



# Vaccine manufacturing at lab scale: A paradigm shift to more affordable vaccines


February 2021



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Accelerate biotechnology



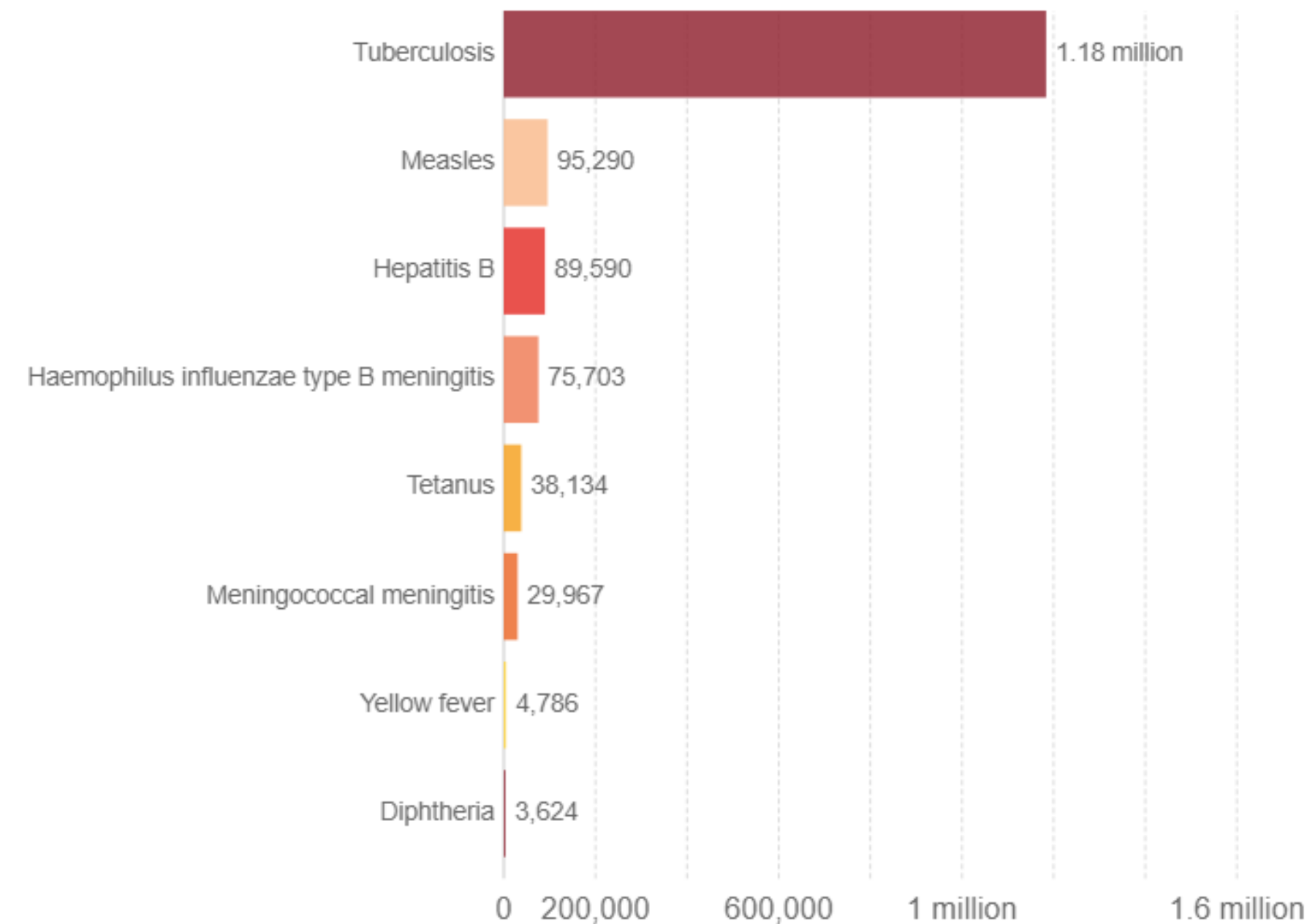


Challenges facing vaccine  
development & manufacturing  
for global health



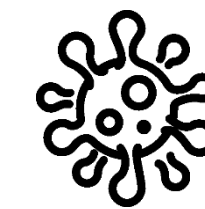
# >8000 people die every day due to preventable diseases

Deaths caused by vaccine-preventable diseases, World, 2017



Source: Institute for Health Metrics & Evaluation (IHME)

OurWorldInData.org/vaccination/ • CC BY



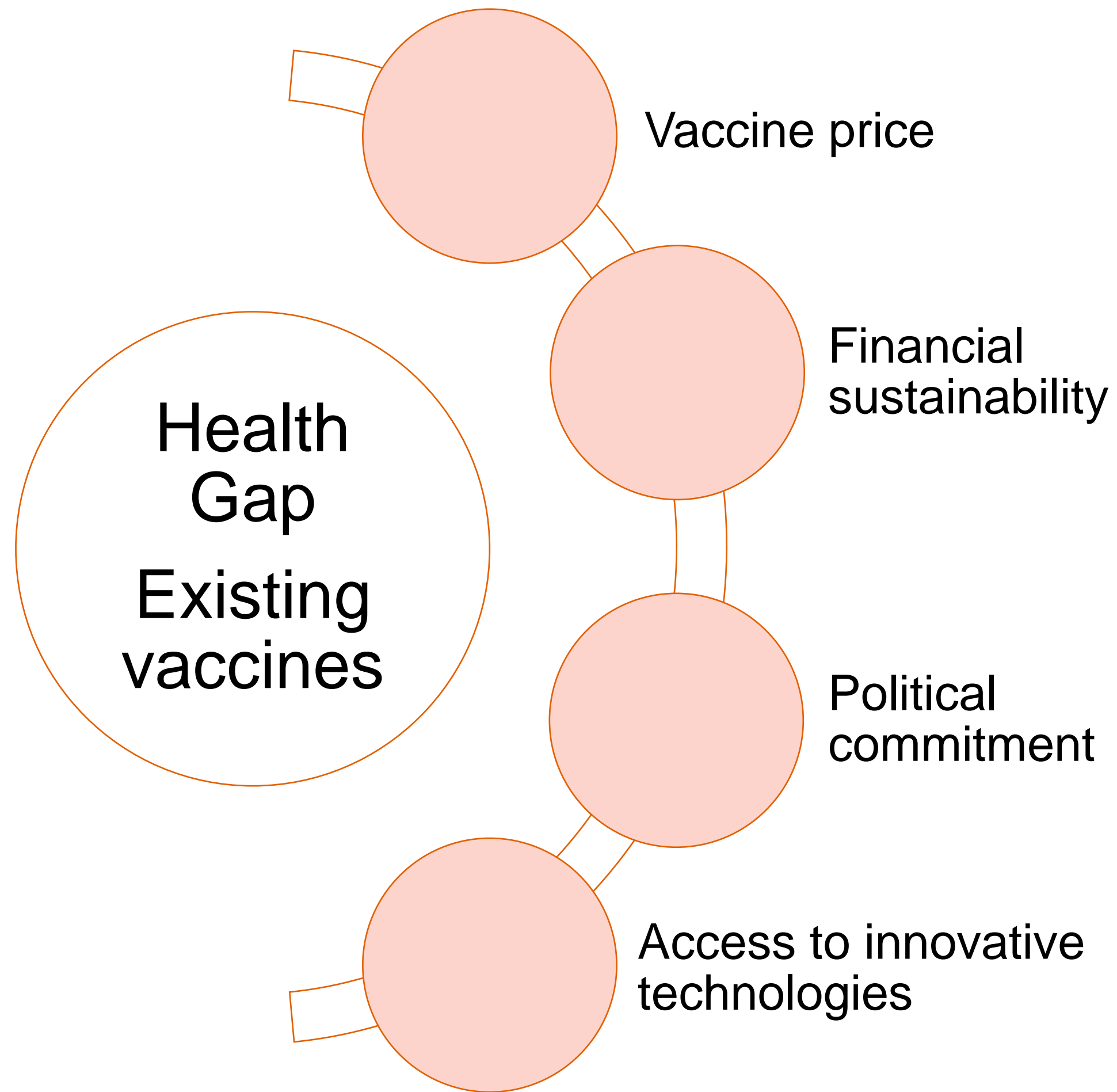
In case of 100% immunization coverage, 1 out of 7 deaths among young children could be prevented with vaccines

**Need to increase availability of cost-effective vaccines**

Vaccination is one of the most cost-effective healthcare interventions, preventing almost 6 million deaths annually worldwide but availability is suboptimal

