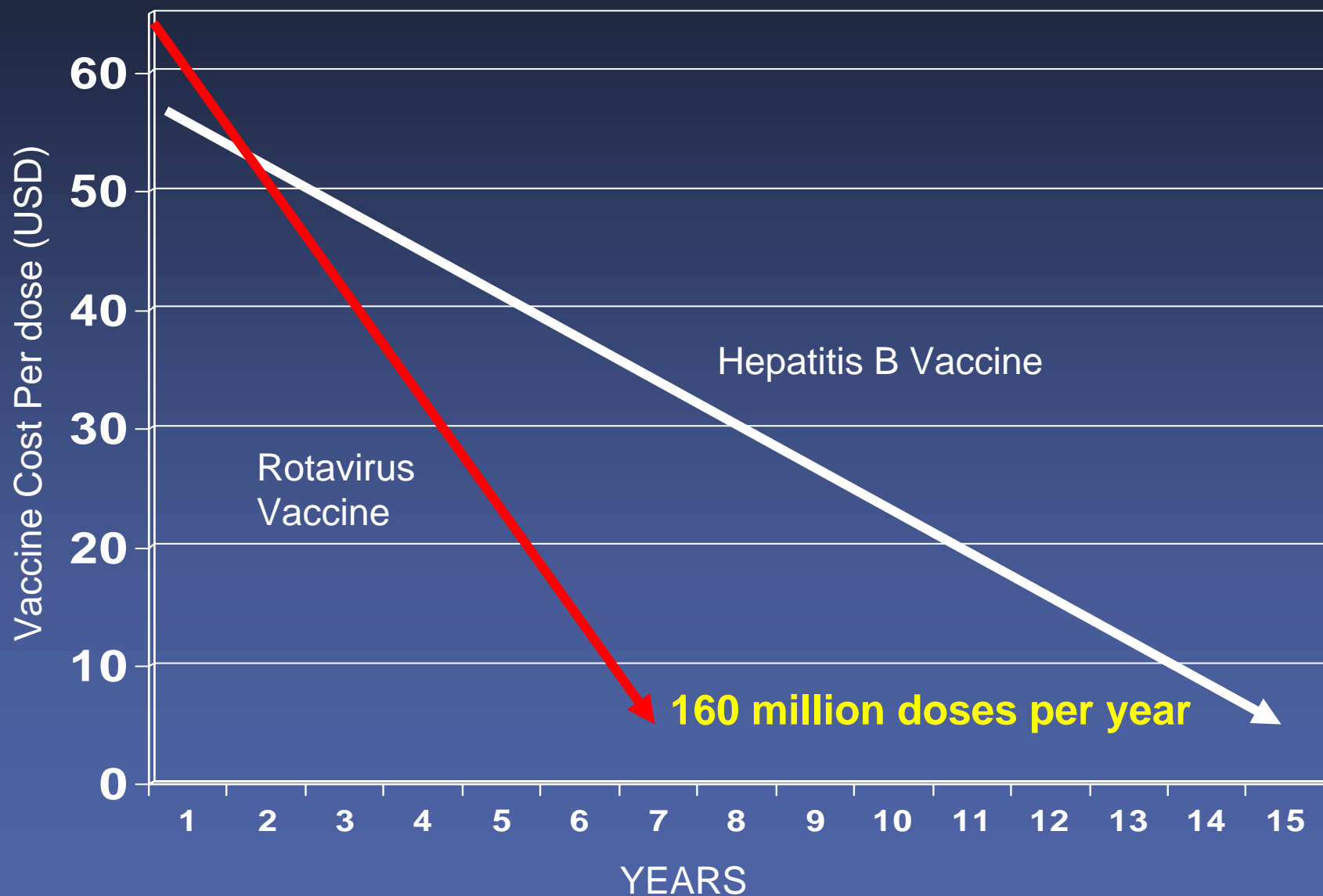


Development and Commercial Manufacturing Challenges for Live Attenuated Rotavirus Vaccines

William H. Wainwright, PhD

Biopharma Consulting Services

Goal of Rotavirus Vaccine Development Initiatives



Advantages of the Live Oral Rotavirus Vaccines

- Two approved vaccines and many promising candidate vaccines in development
- Fairly simple manufacturing process
- Many emerging vaccine manufacturers that are actively involved
 - ✓ Enthusiastic
 - ✓ Adequate to excellent facilities
- Extensive international support

