7 January 2021

COVID-19 Vaccine Efficacy and Safety Workshop

Photo: PATH/Gabe Bienczycki

CCICADA

Fred Cassels

Global Head, Enteric and Diarrheal Diseases

Center for Vaccine Innovation and Access

PATH

1. PATH Center for Vaccine Innovation and Access (CVIA) and CoV-2-RBD219-N1-C1 Vaccine (Baylor and Biological E)

2. SARS-CoV Epidemiology

3. Preclinical safety issues with SARS-CoV vaccines

PATH's CVIA portfolio* includes over two dozen vaccines in development and use across 19 disease targets

DISCOVERY	PRECLINICAL		PHASE 1	PHASE 2		PHASE 3 & REG/PQ	PILOT/ LAUNCH		SCALE-UP	CROSS-PLATFORM
CS230CoPop	Next Gen PCV	TCV LIBP	TB31F (mAb)	Yellow Fever	*ETEC ETVAX*	Respiratory syncytial virus	PCV10	ROTAVAC® - 5CM	HPV	dmLT
GBS hexavalent	COVID NDV-HXP-S	Pfs230/SA-1	cH8/1 LAIV	Maternal pertussis	nOPV 2	P2-VP8 trivalent	ppRTS,S/AS01	ROTAVAC	JE	CHIM
BS Immunogen Design	nOPV 1/3	IRV CDC-9	CPS CHMI	FxRTS,S/AS01	COVID-RBD	NmCV-5	HPV SIHE	Typhoid (TyVAC)	MenAfriVac®	SVM
	cH11/1 LAIV	*Shigella* TM	*Shigella* Invaplex$_{AR-DETOX}$			RTS,S/SMC		ROTASIIL®	MR combination	Bridging transmission measures
		Rh5.2 + Matrix M	IPV-dmLT			MMR			Sabin IPV	COVID-19
			Nipah			Rotavin				Polio NGS for NVT

Indicates non-Gates Foundation funded project.

Indicates projects funded jointly by Gates Foundation and non-Gates Foundation sources.

ENTERIC AND DIARRHEAL DISEASES				MALARIA	RESPIRATORY INFECTIONS AND MATERNAL IMMUNIZATION						ZOONOTIC, EMERGING, AND SEXUALLY TRANSMITTED DISEASES					Other
Rotavirus	ETEC/ *Shigella*	Polio	Typhoid	Malaria	Pertussis	Influenza	Group B Strep	Pneumococcus	Meningococcus	RSV	COVID-19	HPV	Japanese encephalitis	Nipah	Yellow Fever	

* Portfolio snapshot current as of December, 2020; does not include new/ongoing proposal development work in dengue, Zika, or Ebola, nor ongoing support to the Expanded Programme on Immunization in multiple countries.

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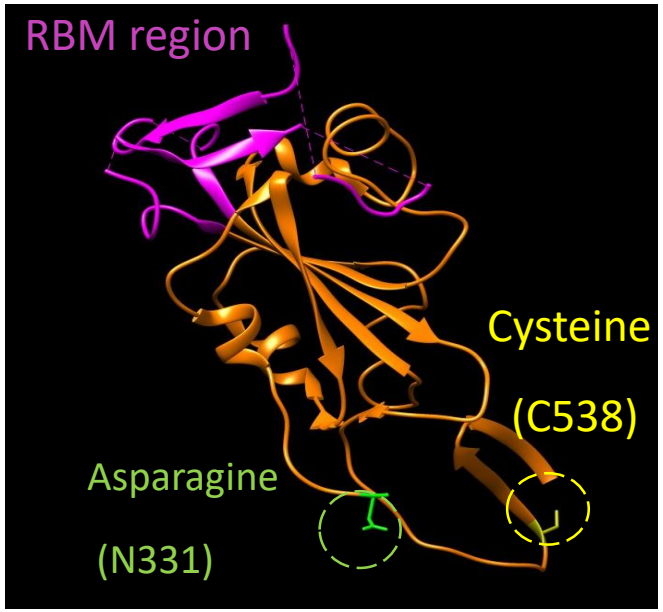
Baylor-Biological E Cov-2-RBD219-N1-C1 Vaccine Milestones in 2020

