Addressing challenges with vaccine manufacturing moving into the future

DCVMN Annual Meeting, Bangkok, October 2015

Dr. Günter Jagschies, GE Healthcare
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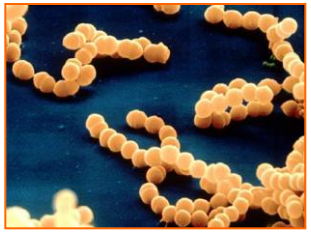
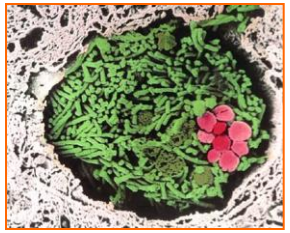
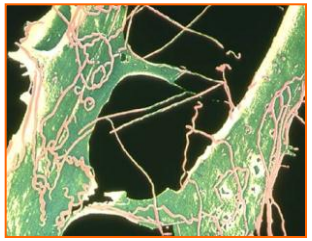
Imagination at work.

Infectious Disease

- Infectious diseases are **caused by microscopic organisms** commonly called **germs** or **pathogens**. Pathogens that infect humans include a wide variety of bacteria, viruses, fungi, protozoa, and parasitic worms.
- In addition, it is assumed that some proteins called prions may cause infectious diseases.

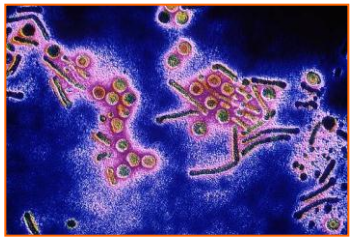
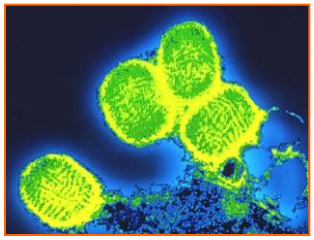
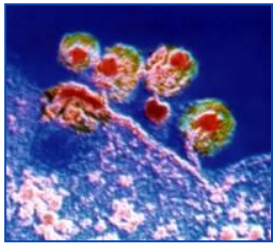
Bacteria

e.g., Streptococcus, Anthrax
Cholera

Virus

e.g., Hepatitis B, Smallpox
HIV

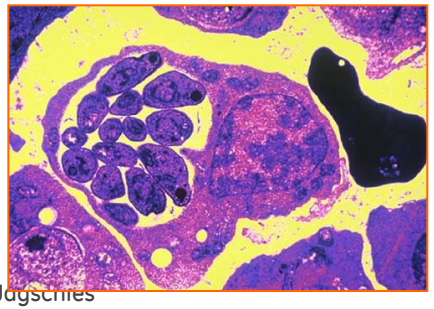




Worms

e.g., Bilharziasis

Protozoa

e.g., Malaria



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Elimination and Eradication of Disease

Jagschies et al. "Handbook of Bioprocessing" in preparation, Elsevier 2016, based on CDC data

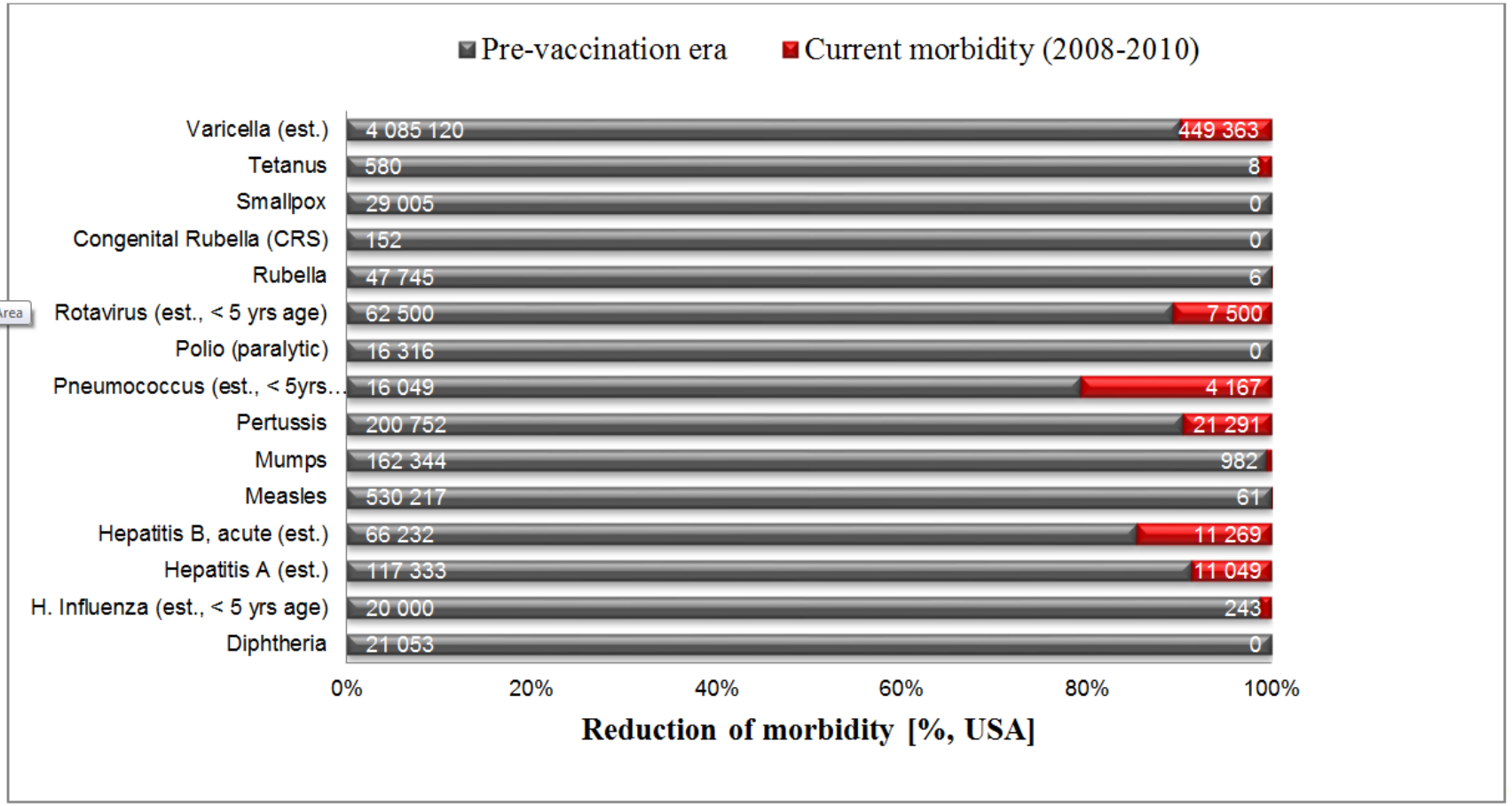
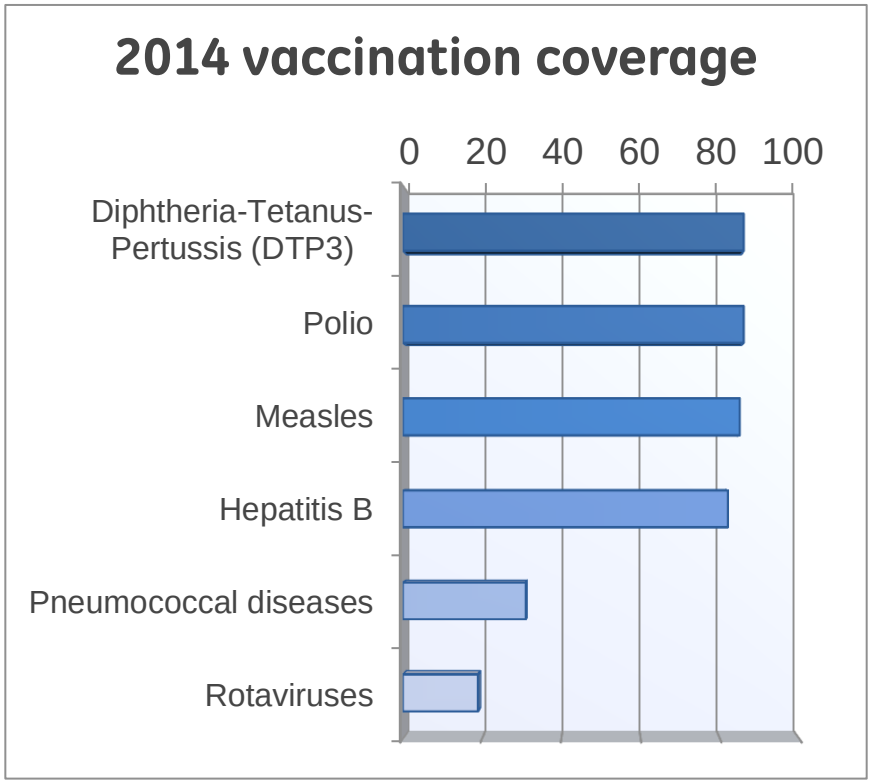


Figure 1–14: Reduction of morbidity with vaccination¶

World Immunization Effect & Coverage

Global mortality (GBD report 2013)

Infection	1990	2013
Diphtheria Tetanus Pertussis	8 032 356 156 138 219	3 276 58 879 60 635
Polio	0	0
Measles	544 474	95 597
Hepatitis B	84 991	68 642
Pneumococcal*	116 770	84 009
Diarrhea#	2 578 732	1 264 079



* Upper respiratory and pneumococcal meningitis

\# all diarrheal diseases, incl. Rotavirus caused (~50% of diarrhea hospitalization w/ children)

