Mainstreaming new immunization technologies

…technologies that will facilitate high coverage with safe and effective immunization.

Goals

- Raise ‘effective’ coverage
  - to GAVI goal and beyond
- Safe administration
  - eliminate contamination, transmission
- Reduce dependence on the cold chain
  - towards elimination

Challenges (1)

- Complexity of current multi-dose vaccine presentations

- 8 vaccines and increasing:
  - inc. 4 liquid, 4 FD plus combinations in 2, 6, 10, 20 dose vials
- High wastage of MDVials:
  - Reluctance to adopt MDVPolicy
  - Refusal to open vials
- Reconstitution
  - Contamination issue
  - Recon. syringes

Challenges (2)

- Complexity of current multi-dose vaccine presentations
- Risk of needle-stick and re-use of needles

- Transmission of HepB, HepC and HIV
  - 20 million HB infections and 500,000 HIV infections
- Risks of re-use to:
  - Client & community
- Risks of needle-stick to:
  - Healthworker, waste handlers and the community

Challenges (3)

- Complexity of current multi-dose vaccine presentations
- Risk of needle-stick and re-use of needles
- Cold chain failures, frozen vaccine

- Cold chain failures cause estimated 5% wastage
- But exposure to freezing of freeze-sensitive vaccines observed to be 75-83%
  - PATH studies in Indonesia 2002-2003

