EPSRC
Engineering and Physical Sciences Research Council

Department of Health & Social Care

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Imperial College London

The Department of Health and EPSRC
Imperial Future Vaccine Manufacturing Research Hub

Progress in novel vaccine manufacturing platforms and technology transfer

This research is funded by the Department of Health and Social Care using UK Aid funding and is managed by the Engineering and Physical Sciences Research Council (EPSRC, grant number: EP/R013764/1). The views expressed in this presentation are those of the author(s) and not necessarily those of the Department of Health and Social Care.

Introduction to the Imperial Future Vaccine Manufacturing Research Hub

Imperial College London

The University of Nottingham

University of BRISTOL

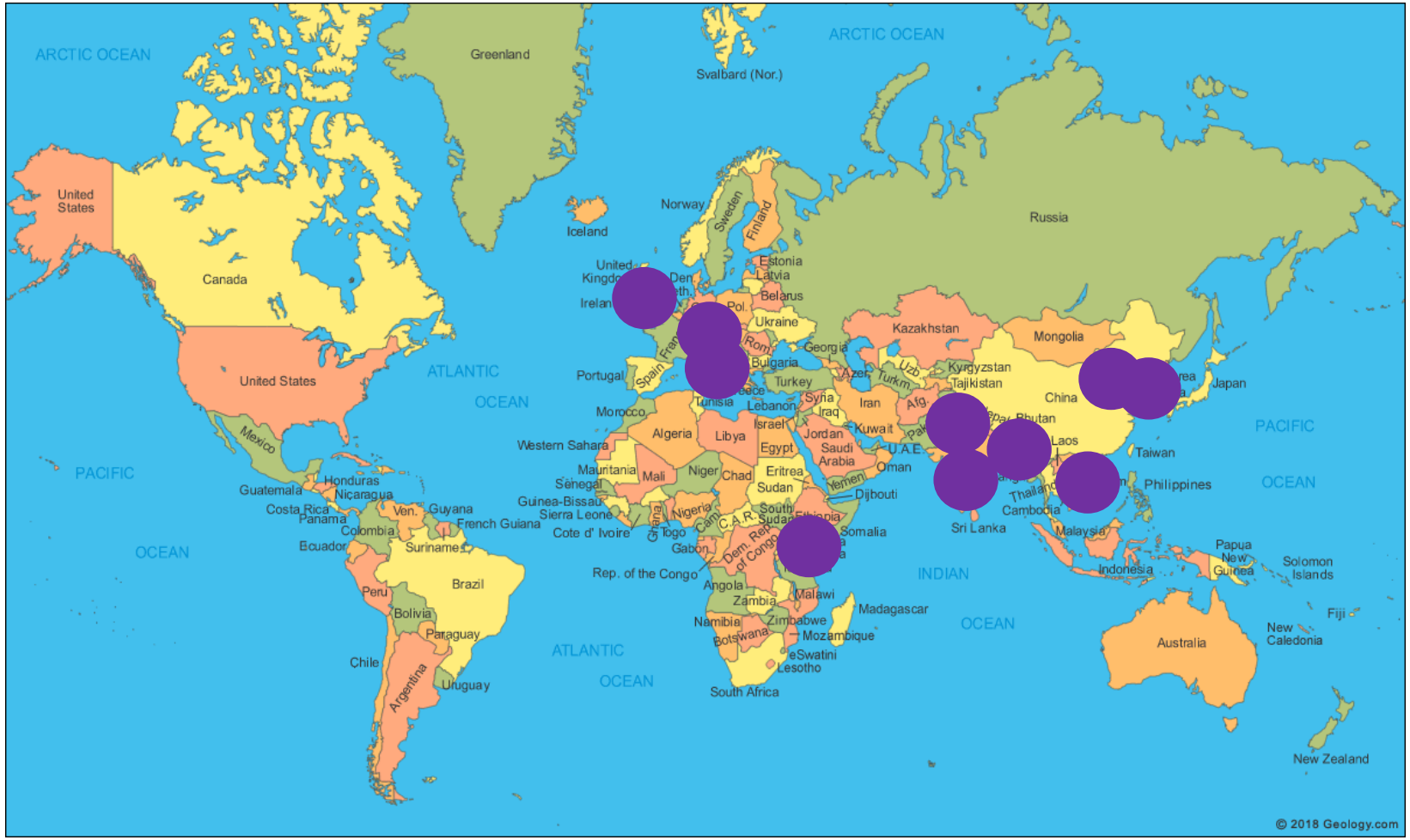
UNIVERSITY OF CAMBRIDGE

NHS Blood and Transplant

Cranfield University

cpi

NIBSC Confidence in Biological Medicines



UNIVERSITY OF LEEDS

Biological E. Limited Celebrating Life Every Day

MINHAI

imBio INNOVATING VACCINES

EXCIVION

Hissen 艾美汉信疫苗（大连）有限公司 Aimei Hissen Vaccine (Dalian) Co., Ltd.