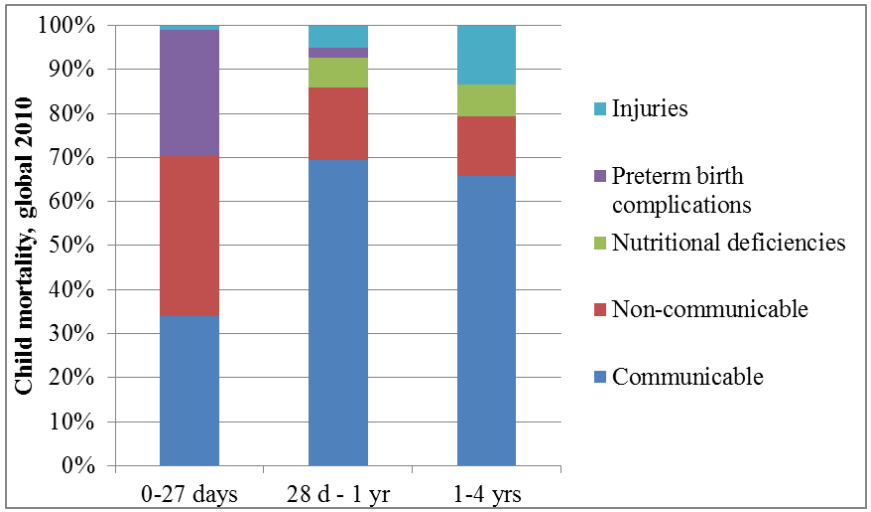
Challenges influencing technical needs and planning for manufacturing

Infectious disease burden

Affordable supply to the poorest

- More than 80% of global mortality from non-communicable diseases (NCDs), but children still being much more at risk from infectious diseases.
- 2013 Global Burden of Disease study found a 24% decline in mortality from infectious diseases since 1990 (2.8 million averted future deaths annually)
- Three big infectious diseases HIV/AIDS, Malaria, and Tuberculosis (TB) still killed 3.5 million people in 2013, the majority of them being children and young adults
- Almost 90% of all deaths from communicable disease occur in low and lower middle income countries
- 2.2 billion cases or 44% of the global prevalence of communicable disease are from 17 diseases that together are referred to as "neglected tropical diseases" (NTDs)

Child mortality driven by infectious disease (~3.3 million below age five)

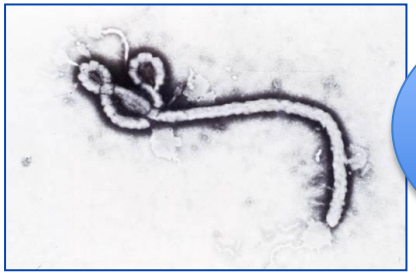


Global Burden of Disease Study 2010, The Lancet

Effective interventions for neglected tropical disease

R&D efforts on Malaria, HIV, and TB

Disease Challenges



Ebola outbreak in West Africa in 2014
has cost > 11,000 lives

Preparedness for new diseases

Action on NTDs

- Viruses for **new diseases**, such as **Ebola**, have surfaced in Africa.
- In addition to new diseases, known **pathogens may change, or mutate**, creating new, virulent strains.
- Mutations in infectious agents result in **resistance to vaccines** as the serotypes they cover are replaced by others.
- With **global travel**, outbreaks spread very fast and may lead to large epidemics.
- With **climate change** disease might spread together with their vectors.
- **Production methods are too old and inefficient** to meet the challenges.
- The prevalence for **neglected tropical diseases** is 2.2 billion, 40% of all communicable diseases and more than twice as high as all cancers globally.
- **Vaccination rates are too low** to prevent pandemic influenza and too low in developing countries to prevent up to 3 million annual child deaths from other infectious diseases (one child every 20 seconds).

Increased vaccination rates

Full coverage of serotypes, regular vaccine updates

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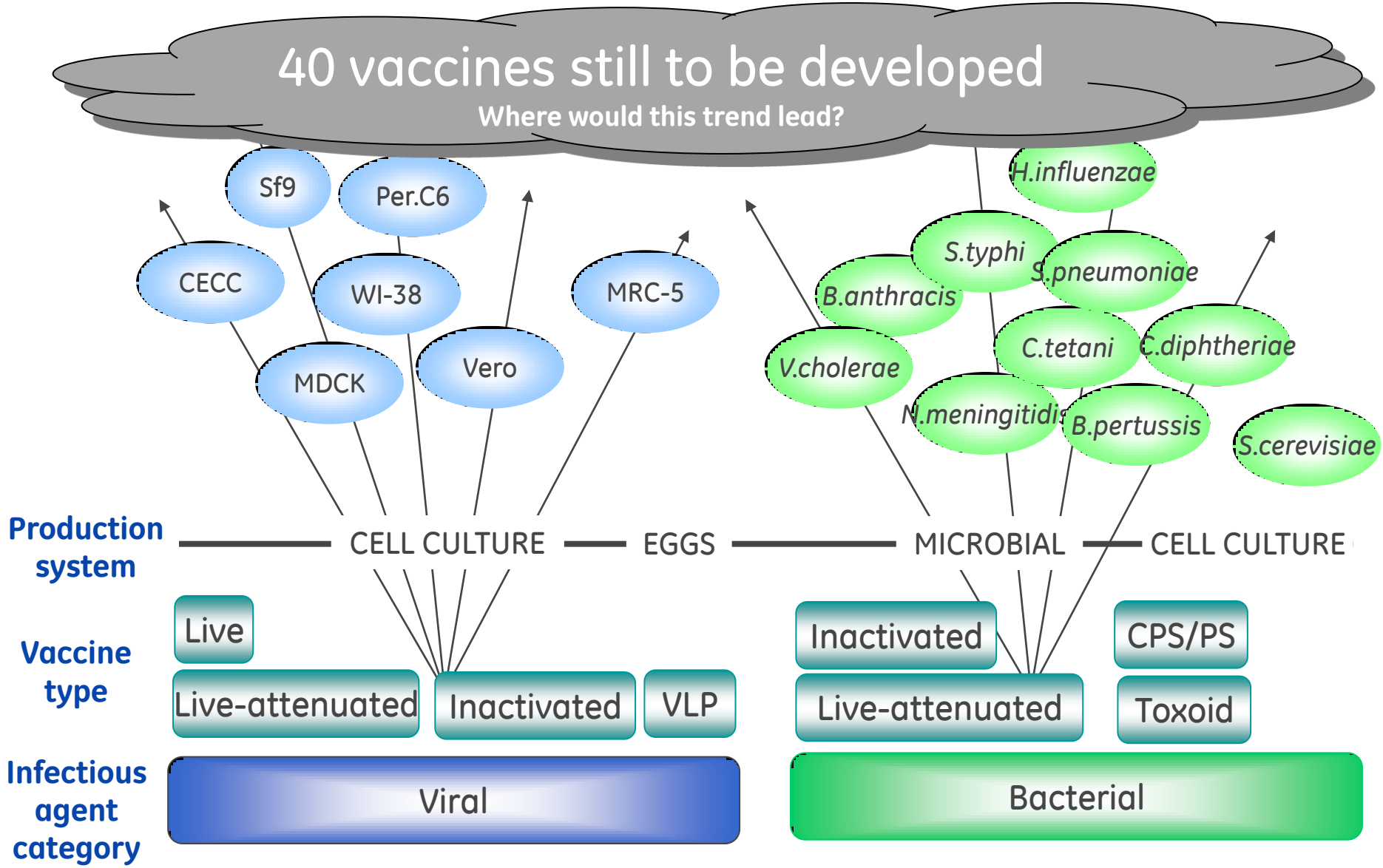
Pathogens without a vaccine

Action on NTDs
New vaccines

Bacteria	Viruses	Parasi
Tuberculosis	HIV	Malaria
Group A streptococcus	HCV	Leishmania
Group B streptococcus	RSV	Schistosoma
Staphylococcus aureus	EBV	Trypanosoma
Shigella	HSV	Toxoplasma
Salmonella	CMV	Brucella
Clamydia	Dengue	Cryptosporidium
Pathogenic E.coli	Enteroviruses	Entoamoeba
Pseudomonas aeruginosa	Ebola	
Clostridium difficile	Marburg hemorragic fever	
Non-typeable Haemophilus	Parvovirus	
Klebsiella pneumoniae	Norovirus	

RSV= Respiratory syncytial (sin-SISH-uhl) virus; EBV = Eppstein-Barr Virus; HSV = Herpes Simplex Virus; CMV = Cytomegalovirus

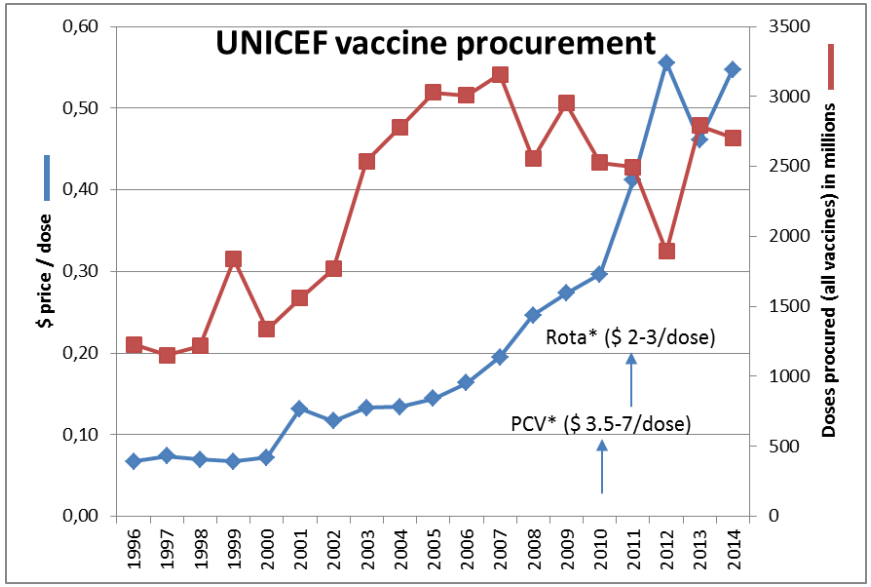
Diversification of Technology



Who are the players?
What are the issues?

