Objectives

- To provide an overview of vaccine development from laboratory bench to approval for licensure
- To describe the purpose and characteristics of clinical vaccine trials
- To highlight that clinical vaccine trials are integral to successful vaccination programmes
- To identify issues in vaccine trials in resource poor settings

Vaccine development process…

- Long
  - multiple steps that each require careful validation
- Collaborative
  - scientific, manufacturing & regulatory organisations
- Expensive
  - US $100-300 million

Primary aims of vaccine development

- To establish vaccine safety, immunogenicity & efficacy in the population for whom the vaccine is intended = target population
- To establish that batches of vaccine manufactured on a large scale are consistent in content & quality

Steps in vaccine development

- Identification of micro-organism
- Studies to determine factors that cause & protect against disease
- Development of animal models
- Development of vaccine candidates
- Preclinical studies of safety & immunogenicity
- Prototype vaccines for human testing
- Efficient manufacturing process
- Extensive clinical evaluation

What is a clinical trial?

- Prospective study designed to assess the effect of an intervention in a group of individuals
- Representative sample of individuals used to make inferences about the effect of the intervention on the target population
- Controlled, randomised & double blind design minimises bias
Essential components of clinical trials

- **Protocol**
  - independent ethics committee

- **Ethical & scientific standards**
  - Declaration of Helsinki 1964

Clinical trials in vaccine development

- **Pre-licensure**
  - Phase I - safety & immunogenicity
  - Phase II - immunogenicity & safety
  - Phase III - efficacy
  - Consistency & bridging studies

- **Post-licensure**
  - Phase IV - effectiveness & safety

Phase I clinical vaccine trial

*Initial data on vaccine safety & immunogenicity*

- Close safety monitoring
  - common and severe reaction
  - conservative stopping rules

- Investigate underlying immune mechanisms
  - immunological memory
  - immediate post vaccination antibody levels

- Subjects = Adults  n=10-100
- Design = controlled or uncontrolled

Phase II clinical vaccine trials

- Identify optimal vaccine regime for Phase III trials
  - vaccine dose, adjuvants, composition
  - minimum number & timing of doses
  - age-specific immune responses
  - shape & duration of immune responses
  - interaction with other vaccines

- Safety
  - local & systemic reaction

Phase II clinical vaccine trials

- Subjects
  - Target group
  - n = 50 - 500

- Design
  - Double blind randomised controlled trial

- Compare vaccine immunogenicity & safety in the target population to the control group
Phase III clinical vaccine trials
Vaccine efficacy in the target population
- Vaccine efficacy
- Active safety monitoring for serious events
- Secondary objectives
  - age-specific effects
  - duration of protection
  - effect on carriage & infectivity of micro-organisms
  - establish laboratory correlate of protection

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Phase III clinical vaccine trials
Vaccine efficacy in the target population
- Subjects
  - Target group
  - n = 1000 - 150,000
- Design
  - Double blind randomised controlled trial

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Consistency studies
- Assess safety & immunogenicity of three consecutive batches of vaccine that are manufactured at commercial scale to demonstrate consistency of manufacture

NCIRS
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No. of test item:
- O: Required for official release testing;
- Δ: Exempted or replaced

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Bridging studies
- Determine effect of change in any one parameter on vaccine’s clinical performance
  - population
  - manufacturing scale
  - formulation
  - dosing schedule

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Vaccine licensure

- Data on vaccine safety, efficacy & manufacture
- Government agencies use strict regulations & international standards to review application
  - Food and Drug Authority (FDA) US
  - Therapeutic Goods Administration (TGA) Australia
- Approval of application - registration
  - Australian Drug Evaluation Committee
  - Vaccine marketed for community use

Requirements for Vaccine Licensure

1. Clearly defined formulation
2. Acceptably pure and potent
3. Suitable quality control
4. Demonstrable reproducibility of lots
5. Acceptable safety
   - In large numbers
   - In diverse populations
   - In target population
6. Suitable protection
   - Best evidence: Direct evidence of clinical protection
   - Surrogate evidence: Suitable immune responses

The granting of a product license for a new drug merely means that any hazards unacceptable to the licensing authority have not been identified.

It does not ensure that a medicine will always be safe in subsequent prescribing practice”.

Liz Swain, SB Director, UK Post-marketing Group
November 2000, Singapore

Limitations of pre-licensure studies

- Direct individual effects of vaccination only
- Indirect population-level effects unknown
  - herd immunity
  - ecological effects
- Some adverse effects not identified
  - Low numbers in trials
    - to detect an attributable risk of
      1/10,000 vaccinees requires 30,000 vaccinees (+30,000 controls)
  - rare
  - delayed onset

Phase IV post-licensure evaluation

- Vaccine effectiveness in the real world
- Disease incidence & severity
- Safety
- Subjects
  - Vaccinees or total population
  - n = variable - millions
- Design = observational
How does this apply to clinical vaccine trials in resource poor settings?

Issues for developing countries
- Poor regulatory and surveillance systems
  - Pre and post licensure
  - India – FDA equivalent has 3 technical staff - pharmacists
- Need to strengthen clinical trial monitoring
  - Lab quality
- Ethical issues
- Rapid increase in number of vaccine production companies

Vaccines and regulatory authorities
- “Trickle down” from industrialised to developing countries
- Approval for vaccine use in some countries comes from national regulatory authorities (NRA), eg FDA, EMEA
- Others lack basic infrastructure to do this
- Development of a Developing Country Vaccine Manufacturers Network

Strengthening capacity for clinical trial monitoring
- WHO set up training curriculum for trial investigators and help for ethics committees and clinical monitors
- Data management support
  - Eg; Templates for case reporting forms
- Quality support for laboratories

Ethical considerations
- Age of consent for children varies
  - US >7 years old, others >12 years old – OLDER
  - Children often required to co-sign consent with parents
- Illiteracy
- No trial should have a placebo arm
- Should vaccine be trialed in developing country at the same time as developed country
  - India Jun 2005 agreed to allow trials of same phase as other countries
  - India – erythromycin vaginal pellets tested on poor illiterate women in West Bengal in 2002, NO regulatory approval
  - Industry sponsored trials with financial inducements
  - Higher disease burden - ?accelerated introduction

Ethics - Rotavirus
- Rotavirus vaccine withdrawn in US after intussusception risk – pending trials in India, Bangladesh, Sth Africa halted
- High disease burden countries
- If vaccine is not safe enough for US, is it OK for other countries
- New vaccine trial needs many more subjects
- Recently licensed in Mexico
Summary

- Clinical vaccine trials are fundamental in pre-licensure vaccine evaluation
- Safety, immunogenicity & protective efficacy are measured in double blind RCT
- Independent ethics review, regulatory approval & trial monitoring are mandatory
- Vaccine evaluation is continued post-licensure
- Resource poor settings – particular issues

Acknowledgements

- International Vaccine Institute

- Thank you for listening!