Development and Commercial Manufacturing Challenges of Live Oral Rotavirus Vaccines

1. Common challenges in the production of any live virus vaccine
 - a) Unique challenges specific to rotavirus vaccines
2. Challenges in the development and manufacturing of vaccines in a developing nation
3. Increasing vaccine supply at an affordable price

Development and Manufacturing challenges for live virus vaccines

➤ Common challenges

- ◆ Adventitious agents
- ◆ Stability
- ◆ High growth with minimal process losses
- ◆ Multivalent infectivity assays

➤ Unique Challenges Specific to Rotavirus

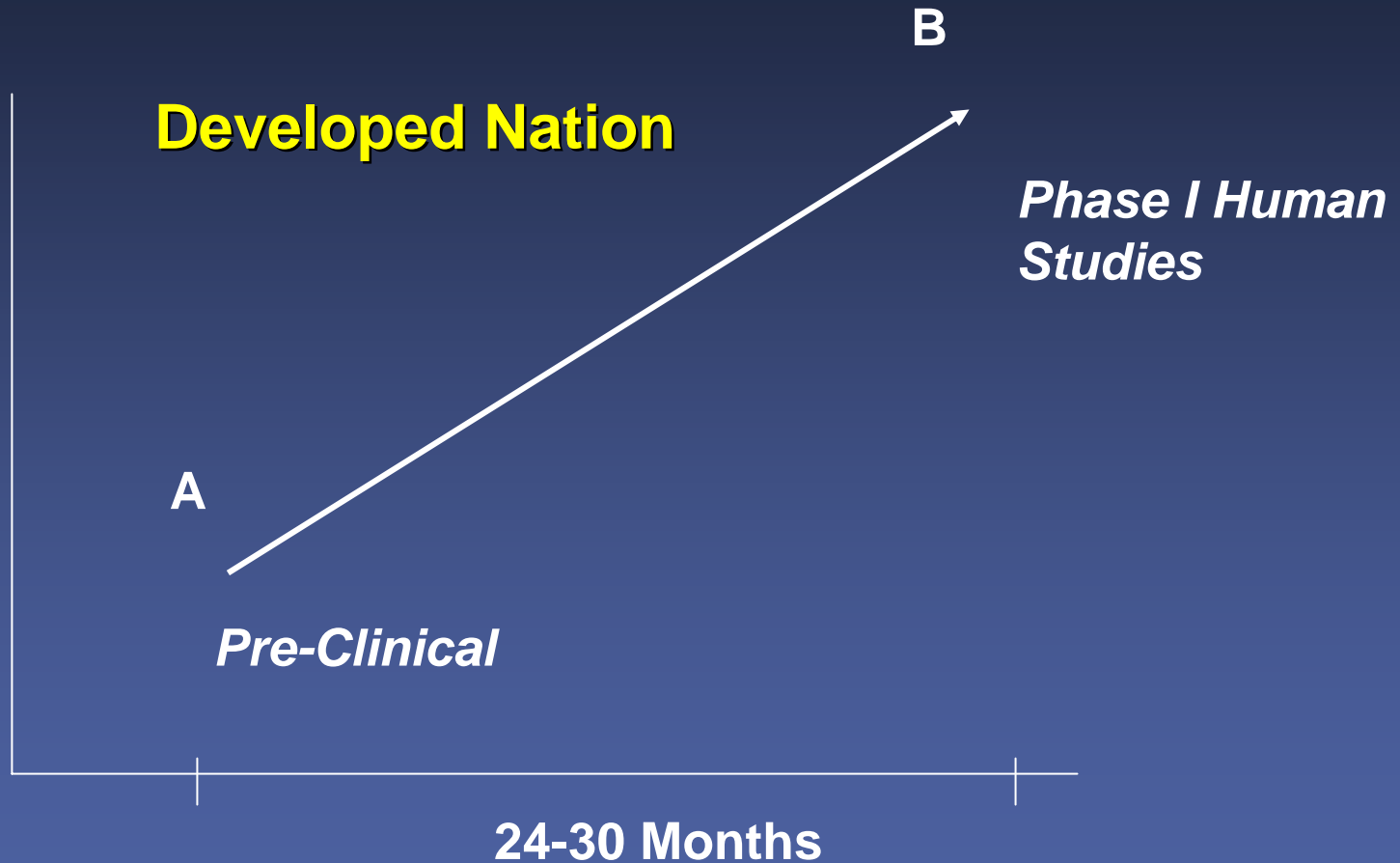
- ◆ Antacid
- ◆ Complex dosage formulation
- ◆ Large scale manufacturing