UNICEF Vaccine Procurement

- Total procurement by UNICEF in 2014 was $ 1,481 M for 2,700 M doses overall
- Since year 2000 average price per dose has increased 5 fold from 10 $cents to 50 $cents / dose
- High value vaccines PCV (Pfizer/GSK) and Rotavirus (GSK/Merck) have been added to the portfolio and represent 44% of total procurement value / stand for almost all of dose price increase since 2009
- High volume vaccine OPV from Western and Indian suppliers has stable to slightly lowered prices from all, represents 14% of value at 60% of doses
- Price developments have no clear pattern between western and other suppliers:
  - Measles: both Sanofi and SSI increased by 100% since introduction
  - HepB: both Crucell and LG decreased by 40-50% since introduction
  - DTP-HepB-Hib: SSI increased by 11% but is $1 cheaper than GSK who decreased price by 16% since introduction



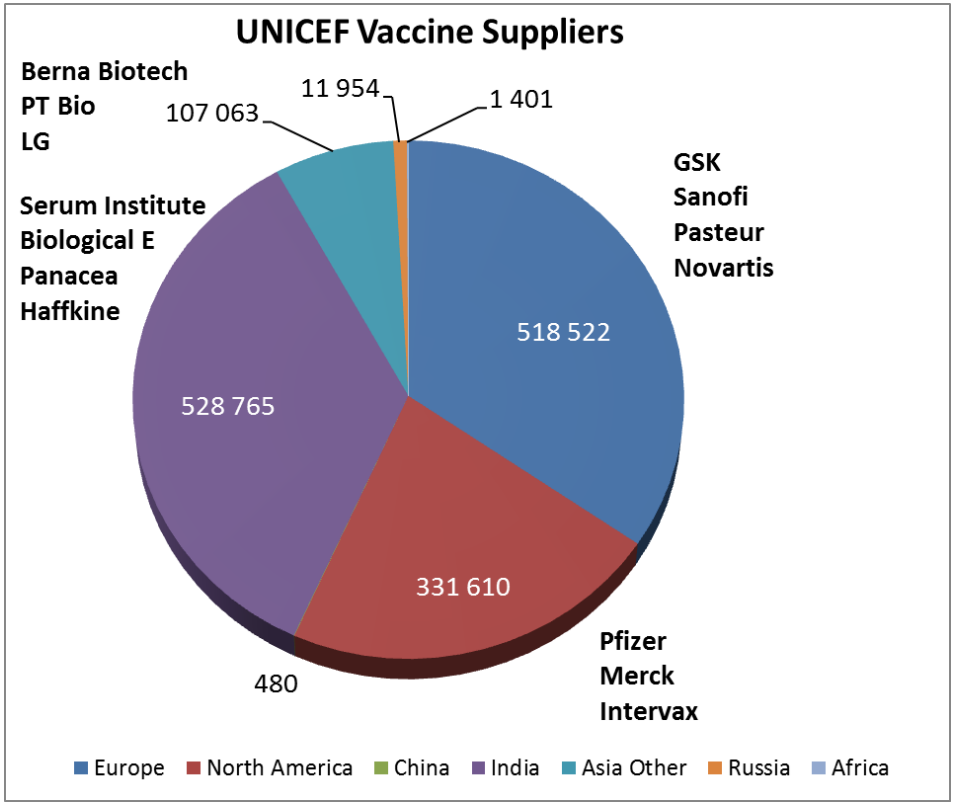
Medicins sans frontier – price in focus

"The price to fully vaccinate a child is 68 times more expensive than it was just over a decade ago, mainly because a handful of big pharmaceutical companies are overcharging donors and developing countries for vaccines that already earn them billions of dollars in wealthy countries. Donors will be asked to put an additional $7.5 billion dollars on the table to pay for vaccines in poor countries for the next five years, with over one third of that going to pay for one vaccine alone, the high-priced pneumococcal vaccine; just think of how much further taxpayer money could go to vaccinate more children if vaccines were cheaper. We think it's time for GSK and Pfizer to do their part to make vaccines more affordable for countries in the long term, because the discounts the companies are offering today are just not good enough."

Rohit Malpani
Director of Policy and Analysis for MSF's Access Campaign.

Vaccine Suppliers to UNICEF

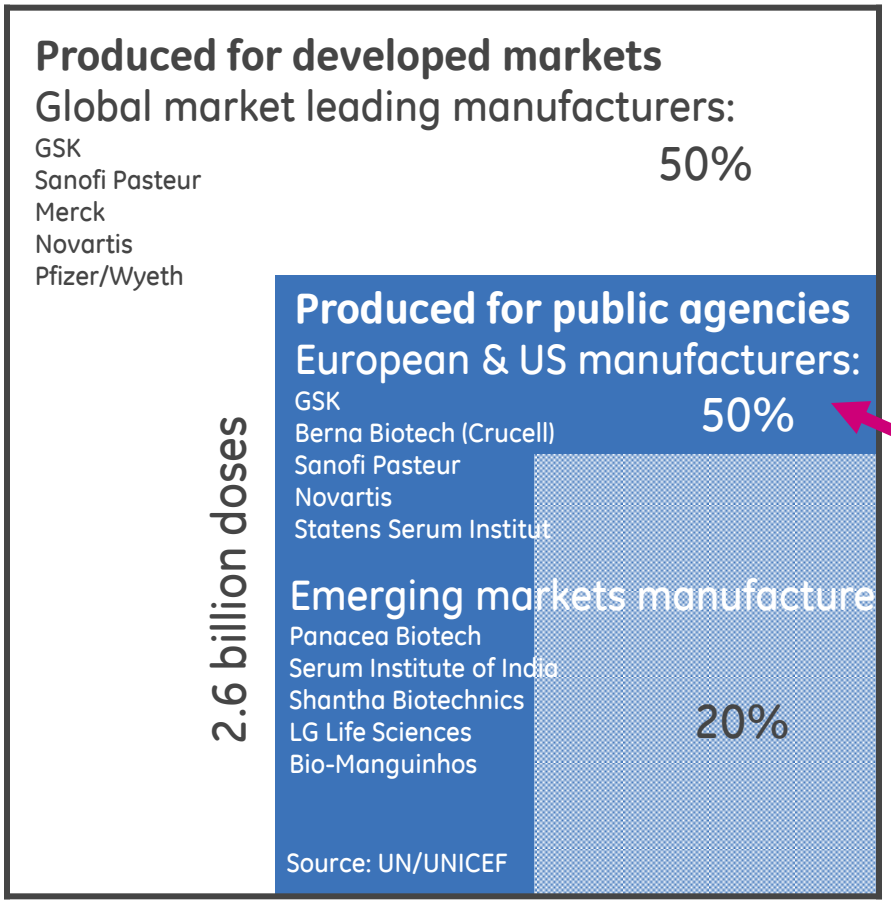
- Two thirds of the UNICEF supply comes from Europe and North America
- The remaining third is delivered by Asian manufacturers
- India is the country with largest share of UNICEF purchase value
- GSK, Serum Institute, and Pfizer are the three largest suppliers to UNICEF at 75% of the total value



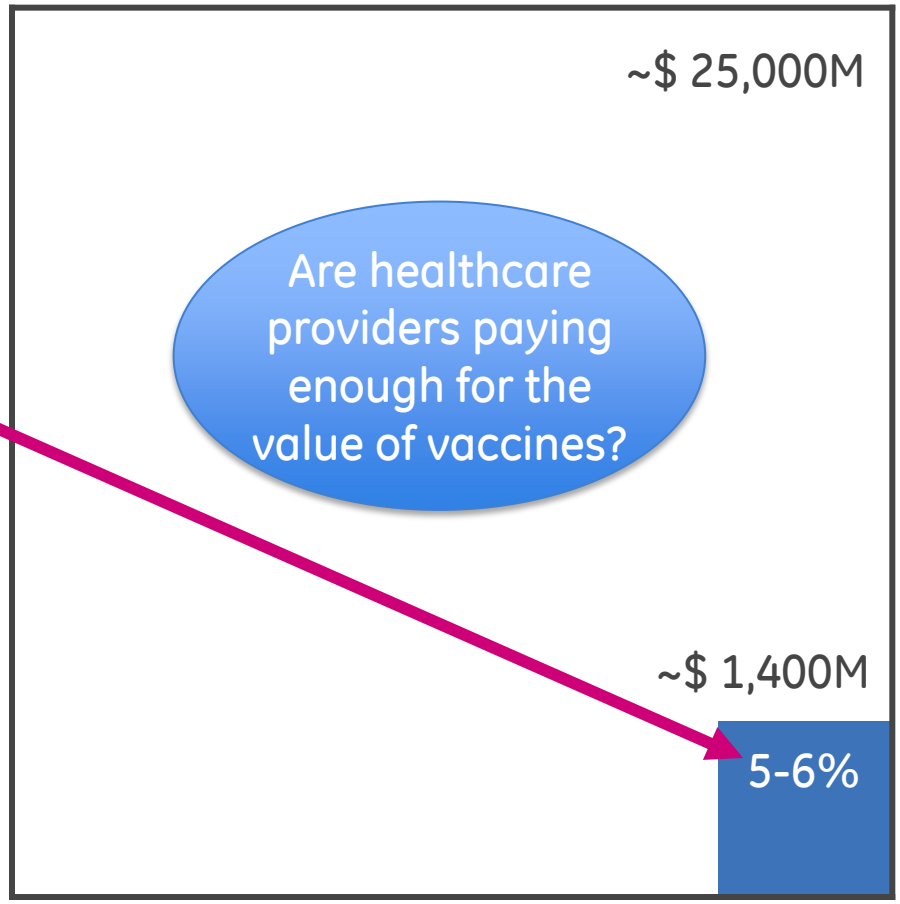
Public Agencies Vaccine Procurement

UNICEF Report 2008, vaccines for expanded national vaccination programs

Global volume doses 2008



Market value 2014



Vaccine ecosystem in danger

Price is not the shortcut to real solutions, summary of an interview with…

Michael Watson
Sanofi Pasteur

- **Two more of the R&D-conducting vaccine producers have bailed out recently: Baxter and Novartis.**
- Perhaps only four of the six that are remaining are of global production scale: GSK, Merck, Pfizer, and Sanofi Pasteur.
- Of these four global companies investing in cutting-edge vaccine R&D, there are only two able to supply each of the key vaccines globally (i.e., MR/MMR, Rota, HPV, PCV, acellular pertussis-based pentavalent and hexavalent combinations)
- Need to move MR/MRR and Yellow Fever production to new technologies and update facilities to meet future demands.
- **The business case for this investment requires the very low price for the vaccines to be increased.**
  - MR/MRR stopped at Sanofi Pasteur, Yellow Fever continued without margin
  - Yellow Fever stopped at Crucell, significant shortage already observed
- Of the nine vaccines UNICEF procures for GAVI (for poorer countries), seven are currently in short supply

- **It's become too cheap to vaccinate populations around the world.** It appears the organizations mentioned above are veering from the goal of providing access to vaccines, to focusing on pushing for the cheapest prices for them.
  - Children don't get the polio vaccine that costs about 12 cents a dose and they don't get DTP, which costs about 19 cents a dose. It is hard to find many things in life as inexpensive and as hard to develop and manage distribution for…
  - "Reducing everything to price," concludes Watson, "is now having negative consequences."