Source: World Health Organization

# Relatively high price results in a health gap

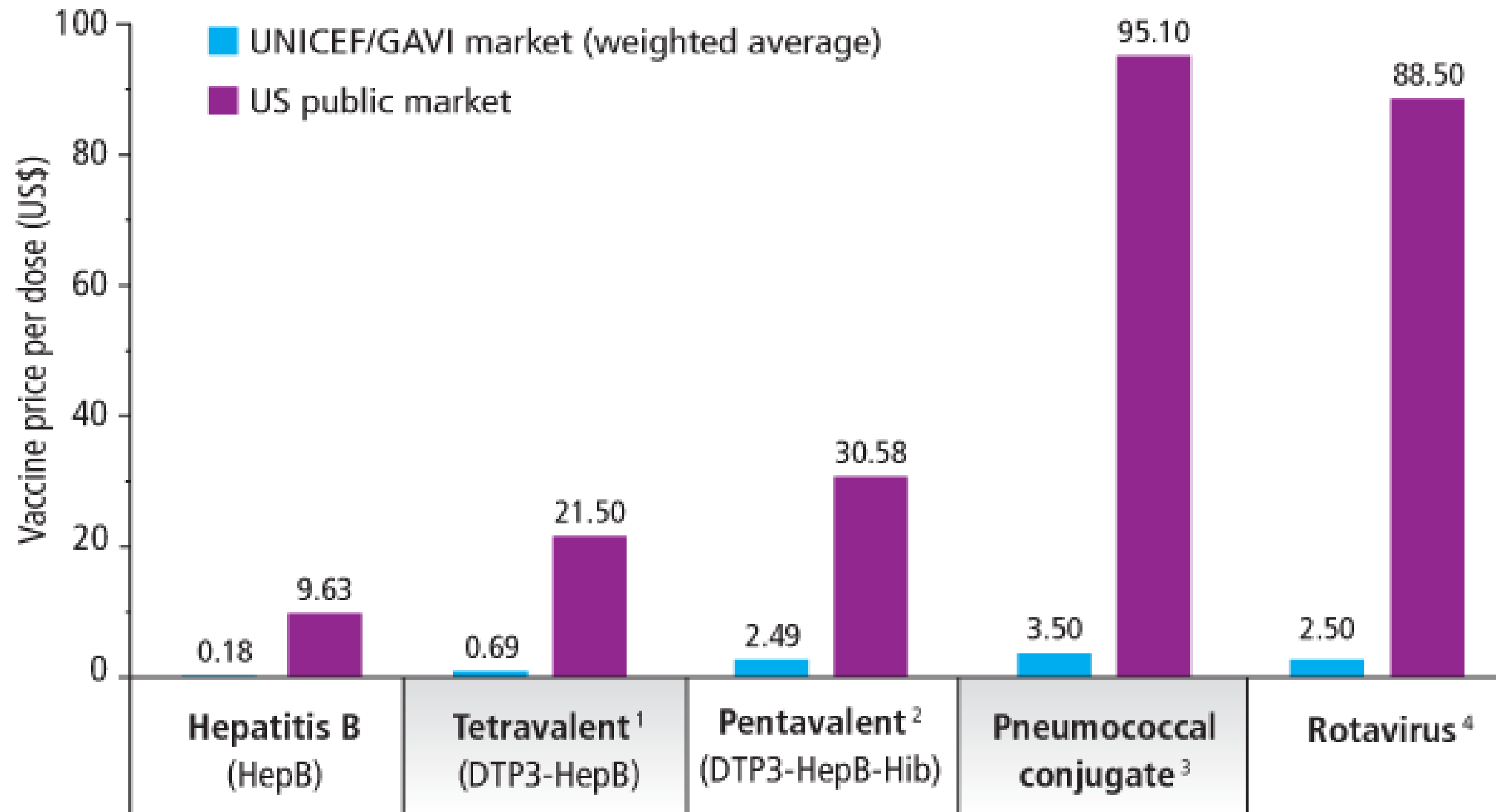


## Vaccination schedule in Somalia

| Antigen | Schedule   |      |       |       |         |
|---------|--|------|-------|-------|---------|
|         | Birth  | 6 wk | 10 wk | 14 wk | 9 month |
| BCG     | █  |      |       |       |         |
| OPV     | █  | █    | █     | █     |         |
| DTP     |  | █    | █     | █     |         |
| Measles |  |      |       |       | █       |
| TT      | Pregnant women at health facilities and WCBA during CHDs |      |       |       |         |

Total number of vaccines used in many countries is less than the 11 vaccines recommended by WHO for infants in all countries

# Global need to further lower vaccine prices



<sup>1</sup> The combination procured by UNICEF is not provided in the US markets - US prices refer to the sum of a DTaP (Diphtheria-Tetanus-Acellular Pertussis) vaccine and a HepB monovalent vaccine.

<sup>2</sup> The combination procured by UNICEF is not provided in the US markets - US prices refer to the sum of a DTaP vaccine, a HepB monovalent vaccine and a Hib vaccine.

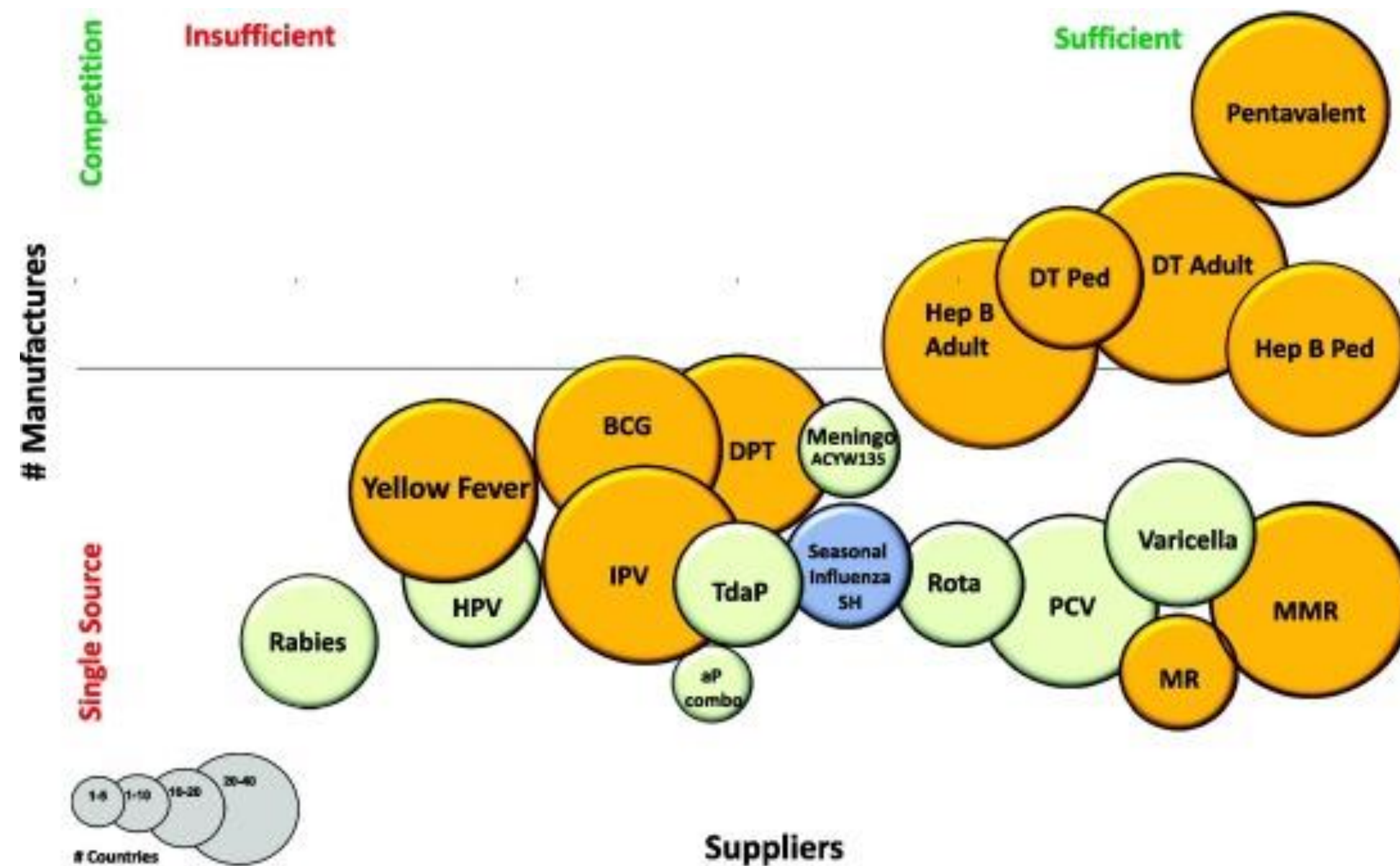
<sup>3</sup> 13-valent vaccine (US markets) and tail price cap under the AMC agreement (UNICEF/GAVI market).

<sup>4</sup> Refers to GSK product procured by GAVI as of 2012.

Vaccines are sold in developing countries at prices systematically lower than in industrialized countries.

