lsmeans=lsmeans1(rename=
                (estimate=_lsmean_ upper=_upper_ lower=_lower_ ));
    ods output tests3=test1;
run;
```


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Sample Output

Summary of Anti-HPV cLIA Geometric Mean Titers by Age and Time from qHPV Vaccination Dose 1 in Mid-Adult Women Having Received qHPV Vaccine, Early Vaccination Group, Day 1 to Year 10 (Per-Protocol Immunogenicity Population)

Assay (cLIA) Time Point†	Early Vaccination Group (N=1,910)					
	24 to 34 Year-olds (N=953)		35 to 45 Year-olds (N=957)		All Subjects (N=1,910)	
	n	GMT (mMU/mL) (95% CI)	n	GMT (mMU/mL) (95% CI)	n	GMT (mMU/mL) (95% CI)
Anti-HPV 6						
Day 1 (qHPV)	605	< 7 (<7, <7)	644	< 7 (<7, <7)	1,249	< 7 (<7, <7)
Month 07	605	437.4 (401.2, 476.8)	644	397.3 (365.4, 431.9)	1,249	416.2 (391.9, 442.0)
Month 12	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 24	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 36	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 48	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 72	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 96	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 120	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Anti-HPV 11						
Day 1 (qHPV)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 07	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 12	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 24	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 36	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 48	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 72	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 96	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)
Month 120	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)	xxx	xxx.x (xxx.x, xxx.x)

Programs Used for Seropositivity Rate

```
data _imm_dt;
   set imm_data;
   &subset;;
   if upcase(compress(assay))="LIA 6";
   if examval > 0 then lexamval=log(examval);
   if lexamval = . then delete;

   if examval => SEROCTPT then ge_cut = 1;
     else if 0 =< examval < SEROCTPT then ge_cut = 0;

    keep an examval lexamval agel35fn ge_cut;
run;
```

```
proc sort data=_imm_dt; by agel35fn; run;
```

```
proc means data=_imm_dt noprint;
   by agel35fn;
   var ge_cut;
   output out=resout n=n sum=m;
run;
```

```
/* Call macro EXACT_CI for calculating the percents >= cut-point and CIs */
%exactci(INDSN=resout, OUTDSN=res_out, SUCCESS=m, TOTAL=n,
         ALPHA=&alpha, PERCENTS=1, METHOD=2);
```

Sample Output

Summary of Anti-HPV Seropositivity Rates by Age and Time from qHPV Vaccination Dose 1
in Mid-Adult Women Having Received qHPV Vaccine, Early Vaccination Group, Day 1 to Year 10
(Per-Protocol Immunogenicity Population)

Assay (cLIA) Time Point†	Early Vaccination Group (N=1,910)					
	24 to 34 Year-olds (N=953)		35 to 45 Year-olds (N=957)		All Subjects (N=1,910)	
	n	SPR (%) (95% CI)	n	SPR (%) (95% CI)	n	SPR (%) (95% CI)
Anti-HPV 6						
Day 1 (qHPV)	605	0.0 (0.0%, 0.6%)	644	0.0 (0.0%, 0.6%)	1,249	0.0 (0.0%, 0.3%)
Month 07	605	98.7 (97.4%, 99.4%)	644	98.1 (96.8%, 99.0%)	1,249	98.4 (97.5%, 99.0%)
Month 12	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 24	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 36	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 48	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 72	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 96	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 120	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Anti-HPV 11						
Day 1 (qHPV)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 07	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 12	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 24	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 36	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 48	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 72	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)
Month 96	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)	xxx	xx.x (xx.x%, xx.x%)

Programming Strategy for qHPV Vaccine Studies

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Strain-specific analysis

- There are actually more than 100 related viruses in human papillomavirus group. Each HPV virus is given a number or type.
- In efficacy trials of multivalent vaccines, the primary endpoint has often been disease with any strain-related or to one of the strains contained in the vaccine.
- An important consideration in assessing strain-specific vaccine efficacy is whether multiple cases of distinct endpoint for a subject are counted.

Special Consideration in Construction of Efficacy Analysis Datasets

- Efficacy analysis includes single endpoint analyzed by HPV types and; composite endpoints analyzed by distinct endpoint.
- Each endpoint is analyzed on multiple populations (FAS, PPE, etc).
- Definition of efficacy populations are very complicated and strain-specific.
- Definition of each case of efficacy (persistent infection, external genital wart, CIN2 or worse, etc.) involves large amount of derivation and nested logic.

Special Consideration in Construction of Efficacy Analysis Datasets (Cont'd)

How to construct efficacy ADaM dataset to adjust for the special need?

- Traditionally, we construct one or more efficacy datasets and each data set has different population flags to be used in final analysis and reporting.
- However, each population flag is associated with different HPV types.

- Alternatively, we construct one intermediate efficacy dataset and create individual efficacy analysis dataset for each analysis population with derived flags of HPV types.
- In each efficacy dataset, we use modularized macro to derive the endpoints of interest.

A Peek at ADEFFAS

AN	TREATMNT	CASEDT	CASEFN	COHORT	DISEASE	HPV	HPVTYPE	LABID	LTFUST	START_DT	VAC1_DT
41378	Placebo	12FEB2013	0	2	CIN3	0	11	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	16	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	18	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	31	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	33	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	35	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	39	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	45	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	51	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	52	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	56	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	58	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	59	PANEL	01APR2008	07JUN2007	07JUN2007
41378	Placebo	12FEB2013	0	2	CIN3	0	6	PANEL	01APR2008	07JUN2007	07JUN2007
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	11	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	16	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	18	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	31	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	33	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	35	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	39	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	45	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	51	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	52	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	56	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	58	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	59	PANEL	17AUG2006	17AUG2006	07NOV2002
41379	HPV Quadrivalent (VAI018I001)	30JAN2014	0	1	CIN3	1	6	PANEL	17AUG2006	17AUG2006	07NOV2002

Summary

- Vaccine trials are typically studying healthy subjects and the sample size are generally larger than drug trials.
- Efficacy analysis in vaccine trials are usually case-driven because of uncertainty of incidence rate of the underlying disease.
- There are special terms in vaccine trials that needs to be understood.
- Vaccines works on viruses that might have more than one strain/type so efficacy and immunogenicity analysis might be strain-specific, thus more thoughts on the construction of ADaM are needed before starting out on programming.
- Vaccine trials could have very long follow-up time. Post-marketing vaccine trials focus on long-term measurement of vaccine effectiveness. Vaccine effectiveness help us understand how the vaccine works in the real world.

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THANK YOU!

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