Incepta

VABIOTECH For a Healthier life

gsk

dcvmn Developing Countries Vaccine Manufacturers Network

Responding to developing world vaccine needs

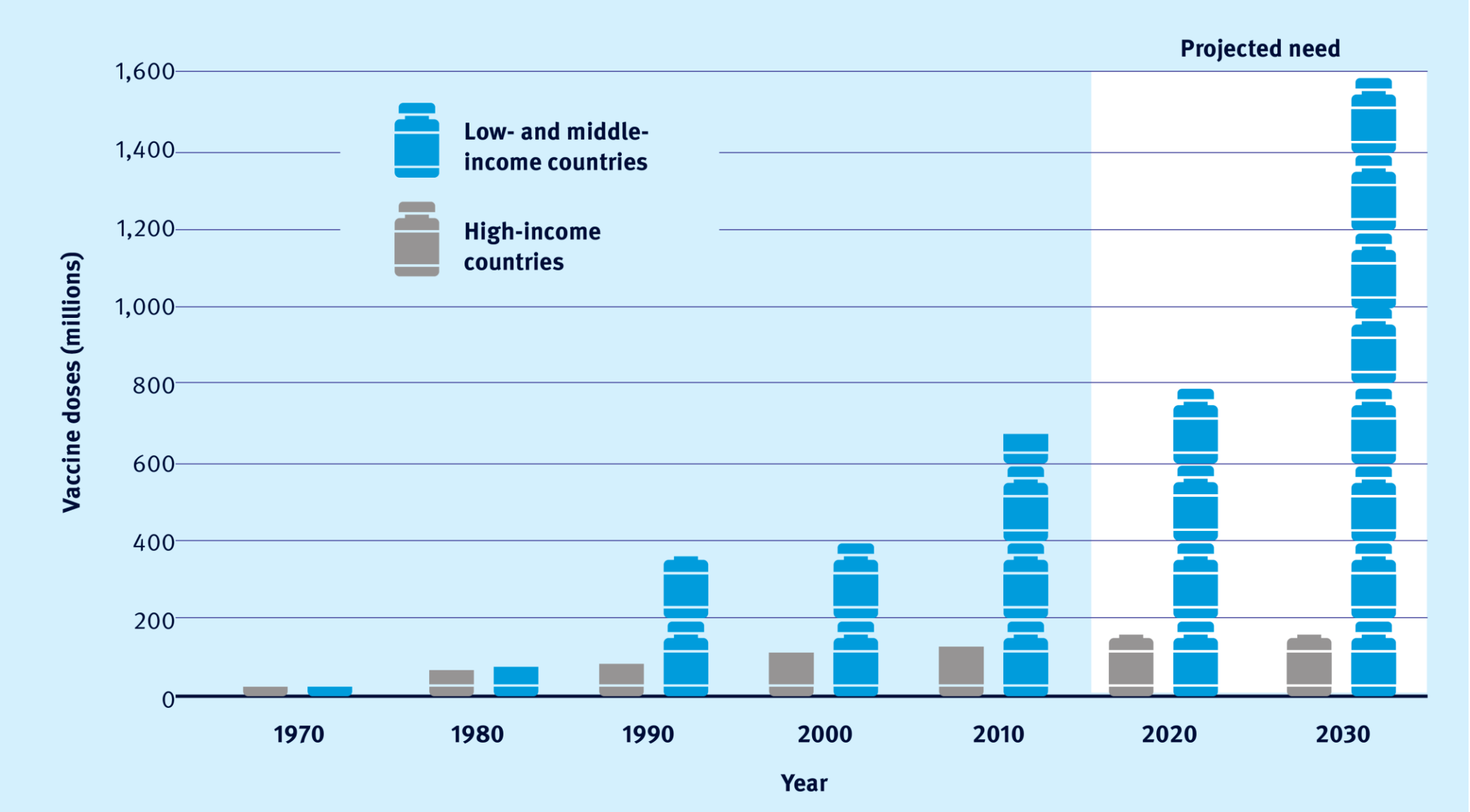
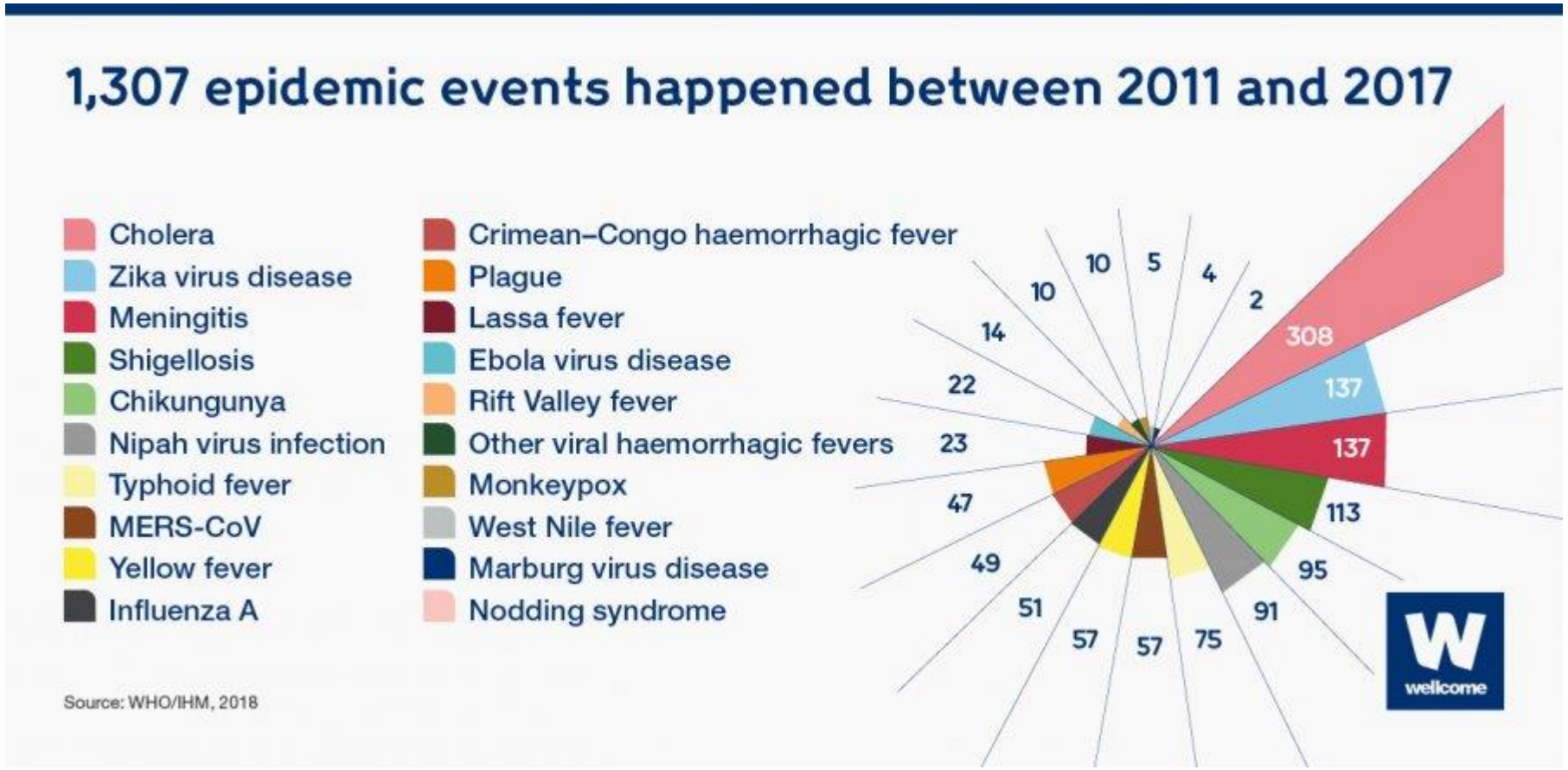


Figure adapted from Rino Rappuoli, Steven Black, and David E Bloom. *Science Translational Medicine.* **2019**. 11, eeaw2888.

Epidemics cost $60 billion economic growth per year



Pathogens targeted by FVMR Hub

Epidemics recorded from 2011-2017		Further diseases focused on by FVMR Hub	
Cholera	Crimean-Congo haemorrhagic fever	Hepatitis E	ETEC
Zika virus	Lassa fever	HPV	EV71 (HFMD)
Meningococcal meningitis	Ebola fever	Pertussis	Nontyphoidal salmonella
Shigellosis	Rift valley fever	Pneumococcal disease	Paratyphoid fever
Typhoid	Influenza	Poliomyelitis	Rabies
Chikungunya		Rotavirus	

