Lessons learnt from cholera vaccine development

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Head Vaccine Development
International Vaccine Institute

MSF/Oxfam vaccines consultation Meeting,
Improving access and stimulating vaccine development for use in resource poor settings.
Geneva, Switzerland
26 January 2010

IVI model for vaccine development

"To promote the health of people in developing countries by the development, introduction and use of new and improved vaccines"

- From: Constitution of IVI (1996)

1. Establish disease burden
2. Vaccine development – available technologies
3. Technology transfer – scale up at the manufacturer
4. Production of GMP consistency lots
5. Clinical trials
6. Licensure
7. Introduction into target populations

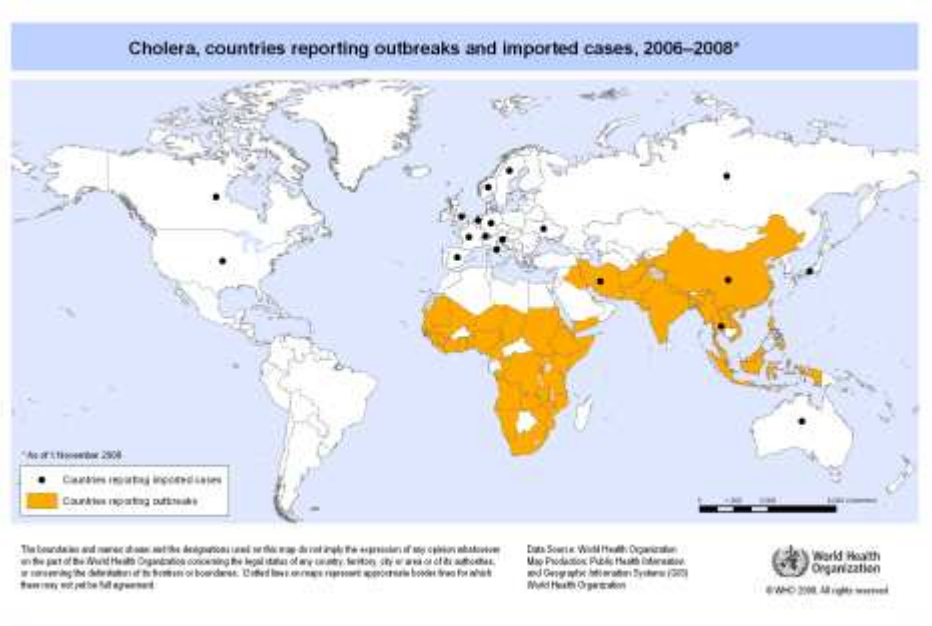
At Granville cemetery, Harare, gravediggers used to dig 45 graves a fortnight. It has risen to 300 every two weeks since November 2008.
Photographs: Robin Hammond/Oxfam/PA

Disease Burden
Cholera

2007
Reported Cases of Cholera
177,963 cases - 4,031 deaths

Cholera cases are under reported

- WHO estimates only 5 - 10% of cases reported
- Likely to exceed 1 million cases annually
- Estimated 120,000 deaths annually
- Mostly in Africa and Asia



Models for vaccine development

Technology from existing manufacturer	Technology from the inventor	Technology developed in house at IVI
Developing country manufacturer, is the technology suitable? Big pharma, lots of strings attached.	NIH, universities, small companies. Technology not fully developed. Consistency? No scale up? GMP compatible? Quality control?	Developed with large scale GMP compatible manufacture of primary importance. Assay development also an important component.
Cholera	**Typhoid conjugate**	**Vi polysaccharide** ***S. paratyphi* A conjugate**

Deliverables

Process that produces a consistent product.
Equipment that is scalable and compatible with GMP.
Chemicals / reagents that are compliant with GMP.
A comprehensive SOP that defines the product.

Assays that control the manufacturing process.
Assays that define the quality of the final product.
SOPs for QC assays.

High degree of confidence that the process will work in a manufacturing facility at production scale.

Candidate for technology transfer

ORC-Vax VaBiotech
Inactivated Inaba and Ogawa (O1) plus O139 cells
Oral delivery
1.5 ml liquid per dose
Buffer not required
First licensed 1997
No WHO prequalified vaccines
Around US $1.00 per dose

VaBiotech ORC-Vax

Suitability for transfer?

Main concerns were Safety and Quality.

WHO guidelines for production and control of inactivated cholera vaccine

Identified two deficiencies

Antigen quantification method

Inconsistent removal of cholera toxin

– and no assay to measure residual toxin

Process and Assay Development

Developed two new ELISA based assays

- O antigen component of the LPS
- Cholera Toxin assay

Reformulated vaccine

- Increased antigen dose
- Removed toxin hyper-producing strain

Addressed GMP issues and made process changes in compliance with GMP standards.