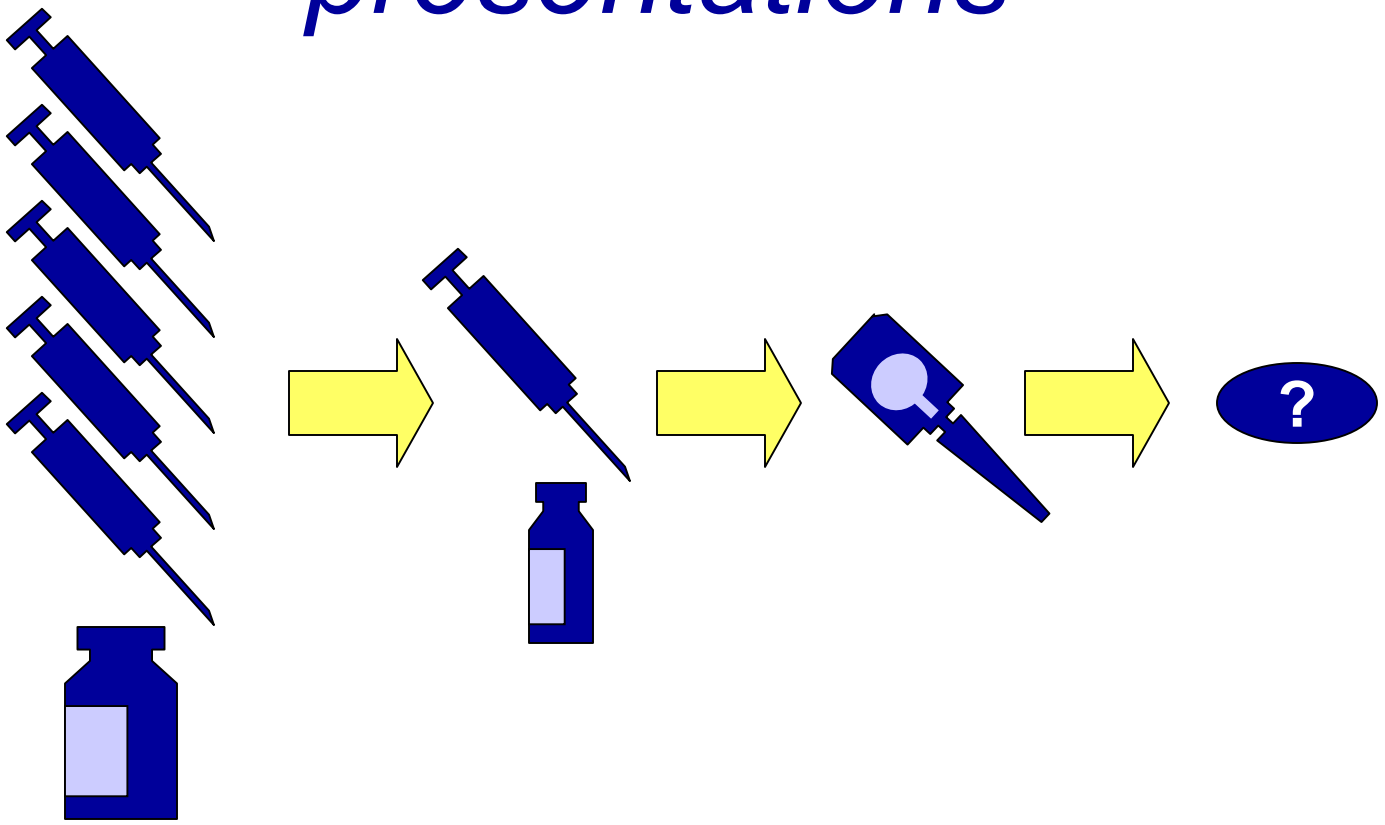
Rationale for 4-point rolling strategy

- **Single-dose**, liquid vaccine presentations
- **Needle-free** administration of vaccine
- **Thermostable** stored under standard drug storage conditions
- **Multiple vaccine combinations,** vaccine antigen co-suspensions

Single-dose, liquid vaccine presentations

Single-dose versus multi-dose vaccine vials for immunization programmes in developing countries. Drain P, Nelson C and Lloyd J, P Bulletin of the WHO 2003, 81 (10)

Towards single-dose presentations



Single v. Multi liquid dose formats

	Multi-dose vial	Single dose vial	Prefilled device
Production	Faster filling rate		
Packaging	Less packaging		
Distribution	Smaller, lighter for transport	Simpler stock	
Cold chain	Smaller coldchain volume		
Safety		Less risk of contamination use of Thiomersal More accurate dose delivery	No risk of contamination No use of Thiomersal More accurate dose delivery
Syringe usage			No syringe required
Vaccine wastage		Less vaccine wastage	Least vaccine wastage
Coverage rates		Less reluctance to open a vial	Facilitates innovative outreach strategies Less reluctance to open a vial
Medical waste	Smaller waste volume	Most volume to dispose	Least volume to dispose

Slower filling rate
Equipment investment

x 6

x 8

Cost & wastage trade-off

Estimated manufacturing costs (US $) per dose, including an injection device and excluding cost of vaccine solution, for 10-dose vials, 1-dose vials, or prefilled AD device by a hypothetical vaccine producer in a developing country

Manufacturing Costs(1)	10-dose vial	1-dose vial	Prefilled AD device
Production (labor and equipment)(2)	$0.015	$0.040	$0.042
Material packaging and syringe(3)	$0.090	$0.217	$0.200
Vaccine overfill adjustment(4)	100%	113%	98%
Total Manufacturing Cost	$0.105	$0.257	$0.242

1. Based on a production rate of 120 units/minute, with manual inspection and packaging, and a US$5,000/year direct labor rate.
2. Includes quality control tests, facility and utility costs, and equipment depreciation, based on a 10-year life span for all manufacturing equipment.
3. All costs include vial/device, stopper, aluminum crimp seal, label, carton or pouch, box, and a $.04 vaccine vial monitor. Vials include a $.07 auto-disable syringe.
4. Based on recommended levels of overfill for injectable vaccines.