Profit & Loss (P&L) for Vaccine Businesses

Manufacturing cost > 50%

- Compares to >15% in protein therapeutics

Factors enabling low pricing
("one dose for the cost of a cup of tea")

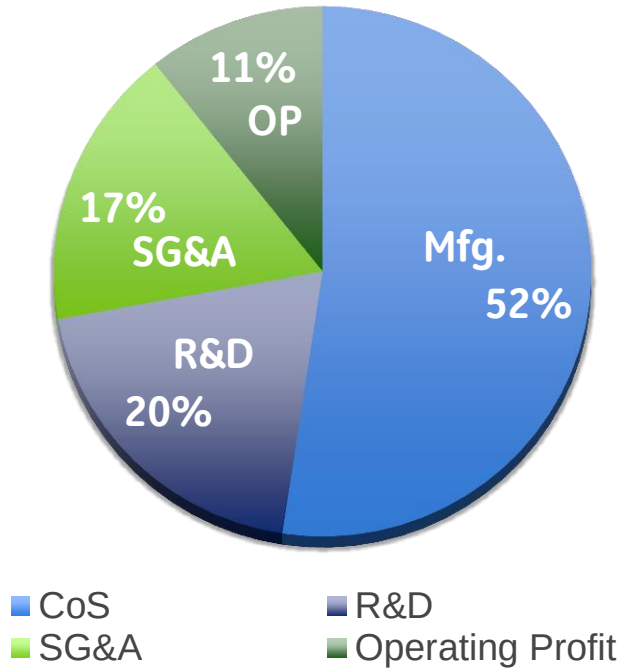
- Companies with supply of basic pediatric vaccines only have low current R&D efforts
- Companies with distribution mainly via UN institutions have low SG&A costs
- Private ownership less sensitive to operating profit pressure

Driving the future

- R&D is key to enable the development of vaccines with better safety and acceptance
- Without R&D neither the remaining nor the new threats will be addressed
- R&D provides competitiveness with improved processes for lower costs and better responsiveness

Typical P&L for vaccine businesses (no or little other business)

Annual Report 2009: Crucell, incl. Berna Biotech



- Legacy technology distorts economics
- Limited process intensification
- Little flexibility

World Immunization Week 2015 (WHO)

We must ensure that…

What needs to happen on new developments & with production preparedness

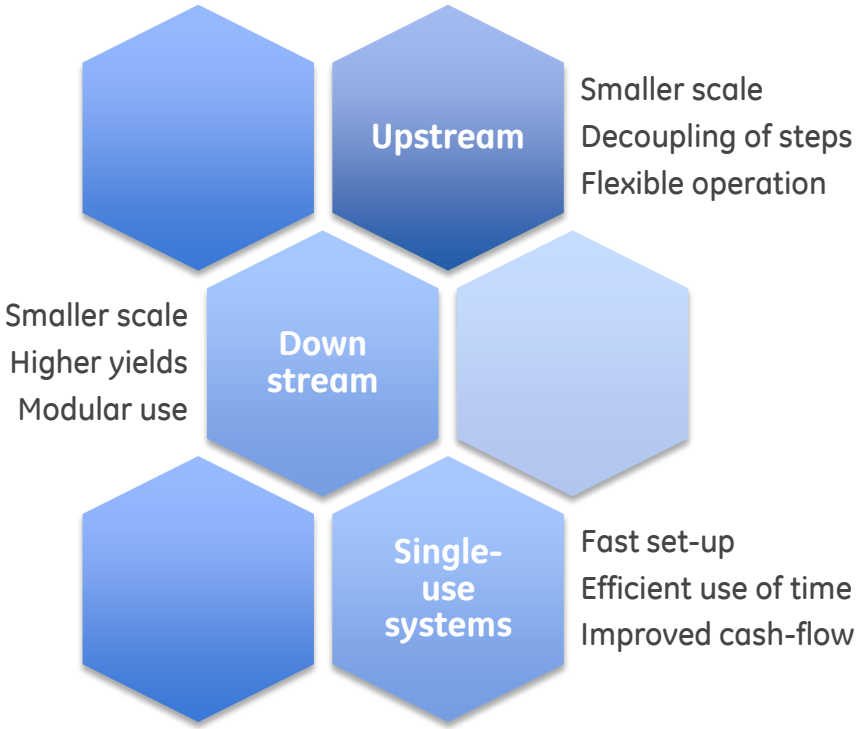
What are the key issues to be addressed?

- Prevent resistance to vaccines
- Develop vaccines for the ”big three” (HIV, Malaria, TB)
- Platform vaccine technology and processing
- Upgrade manufacturing networks and process yields
- Secure supply for pandemic influenza
- Solve affordability versus R&D investment issue
- Bring up vaccination rates everywhere

Every dollar spent on vaccination returns between $7 and $20 in avoided costs related to therapy / disease management.

Vaccine technology platform discussion

R&D response to improve how things have always been done ?

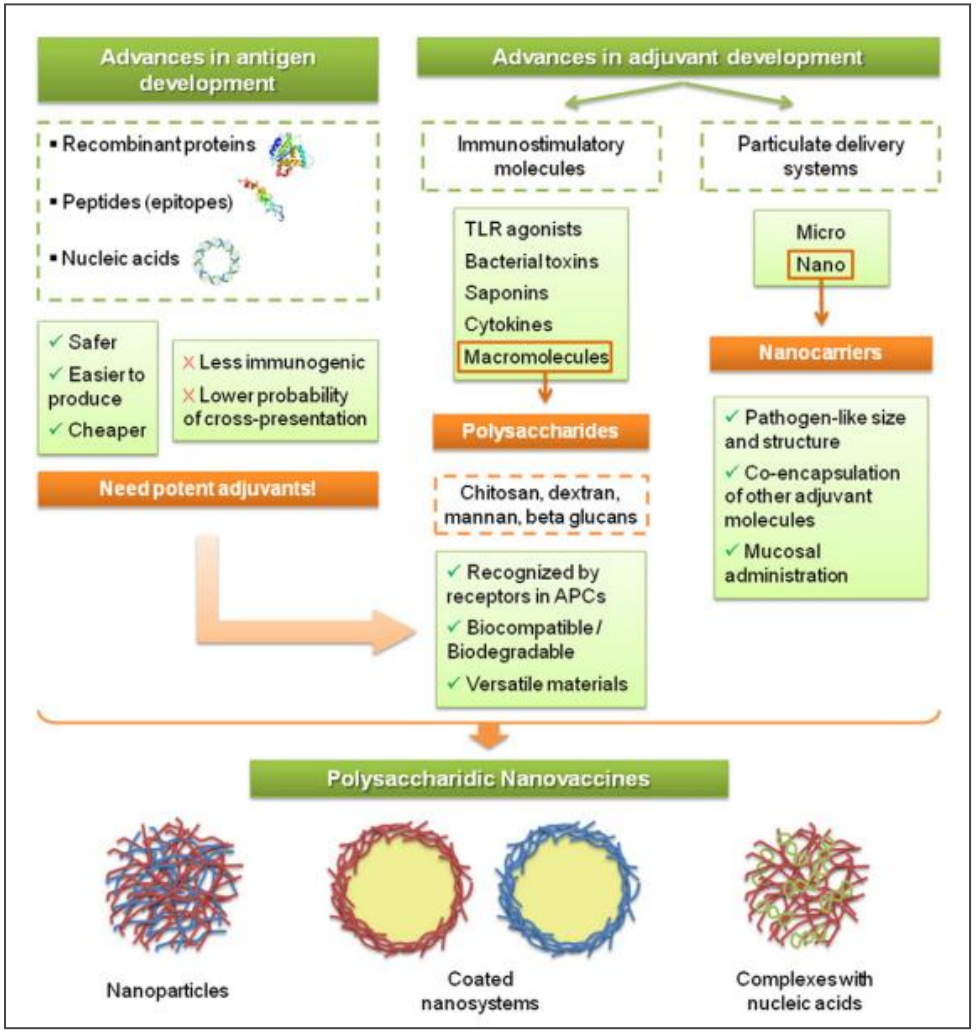


- Fewer vaccine technologies, e.g., VLPs or similar standard
- One cell substrate for viral vaccines
- Standard harvest & purification steps – impurity removal
- Use standard equipment (modules) in highly flexible facilities
- Standard, multipurpose analytic platforms
- Standardize and simplify delivery to patients, localize supply capability, consider preparedness for ramp-up of demand
- Adjuvant, dose sparing, but is it safe (see pandemic influenza and narcolepsy)?

Example hypothesis for future vaccines

AS Cordeiro, MJ Alonso, M de la Fuente "Nanoengineering of vaccines using natural polysaccharides", Biotechnology Advances 33 (2015) 1279–1293

- Advances in biological and microbiological technologies have increased the knowledge of pathogens and led to the development of newer and safer subunit antigens.
- These antigens are less effective in inducing protective immune responses and require parallel development of potent adjuvants such as immuno-modulating molecules and particulate delivery systems.
- Polysaccharide-based nano systems have demonstrated potential to be successfully used in vaccine formulations.