Process optimisation / intensification that benefits manufacturers more globally

Hub vaccine innovative technologies

GMMA

Easy scale-up

Mature

Slow

Human glycosylation not possible

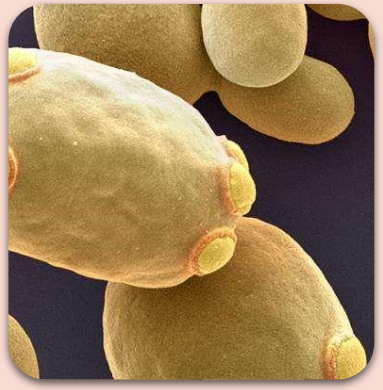
Baculovirus

Thermostable

Rapid

Feasible scale-up

Technologically complex



Yeast

Easy scale-up and high yield

Low risk of contamination

Downstream purification challenging

RNA

Rapid

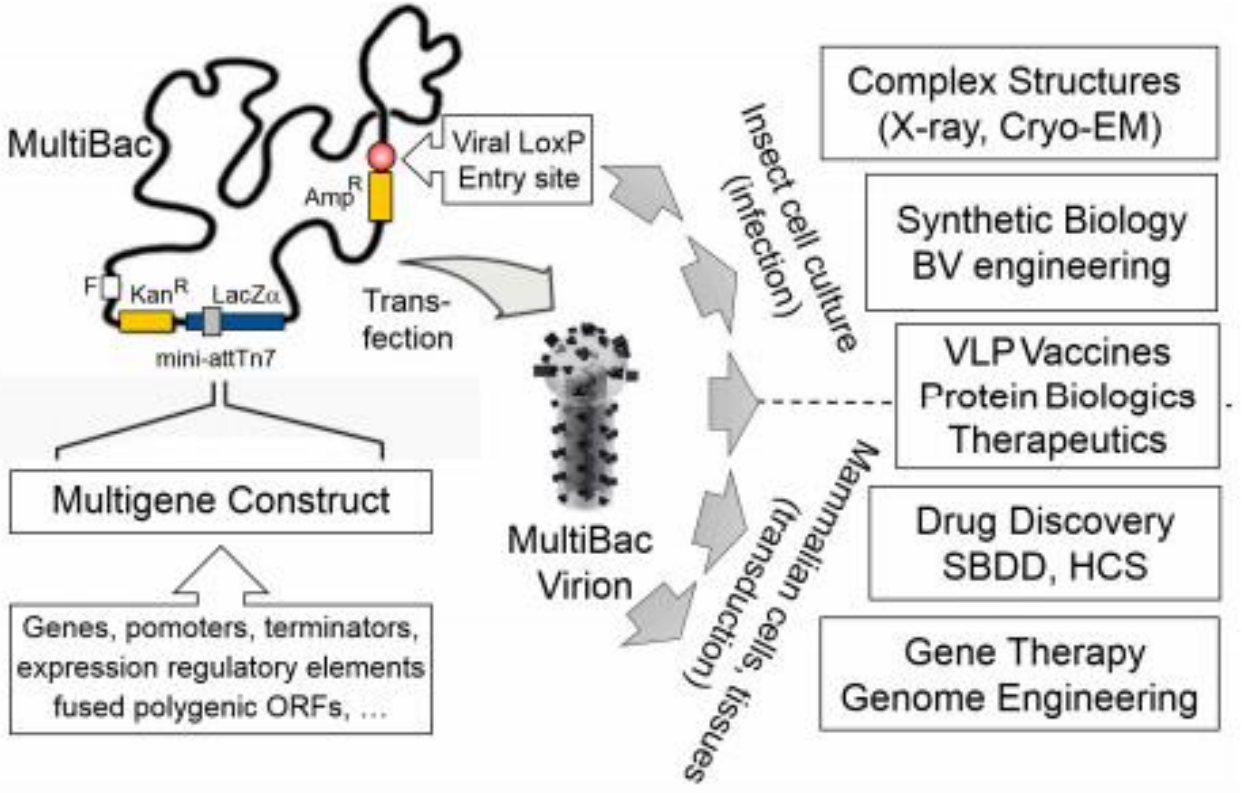
Low cost

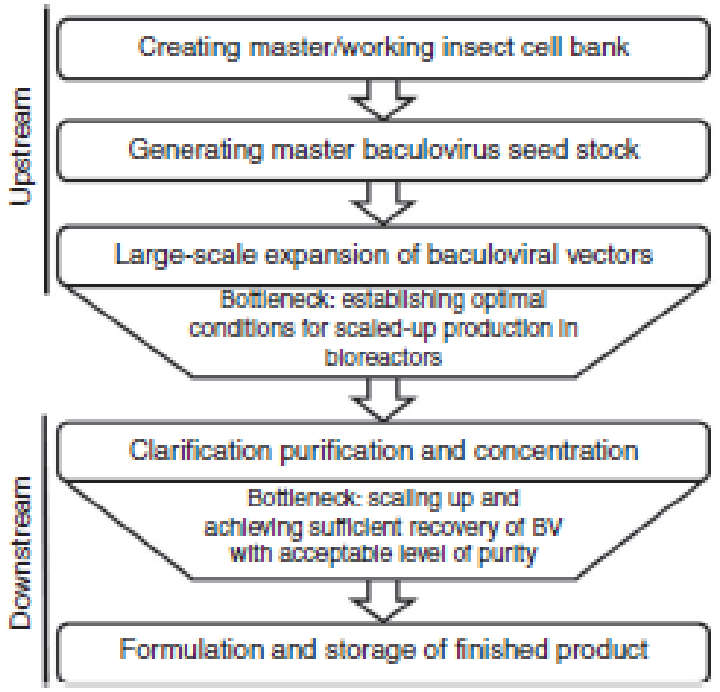
Synthetic and cell-free

Immature

Decreasing risk

Baculovirus

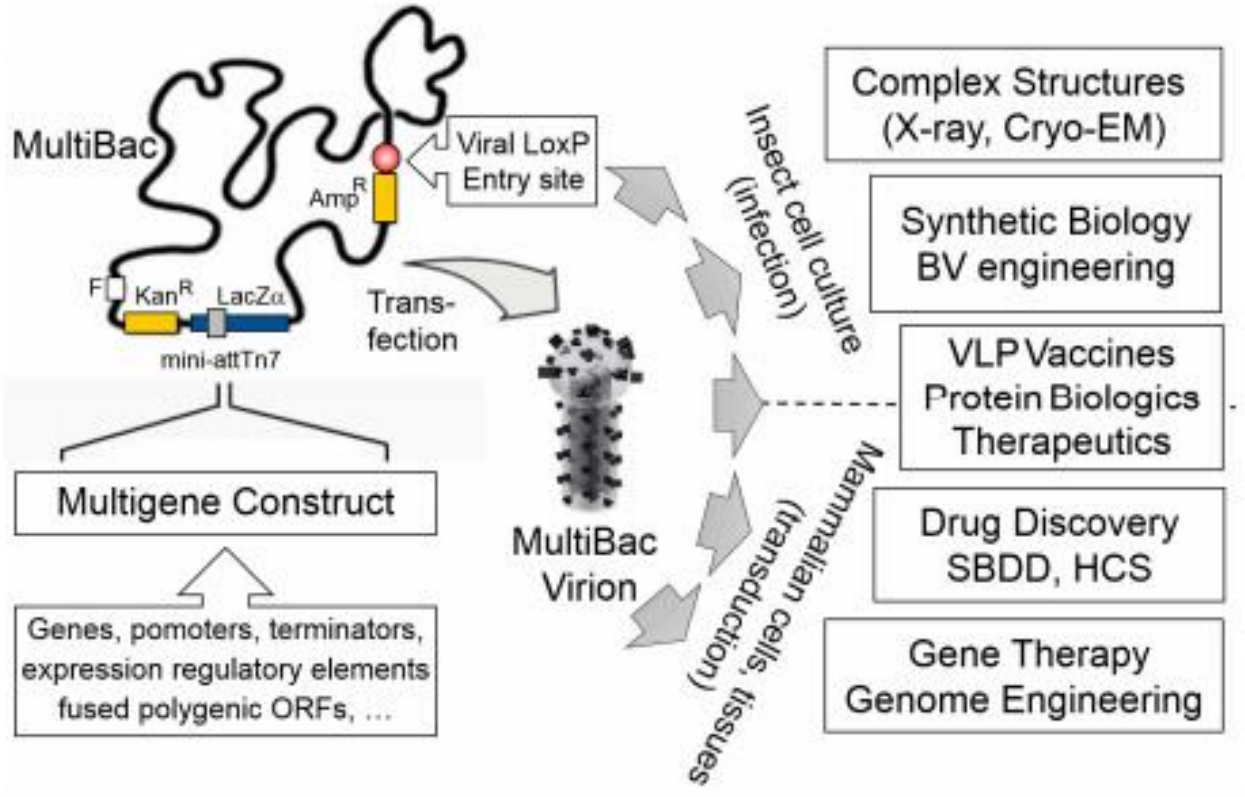




Time from gene to 1 million doses = 47 days, < 7 weeks

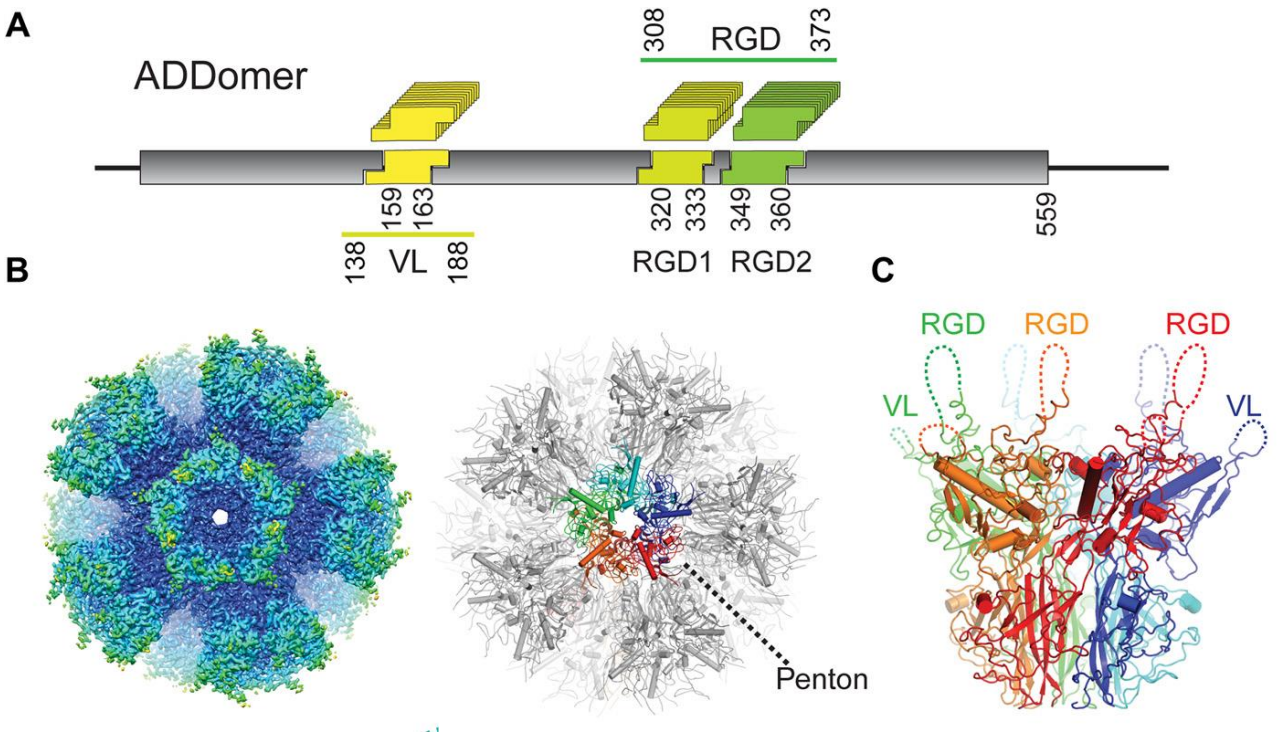
T. W. Kwang, X. Zeng, S. Wang. *Methods & Clinical Development*. 2016: 3: 15050.