Need for pricing to fall further (<\$1 per dose) to ensure better coverage and sustainable supply

# Cost-effective and innovative technologies for a better vaccine supply



Well established and under-used vaccines supplied by Developing Country Vaccine Manufacturers are mainly based on **conventional technologies**

Investment hurdles are imposed for the conventional technologies (cell factories, microcarriers) due to the need for large and expensive manufacturing facilities (high CAPEX) and operations (high OPEX)

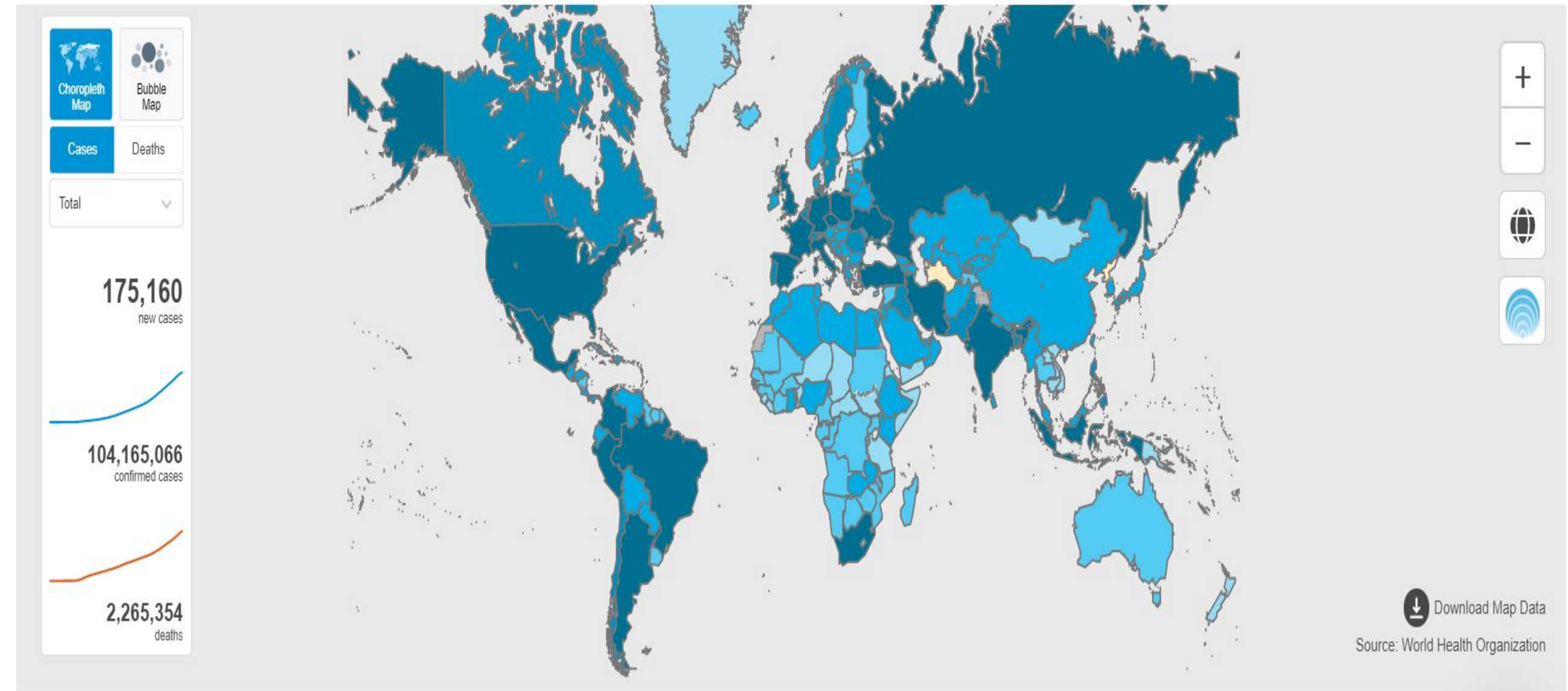
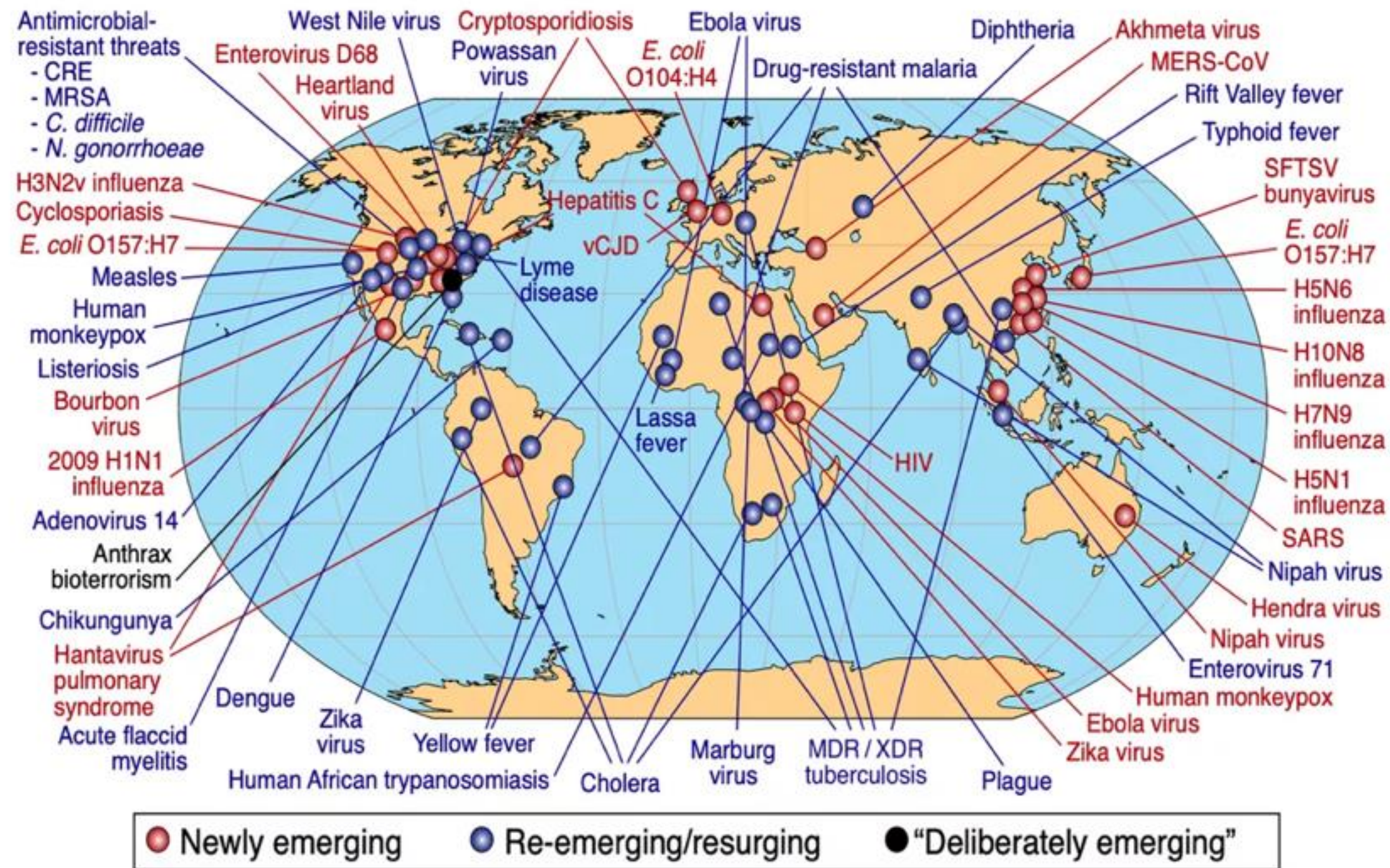
**Need for cost-effective and innovative technologies to assure more competition and cost-effectiveness**

Sources: Sonia Pagliusi et al, Vaccine 2020  
<https://www.dcvmn.org/>



# (Re)emerging diseases exert a significant global health threat

- Globalization
- Migration
- Armed conflicts
- Population & Urbanization
- Climate change



Cases Coronavirus Disease globally (Feb 2020), WHO

- Chikungunya Dec 2013 - Mar 2015 (Americas)
- >1.3 million cases in 44 countries
- Ebola 2014 (W.Africa)
- 20,206 cases, 7905 deaths
- MERS-CoV 2012 - 2017 (Global)
- Affecting >212 countries and territories
- COVID-19 2020 (Global)
- >100M cases, >2.2 M deaths



# Increased demand for vaccines requires novel way of manufacturing

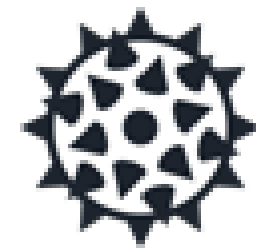


## Low cost & low investment

To ensure global availability

Very low COGs  
(<\$1 / dose) critical  
&

Focus on low CAPEX and low  
OPEX lowering the barrier for  
new investments



## Broad applicability

High diversity of vaccine  
modalities

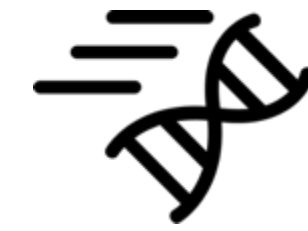
Broadly applicable  
manufacturing platform  
needed



## Capacity & Flexibility

Multiple threats ranging from  
regional diseases (Nipah,  
Lassa, Ebola) to major global  
outbreaks (COVID-19)

