World Health Organization - WHO

Potency testing of whole cell pertussis vaccine(s): WHO perspective

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Critical points in evaluation of pertussis vaccines

- ✓ LABORATORY TESTING: QC
  - POTENCY
  - TOXICITY

- ✓ CLINICAL TESTING
  - PROTECTION IN HUMANS
  - SAFETY

Correlates of protection: a basis for potency test

- 19 vaccines tested; more than 36 000 children involved in MRC trials (follow up for 2-3 years)
- Correlation between protection in children and:
  - Protection in mice
  - Production of agglutinin in mice
  - Production of agglutinin in children

Is it still the case with current wP vaccines?

If so, is it worth to explore production of agglutinins as an in vitro test?

If not, what are the correlates of protection to be considered as potential replacement of protection in mice?

Unresolved issues after early trials

- ✓ Which test is the most direct measure of the factor or factors responsible for protection in children?
- ✓ Do we have the answer today?
- ✓ Is there any other parameter than protection in mice that correlate with protection in humans?

Current understanding of protection in humans?

1. Value of neutralizing antibodies?
   - ✓ Which *B. pertussis* antigens are crucial for protection (PT, FHA, Prn, Agg)?
   - ✓ Importance of avidity of ab?
   - ✓ A need for standardization of assays?
2. Value of CMI in the protection?
   - ✓ The importance of cytokine profile?
3. Duration of immune responses following primary immunization
4. Correlation with the vaccine efficacy?

Potency test: scientific principle

- ✓ Correlation with protection in children – confirmed in early trials
- ✓ Intracerebral mouse protection test
- ✓ Potency determined by comparison with reference calibrated against IS
- ✓ Not less than 4 IU per single human dose
- ✓ Scientifically: one of the best examples of potency testing of biologicals
- ✓ Valuable test for lot release

Why should we consider an alternative?

Is current test scientifically correct?

What is wrong with the current test?

Difficult to:

- perform?
- validate?
- pass 4IU?

OR

Need to:

- follow 3Rs trend?
- shorten duration of test?
- simplify approach for lot release?

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Potency test in current WHO requirements (TRS 800, 1990)

- ✓ The assay (intracerebral mouse protection test) and the method of calculation: should be approved by the NRA
- ✓ Potency: not less than 4.0 IU per SHD
- ✓ Details of the assay, calculation, validation, estimation of potency in small print
- ✓ Estimated potency not less than 4.0 IU and lower fiducial limit (P=0.95) of the estimated potency is not less than 2.0 IU
- ✓ Additional tests may be carried out and all valid tests combined in the GME
- ✓ In some countries an upper limit of potency is specified

Ivana Knezevic, WHO/FCH/IVB/QSB, March 2005

Difficulties with the current potency test

- Technical
- Assay validation
- Duration of the test
- Analysis of the results (GMT or a single assay?)

✓ Is it difficult to meet 4IU?

✓ What is the percentage of batches rejected because of potency lower than required? By manufacturers? By NCLs?

The interpretation of the potency results: difficulties

✓ Comparison with potency of "in-house reference" (an equivalent standard vaccine?)

✓ If one test pass and one fail, how many additional tests should be performed?

✓ If tested vaccine pass 4 IU per SHD, is it a guarantee of clinical efficacy in humans?

Revision of current WHO requirements for wP

- ✓ WHO Informal Consultation on Standardization and Control of pertussis vaccines, 17-18 March 2005, WHO, HQ
- ✓ Potency test:
  - Potential improvements of Kendrick test
  - Rationale for the development of an alternative
  - Prerequisites for A RELEVANT alternative
  - Distinguish ALTERNATIVE from AN ADDITIONAL TEST
- ✓ Monitoring progress continue

Potential improvements of Kendrick test

- ✓ At the level of:
  - Technical details (no of animals, challenge etc)
  - IS
  - Validation of the assay
  - Challenge strain – a need for repository?
  - Recording of results: humane end points?
  - Calculation and statistical validity of the test

Alternatives to Kendrick test

Alternative to mouse protection test in vivo should:

- ☞ be based on the same scientific principle – measurement of protection in vivo
- ✒ be transparent (what is measured?)
- ✓✎ be sensitive at least as current test is (to be able to distinguish potent vs sub-potent vaccines)
- ✓✎ be specific to detect protective response
- ✕✎ well established validity criteria
- ✖✎ simpler than current test
- ✗✎ correlate at least with Kendrick test
- ✗✎ correlate with efficacy in humans
  - direct correlation with clinical data?

WHO Informal Consultation and way forward

1. To get advice on the appropriate revision of Req for wP, including potency and toxicity testing – March 2005
   - To agree on the next steps towards the improvement of current requirements
   - To submit revised req to the ECBS 2005
2. To consider a need for an alternative to Kendrick test

✓ If needed, to get consensus on the direction in the development of an APPROPRIATE alternative (functional assay?)

3. To get consensus on further developments of International Standards and standardization of test methods/reagents