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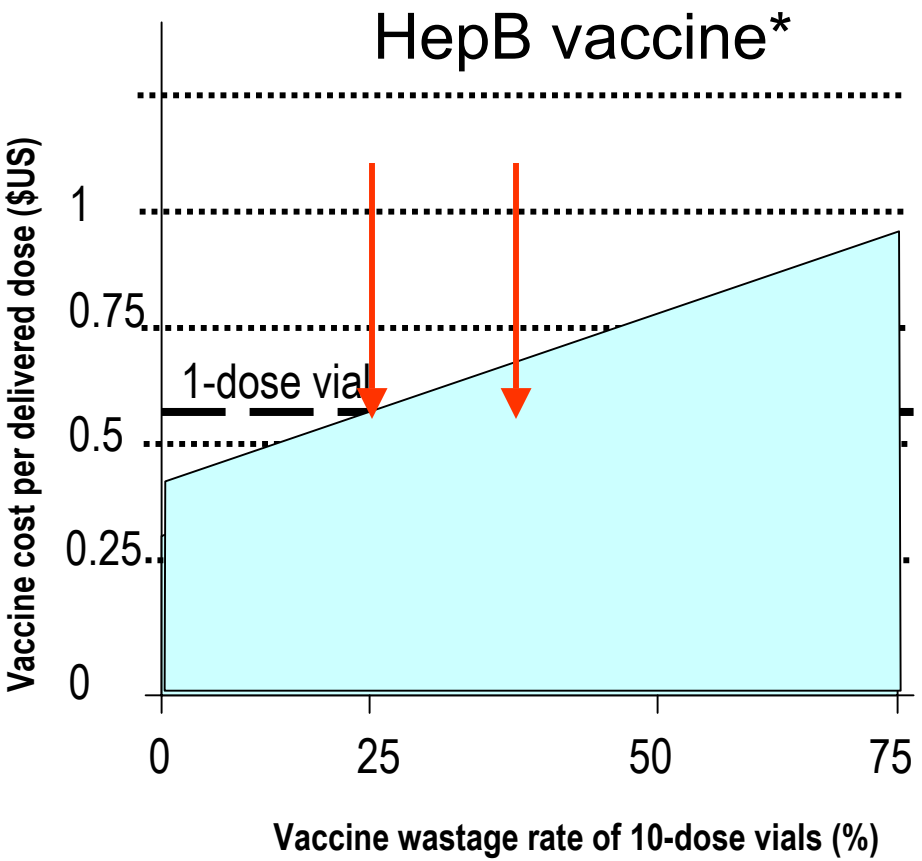

(UNICEF Projections 2002)*

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20 years of 'plastic prefill' (Uniject) development

Recent experience

- 9 million TT doses 2002-2005
  - **Mali**
  - Afghanistan
  - Ghana
  - S Sudan
  - Somalia
  - Burkina Faso

•340 non-literate TBAs used TT-Uniject at community posts.

•Easily trained.

•Safely and correctly used TT-Uniject.

•Acceptability high—women prefer being immunized by people from their own community.

•Use of TBAs may increase coverage by

•Mobilizing population

–Better identification of those needing vaccination

–Reducing rumors

Lessons learned

- Long (and costly) process for pharma adoption of prefill system
- Prefill economics favor higher value products
- System costs offset price premiums
- Move from multi-dose to single dose (prefill or vial) is challenging
- System changes profound for BOTH pharma producers and program users
- Prefill value added not easily recognized by procurement agencies