Large capacity, multi-product  
flexible facility



## Rapid response

Following outbreak  
vaccines are pivotal in crisis  
management

Rapid response and ramp-  
up essential

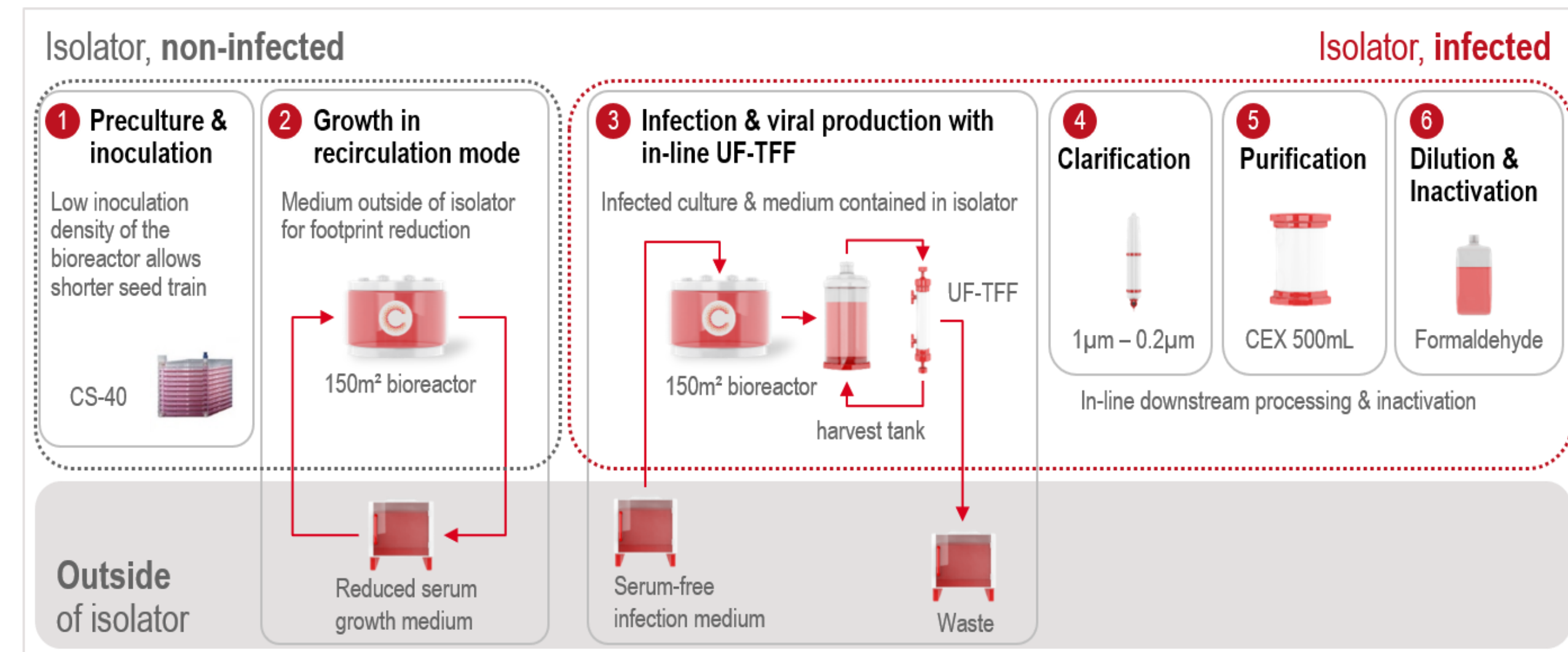


Manufacturing at lab scale:  
A novel way of manufacturing



# Batavia's proven solution: HIP-Vax<sup>®</sup> technology

- HIP-Vax<sup>®</sup> supports high vaccine yields in small footprint
  - Output equivalent to 1000L bioreactor at 50L harvest scale
- Low OPEX, low COGs
- Commercial manufacture at lab scale
- Developed in grants funded by Gates Foundation
  - Grants for polio (sIPV, nOPV), measles and rubella vaccines
- Expanded in other collaborations
  - CEPI: Lassa fever, Nipah
  - DTRA: Marburg
- Applicable to major vaccine modalities
  - Viral vectors (VSV, MV, Adeno), inactivated & live attenuated vaccines
  - All major manufacturing cell substrates - vero, MRC-5, HEK-293





# Fixed-bed bioreactors replacing equivalent manufacturing technologies

| scale-X™          | #RB<br>(850cm <sup>2</sup> ) | #CF40<br>(25.280cm <sup>2</sup> ) | Stirred tank<br>(Cytodex, 3 g/L) |
|-------------------|------------------------------|-----------------------------------|----------------------------------|
| 10m <sup>2</sup>  | ~120                         | ~4                                | ~15L                             |
| 30m <sup>2</sup>  | ~360                         | ~12                               | ~50L                             |
| 200m <sup>2</sup> | ~2,400                       | ~80                               | ~300L                            |
| 600m <sup>2</sup> | ~7,000                       | ~240                              | ~1000L                           |





A row of small glass vials containing pink liquid, arranged on a curved metal tray inside a laboratory setting. The vials are filled with a vibrant pink liquid and are positioned on a polished, reflective metal tray. The background is a dark, out-of-focus laboratory environment with some blurred lights and equipment. The overall scene suggests a scientific or medical laboratory setting.

Case study: low-cost  
inactivated polio vaccine



# Inactivated polio vaccine price not in line with mass global use

IPV prices per dose 2018-2019 actual, 2020-2022 predictions

UNICEF Market Update 19Sept 2019

| Presentations | 2018    | 2019    | % increase over 2018 | 2020    | 2021    | 2022    |
|---------------|---------|---------|----------------------|---------|---------|---------|
| 1 dose        | \$ 2.80 | \$ 3.50 | 25%                  | \$ 2.80 | \$ 2.80 | \$ 2.80 |
|               |         |         |                      |         |         |         |
| 5 dose        | \$ 1.90 | \$ 2.95 | 55%                  | \$ 3.10 | \$ 3.10 | \$ 2.50 |
|               | € 0.96  | € 2.06  | 115%                 | € 2.06  | € 2.06  | € 2.06  |
|               |         |         |                      |         |         |         |
| 10 dose       | € 0.75  | € 1.81  | 141%                 | € 1.81  | € 1.81  | € 1.81  |

Need for pricing to fall to <\$1 per dose



# Inactivated polio vaccine manufacturing capacity not in line with demand

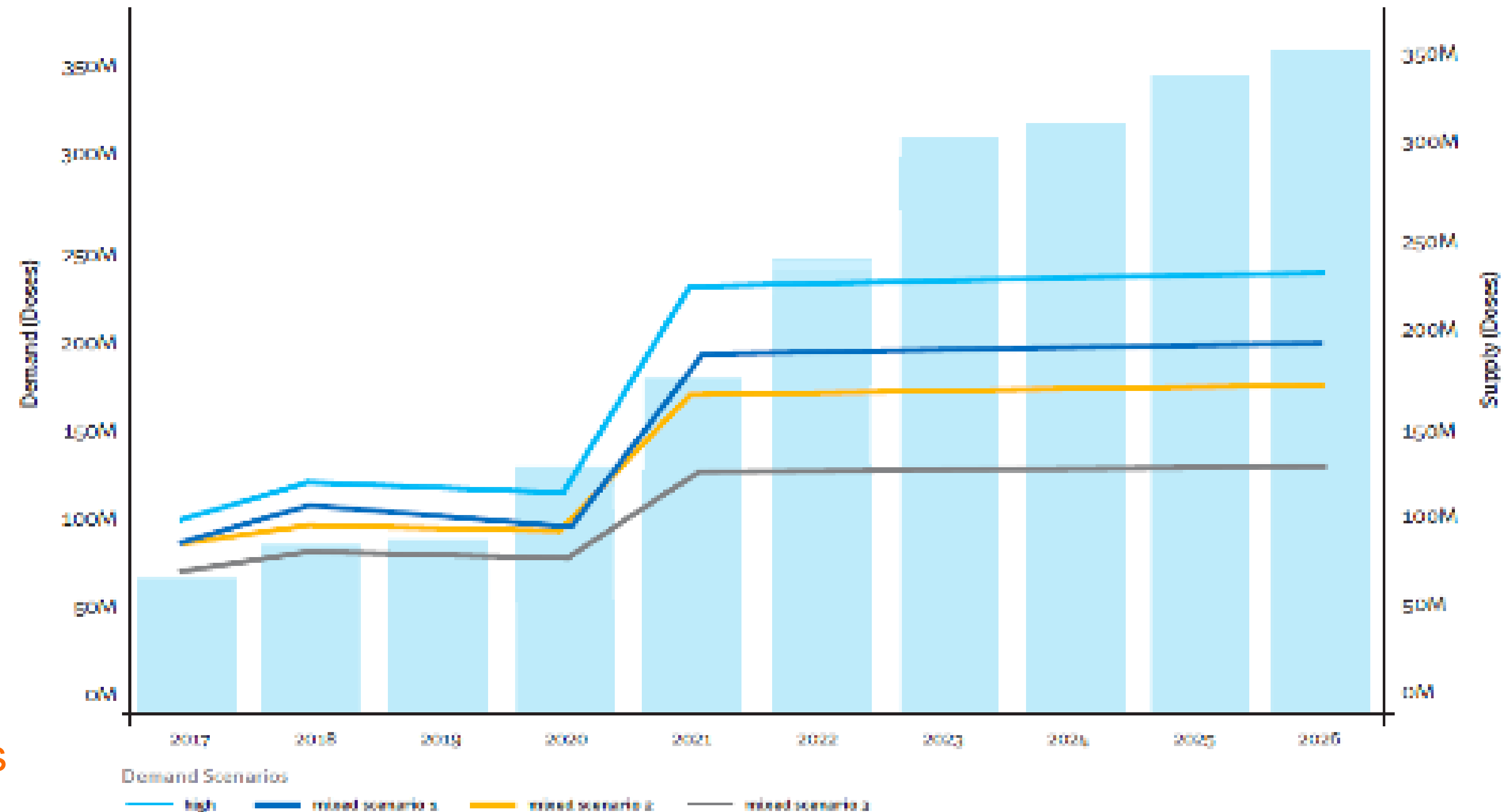
The world continues to struggle with IPV availability and supply at an affordable cost

As the world moves toward **complete polio eradication**, use of **OPV** (which can result in vaccine associated paralytic poliomyelitis (VAPP) through circulating vaccine-derived polioviruses (cVDPVs) will be phased out and replaced by **IPV**.