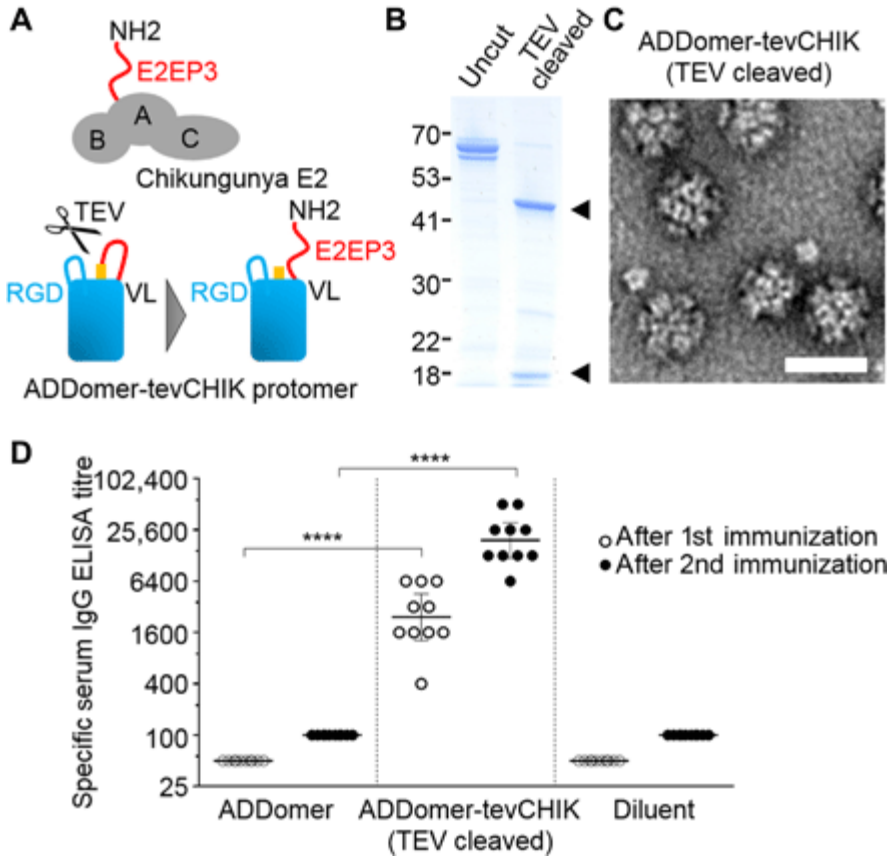
Influenza and Rabies – Vabiotech, Vietnam



Secondment of Vabiotech staff in University of Bristol in 2019, another planned in 2020.
Avian influenza: **global.**
Rabies: **Infection causes tens of thousands of deaths every year, mainly in Asia and Africa.**

Baculovirus - ADDomer





Charles Vragniau, Joshua C. Bufton, Frédéric Garzoni, Emilie Stermann, Fruzsina Rabi, Céline Terrat, Mélanie Guidetti, Véronique Josserand, Matt Williams, Christopher J. Woods, Gerardo Viedma, Phil Bates, Bernard Verrier, Laurence Chaperot, Christiane Schaffitzel, Imre Berger, and Pascal Fender. "Synthetic self-assembling ADDomer platform for highly efficient vaccination by genetically encoded multiepitope display." ***Science Advances***. 2019. 5: eaaw2853.

Hand, foot and mouth disease – Dalian, China

艾美汉信疫苗（大连）有限公司
Aimei Hissen Vaccine (Dalian) Co., Ltd.

"In most cases, the disease is mild and self limiting, with common symptoms including fever, painful sores in the mouth, and a rash with blisters on hands, feet and buttocks. However, **more severe symptoms such as meningitis, encephalitis and polio-like paralysis may occur.**"

Each year in Vietnam alone, around 50,000 – 100,000 HFMD cases, including several deaths, are reported.

In 2011, a **large outbreak of hand, foot and mouth disease (HFMD) in Vietnam** resulted in 113,121 children seeking medical attention, of whom 170 died. **The economic cost posed by HFMD is $90 million/year in Vietnam.**

Vabiotech will export to Vietnam.

In 2019, cases were reported in Bangladesh (based on clinical features, as laboratory diagnostic facilities are lacking). China is largely affected.

Chikungunya – Dalian, China

Table 1
Epidemiological findings of CHIKV across the globe.

Country	Epidemiological findings	Genotype	Ref.
Africa			
Zimbabwe	Since 1952, several epidemics have been reported in Zimbabwe. A large outbreak occurred during 1999–2000. Several cases of local transmission were documented in late 2013 and 2016.	ECSA	65
Tanzania	The first outbreak of CHIKV was recorded in Makonde Plateau, Tanzania in 1952. A combined outbreak of DENV and CHIKV was recorded in 2011–2014. About 7.7% and 1.8% seroprevalence was found in Pemba Island and Tosamaganga, respectively.	ECSA	33,66,67
Nigeria	An epidemic that affected thousands of people occurred in 1969.		
Burundi	The first outbreak was reported in 1980–1982.	ECSA	68
Kenya	The first outbreak occurred in 1982, followed by other severe epidemics with an attack rate of 75% in Lamu and Mombasa in 2004. Over 150 Kenyan people have died because of CHIKV. A combined outbreak of DENV and CHIKV was recorded in 2013.	ECSA, IOL	28,69
Senegal	The first outbreak occurred in 1983, followed by a number of outbreaks up until 1999. A few more cases were identified in 2006.	ECSA, West African	38
Uganda	Uganda experienced several outbreaks during 1985–1971.	ECSA	70,71
Malawi	The first outbreak occurred in 1987–89. A few cases were reported in 2001 and 2015.	ECSA	72,73
Sudan	About 12% of the population was positive for CHIKV in 1989. Other outbreaks occurred in 2005, 2012, and 2013. Seroprevalence of 1.8% was reported in 2016.	Not studied	74
Central African Republic	An outbreak occurred in 2000–2003 that infected thousands of people.	ECSA	75
Comoros	Comoros experienced a severe outbreak in 2005 with an infection rate of 60%.	IOL	76
Madagascar	Two epidemics that occurred in 2006 and 2009 have been recorded. The IgG and IgM seroprevalence varied between 5% and 45%.	ECSA, IOL	77,78
Cameroon	CHIKV was reported in 2006 in two main cities, i.e., Douala and Yaoundé. Seroprevalence was 51.4% in 2006.	ECSA	37,79
Benin	Seroprevalence was 36.1% in 2006 and 2007.	Not studied	80
Mayotte	The only outbreak was reported in 2005–2006, with seroprevalence of 37.2%.	Not studied	81
Mauritius	Mauritius experienced a major epidemic in 2005–2006 and about 51% of the population was suspected to have CHIKV.	ECSA, IOL	82
Gabon	In 2010, 36.6% of a total 4287 suspected cases had confirmed CHIKV.	ECSA	36,83
Guinea	The first outbreak occurred in June 2012; almost 36% of the population was positive for CHIKV.	ECSA, West African	84
Congo	The first outbreak occurred in 2011. As of July 26, 2014 approximately 11 083 suspected cases were reported, with the maximum cases reported from Makélékélé, Brazzaville.	ECSA	30,75
Equatorial Guinea	More than 100 cases of CHIKV were documented during 2002–2006. In 2012, Papua New Guinea experienced a severe outbreak that spread to eight provinces.	ECSA	84,85
Asia			
Cambodia	The first case was identified in 1961 and the virus re-emerged in 2011when 24 patients had positive RT-PCR and ELISA. In 2012, another outbreak occurred in Trapeang Roka Kampong Speu with a seroprevalence rate of 44.7%.	Asian, ECSA, IOL	47,86,87
India	The first outbreak occurred in Kolkata in 1963, followed by a number of other outbreaks in Maharashtra, Andhra Pradesh, Tamil Nadu, and Barsi from 1964 to 1973. The virus reappeared in 2006 and badly hit 13 Indian states including Gujarat, Kerala, Tamil Nadu, Andhra Pradesh, Madhya Pradesh, Maharashtra, and Karnataka. About 2994 individuals out of a total 60 777 suspected chikungunya cases lost their lives. Lakshadweep experienced a small outbreak in 2007. One lac people were again infected with CHIKV in 2008 in Kerala. During subsequent years, several other large outbreaks occurred in Maharashtra, Andaman and Nicobar Islands, West Bengal, Orissa, Rajasthan, and Puducherry. In 2010, the seroprevalence rate was 9.91% in the National Capital Region of India. Mumbai reported a 12.5% seroprevalence rate in 2016.	Asian, ECSA, African, IOL	88–93
Philippines	CHIKV was first identified in 1965, followed by several sporadic cases in Masbate, Cebu, Cavite, Luzon Island, and Mindanao.	Asian, ECSA	94
Vietnam	CHIKV was first identified in the 1960s, mainly associated with the Vietnam War. In 1966, 10 American soldiers were infected with CHIKV. In 1967, anti-CHIKV antibodies were detected in a large number of children.	Asian	95–97
Thailand	46 000 suspected cases were reported in the 1960s. In 2008, 244 people had confirmed CHIKV. Approximately 31% of the population was infected in the 1962 Bangkok outbreak. Bueng Kan experienced a severe outbreak in 2013.	Asian, ECSA, IOL	93,98–100

With climate change we predict this will be seen to increasingly affect an even wider geographical distribution.