Needle-free administration of vaccine

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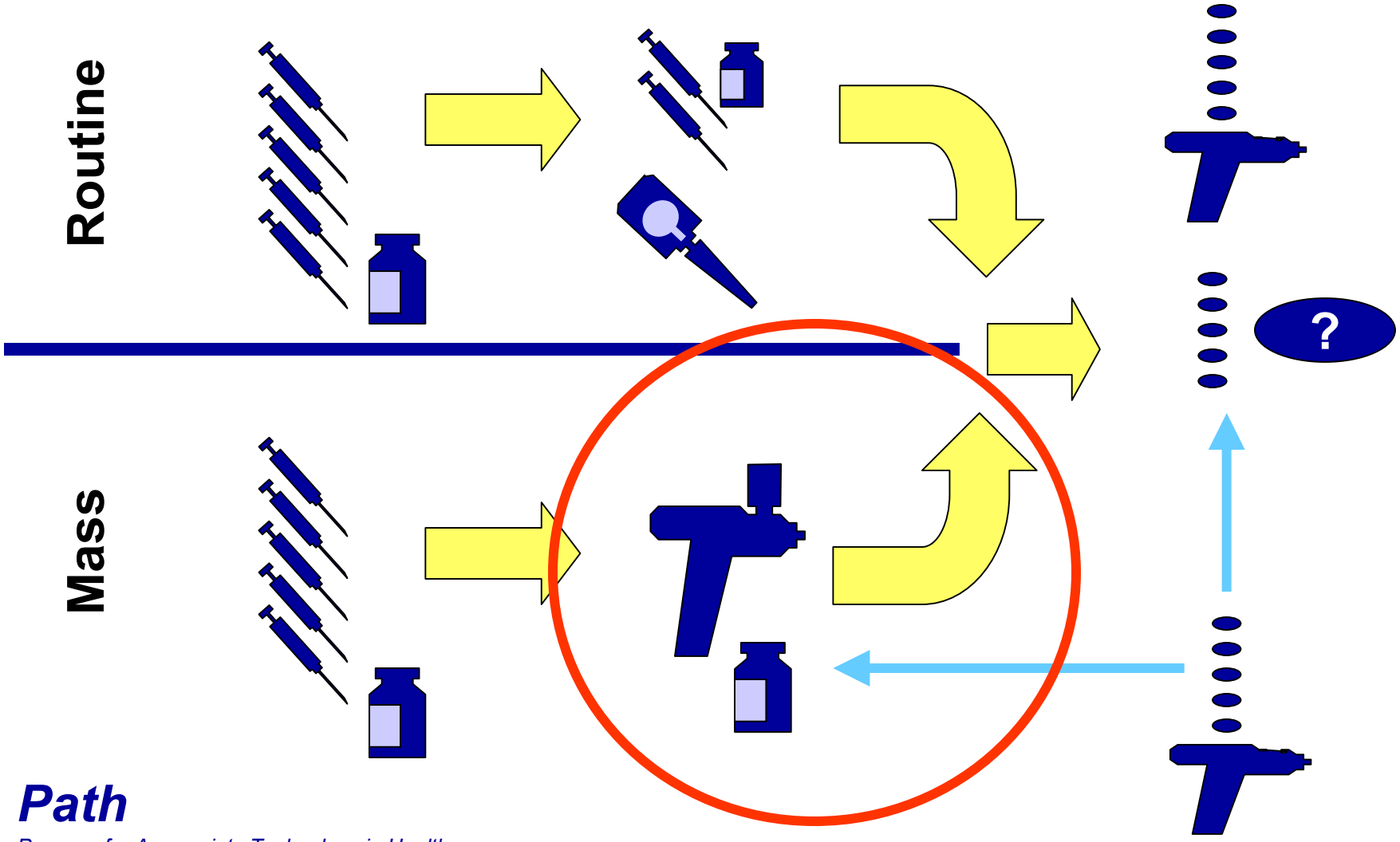
Towards needle-free/ non-invasive



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Mass immunization

Syringes

- Simultaneous campaign via multiple posts
- Period a few days
- All health staff mobilized
- Supplies distributed

Jet injectors

- Campaign by sequential zone
- Period several months
- Trained mobile teams
- Supplies carried

Benefits v. challenges

Benefits

- Greater safety
- Less supplies
- Less disposal
- Greater speed
- Better quality

Challenges

- Contamination history
- Lifting WHO ban
- Sterilization
- Timeliness of product