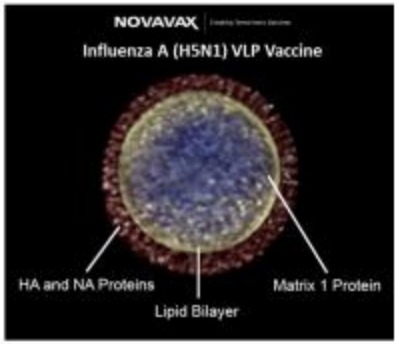
Perspectives on Recombinant Baculovirus-Sf9 Platform Development and Manufacturing Process

BioProcessing JOURNAL

TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Article Published Online: 29 July 2013

Rapid Manufacture and Release of a GMP Batch of Avian Influenza A(H7N9) Virus-Like Particle Vaccine Made Using Recombinant Baculovirus-Sf9 Insect Cell Culture Technology



BioProcessing JOURNAL

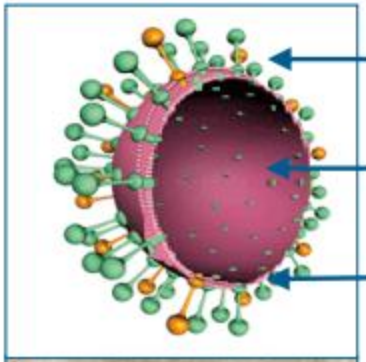
TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Article Published Online: February 10, 2015

Rapid Manufacture and Release of a GMP Batch of Zaire Ebolavirus Glycoprotein Vaccine Made Using Recombinant Baculovirus-Sf9 Insect Cell Culture Technology

Novavax Nanoparticle Vaccines

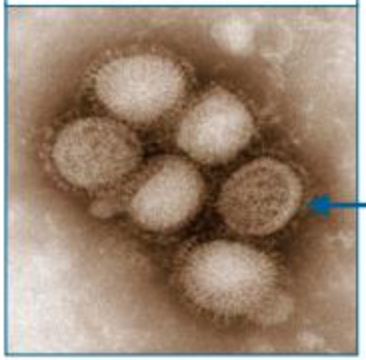
Virus-Like Particles (VLP)
Seasonal & Pandemic Influenza



HA, NA Protein

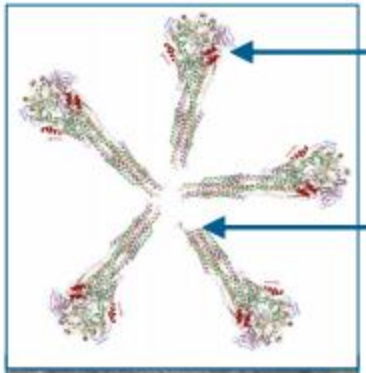
Empty - No genetic material

M1 Matrix Protein



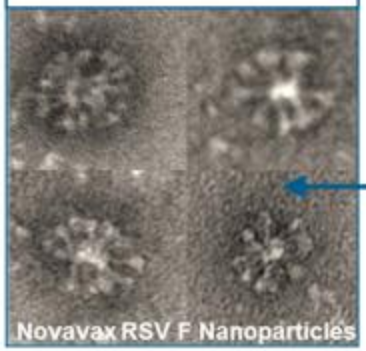
Configuration and size of the virus without RNA genome

Recombinant Protein Micelles
RSV, Rabies, Ebola



Hydrophilic head of protein particle

Hydrophobic tail of protein particle



Protein particles form micelles for efficient antigen presentation:
- Single antigen
- Repeating unit

Vaccine manufacturing

Substrate Dev	Fermentation Cell Culture	Clarification	Concentration	Purification	Formulation	Filling	Release
•Bacteria •Eggs •Cell lines	•Bioreactors •Culture conditions	•Filtration	•Chromatography •Filtration •Sucrose Centrifugation				•Analytical methods

Major challenges

Substrate Dev	Fermentation Cell Culture	Clarification	Concentration	Purification	Formulation	Filling	Release
•Product titer	•Yield •Scale-up •Consistency	•Yield •Aggregation	•Yield •Aggregation •DNA removal		•Potency		•Analytical precision •Number of methods

Recent and emerging technologies

Substrate Dev	Fermentation Cell Culture	Clarification	Concentration	Purification	Formulation	Filling	Release
•Vaccine technologies •Cell lines •Expression systems	•Disposable bioreactors •Microcarrier •Animal-free culture media	•Filters	•Novel Chromato-graphy resins •Single-use equipment		•Adjuvant		•Analytical methods •Bioassays

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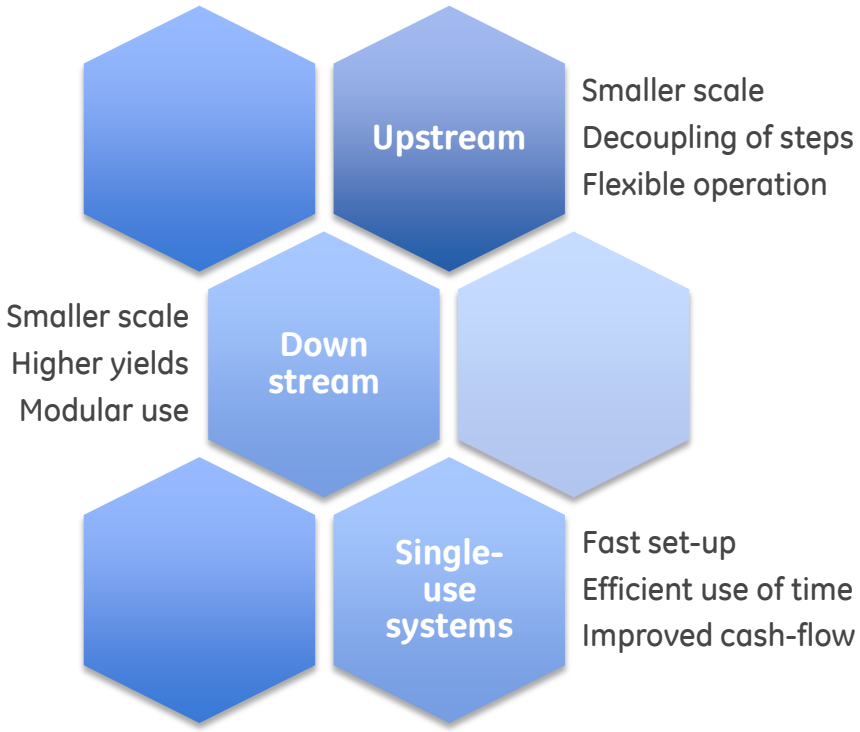
Elements of the improvement effort

Complex designs & processing scenarios need multipoint optimization

Once deployed smartly, the combination of such…



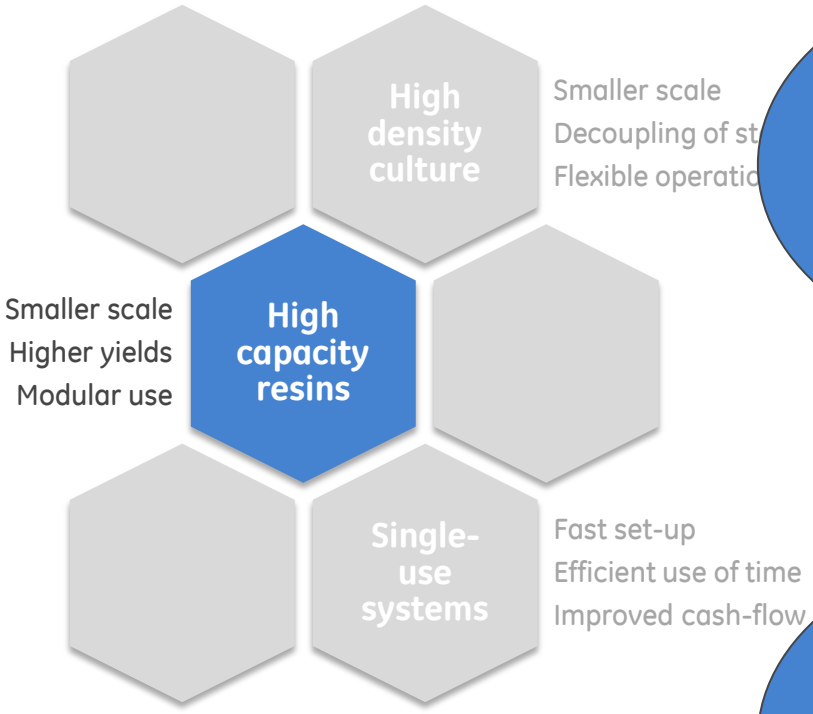
…improvement elements will yield the cost targets

Isolated improvements will hardly result in significant savings, nor can they be justified due to the resulting "cost of change"

To get away from costly and inflexible legacy manufacturing concepts. Process designs need to enable smaller scale operations with:

- Higher productivity of each step
- Flexibility from modular unit operations and from scheduling freedom
- Single-use equipment as a means to delete non-productive activities from the operation

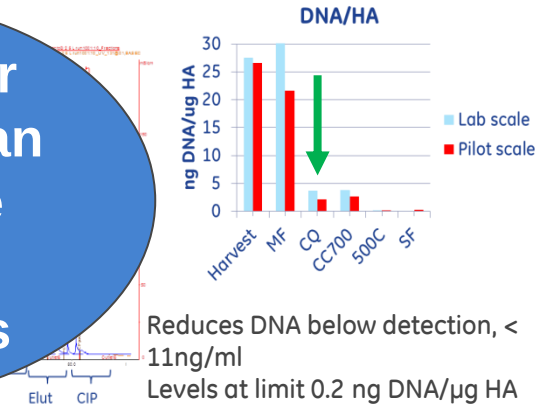
Cell based Influenza pilot case study



Capto Q and Capto Core 700 operated in flow-through mode can be connected in series, as one integrated step !

Focus on removal of DNA - Capto™ Q

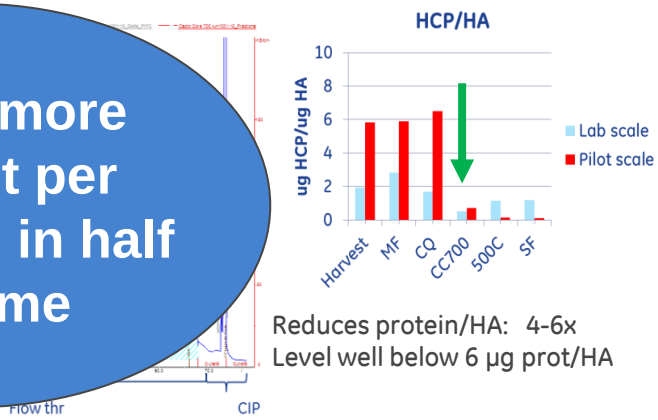
10 fold lower resin cost than comparable legacy Q adsorbers