Hepatitis E and HPV – Incepta, Bangladesh

Hepatitis E

Hepatitis E is found worldwide, but the **disease is most common in East and South Asia**.
WHO estimates that hepatitis E caused approximately **44, 000 deaths in 2015** (accounting for 3.3% of the mortality due to viral hepatitis).

HPV

Estimated 266,000 deaths and 528,000 new cases in 2012. **A large majority (around 85%) of the global burden occurs in the less developed regions**, where it accounts for almost 12% of all female cancers.

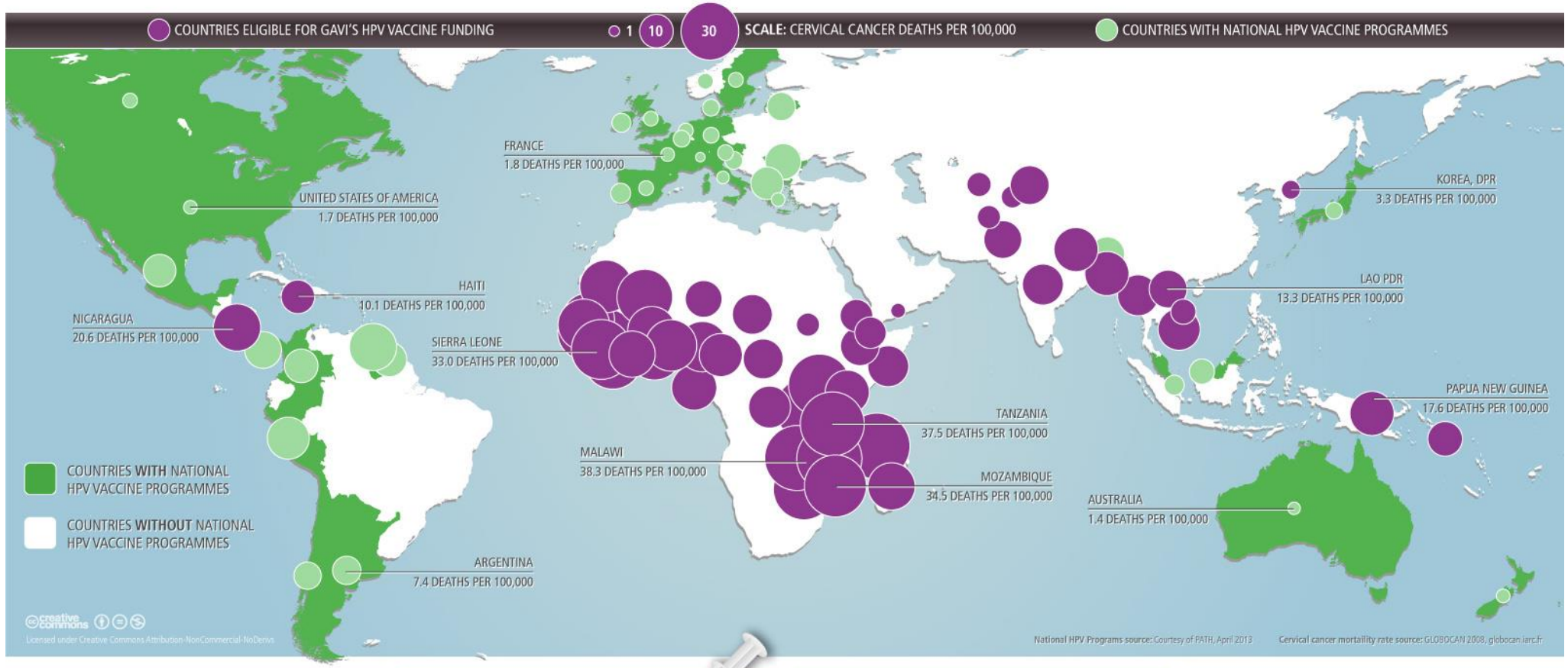
Secondment of Incepta staff in Imperial College London in 2019. Collaborations with NIBSC planned.

GAVI ALLIANCE

SAVING LIVES AND PROTECTING HEALTH THROUGH IMMUNISATION IN DEVELOPING COUNTRIES

GAVI ALLIANCE TACKLES CERVICAL CANCER

EVERY YEAR, 275,000 WOMEN DIE OF CERVICAL CANCER. OVER 85% OF THOSE DEATHS ARE IN DEVELOPING COUNTRIES



CHANGING THE BALANCE

GAVI's support for HPV vaccines will help redress the inequity, delivering vaccines to countries with the highest burden.

ABOUT HPV VACCINE

Safe and effective, human papillomavirus (HPV) vaccines protect against 70% of cervical cancer.

LOWERING THE PRICE

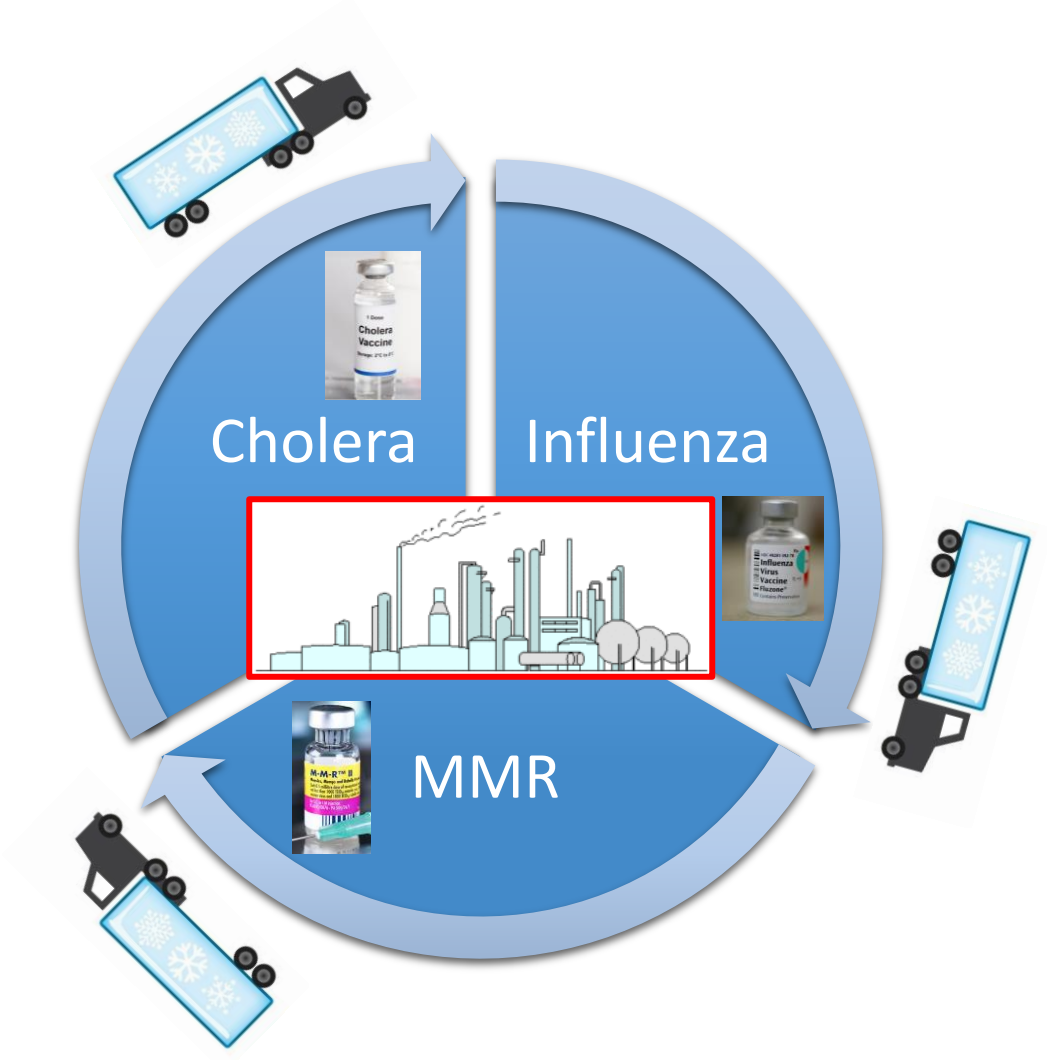
The new low price of US $4.50 per dose marks a two-thirds reduction on the current lowest public sector price.

