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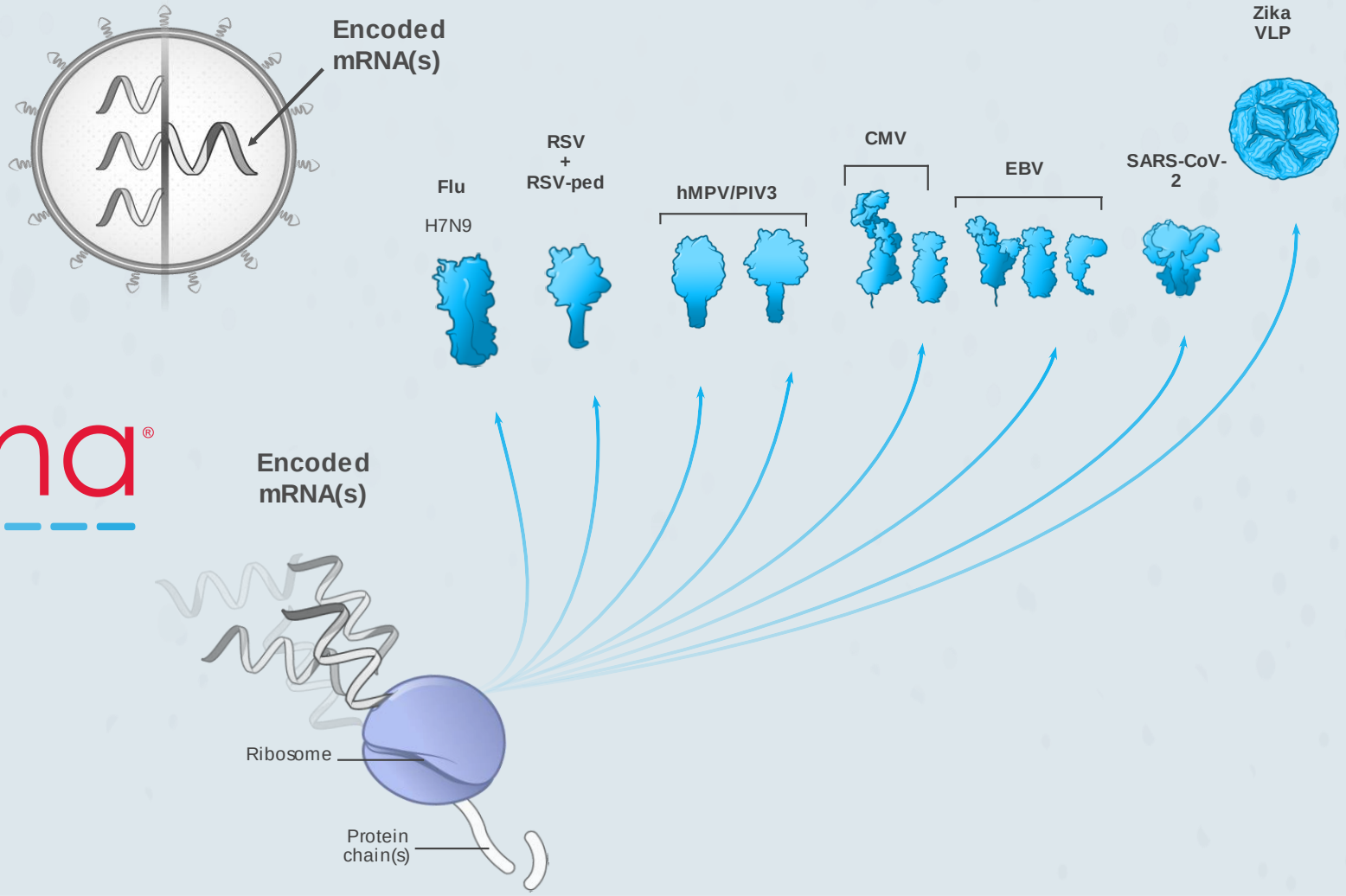