- Receptor-binding domain (RBD) of SARS-CoV-2 spike protein expressed in yeast (*Pichia pastoris*) formulated on alum plus CpG 1018 from Dynavax (funding NIH, other)
- The vaccine and closely related prototypes induce high levels of VNA in mice, NHPs and safe and protective immunity
- Since early November, the vaccine is undergoing clinical testing – phase 1/2 – in five sites in India (BMGF, BioE)



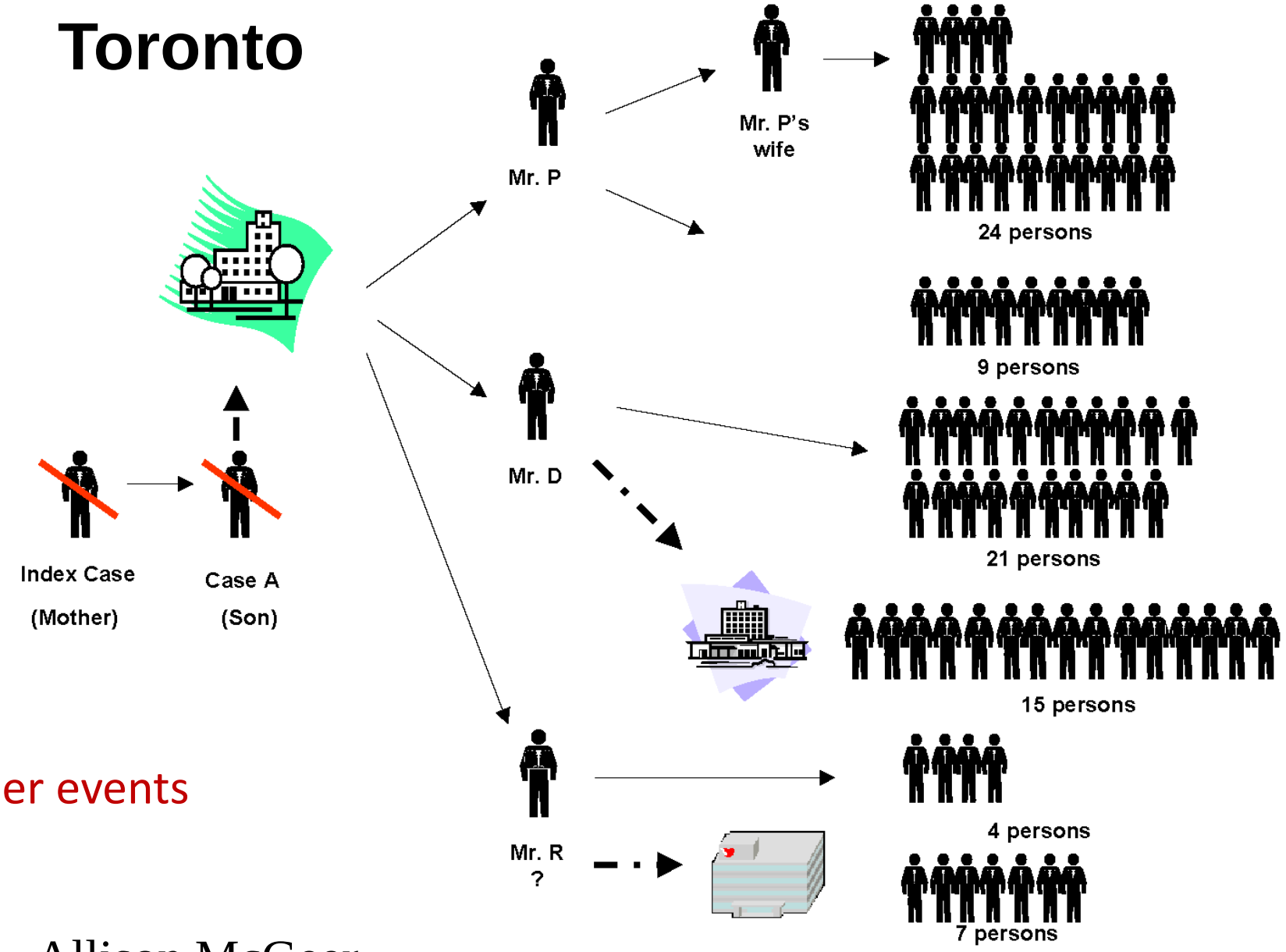
- Biological E capacity for >1 B protein doses and formulation for >500M doses of a recombinant protein-based vaccine for phase 3 India toward EUL (CEPI, BioE)