Technology Transfer

to Shantha Biotechnics (India)

Selection of a qualified manufacturer

Training at IVI (2 weeks duration)

- ***2 Production staff***
- ***1 Quality control***
- ***1 Project manager***

Production process

In process control

- Formulation
- Lot release assays

Scale up at Shantha

Scale up issues

Scale up at the manufacturer very successful

Batch size 400 litres

- Yields as measured by OD_{600} were similar to those obtained at IVI laboratory scale.
- Minor scale up and GMP issues had to be addressed.
- Quality control assays successfully introduced to
  - Control manufacturing process
  - Assure quality of final product

Safety and immunogenicity

(Phase II)

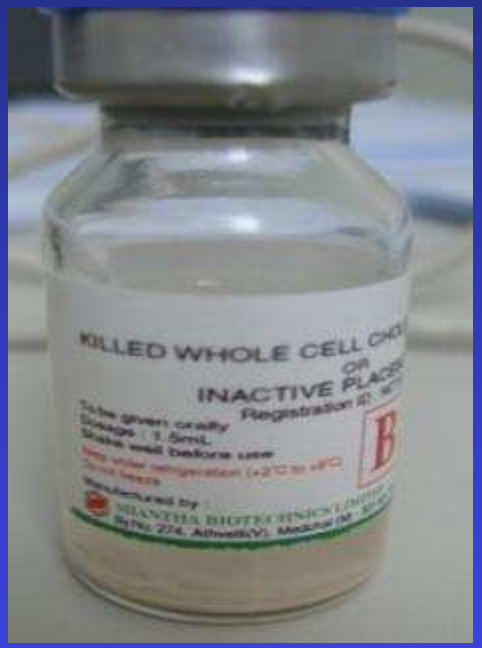
SonLa, Vietnam

Kolkata, India

Phase II Studies:

Safety and Immunogenicity

- Safety: Vaccine safe.
- Immunogenicity: Superior vibriocidal responses compared to existing Vietnamese vaccine and Internationally licensed Swedish vaccine.
- Results similar in non-endemic (SonLa) and endemic (Kolkata).



Does the Vaccine work?
Clinical trials

- Phase III trials (65,000 persons)
  - Efficacy trial (Protection from disease)

  Vaccine provided 70% protection and was very safe.

THE LANCET

Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial

Dipika Sur, Anna Lena Lopez, Suman Kanungo, Allison Paisley, Byomkesh Manna, Mohammad Ali, Swapan K Niyogi, Jin Kyung Park, Banawarilal Sarkar, Mahesh K Puri, Deok Ryun Kim, Jacqueline L Deen, Jan Holmgren, Rodney Carbis, Raman Rao, Nguyen Thu Van, Allan Donner, Nirmal K Ganguly, G Balakrish Nair, Sujit K Bhattacharya, John D Clemens

Licensure

Licensure
24 February 2009

Government of India
Central Drugs Standard Control Organisation
Directorate General of Health Services
FDA Bhawan, New Delhi – 110 002 (India)

Form-46

(See rules 122-B and 122-D and 122-DA)
Permission/approval for manufacture of new drug formulation

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Number of the permission and date of issue **MF-176/09**

M/s. Shantha Biotechnics Limited, Survey No. 274, Athvelli Village, Medchal Mandal, Ranga Reddy-Dist, Andhra Pradesh.(address) is hereby granted permission/approval to manufacture the following new drug formulation under rule 122-B/122-D/ ~~122-DA~~ of the Drugs and Cosmetics Rules-1945, namely:

(1)	**Name of the drug**	:	**Killed Bivalent (O1 & O139) whole cell Oral Cholera vaccine.**
(2)	**Dosage Form**	:	**Liquid vaccine for Oral Administration.**
(3)	**Composition**	:	**As per Annexure.**
(4)	**Indication**	:	**For active immunization against Vibrio cholera.**

Date: 11 FEB 2009

Signature:
(Dr.Surinder Singh)
Drugs Controller General (India)
(Name & Designation of Licensing Authority)