DRAMATIC ACCELERATION

By 2020, over **30** million girls in more than **40** countries will be vaccinated against HPV

The first GAVI-supported HPV vaccines will be delivered in May 2013.

Supply Chain: centralised vs decentralised manufacture



FVMR Hub calls that support industrial vaccine manufacturing

DCVMN-based calls
- **Supply Chain Workshop**

DCVMN-based calls
- **Consultancy**

DCVMN-based calls
- **QC training**

UK-based SMEs

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Supply Chain Efficiency

The FVMR Hub aims to improve existing, centralised supply chain pipelines

Quality by Design and Supply Chain Modelling Workshop organised / hosted by FVMR Hub

Attendance from DCVMN Members from Developing Countries

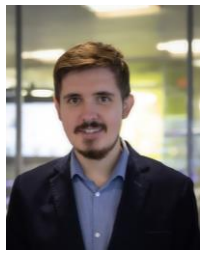
Hanoi, Vietnam

24 – 27 November 2019

Already 40 registered attendees!

Please check DCVMN website




dcvmn
Developing Countries Vaccine Manufacturers Network

Imperial College London

Workshop on Supply Chain Management:
Quality by Design and Supply Chain Modelling
25-28 November 2019, Hanoi, Vietnam.

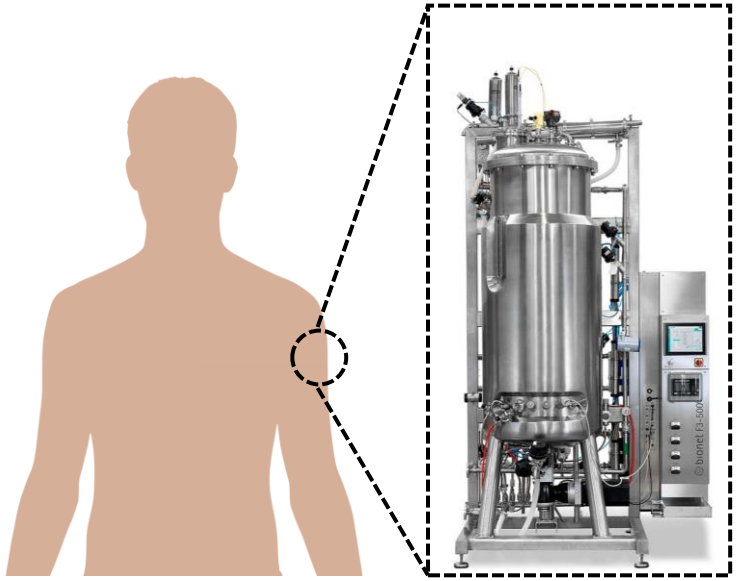
Scope: In Partnership with DCVMN, the Future Vaccine Manufacturing Research Hub (FVMR Hub), led by Imperial College London, will deliver an educational content on quality by design methodology and vaccine supply chain modelling & optimization. The workshop aims to define current challenges in vaccine development as well as supply chains in developing countries and discuss proposed solutions to the identified challenges.

QbD: Quality by design (QbD) is a systematic approach to product development that begins with predefined objectives and emphasizes product and process understanding and controls based on sound science and quality risk management (ICH Q8). The emphasis of QbD began with the recognition that increased testing does not necessarily improve product quality and cost-effectiveness; however, quality must be built into the product from the R&D. The regulatory agencies encourage risk-based approaches and the adoption of QbD principles in product development and manufacturing.

Supply Chain modelling will focus on theoretical and interactive discussions:
Theoretical background for vaccine supply chain modelling:

- Understanding the fundamentals and importance of supply chain modelling for vaccines

RNA – Professor Robin Shattock



Prof Robin Shattock
Director of ICL's FVMR Hub

More detailed RNA presentation on Day 3

RNA synthesis enables rapid manufacturing

CEPI

Optimisation and generation of suitable DNA template encoding the antigen of interest

In vitro RNA transcription followed by hydrolysis of the DNA template and purification of the RNA

Release of bulk RNA

Formulation, fill and finish

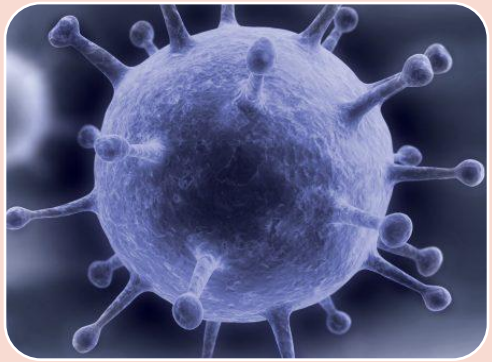
Performance of preclinical toxicology

Release of product for distribution

Our objective is to demonstrate the utility and flexibility of an innovative, broadly applicable synthetic saRNA vaccine platform that enables tailored “just in time” vaccine production to improve regional and global preparedness for foreseeable recurrent outbreaks with viral pathogens.

We acknowledge the financial support provided by the Coalition for Epidemic Preparedness Innovations (CEPI) for our work under an award agreement entitled RapidVac.

RNA – Professor Robin Shattock

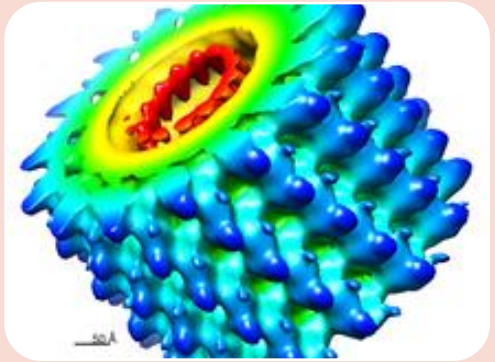


Influenza

Ferret studies

Rabies

Mice studies



Marburg

Guinea pig studies

RNA presentation on Day 3

We acknowledge the financial support provided by the Coalition for Epidemic Preparedness Innovations (CEPI) for our work under an award agreement entitled RapidVac.