Challenges in the Development and Manufacturing of Vaccines in a Developing Nation

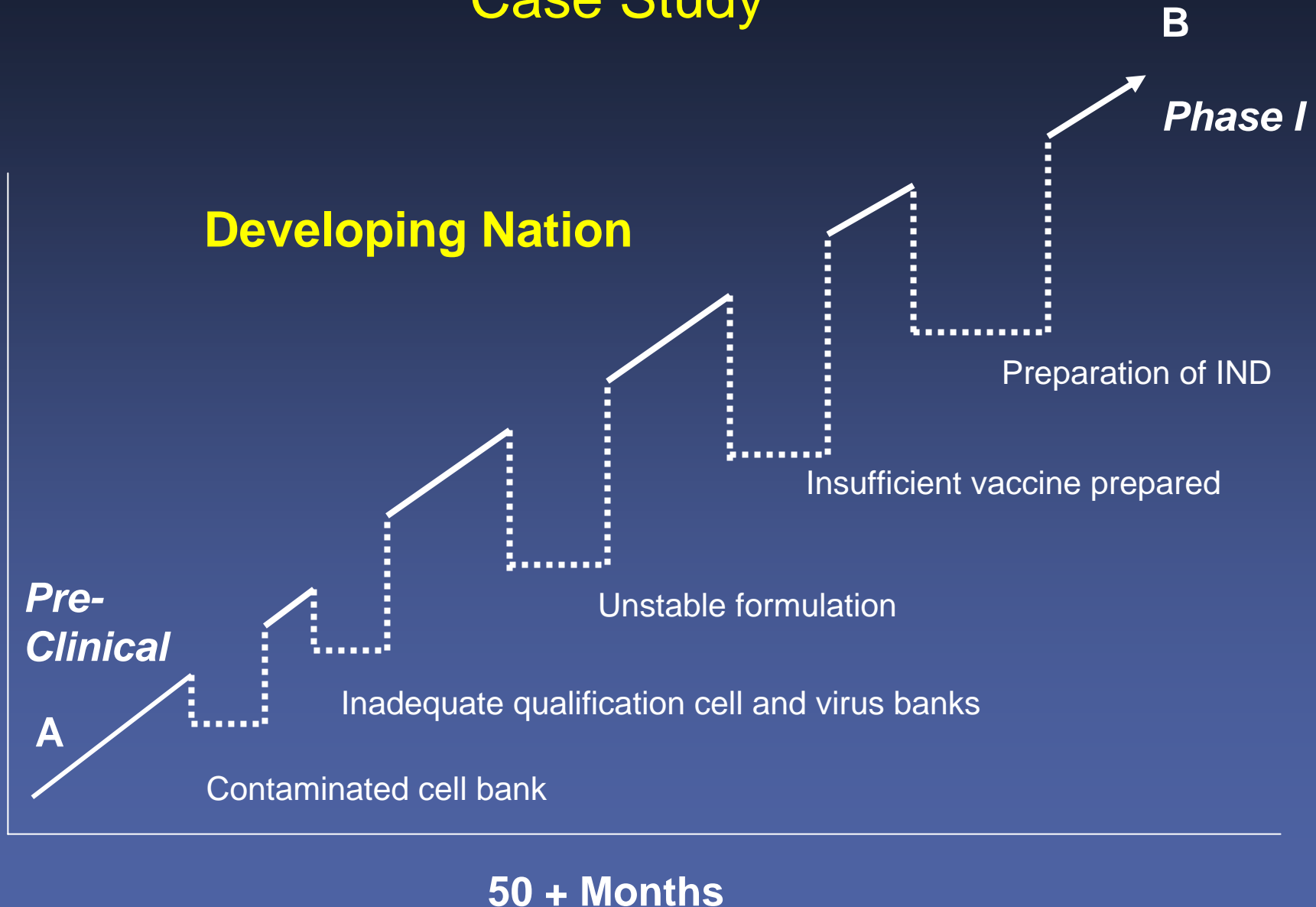
- **Funding**
- **Clinical development**
- **Project Management**
- **Personnel**
- **Quality Assurance and Quality Control**