Thermostable vaccine

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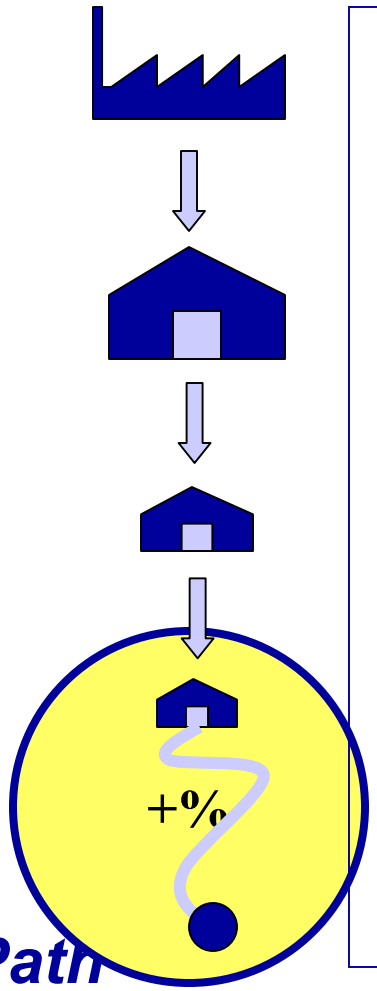
PATH is working in this area with funding from GF (through the Affordable Technologies for Health project) and USAID (HealthTech)

Towards thermostable vaccine



- Introduce ‘E’-monitoring of vaccine stores
- Eliminate vaccine freezing in transport and storage
- Introduce and fully utilize VVMs
- Take certain vaccines beyond the cold chain

- Vaccines heat and freeze stable:
  - Antigen particles
  - Dried & co-suspended
- Vaccines stable liquids for injection
- Vaccines stable dry powder for non-invasive administration

Proof of principle…

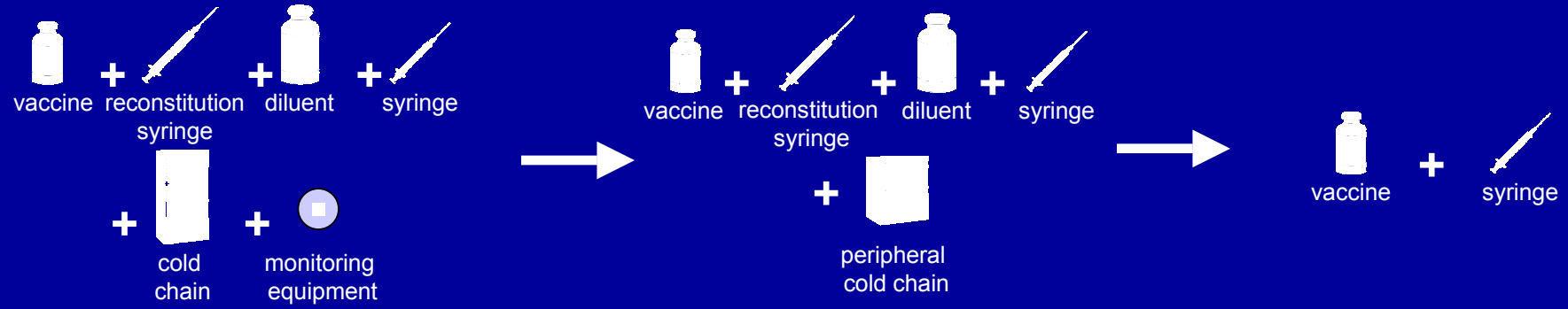
Vaccine	Results	Year
Measles	Titre drop of less than 1 log Plaque Forming Unit (PFU)/ml after 120 days at 37°C or 14 days at 45°C	2001
Tetanus Toxoid (TT)	Less than 10% drop in activity after 35 weeks at 45°C. Heat stability of dried TT suspended in oil and perfluorocarbon has also been shown.	Prior to 1999
Diptheria-Tetanus-Pertussis (DTP)	Four of five results showed unaltered potency after 3 months at 60°C and after 1 year at 37°C	Prior to 1997
Oral Polio Virus (Sabin 1)	Heat-stabilization of trehalose-dried vaccine for 1 week at 45°C.	1993
Influenza (A/PR/8/34) and Tetanus	Heat-stabilization of spray-dried vaccine with adjuvants is demonstrated after 9 months at 37°C.	1991-1998
Measles	Titre drop of less than .75 log Cell Culture Infected Dose (CCID)/ml after 15 days at 45°C, and less than .5 log after 30 days at 37°C.	2002