World's need for IPV is growing rapidly beyond today's available capacity

Current costs of IPV are at least 10-fold higher than OPV

Urgent need to increase capacity and decrease costs





# Highly Intensified, low-cost vaccine manufacturing platform: HIP-Vax<sup>®</sup>

## 1. Optimized cell line and production medium

- Target: >2-fold increase in virus productivity

## 2. High Cell Density Bioreactor

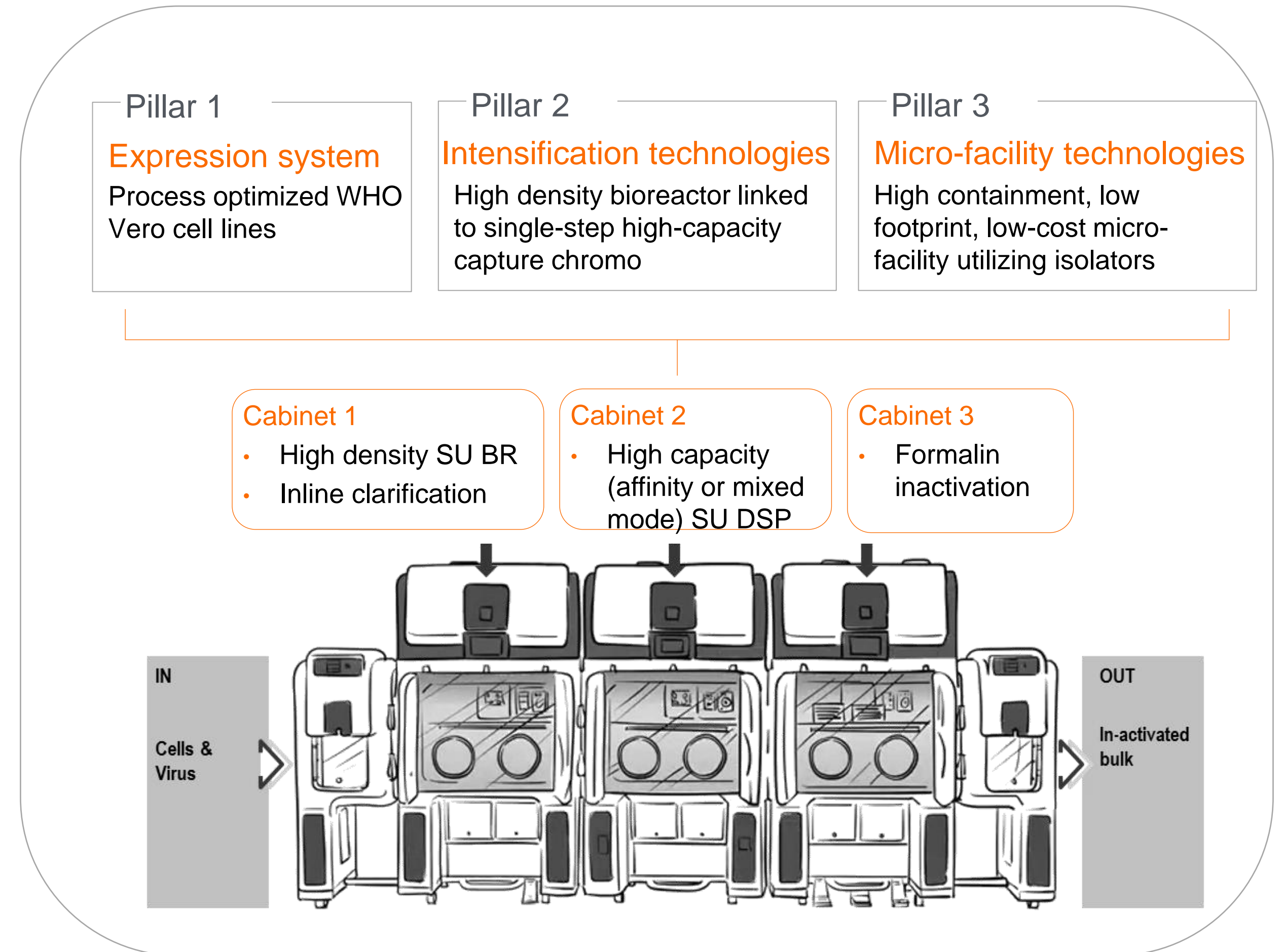
- Target: >20-fold increase in cell density and virus productivity) and

### Affinity Purification Membranes

- Target: 2-fold increase in recovery, single step purification

## 3. Integrated continuous process

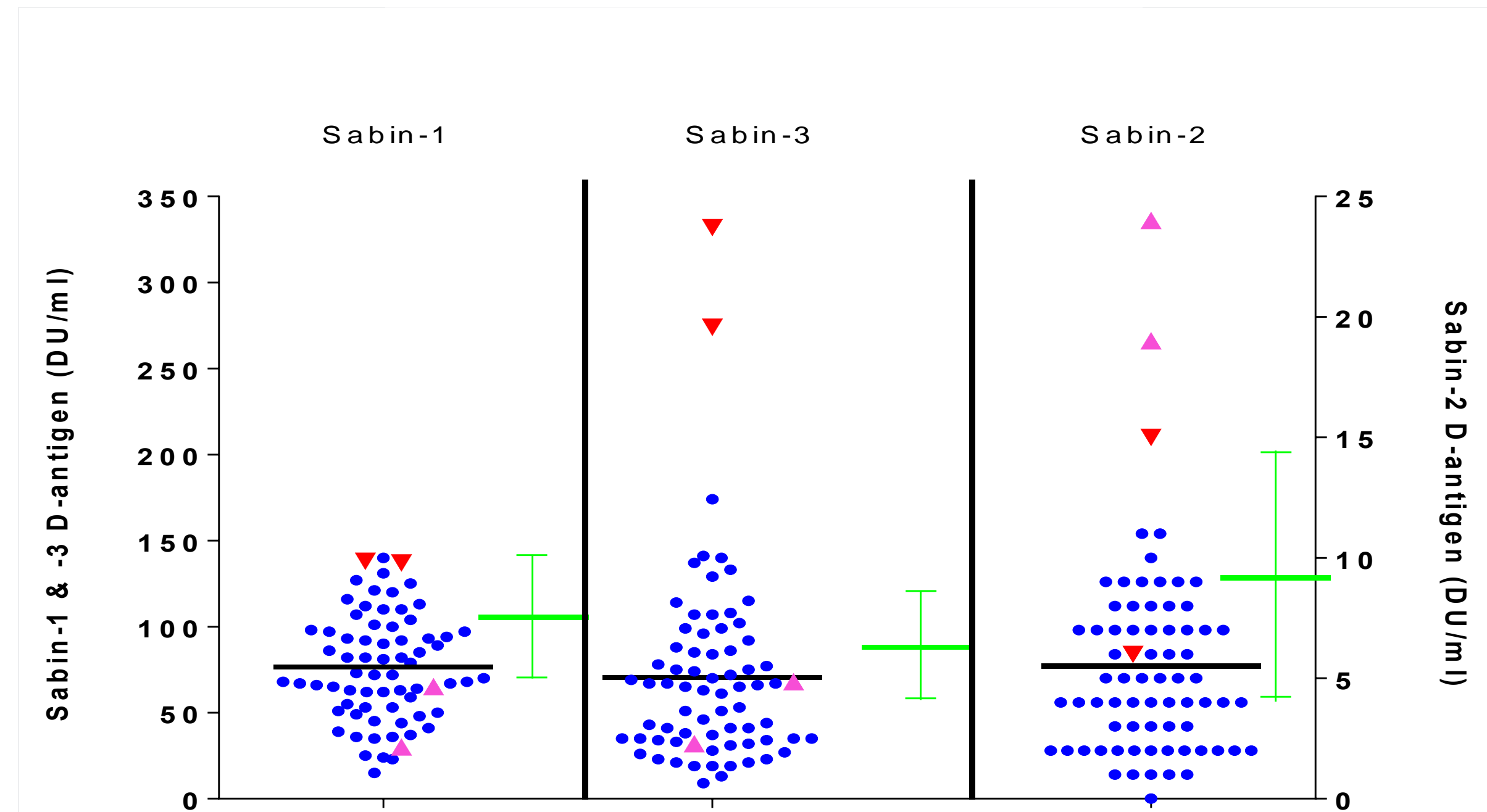
- Linked process in modular isolators – small footprint, low cost (OPEX and CAPEX), high containment manufacturing environment





