Vaccine Effectiveness vs Efficacy

- **Effectiveness** = measurement of vaccine protection based on data usually gathered from observational studies

- **Efficacy** = measurement of vaccine protection based on data gathered from randomized, controlled clinical trials
Vaccine Development and Evaluation

- Immunogen Characterization
- Non-Clinical & Pre-Clinical Studies
- Develop Manufacturing Process

Phase I  Phase II  Phase III

Licensing & Recommendations

Phase IV
Post - Marketing Surveillance / Effectiveness Studies

Adapted from Plotkin – Orenstein Vaccines 4th ed.
Another Option

- Immunogen Characterization
- Non-Clinical & Pre-Clinical Studies
- Develop Manufacturing Process

- Phase I
- Phase II
- Phase III

Effectiveness Studies

Licensing & Recommendations

Phase IV
Post-Marketing Surveillance
Hepatitis A Vaccine
An Example Relevant to Dengue Vaccines?

“Similarities”
- Acute, endemic disease with cyclical epidemics
- Relatively low force of infection ($R_0$)
- Focal transmission within communities
- Transmission across wide range of ages
- Antibody mediated protection

Differences
- Transmission not vector-borne
- Single serotype
Hepatitis A Vaccine Effectiveness Study
Butte County, CA: 1995-2000
Hepatitis A Incidence, by Year
Butte County, CA, 1980-1995

From: Averhoff et al. JAMA 2001; 286:2968-2973
Hepatitis A Incidence, California Butte and Contiguous Counties

From: Averhoff et al JAMA 2001; 286:2968-2973
Hepatitis A Butte County, CA

- Hepatitis A
  - Nationally reportable disease
  - Reportable disease in California
  - Prior to 1985 = infectious hepatitis (syndromic)
  - ~ 1985 diagnostic testing widely used – IgM anti-HAV
Hepatitis A Vaccine Effectiveness Study
Butte County, CA: 1995-2000

- Target population – children 2-12 years old (~30,000)
- Vaccine delivery and monitoring
  - Vaccination registry
  - Adverse event monitoring (throughout –
    - Enhanced / stimulated surveillance + laboratory diagnostics for all suspect cases of hepatitis A and laboratory reporting

From: Averhoff et all JAMA 2001; 286:2968-2973
**Hepatitis A Vaccine Effectiveness Study**  
**Butte County, CA: 1995-2000**

- **Vaccine**
  - Merck, inactivated hepatitis A (VAQTA) – pediatric formulation
  - Schedule: 2-dose at 0 & 6-12 months
  - 1995 – not license and delivered under IND with informed consent
  - 1996 – vaccine licensed, used vaccine information statement
  - Provided free of charge

From: Averhoff et al. JAMA 2001; 286:2968-2973
Hepatitis A Vaccine Effectiveness Study
Butte County, CA: 1995-2000

- Vaccination coverage
  - ~62% first dose
  - ~40% 2-dose series

From: Averhoff et al; JAMA 2001; 286:2968-2973
Effect of Hepatitis A Vaccination on Disease Incidence, Butte County, CA 1991-2000

Vaccinated Age Groups
1995-2000

Averhoff et al. JAMA 2001; 286:2968-2973
Hepatitis A Incidence, by Year
Butte County, CA, 1980-2000

From: Averhoff et al JAMA 2001; 286:2968-2973
Hepatitis A Incidence, California Butte and Contiguous Counties

Source: National Notifiable Disease Surveillance System, CDC; 2000 data are provisional
Effectiveness of Hepatitis A Vaccination – Israel, 1999-2003
Hepatitis A in Israel

- Very high incidence of disease documented
- Significant differences in disease rates between Jewish and non-Jewish populations
- National passive surveillance for “infectious hepatitis” since 1950’s with diagnostic testing more common since 1993
- Active surveillance for hepatitis A established in Jerusalem from 1999 – 2003 to validate passive surveillance system, including household case finding.
Hepatitis A Vaccination, Israel

- 1996 - inactivated hepatitis A vaccine (HAVRIX, GSK) licensed in a 2-dose schedule
- 1999 - a universal campaign to vaccinate 18-24 month olds initiated
- Most vaccines provided in the public sector and coverage equal in Jewish and non-Jewish populations
- 2001- 2002 - 90% 1\textsuperscript{st} dose coverage and 85% 2\textsuperscript{nd} dose coverage.
- Low coverage in other age groups based on pediatric versus adult dose sales data, though 30,000 young adults vaccinated in a clinical trial of the Merck vaccine
Effect of Hepatitis A Vaccination of Toddlers on Disease Incidence, Israel

Dagan et al. JAMA 2005
Age-specific Effects of Toddler Hepatitis A Vaccination, Israel 1999-2004

Dagan et al. JAMA 2005
Conclusions

- Population-based observational studies can be used to estimate vaccine effectiveness

- Some caveats
  - Need for laboratory confirmed diagnosis of syndromic surveillance events
  - Need for validation of surveillance systems
  - Need for accurate estimates of dose-specific vaccine coverage

- Following demonstration of vaccine efficacy in a Phase 3 trial, effectiveness studies can be performed pre- or post- licensure with appropriate protection of human subjects