



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



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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?

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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?

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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?

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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

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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?

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

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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?

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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?

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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

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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

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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?

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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

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