Project Management

Knowing what to do and when to do it



Rotavirus Vaccine Development Case Study



Personnel Available for Rotavirus Vaccine Development

➤ Developed world

- ✓ Low turnover
 - ◆ Experience is retained
- ✓ Adequate supply of highly trained people
 - ◆ 50 – 75 well trained individuals per vaccine development project

➤ Developing world

- ✓ High turnover
 - ◆ One person leaves a project is stopped
- ✓ Limited number of trained staff
 - ◆ 10- 15 individuals with 0 -2 years experience per vaccine development project

Quality Assurance and Quality Control

Cost of Compliance

***Large
Multinational***

=

Quality Standards

***Emerging
Manufacturers***

- Extensive financial resources
- Wealth of QA/QC Talent
- Ratio 4 production to 1 QC/QA

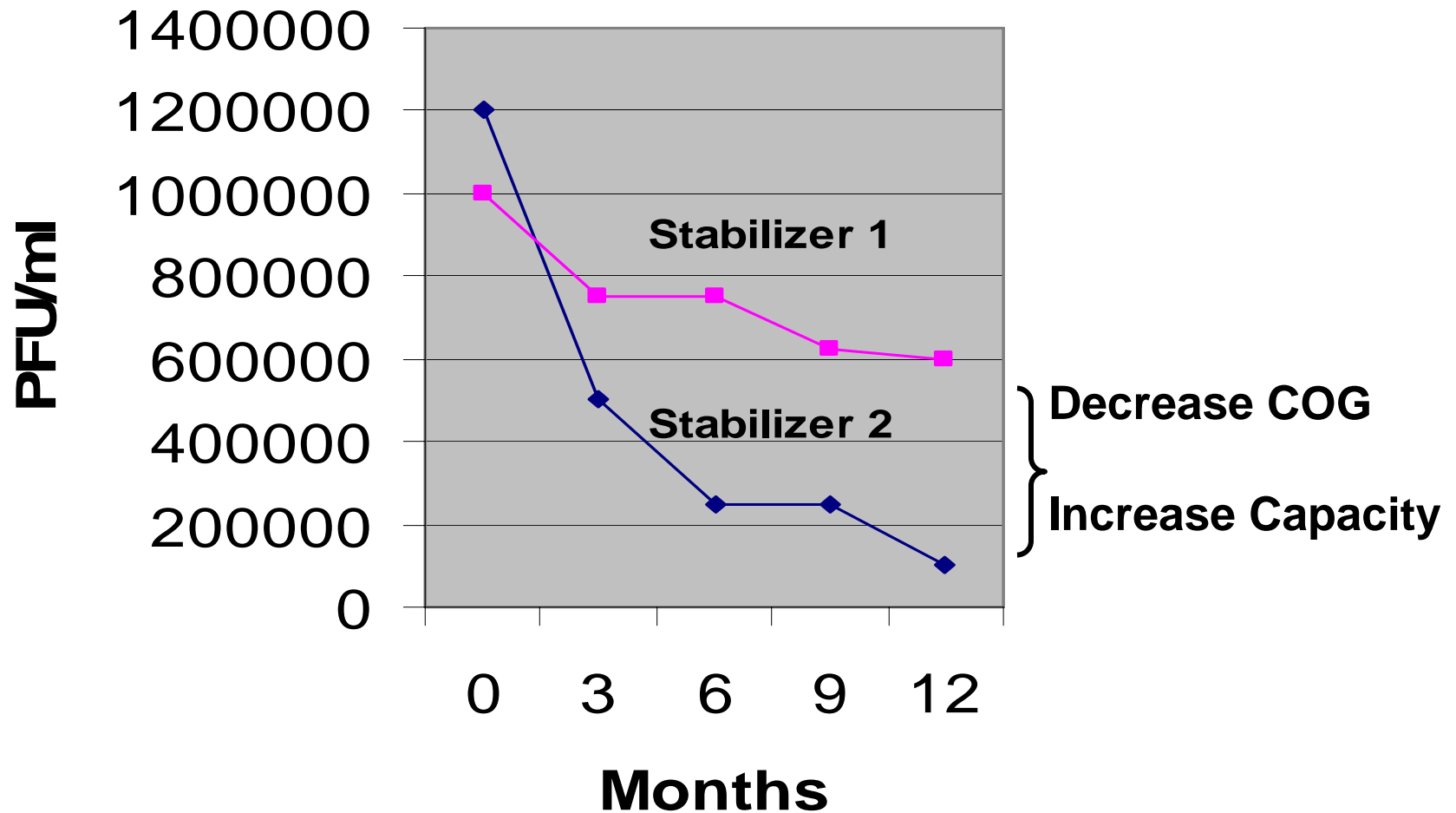
- Limited financial resources
- Limited QA/QC expertise
- Ratio 15 production to 1 QC/QA