Texas Children's Hospital
Baylor College of Medicine
National School of Tropical Medicine
Biological E. Limited
Celebrating Life Every Day
PATH
DYNAVAX

Spread of SARS from Hotel Metropole

Superspreader event

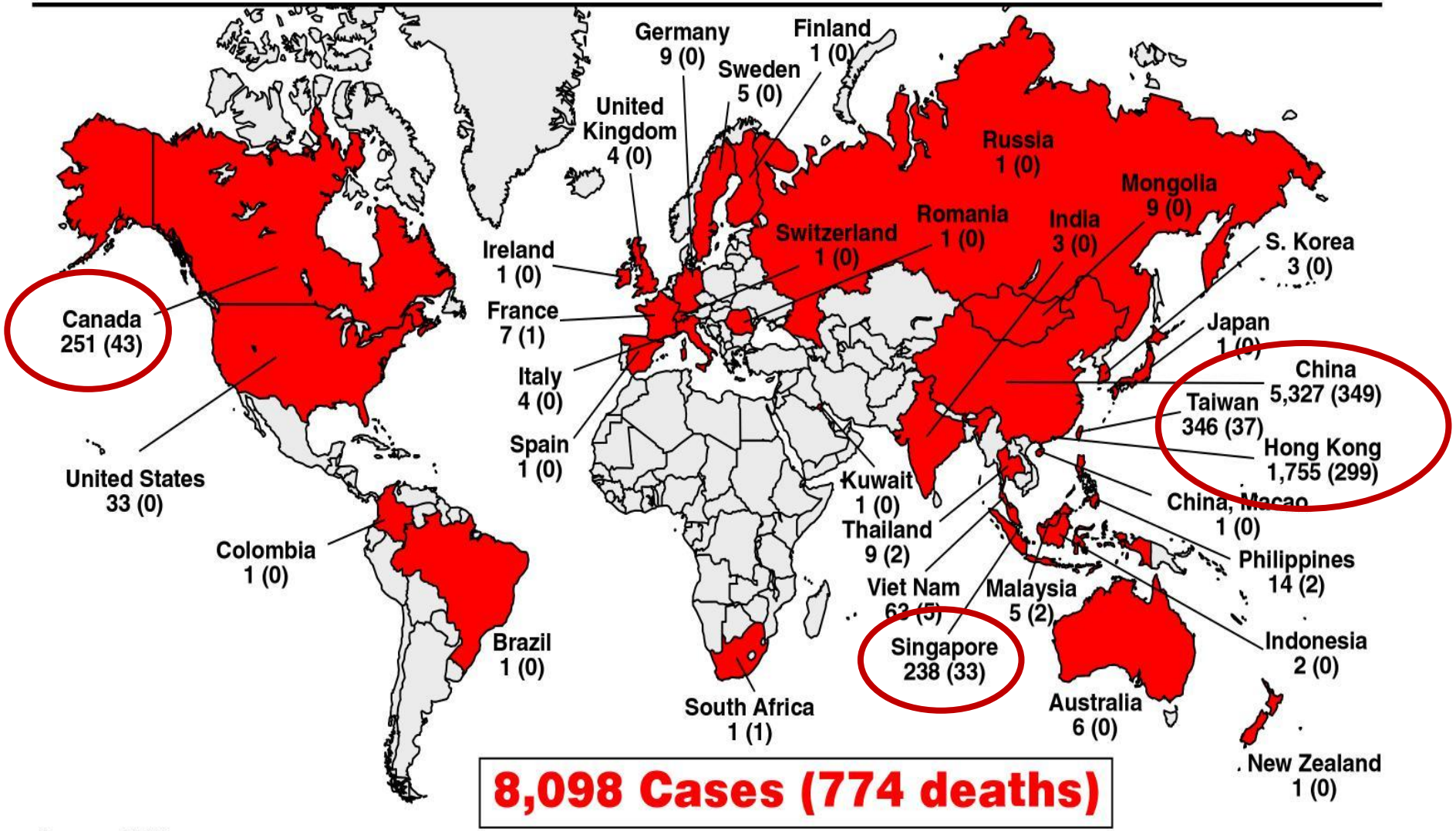
Toronto



Superspreader events

Allison McGeer

Cumulative Reported Cases of Severe Acute Respiratory Syndrome (SARS), Sept. 26, 2003



Source: WHO

COVID-19 87,225,457 Cases (1,884,266 deaths)

Animal Model	Vaccine[1]	Protection[2]	Immunopathology[3]
Mice	Whole virus[tr]		
	w alum	Yes	Yes
	Whole virus[25,tr]		
	w alum	Yes	Yes
	wo alum	Yes	Yes
	VLP[17,tr]		
	w alum	Yes	Yes
	wo alum	Yes	Yes
	S Protein[tr]		
	w alum	Yes	Yes
	wo alum	Yes	Yes
	VEE Vector[15]		
	for N protein	No	Yes
	for S protein	Yes	No
	Vaccinia vector[18]		
	for N protein	No	Yes
	for S protein	Yes	?No
Ferrets	Whole virus[11]		
	w alum	Yes	Yes
Nonhuman Primate[4]	Whole virus[11]		
	w alum	Yes	Yes
Hamsters	Whole virus[22]		
	w ASO1	Yes	No

K. Tseng…R. Couch, Immunization with SARS Coronavirus Vaccines Leads to Pulmonary Immunopathology on Challenge with the SARS Virus. PLoS One, April 2012

B. Graham, VRC NIAID: Avoid Th2, induces IL4 and IL13—IL4 is mucus inducing, small airway obstruction (≤ age 2 y.o., RSV experience); IL13--inhibits CD8 delaying viral clearance

Box 1

Vaccine enhanced disease

While enhanced disease is usually associated with flaviviruses, pre-existing immunity induced by natural infection or vaccination to feline coronavirus (FCoV) can lead to antibody-dependent enhanced disease. This occurs mostly under experimental conditions but seems to be rare in the field[91]. Vaccination with formalin inactivated vaccines, DNA-based vaccines, RNA-based vaccines, VLP-based vaccines and MVA-vectored vaccines against SARS-CoV-1 has resulted in complications like increased