# Selection of higher producing cell substrates by sub-cloning

Sabin polio virus propagation in Vero 10-87 sub-clones





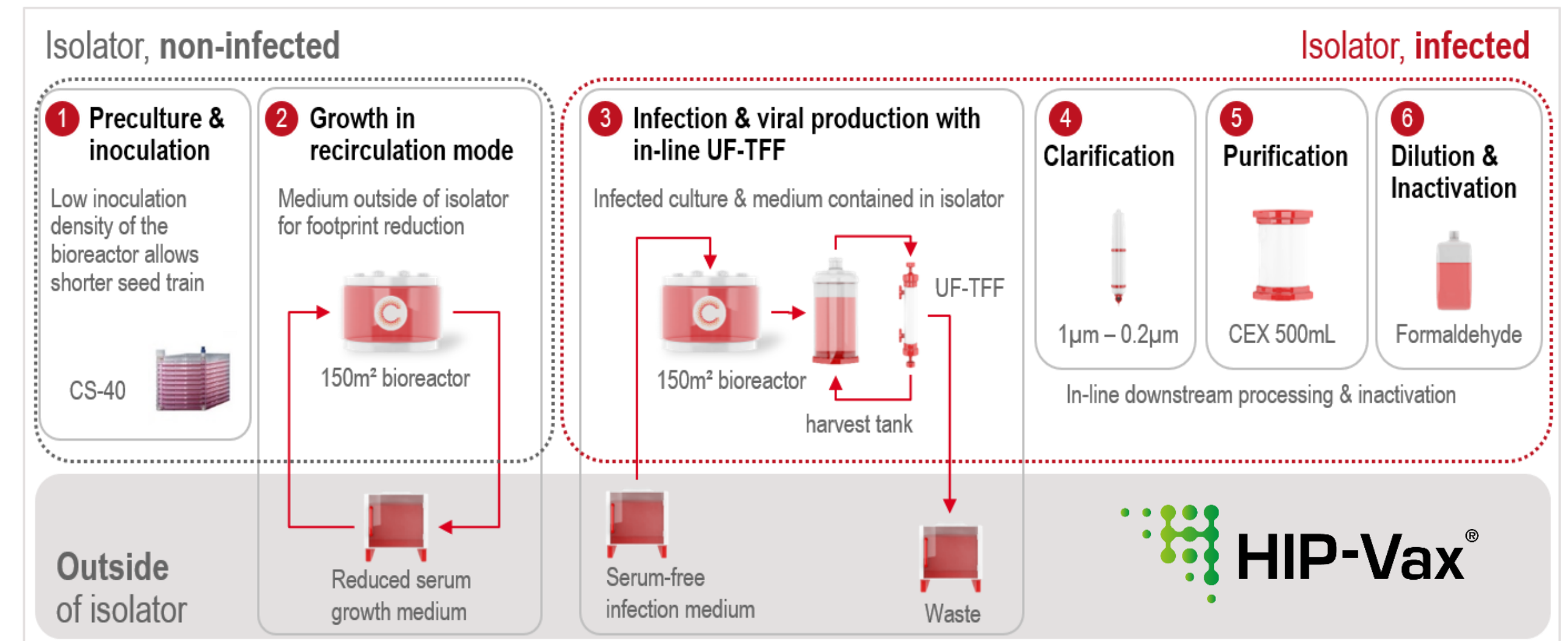
# Low-cost sIPV manufacturing solution: A Gates Foundation funded initiative

Process and equipment designed around each other

Equipment: Univercells NevoLine™  
using scale-X™ bioreactors



Process: Batavia Biosciences  
Highly Intensified Process (HIP-Vax®)



Equipment for process intensification & Integration

High cell density, small footprint bioreactor, in-line single step purification  
And small footprint containment (GAPIII) isolators

Manufacturing process & Biological materials

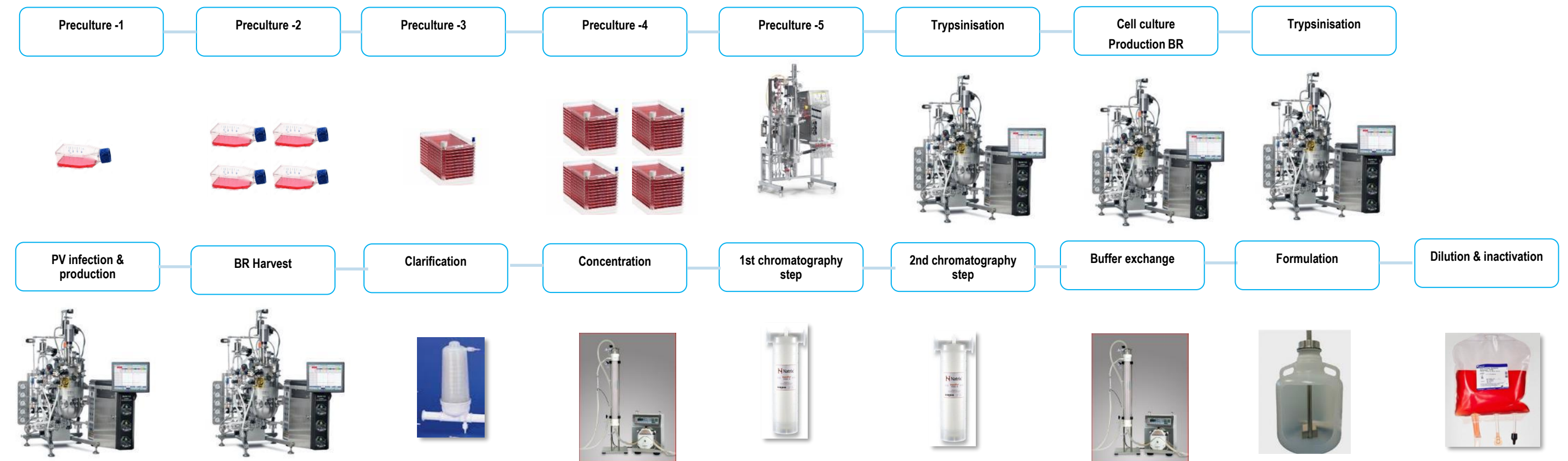
GMP cell line (Vero / MRC-5 / 293) & virus seeds, manufacturing process, Analytical assays, Inactivation



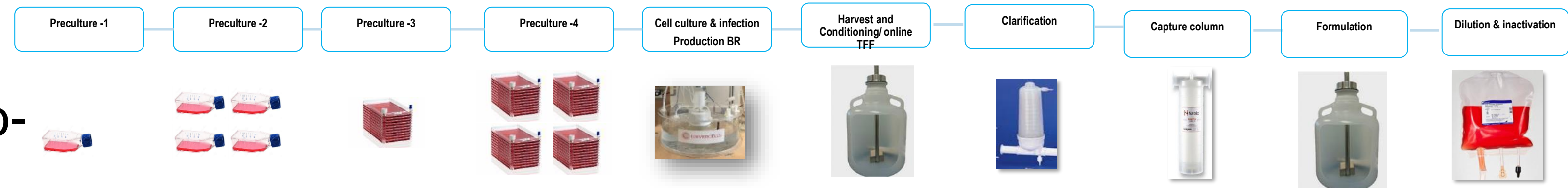
# Breakthrough alternative for conventional processing



Polio vaccine production  
Conventional



Polio vaccine production  
Isolator-based micro-facility



Reduction in footprint, CAPEX, OPEX and CoG's



# Where are we today and line of sight: a price of <\$1/dose is feasible

## Optimized cell line

- 2-fold increased virus production

## High density bioreactor

- 30 million cells per mL

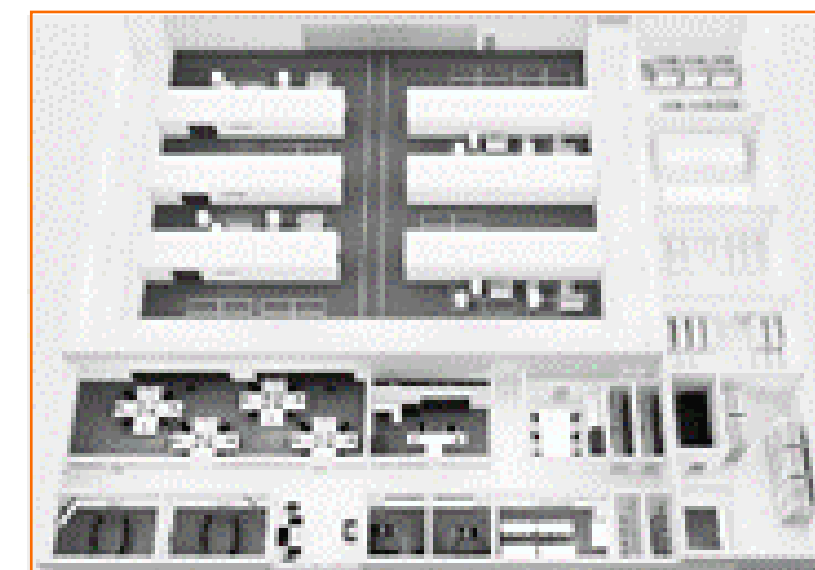
## High efficiency purification

- >70% recovery, >95% purity from single chromatography step process

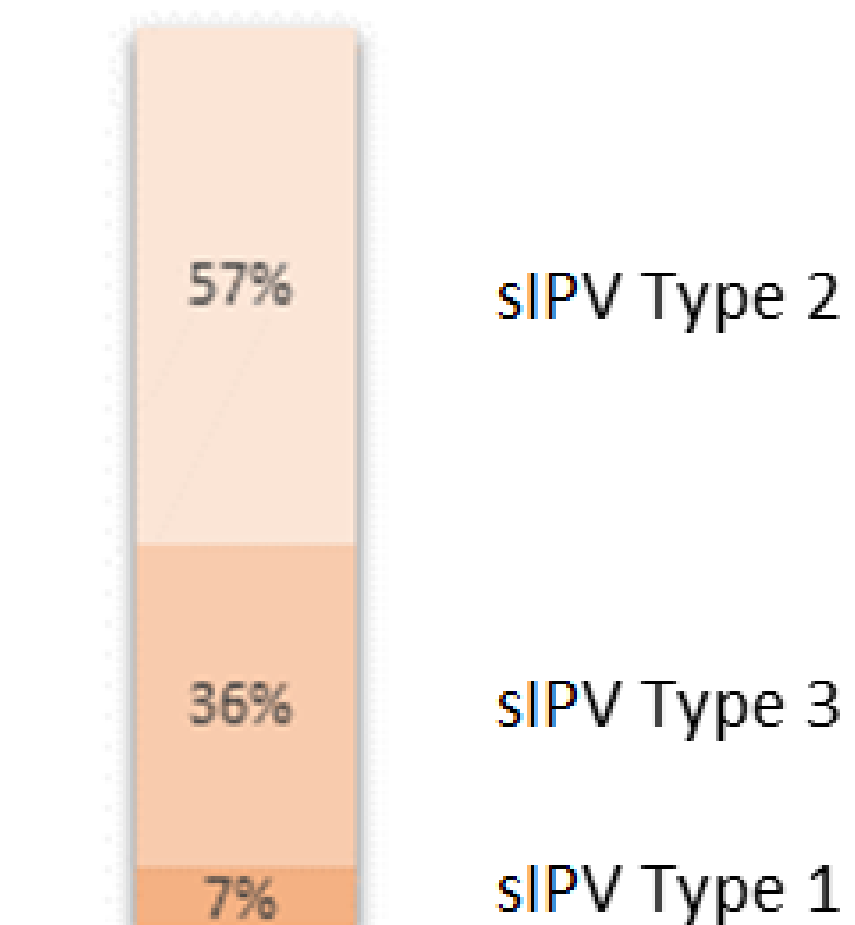
## Reduced process length / increased facility throughput