Towards no cold chain

Current Vaccines	Stable Dry Vaccines	Stable Liquid Vaccines

Freeze-dried

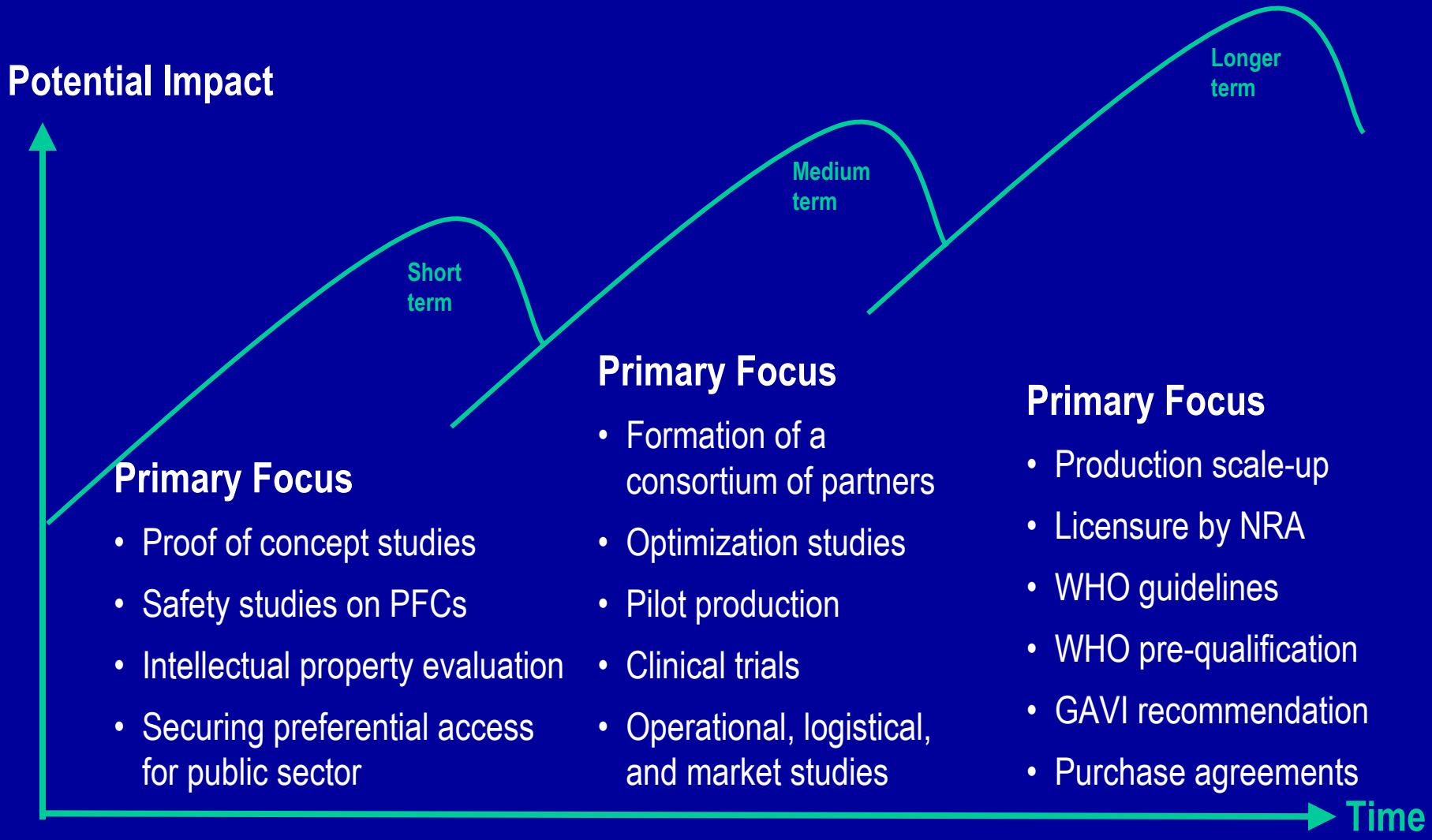
(measles, BCG, Hib, yellow fever)