FVMR Hub calls that support industrial vaccine manufacturing

DCVMN-based calls
- **Supply Chain Workshop**

DCVMN-based calls
- **Consultancy**

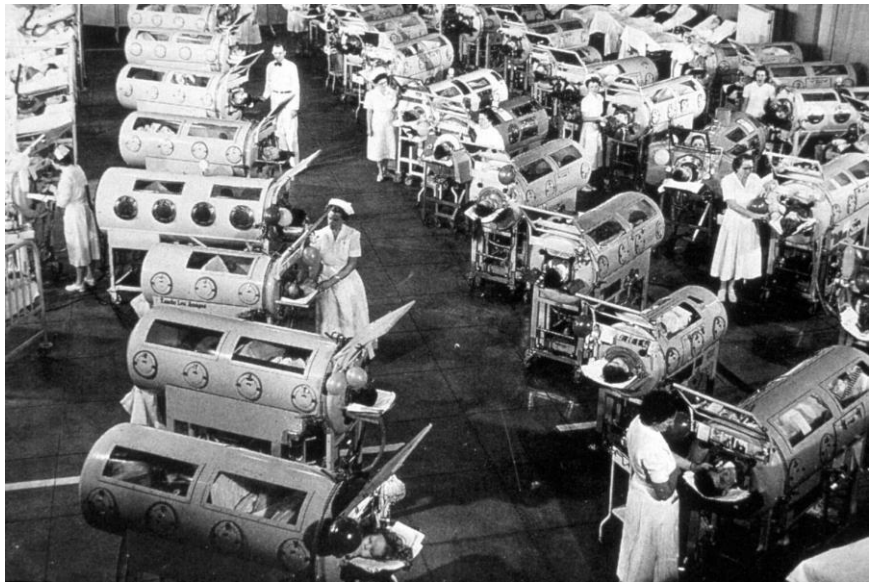
DCVMN-based calls
- **QC training**

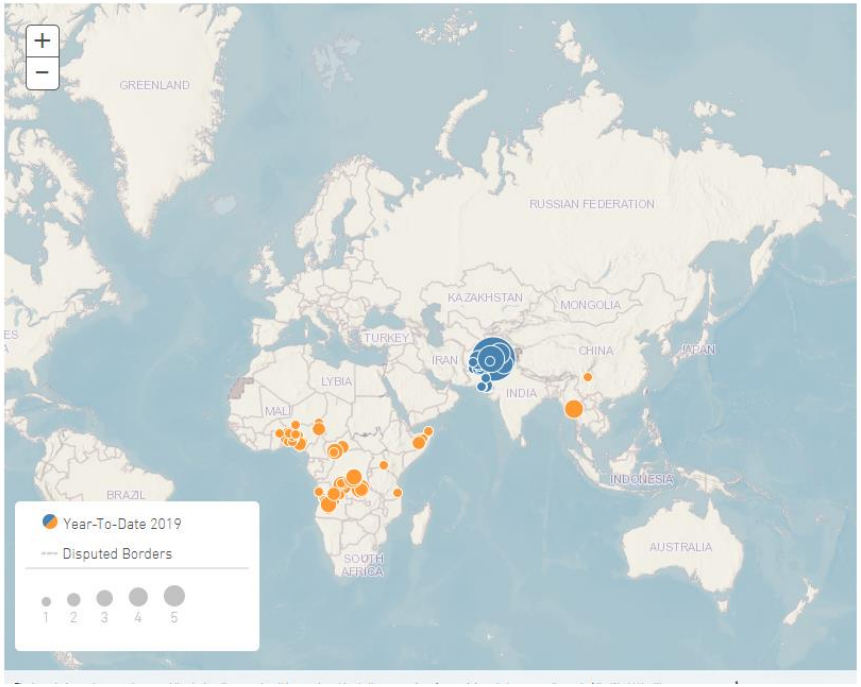
UK-based SMEs

Polio – Beijing Minhai Biotechnology

Poliomyelitis (polio) cases decreased by over 99% since 1988, but polio remains (78 wild poliovirus (WPV) cases reported thus far from 1 January –20 September 2019; in comparison, 33 WPV cases were reported in all of 2018).

Endemic in Afghanistan, Nigeria and Pakistan.





- DCVMN member: Minhai, $49,000 support from the FVMR Hub.
- 2nd DCVMN member has won support of $40,000.

Further Call via DCVMN: expected Jan 2020

Imperial College London

dcvmn Developing Countries Vaccine Manufacturers Network

SECOND CALL FOR PROPOSALS

THE DEVELOPING COUNTRIES VACCINE MANUFACTURERS NETWORK's (DCVMN) OPEN CALL FOR EXPRESSION OF INTEREST IN COLLABORATIVE PROJECTS WITH FUTURE VACCINE MANUFACTURING RESEARCH HUB (FVMR)

GUIDANCE FOR APPLICANTS

DCVMN International periodically sponsors technical assistance provided to member companies by internationally-reputable expert consultants and/or service firms, to improve manufacturing technology, processes or quality control systems. The objective is to increase availability of high-quality vaccines globally.

1. Purpose

As announced on the DCVMN website in January 2018, a novel partnership has been launched to support responsible innovation for manufacturing in emerging countries and to improve the response to life-threatening outbreaks through the rapid deployment of vaccines. (cf. http://www.dcvmn.org/DCVMN-and-the-Future-Vaccine-Manufacturing-Hub).

DCVMN member companies will be notified once call is announced.

FVMR Hub calls that support industrial vaccine manufacturing

DCVMN-based calls
- **Supply Chain Workshop**

DCVMN-based calls
- **Consultancy**

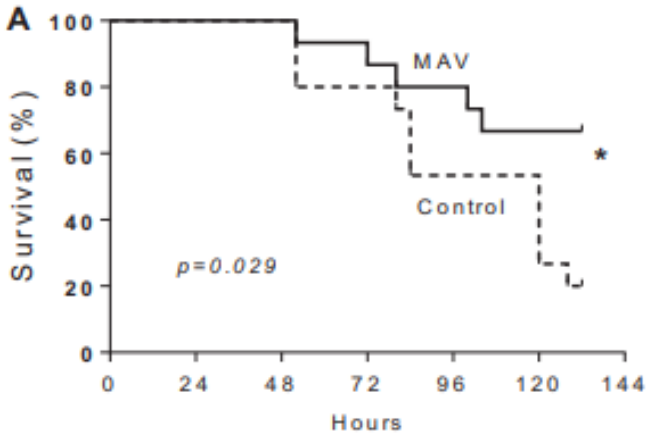
DCVMN-based calls
- **QC training**

UK-based SMEs

Pneumococcal disease – ImmBio and NIBSC

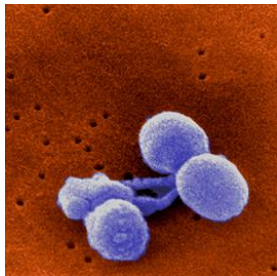
PnuBioVax™ is a protein-based vaccine, with good Phase 1 clinical safety and immunogenic data, and is Phase 2-ready.

In pre-clinical studies, PnuBioVax™ was shown to be immunogenic against all S. pneumoniae strains tested to date regardless of the serotype.



Supported by NIBSC, ImmBio are looking to improve ELISA assays to quantify antigen components.

Win-Yan Chan, Claire Entwisle, Giuseppe Ercoli, Elise Ramos-Sevillano, Ann McIlgorm, Paola Cecchini, Christopher Bailey, Oliver Lam, Gail Whiting, Nicola Green, David Goldblatt, Jun X. Wheeler, Jeremy S. Brown. *Infection and Immunity*. 2019. 87(3): e00846-18.