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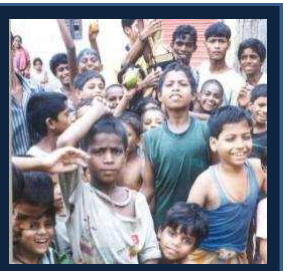
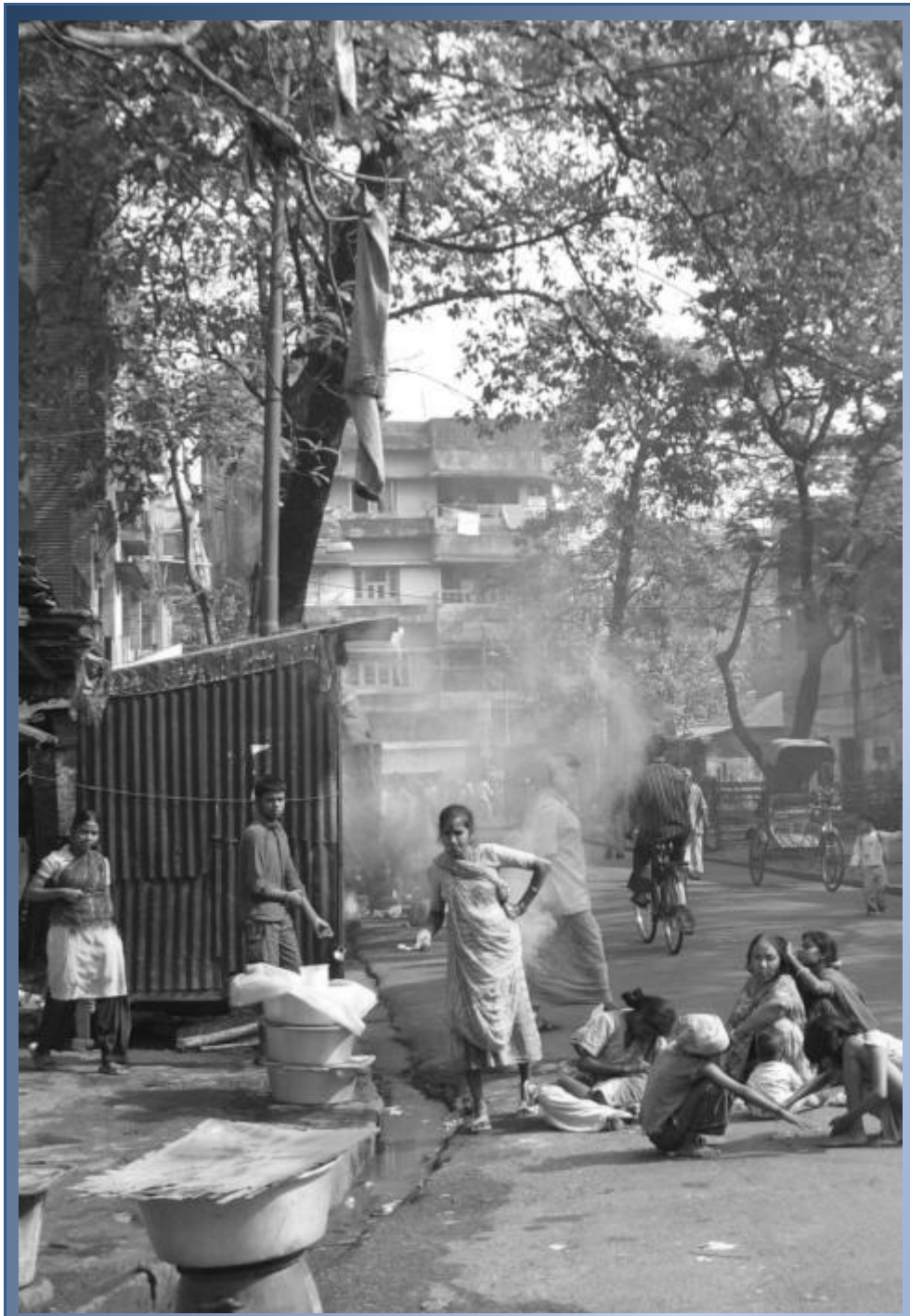
Lessons learnt



- Don’t assume that a technology acquired from a technology provider meets all the regulatory requirements.
- Suitable assays to assess quality are a critical component of vaccine manufacturing.
- Before technology transfer is attempted make sure the process is well understood and documented in the form of comprehensive SOPs.
- Don’t assume that the technology partner will follow the SOP.
- Scale up and GMP manufacture always presents challenges, what works in the lab does not necessarily work in production.
- Technology transfer does not finish when the training is completed, be ready to trouble shoot once production starts.
- Trust and understanding between the parties (particularly during technology transfer) is very important for a successful outcome.
- Approval to conduct trials usually takes longer than planned.
- Trials can be further delayed by unplanned events such as flooding and political problems.
- Negotiate terms of the agreement with all parties involved at the beginning of each project.



Thank you

Vaccines don’t save lives

Vaccination does