Liquid

(liquid Hib, hepatitis B, DTP, TT, DT, Td)

Development of a stable liquid vaccine



Manage a portfolio of interventions and continuously assess risk vs. potential return when allocating resources

Multiple vaccine combinations

Towards fewer contacts..

- Co-suspensions of inert antigen particles
  - Permit more antigen combinations
  - Permit shorter development track
- Controlled release opportunities
  - Encapsulation of particles
  - Low hydroscopicity
- Alternative powder formats
  - Particle size control <5 microns to >40 microns
  - Options for inhalation, paste or cake deposition

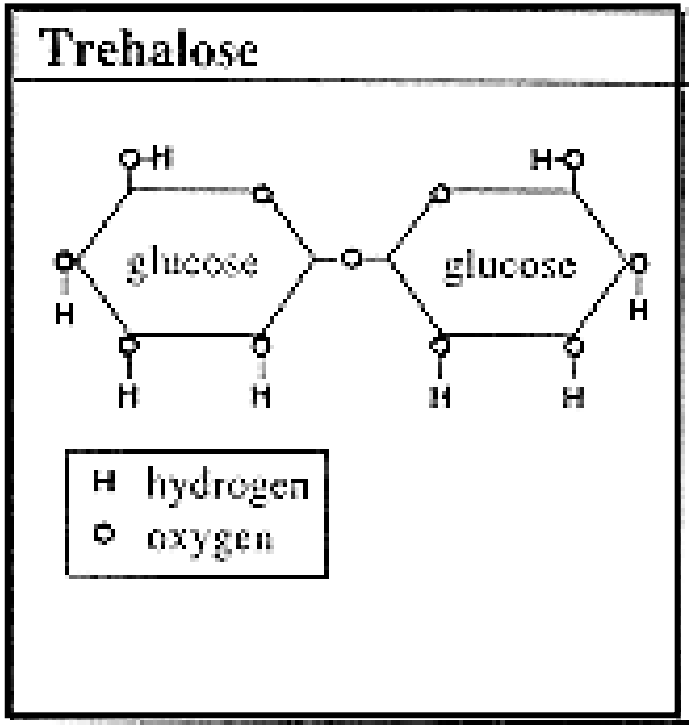
Vision

- **Today:**
  - Safety Syringes + MDVs + cold chain + VVMs for routine and mass immunization
- **In 5-10 years:**
  - Reduced dependence on the cold chain
  - Prefilled injection devices for liquid combos
  - Safety Syringes + MDVs for trad.vaccines in routine immunization
  - Jet injection + MDVs for mass immunization
- **In 10-15 years:**
  - Stabilized liquid single-dose, combination vaccines
  - Needle-free administration for all immunizations

Thank you!

Sugar glasses

- present in high concentrations in **cryptobionts**: dry out completely completely and regain full metabolic activity with water
- **very unreactive**, because the two glucose moities are joined by a low energy glycosidic bond that **makes trehalose non-reducing** and **very stable to hydrolisis**
- ability to hydrogen bond to phospholipid membrane and proteins by **substituting for structural water**
- solidify as a **heat stable glass** rather than crystallization



Potential for suspension in perfluorocarbon liquid