Imperial's FVMR Hub and NIBSC

ELISA and Pneumoccocal

GMMA

Many pathogens

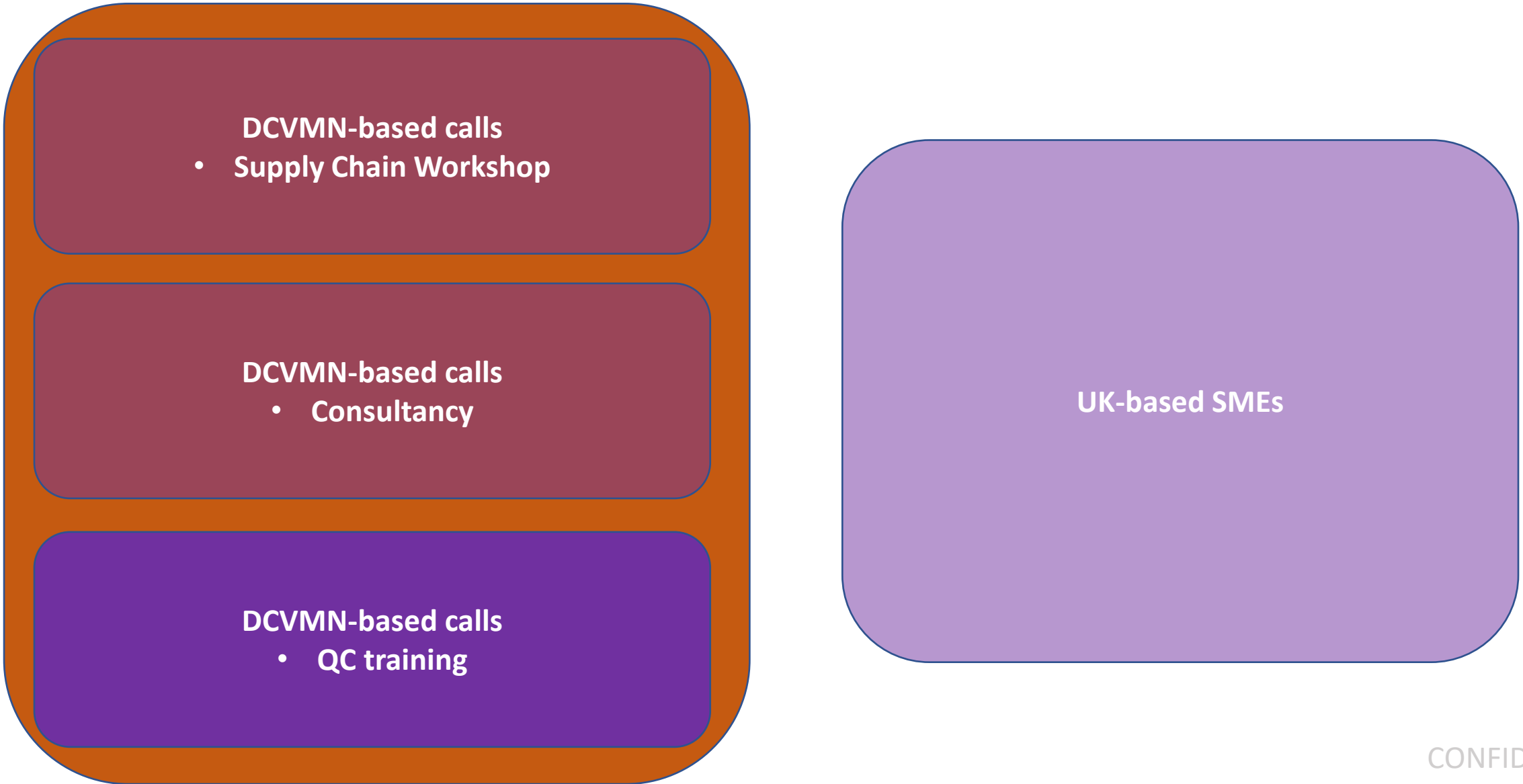
Marburg and Rabies
Freeze drying

Automated filling
Freeze-drying facilities

The **training will support manufacturers to improve the accuracy and efficiency of their vaccine testing such as batch release and QC assays** for the following disease areas:

1. Tetanus
2. Pertussis
3. Rabies
4. Polio (new Sabin IPV)
5. Porcine circovirus
6. Meningitis
7. Influenza
8. HPV
9. Hep A / B

FVMR Hub calls that support industrial vaccine manufacturing



Imperial's FVMR Hub: NIBSC and DCVMN Training

Imperial College London

NIBSC Confidence in Biological Medicines

dcvmn Developing Countries Vaccine Manufacturers Network

CALL FOR EXPRESSION OF INTEREST

THE DEVELOPING COUNTRIES VACCINE MANUFACTURERS NETWORK's (DCVMN) OPEN CALL FOR EXPRESSION OF INTEREST IN QC/QA TRAINING WITH IMPERIAL COLLEGE LONDON'S FUTURE VACCINE MANUFACTURING RESEARCH HUB (FVMR)

GUIDANCE

DCVMN International periodically sponsors technical assistance for its member companies. This assistance comes from internationally-reputable expert consultants and/or service firms with the aim to improve manufacturing technology, processes or quality control systems. Our objective is to increase the availability of high-quality vaccines.

Purpose. In order to enable the efficient registration and WHO Prequalification of vaccines

2-page EoI. Deadline: 30 Nov 2019.

dcvmn Developing Countries Vaccine Manufacturers Network

The **training will support manufacturers to improve the accuracy and efficiency of their vaccine testing such as batch release and QC assays** for the following disease areas:

1. Tetanus
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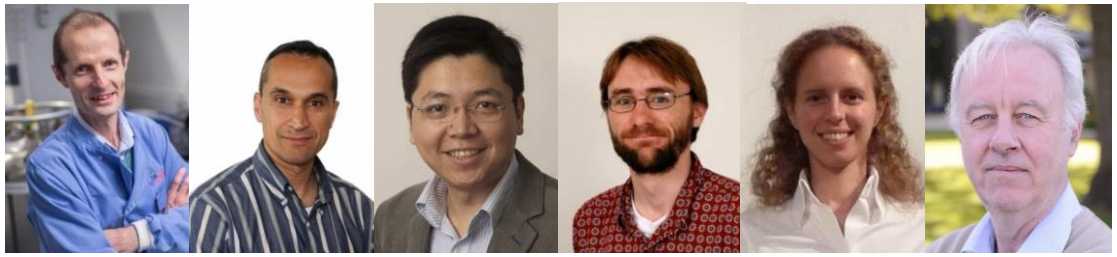
Future Vaccine Manufacturing Hub



Adaptive, Modular, Responsive to Disease X.

Future Vaccine Manufacturing Hub Outputs

Publications

1. Charles Vragniau, Joshua C. Bufton, Frédéric Garzoni, Emilie Stermann, Fruzsina Rabi, Céline Terrat, Mélanie Guidetti, Véronique Josserand, Matt Williams, Christopher J. Woods, Gerardo Viedma, Phil Bates, Bernard Verrier, Laurence Chaperot, Christiane Schaffitzel, Imre Berger, and Pascal Fender. "Synthetic self-assembling ADDomer platform for highly efficient vaccination by genetically encoded multiepitope display." *Science Advances*. 2019. 5: eaaw2853.
2. Ankur Matreja, Gordon Dougan. "Molecular epidemiology and intercontinental spread of cholera." Vaccine. 2019. https://doi.org/10.1016/j.vaccine.2019.07.038.
3. Anna K. Blakney, Paul F. McKay, Bárbara Ibarzo Yus, Yoann Aldon, and Robin Shattock. "Inside out: optimization of lipid nanoparticle formulations for exterior complexation and in vivo delivery of saRNA." *Gene Therapy*. 2019. https://doi.org/10.1038/s41434-019-0095-2
4. Zoltán Kis, Maria M. Papthanasiou, Raul Calvo-Serrano, Cleo Kontoravdi, and Nilay Shah. "A model-based quantification of the impact of new manufacturing technologies on developing country vaccine supply chain performance: a Kenyan case study." *Journal of Advanced Manufacturing and Processing*. 2019. https://doi.org/10.1002/amp2.10025
5. Anna K. Blakney, Paul F. McKay, Dennis Christensen, Bárbara Ibarzo Yus, Yoann Aldon, Frank Follman, Robin J. Shattock. "Effects of cationic adjuvant formulation particle type, fluidity and immunomodulators on delivery and immunogenicity of saRNA." *Journal of Controlled Release.* 2019. 304: 65-74.
6. Maria M. Papthanasiou, Baris Burnak, Justin Katz, Nilay Shah, Efstratios N. Pistikopoulos. "Assisting continuous biomanufacturing through advanced control in downstream purification." *Computers & Chemical Engineering*. 2019. 125: 232-248.
7. Anna K. Blakney, Paul F. McKay, Bárbara Ibarzo Yus, Judith E. Hunter, Elizabeth A. Dex, and Robin J. Shattock. "The Skin You Are In: Design-of-Experiments Optimization of Lipid Nanoparticle Self-Amplifying RNA Formulations in Human Skin Explants." *ACS Nano*. 2019. 13(5): 5920-5930.

Anna K. Blakney was awarded a Provost's Award for excellence in animal research for the above work.

8. Anna K. Blakney, Gokhan Yilmaz, Paul F. McKay, C. Remzi Becer, Robin J. Shattock. "One Size Does Not Fit All: The Effect of Chain Length and Charge Density of Poly(ethylene imine) Based Copolymers on Delivery of pDNA, mRNA, and RepRNA Polyplexes." *Biomacromolecules*. 2018. 19(7): 2870-2879.
9. Anna K. Blakney, Paul F. McKay, Robin J. Shattock. "Structural Components for Amplification of Positive and Negative Strand VEEV Splitzicons." *Frontiers in Molecular Biosciences*. 2018. 5: 71.
10. Luke Muir, Paul F. McKay, Velislava N. Petrova, Oleksiy V. Klymenko, Sven Kratochvil, Christopher L. Pinder, Paul Kellam, Robin J. Shattock. "Optimisation of ex vivo memory B cell expansion/differentiation for interrogation of rare peripheral memory B cell subset responses." *Wellcome Open Research*. 2018. 2: 97.
11. Zoltán Kis, Robin Shattock, Nilay Shah, Cleo Kontoravdi. "Emerging Technologies for Low-Cost, Rapid Vaccine Manufacture." *Biotechnology Journal*. 2019. 14: 1800376.

Awards

Anna K. Blakney was awarded a Provost's Award for excellence in animal research.
Alex Brogan was awarded the Postdoc and Fellows Development Centre (PFDC) Reps Award 2018.
Yunqing (Frank) Zhu was appointed as Professor at Tongji University in Shanghai.
Alex Brogan was appointed Lecturer at King's College London.

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