Reduces DNA below detection, < 11ng/ml
Levels at limit 0.2 ng DNA/µg HA

Focus on removal of HCP - Capto™ Core 700

20 fold more product per liter resin in half the time



Reduces protein/HA: 4-6x
Level well below 6 µg prot/HA

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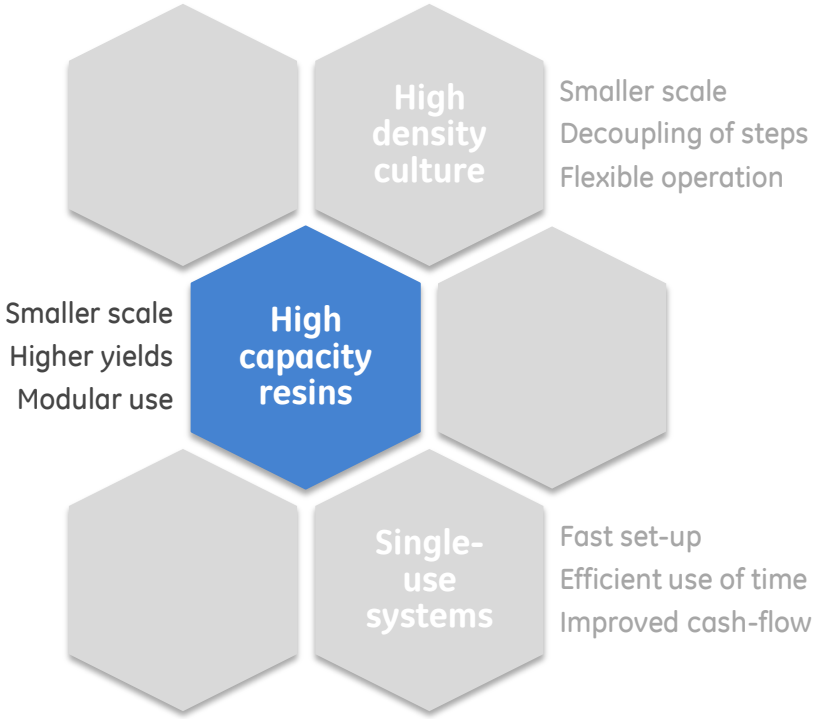
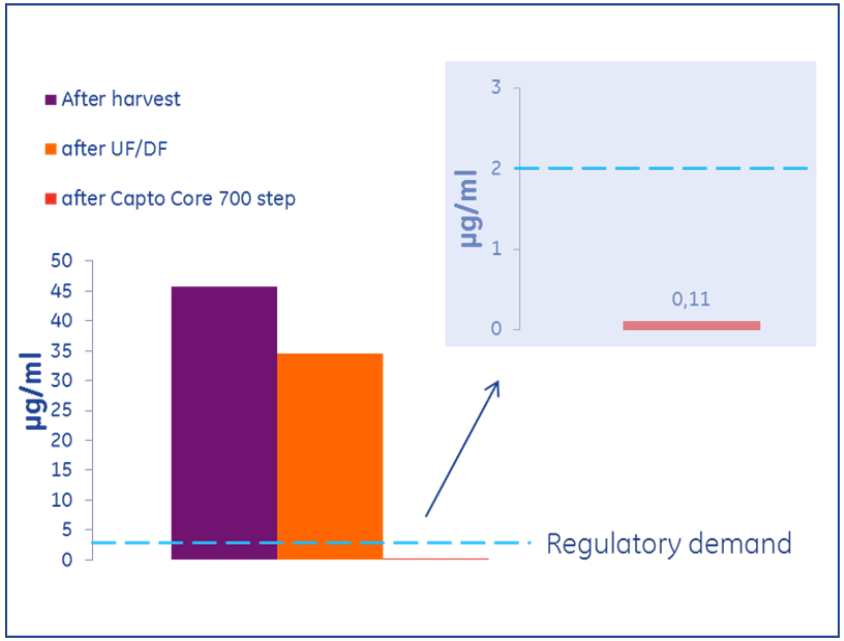
Egg based Influenza case study



Ovalbumin reduction over Capto™ Core 700



Conclusions

- HA recovery over Capto Core 700 step > 90%
- Excellent ovalbumin reduction

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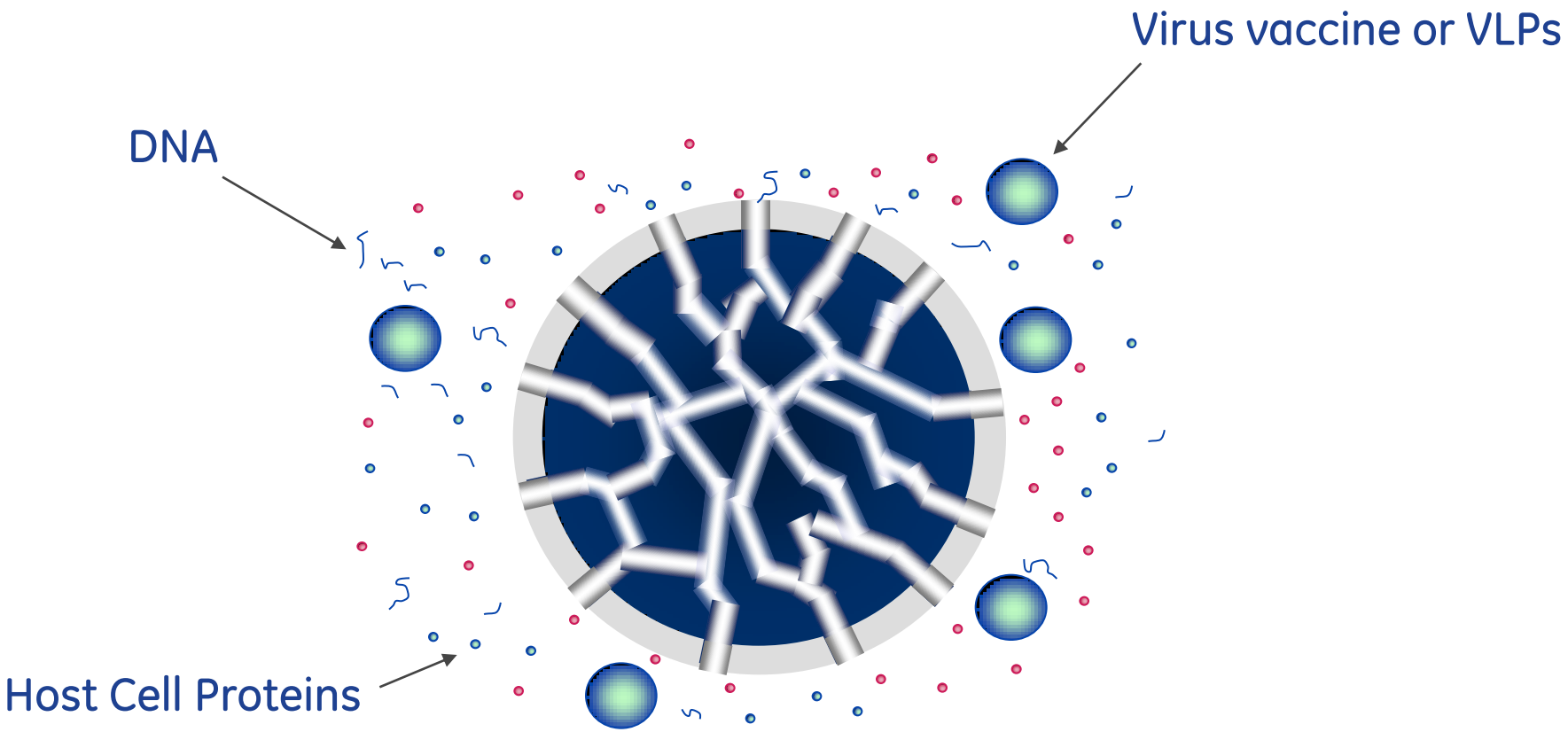
Core beads – the application principle



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Single-Use Vaccine Mfg. Case Studies

Product	Purpose	Cell Line	Bioreactor Scale/type	
West Nile subunit vaccine	GMP Mfg. for Client Partner	S2 Insect cells	XDR-200 mammalian	IND filed
YF Inactivated Virus vaccine	GMP Mfg. for Xcellerex Product	Vero cells microcarriers	XDR-50 mammalian	IND filed
recombinant Protective Antigen (rPA)	DoD Accelerated Mfg. Contract	Pfenex pseudomonas bacteria	XDR-50 microbial	
Swine flu H1	DoD Accelerated Mfg. Contract Live Fire	Pfenex pseudomonas bacteria	XDR-50 microbial	
Swine flu H1N1 VLP	GMP CMO Contract	SF-9 Insect cells	XDR-1000	
Dengue soluble antigen 4 serotypes	GMP mfg. for clinical trials	Insect cells	XDR-200	IND filed

Günter Jagschies
GE Healthcare Life Sciences
Uppsala, Sweden

Yellow Fever Vaccine Mfg. Experience
Vero cell based, killed virus vaccine

Ist Gen process:

- Cytodex 1, 50L scale USP, titer = 1 x E8 pfu/mL
- SF and protein free medium
- 25L DSP process, validated BPL virus kill step
- alum adjuvanted
- Yield: 60 purified doses/L (8.6 log 10/0.5mL)
- 4 GMP batches, IND filed, Phase 1 trial complete

2nd Gen process – COGS reduction, efficiency improvements:

- USP: cell density improved by 2x, bead to bead process
- DSP: Improved yield from 25% to 75% at RT
- Overall improved combined yield TBD – expect 200 doses/L
- Removed UF/DF, introduced chromatographic separations
- Eliminated ultracentrifuge step
- Lowered HCP to <200 ng/mL, DNA to < 10 pg/mL

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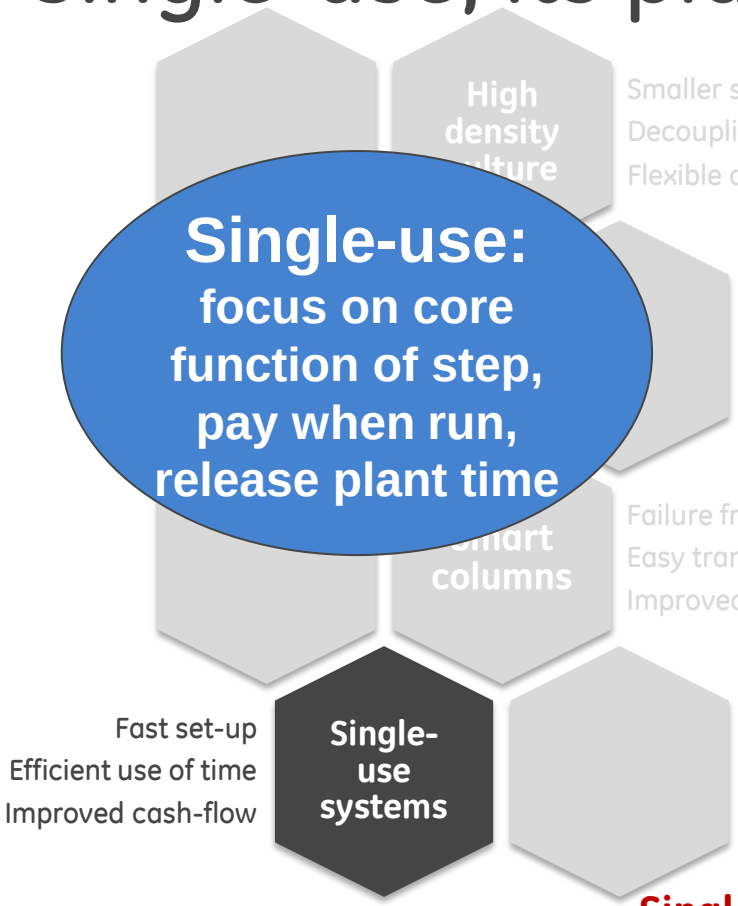
Single-use, its place in a strategy