## Virus yields

- 20 batches ( $\pm 13.6$ M doses) per yr per POD (> 40M doses “micro-facility with 4 pods)



## Polio vaccine CoG's



- Calculated CoG's equal to  **$\approx \$0.40/\text{dose}$**
- Location of manufacturing impacts CoG's

Serotype contribution to the CoG's

Fully loaded CoG's model (BioSolve) including F/F, personnel, facility costs, materials, etc



# Industrial manufacturing at lab scale in low cost “micro-facilities”

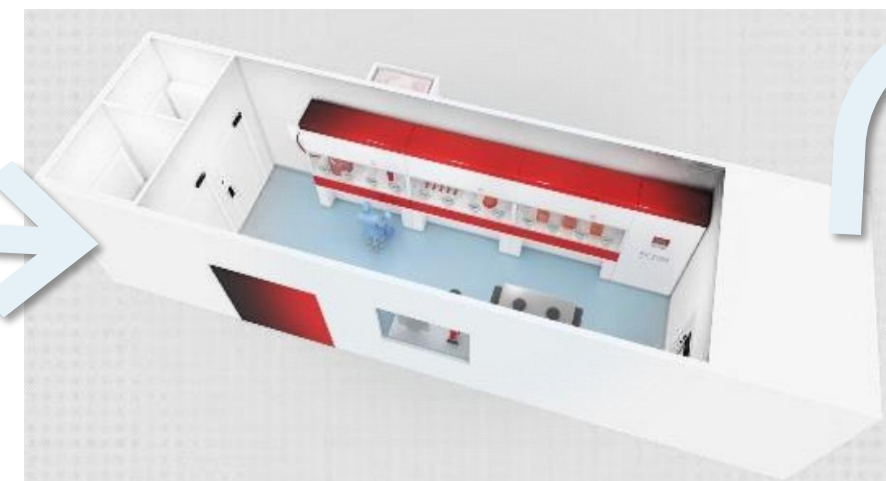
## 1 Miniaturization of equipment in a micro-facility

- **Intensification** of unit steps
- **Chaining** into a continuous process



## 2 Micro-facility can be placed in BSL3 pod

- **Footprint reduction** enables isolators to be placed in container-sized **BSL 3** pod



## 3 micro-facility based production

- **Pod-based facility** with a simplified infrastructure



### Industrial production at lab scale

- Highly intensified process allows miniaturization of commercial manufacturing

### Delivers low CoGs

- Step change in manufacturing scale and yields significantly reduces CoGs

### Broadly applicable to viral vaccines

### High containment and safety

### Rapid response to global threats

- Factory operational in few months
- Can be implemented in new or existing facilities
- Plug & Play system: can be rapidly deployed in-country-for country manufacture



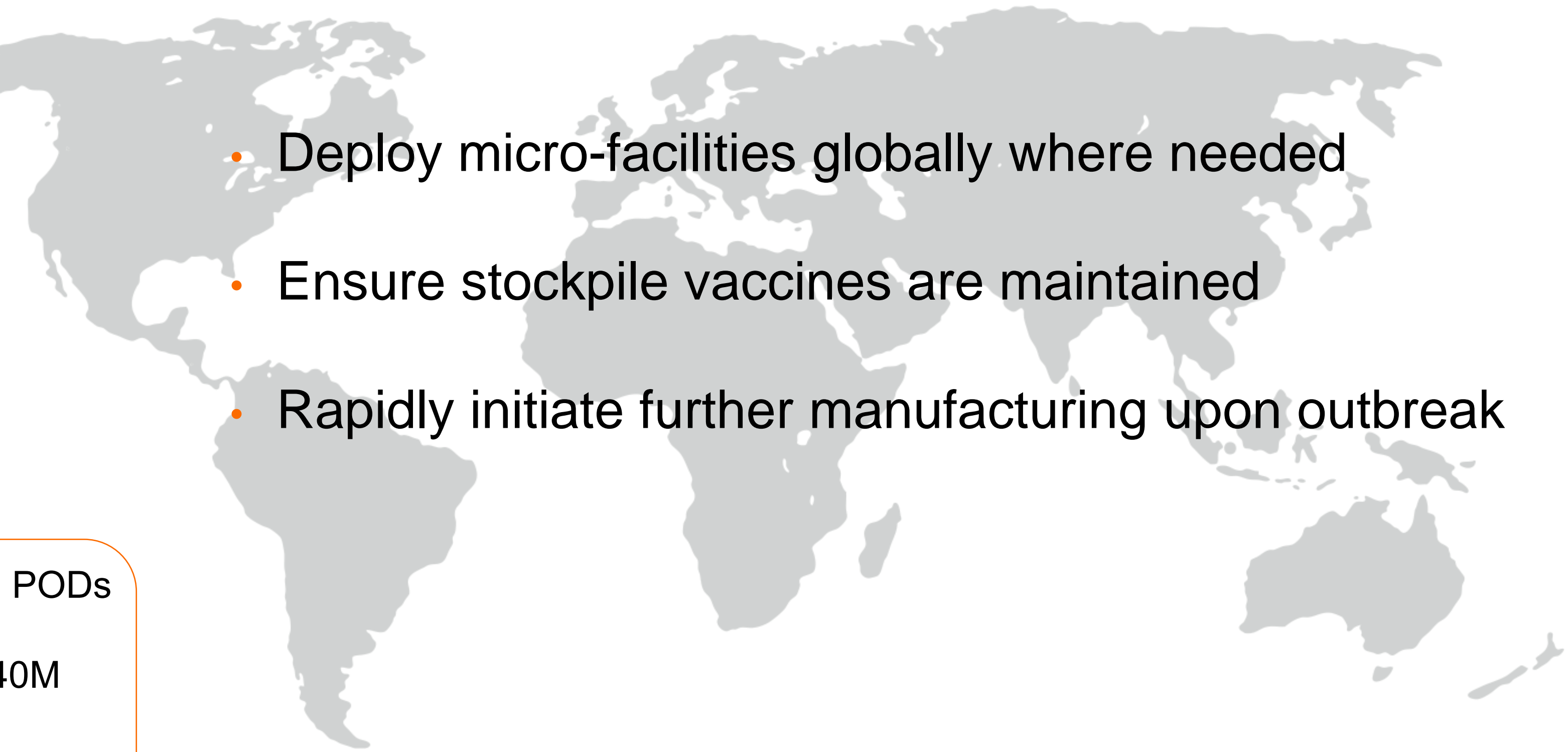
# Rapid response vaccine manufacturing



~ 1500M<sup>2</sup> flexible facility with 4 “micro-facility” PODs

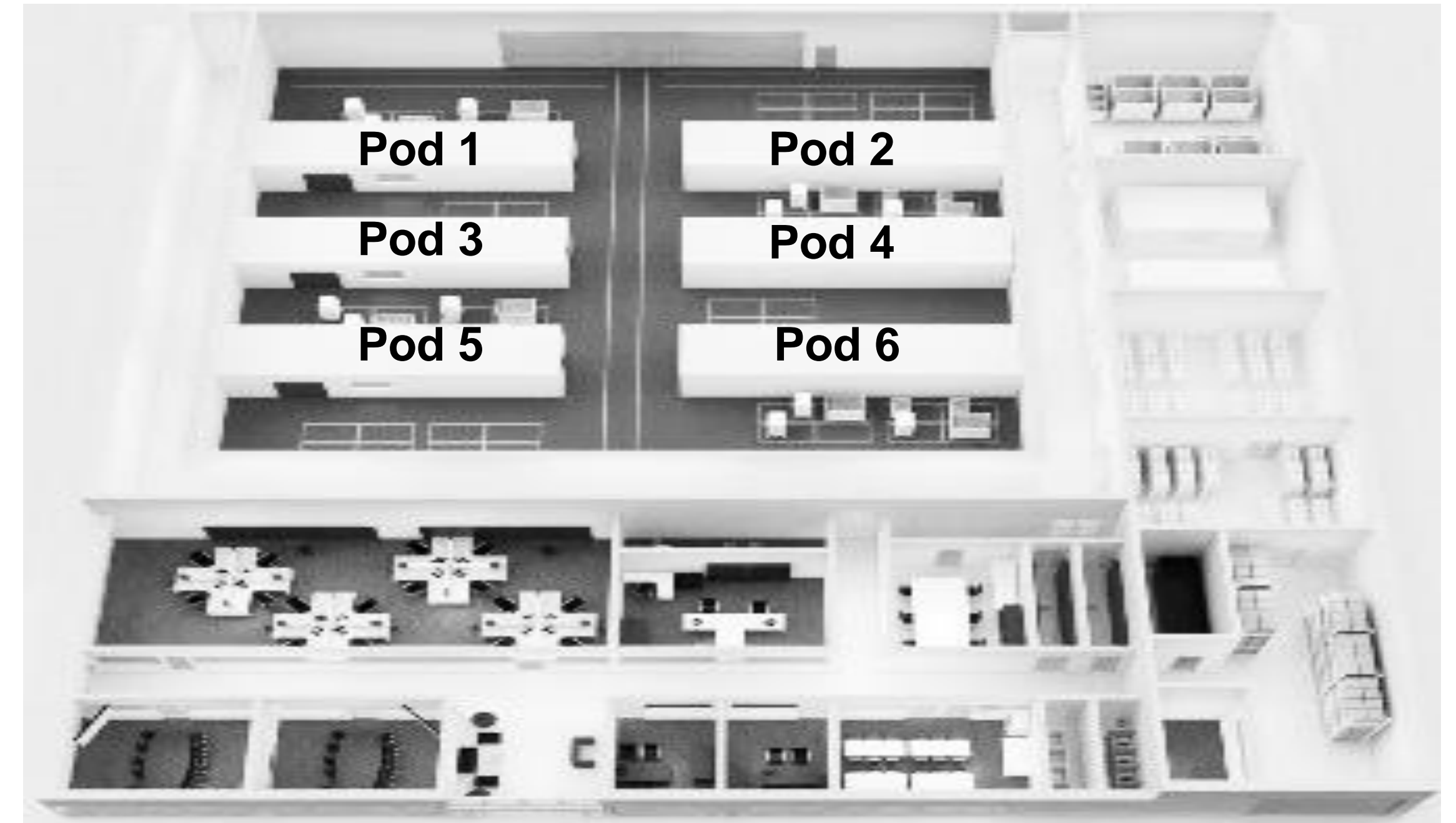
CAPEX of ± €25M capable of delivering >40M doses trivalent IPV vaccine / year