Increase Vaccine Supply at an Affordable Price

Goal: 160 million doses per year @ \$0.50 per dose

- 1. Need manufacturers from developing countries**
 - a) **Cost of manufacturing drives process decisions**
- 2. Increase productivity: Improve yield by increasing the number of doses produced with minimal capital investment**
 - a) **Examples: Hepatitis B, MMR, Bacterial Vaccines**
- 3. Stable vaccine using an inexpensive and convenient delivery system**
 - a) **75% of the COG can be attributed to the formulation and package design**

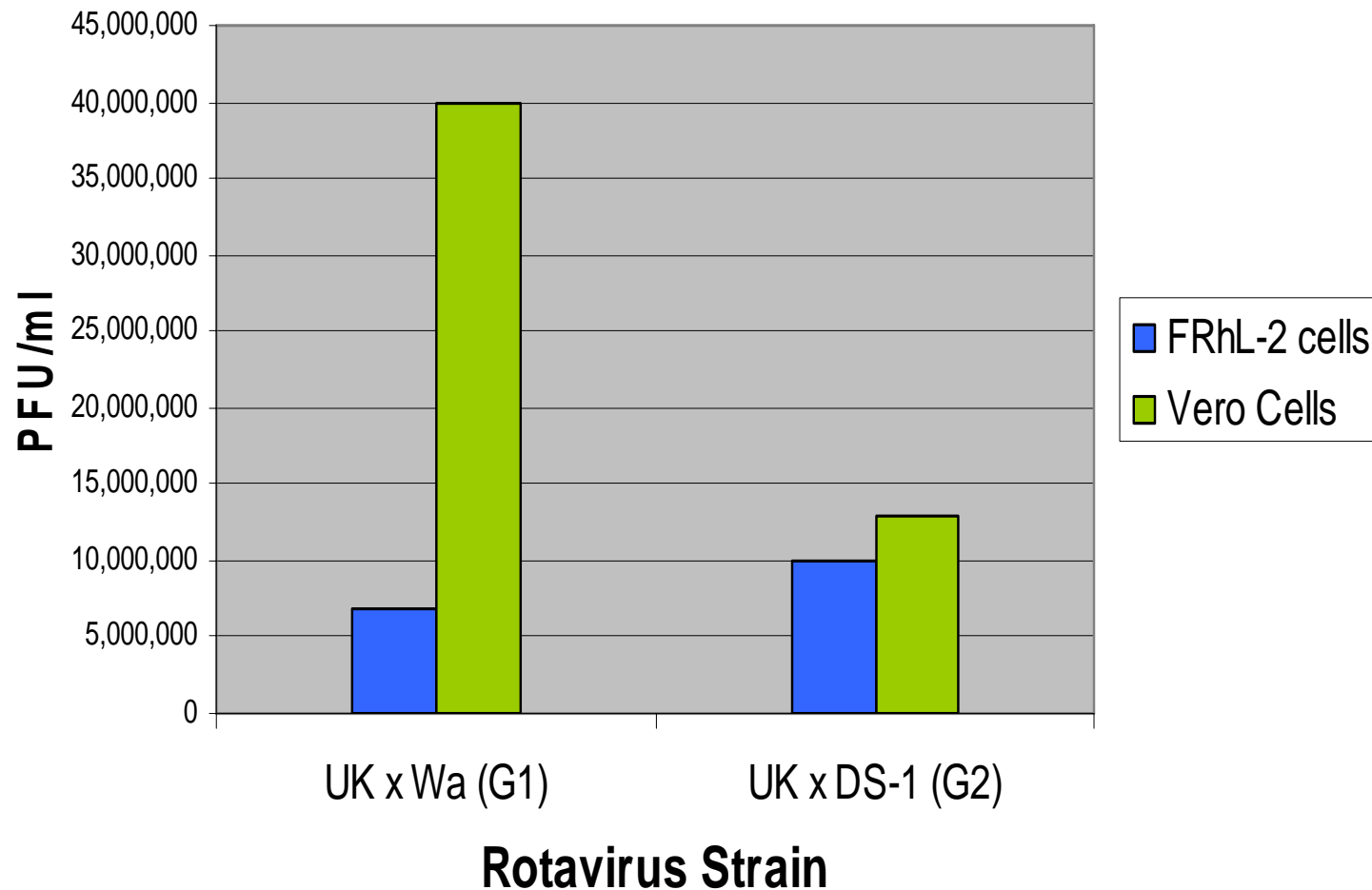
Stability of Rhesus Rotavirus Vaccine



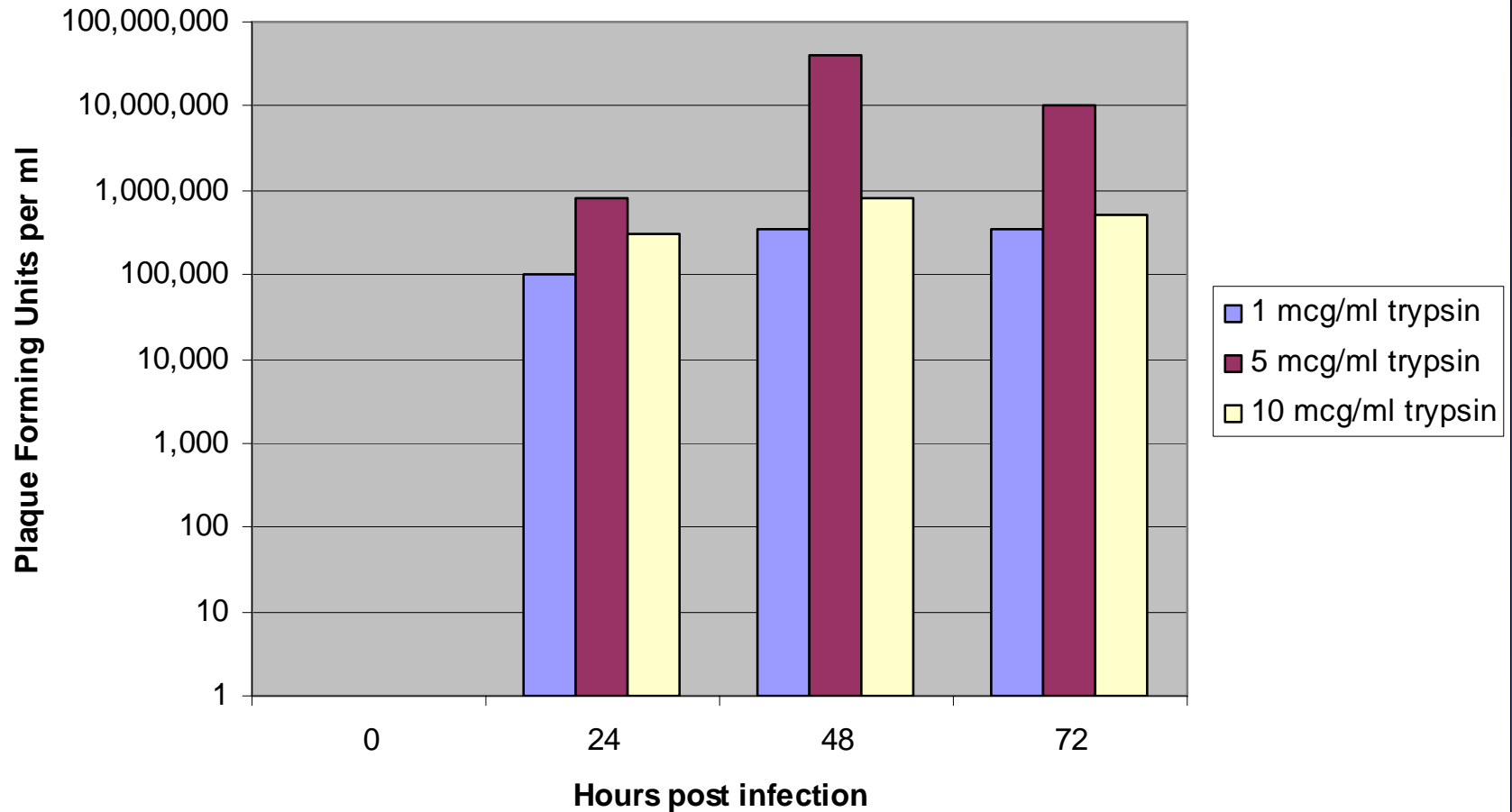
Critical Process Attributes Affecting Manufacturing Costs