Problem statement:

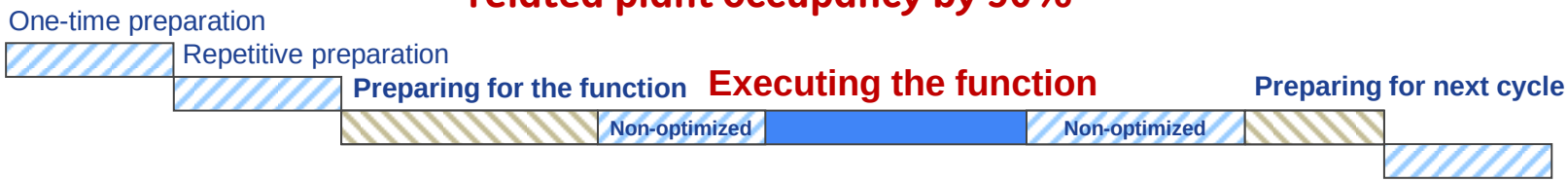
- One-time and repetitive step preparation can take more time than the step itself
- Waiting for hand-over between steps is standard in non-integrated processes
- Classic equipment requires significant capital long before revenue generation starts

Value added work

Non-value added work

Necessary non-value added work

Single-use can shrink the process related plant occupancy by 50%



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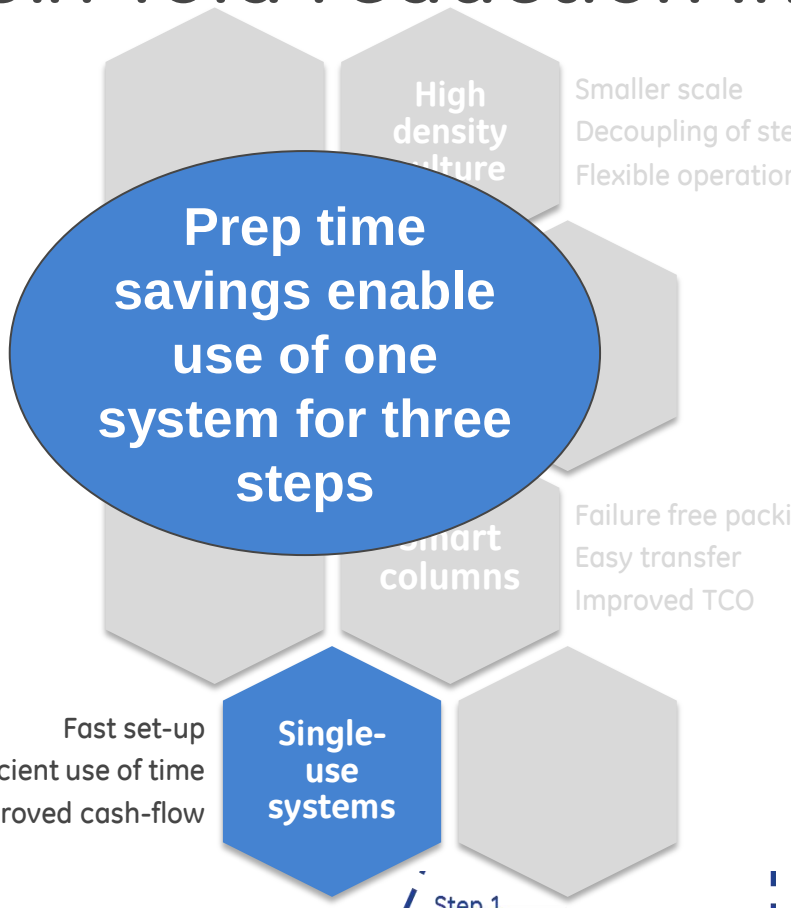
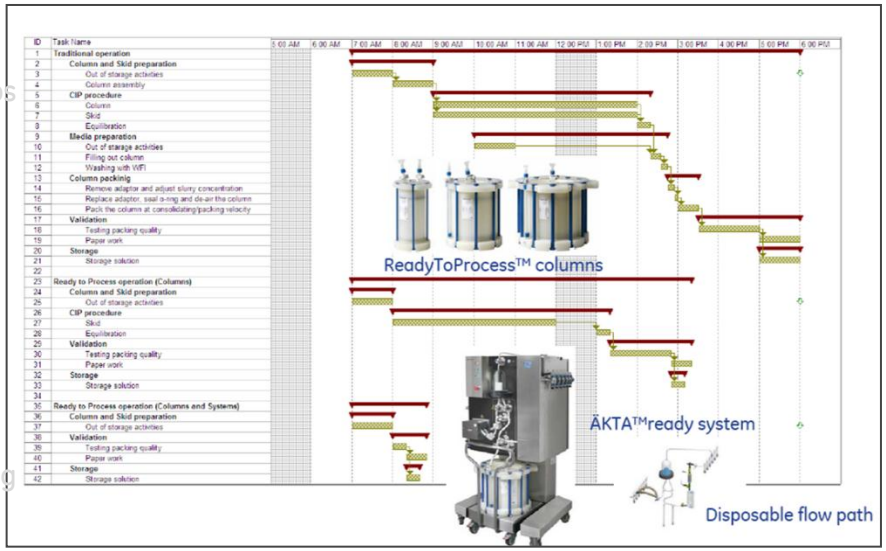
Uppsala, Sweden

Six-fold reduction in setup time





Delete non-value added activities

ÄKTA™ready chromatography system & columns

- System preparation incl. column packing down from 11 hrs to < 2 hrs
- Disposable flow path, 30 min to next run
- One system for all chromatography in a vaccine process

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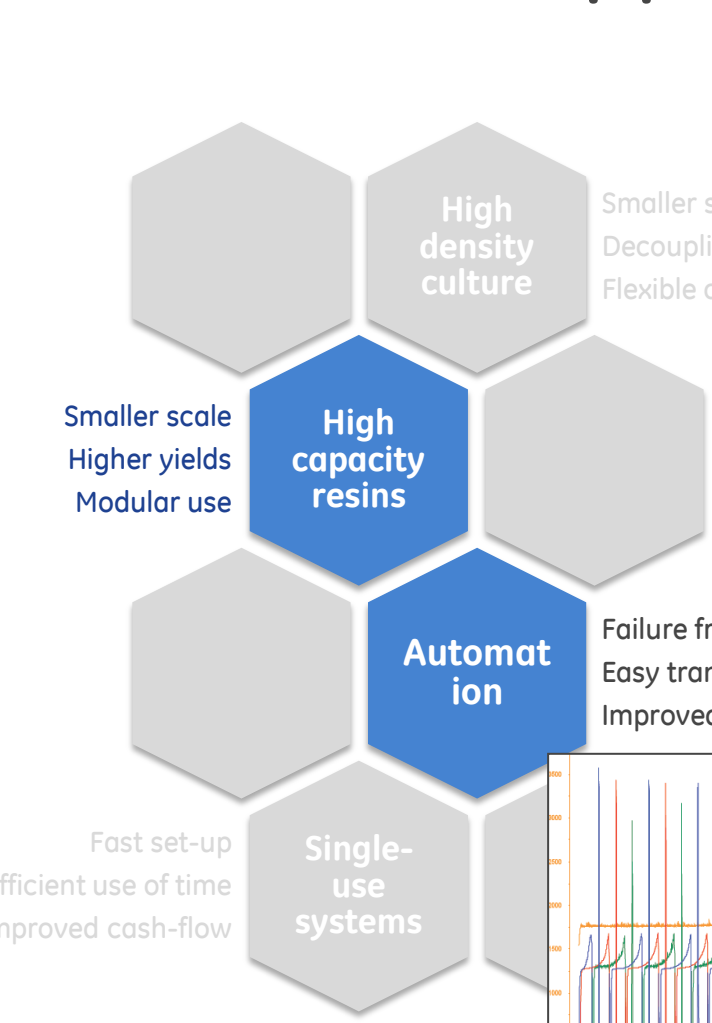
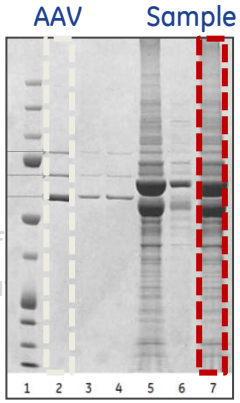
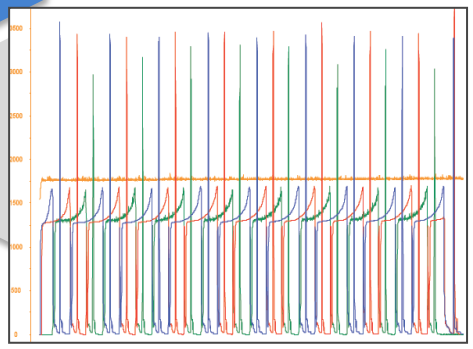
Additional opportunities







Specifically selective resins for vaccine purification for Influenza and Adeno Associated Virus (AAV)

Columns with automated packing and low operator dependency. Smooth site transfer with minimal risk for time losses and failures

Continuous chromatography reduces resin volume by up to 50% and improves yield to near 100%. Simple, smart controls.