Possibility to expand to more POD's

- 
- Deploy micro-facilities globally where needed
  - Ensure stockpile vaccines are maintained
  - Rapidly initiate further manufacturing upon outbreak



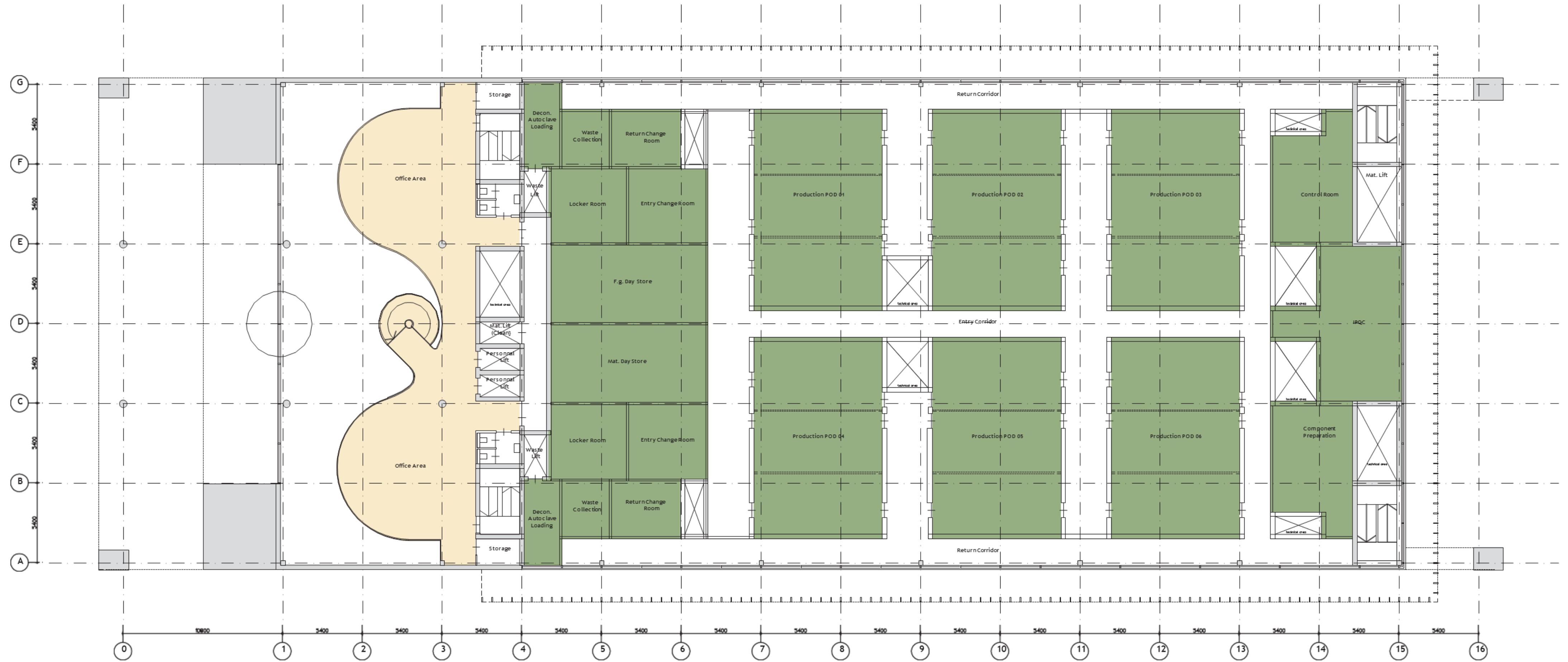
# Application in small footprint, low cost, flexible manufacturing facility



GMP POD's are stand-alone GMP suites, offering flexible & modular vaccine manufacturing  
POD's are housed "clean warehouse" building, dramatically lowering CAPEX and construction timelines

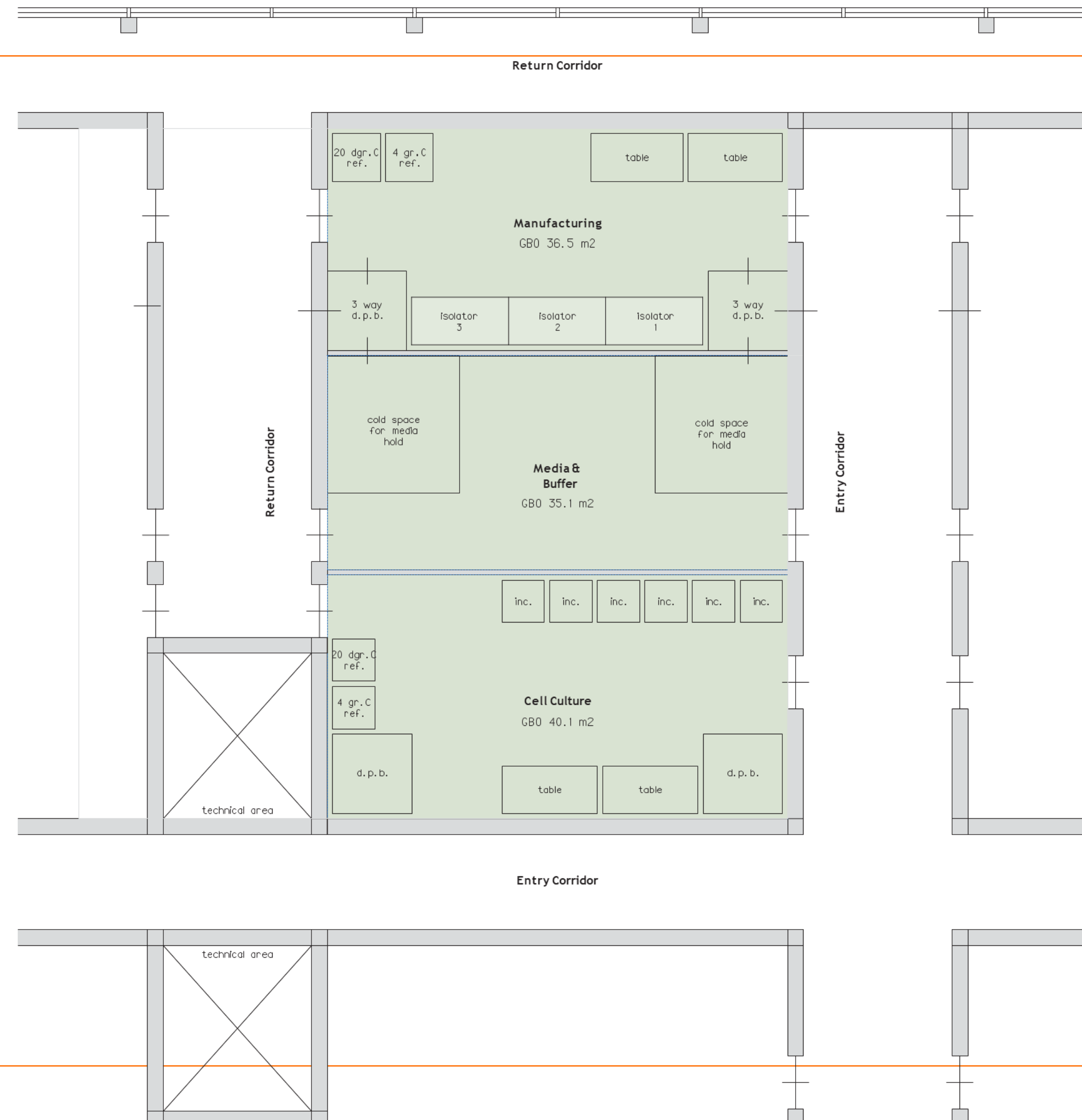


# POD-based facility





# Single POD







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