- Choice of cell substrate
- Trypsin levels
- Bioreactors versus cell factories
- Multiplicity of infection
- Single or multiple harvests
- Choice of stabilizers
- Choice of delivery systems

Effect of Cell Substrate on Growth of UK Bovine Reassortant Viruses



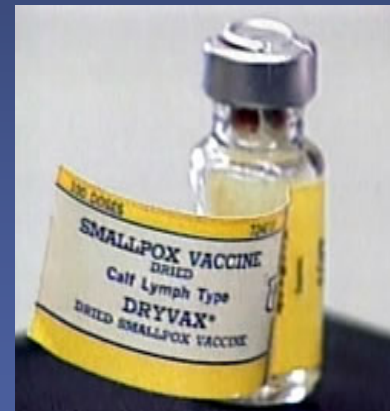
Effect of trypsin concentration on growth of Rhesus Rotavirus



Smallpox Eradication



~~Production
Methods~~



Delivery System

Polio Eradication (?)

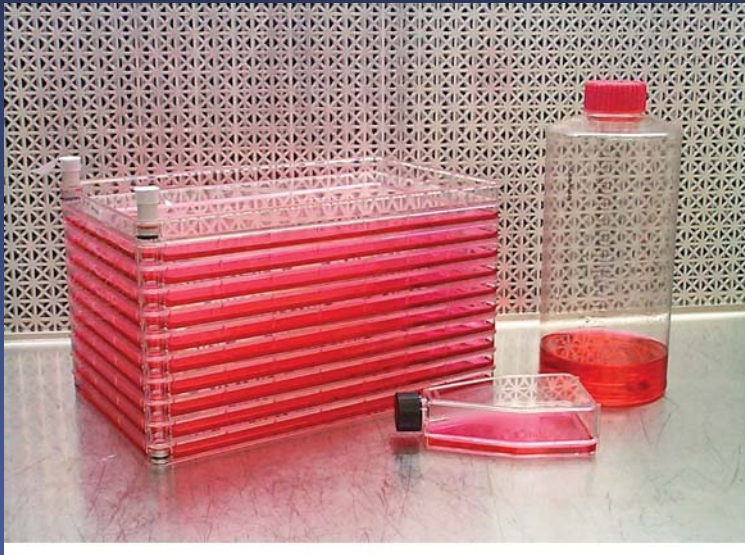


~~Production
Methods~~



Delivery system

Rotavirus Vaccine Supply



- ✓ Antacid + virus
- ✓ Single multi-dose container
- ✓ Refrigeration stable
- ✓ Liquid or Powder
- ✓ Minimal Virus Loss

~~Production
Methods~~

Delivery system

Recommendations

- Continue to encourage and support many vaccine manufacturers
- Expand training network in developing nations
- Improve human resource practices
- Spend the time and effort to develop robust and high yielding processes and inexpensive formulation and deliver systems