infiltration of eosinophils (suggesting a T_{h2} type immunopathology) into the lung or liver damage after challenge with the virus in different animal models[92-95]. It has been speculated that enhanced disease is driven by non-neutralizing antibodies to S, but has also been shown to be triggered by N-based vaccines[93,96,97]. *Bona fide* antibody dependent enhancement for SARS-CoV-1 even by neutralizing antibodies has been shown *in vitro* while the same antibodies then protected *in vivo*[98]. In addition, several vaccine candidates against SARS-CoV-1 induced protective immunity in animal models without signs of enhanced disease. Enhanced disease has also been reported in rabbits after natural infection and re-challenge with MERS-CoV in the absence of neutralizing antibodies[99]. Mice vaccinated with an inactivated MERS-CoV vaccine and then challenged with infectious virus showed enhanced infiltration of easinophiles into the lung even despite the presence of neutralizing antibodies. Of note, as with many SARS-CoV-1 vaccines, these mice controlled the virus better than animals in the control group[100]. The mechanism behind this phenomenon is still unclear and the data is murky. In this context it is also important to note that enhanced disease is not necessarily based on antibody dependent enhancement but could be caused by other mechanisms as well. It seems, given the right circumstances, enhanced disease induced by natural infection or vaccination can be forced in animal models. However, even in animal models there is currently no evidence for SARS-CoV-2 enhanced disease. Nevertheless, monitoring for the occurrence of this phenomenon pre and post marketing of vaccines is paramount, especially once titers start to wane.

F. Krammer, SARS-CoV2 Vaccine Development
Nature, 23 Sept 2020