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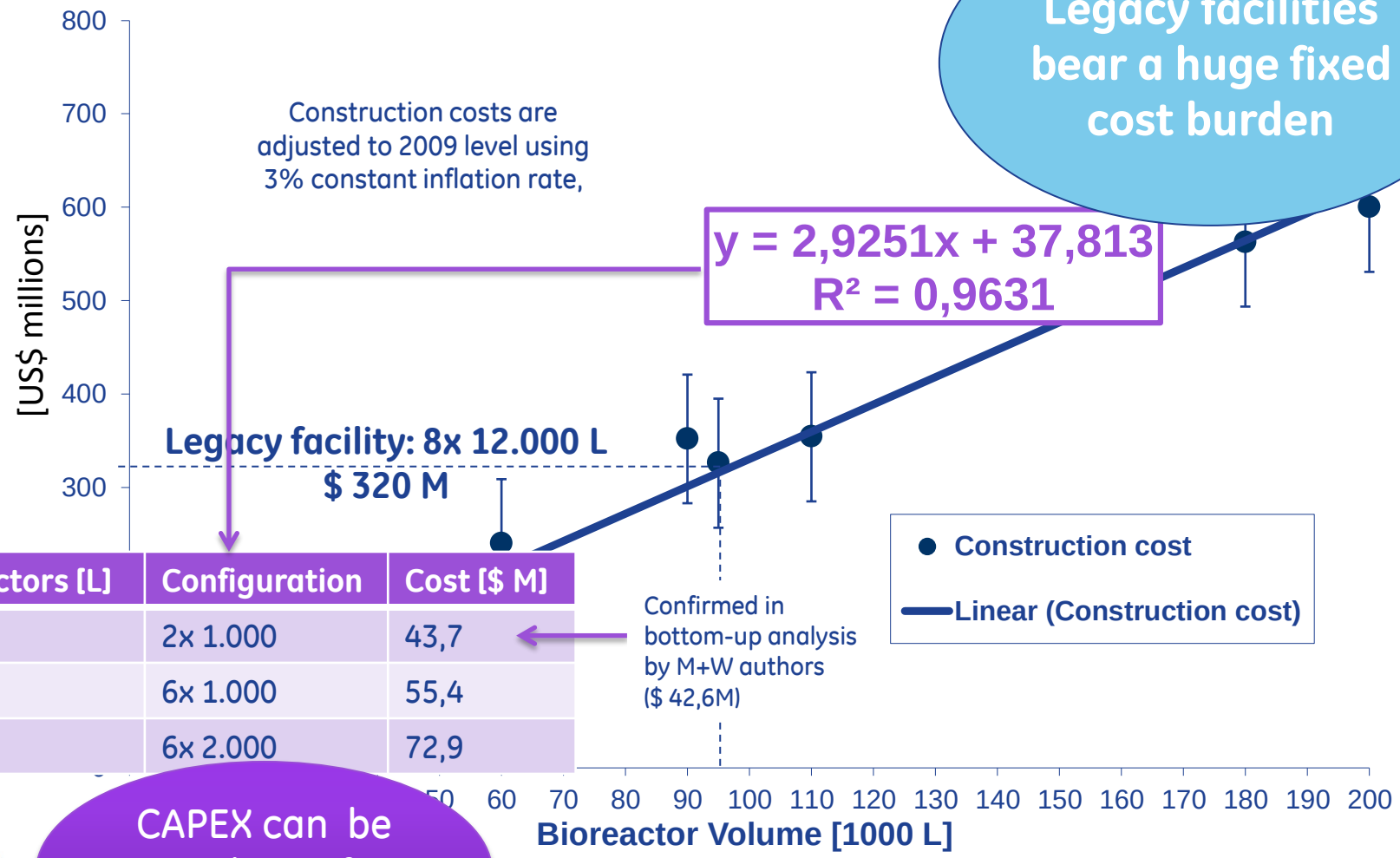
Pandemic Influenza – a global challenge

- This is not just about a pandemic, but about the whole direction of a country's or region's health care policy
- Preparedness includes a solid every day basis of vaccine manufacturing AND an ability to ramp up one particular vaccine production if or when needed.
- The combination of capability for the normal situation with the ability to respond to an emergency requires efficient coordination, infrastructure support, and collaboration.
- Today it is unlikely that one organization or one country can do this alone.

Small facility investment cost

Published CAPEX values: large stainless steel plants



Bioreactors [L]	Configuration	Cost [$ M]
2.000	2x 1.000	43,7
6.000	6x 1.000	55,4
12.000	6x 2.000	72,9

CAPEX can be 30% lower for single-use facility

Elements of an Emergency Ramp-up

- Have a vaccine technology ready-to-go, you can't hope for such technology to become available when the emergency happens.
- Have ongoing production and solid production experience with the staff managing and operating the facilities.
- Have facilities with re-configurable production areas enabling a switch to the emergency program.
- Have facilities with additional space to grow production under the emergency program: surge capacity
- Have similar facilities throughout the country or region that can do the same things when needed, in the same way.
- Have a scale up concept verified that grows production through adding lines rather than through increasing the size of the line (the latter requires to re-design the entire plant).
- Assume the worst: 50% of the workforce will get sick, borders will close, delivery agreements will not be met, national interests and protection will be prioritized

Final word on the money…

Sources of cash to pay (more) for vaccines

A different perspective on the debate about vaccine affordability, rather targeting the illegal or unwanted…

Illegal drugs: $ 300-400 billion

Illegal small arms: $ 5-10 billion

Global corruption:
$ 2,600,000,000,000/yr
(OECD)[2]

State leader embezzlement:
$ 30,000,000,000
(Transparency International)[3]

[3] 10 known leaders of countries with average GDP per capita < $ 1,000 (total during their time in power)

Avg armed conflict:
$ 250,000,000,000/yr
(CCC)[4]

The African Union (2002) estimates that 25% of the GDP of African states or $148 billion, is lost to corruption every year.

Profit[1] top vaccine players (2014):
$ 4,000,000,000/yr
(Sanofi, Merck, GSK, Pfizer, Novartis)
Vaccines only

A country with an income per capita of $ 2000 could expect to see its income rise to $ 8000 in the long run.

Without peace there cannot be development and the Millennium goals become unattainable.

For the period 1990-2008 (18 years) there were 132 actual conflicts. CCC assumes 4 per year each lasting 4 years

Child mortality could fall as much as 75 percent

There is a heated debate about vaccine pricing by the leading manufacturers. While correct in a number of observations, this debate may not focus on the right target…

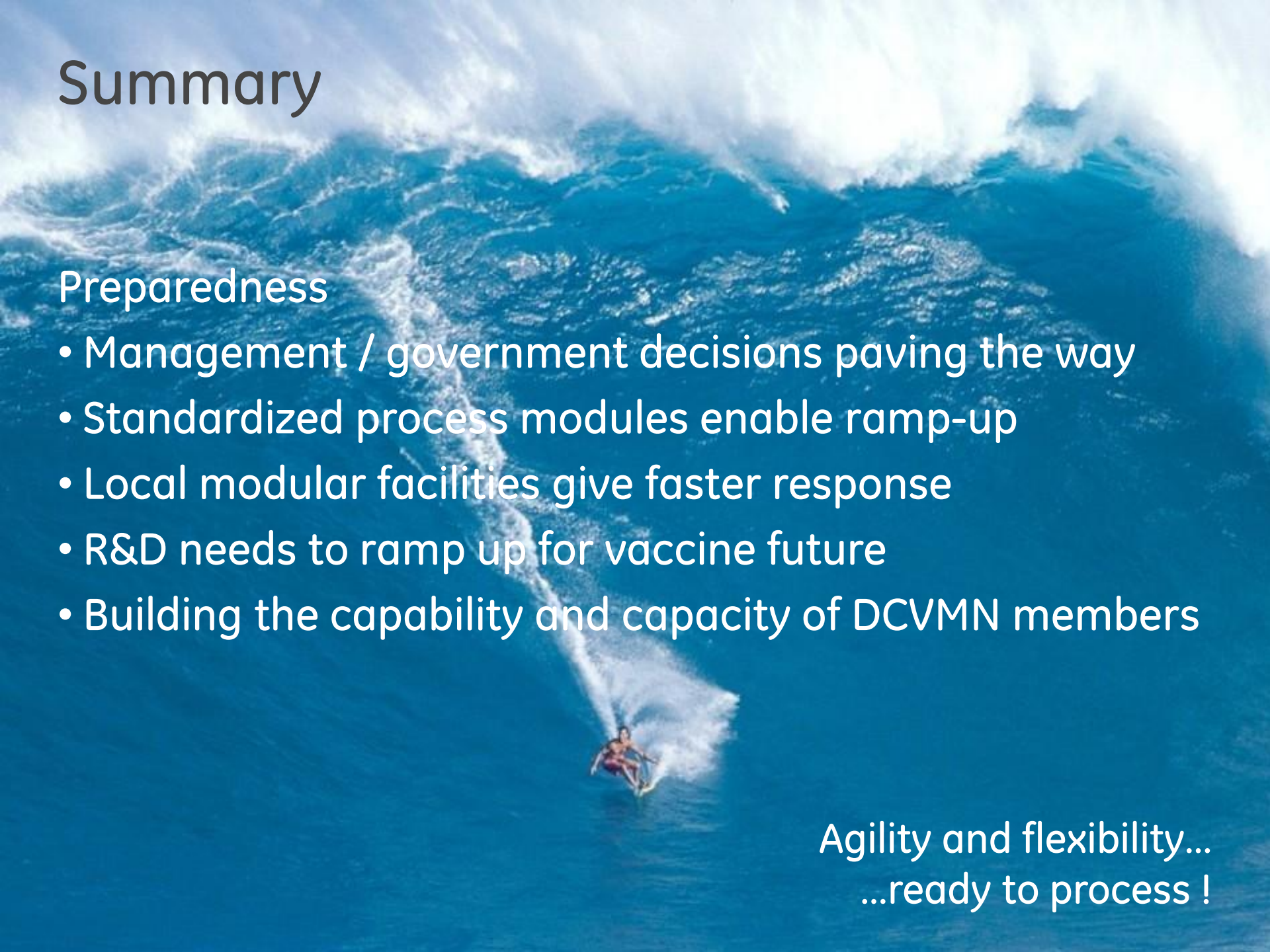
[4] Copenhagen Consensus Center 2012

[2] Corruption is not just a problem of the developing world

[1] author's profit estimate: 15%

World Immunization Week 2015 (WHO)

Summary



Preparedness

- Management / government decisions paving the way
- Standardized process modules enable ramp-up
- Local modular facilities give faster response
- R&D needs to ramp up for vaccine future
- Building the capability and capacity of DCVMN members

Agility and flexibility…
…ready to process !

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Thank you!
Q&A

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imagination at work