First Vaccines Day

April 14, 2020

Forward-looking statements and disclaimers

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended including, but not limited to, statements concerning; the impact of the SARS-CoV-2 pandemic on the Company's clinical trials and operations; the timing and finalization of a dose-confirmation Phase 2 study and planning for a pivotal Phase 3 study for mRNA-1647; the status and outcome of the Phase 1 clinical trial for mRNA-1273 being conducted by NIH; the next steps and ultimate commercial plan for mRNA-1273; the size of the potential market opportunity for mRNA-1273; the size of the potential commercial market for novel vaccines produced by Moderna or others; the potential peak sales for the Company's wholly-owned vaccines; the probability of success of the Company's vaccines individually and as a portfolio; and the ability of the Company to accelerate the research and development timeline for any individual product or the platform as a whole. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this press release are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others: whether the interim or final Phase 1 results for mRNA-1647 and mRNA-1893 will be predictive of any future clinical studies for these or other development candidates with the same LNP formulation; preclinical and clinical development is lengthy and uncertain, especially for a new class of medicines such as mRNA, and therefore our preclinical programs or development candidates may be delayed, terminated, or may never advance to or in the clinic; no mRNA drug has been approved in this new potential class of medicines, and may never be approved; mRNA drug development has substantial clinical development and regulatory risks due to the novel and unprecedented nature of this new class of medicines; despite having ongoing interactions with the FDA or other regulatory agencies, the FDA or such other regulatory agencies may not agree with our regulatory approval strategies, components of our or filings, such as clinical trial designs, conduct and methodologies, or the sufficiency of data submitted; the impact of the COVID-19 pandemic on the operation of the Company's clinical trials, pre-clinical work, and overall operations, including delays and inability to progress with certain clinical trials; and those risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.

This presentation also contains estimates, projections and other statistical data made by independent parties and by Moderna relating to market size and growth and other data about Moderna's industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of Moderna's future performance and the future performance of the markets in which the Company operates are necessarily subject to a high degree of uncertainty and risk.

Certain of the information contained herein is based upon or derived from information provided by third parties and industry sources. While the Company believes that such information is accurate and that the sources from which it has been obtained are reliable, the Company has not independently verified the assumptions on which such information is based. The Company makes no guarantee, express or implied, as to the accuracy and completeness of such information and has neither reviewed nor endorsed the content of third party information.

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Agenda

Introduction of mRNA Vaccine Platform	*Stéphane Bancel, CEO*	*8:00-8:20 AM*	*20 min*
Clinical Trial POS	*Andrew W. Lo, MIT Sloan School of Management*	*8:20-8:40 AM*	*20 min*
Traditional Vaccines Overview	*Paul T. Heath, Vaccine Institute, St George's, University of London*	*8:40-9:20 AM*	*40 min*
mRNA Vaccines Differentiation	*Stephen Hoge, M.D., President*	*9:20-9:50 AM*	*30 min*
Coffee Break		*9:50-10:00 AM*	*10 min*
Vaccines Against Infections From Mother to Baby	*Tal Zaks, M.D., Ph.D., Chief Medical Officer*	*10:00-10:30 AM*	*30 min*
Vaccines Against Respiratory Diseases	*Tal Zaks, M.D., Ph.D., Chief Medical Officer* *Flor Munoz-Rivas, M.D., Baylor College of Medicine* *Mark R. Denison, MD, Vanderbilt University Medical Center* *Tal Zaks, M.D., Ph.D., Chief Medical Officer* *Juan Andres, Chief Technical Operations and Quality Officer*	*10:30-12:10 PM*	*100 min*
ACIP Overview/Framework	*Kathryn M. Edwards, M.D., Sarah H. Sell and Cornelius Vanderbilt Professor of Pediatrics*	*12:10-12:40 PM*	*30 min*
Conclusion	*Stéphane Bancel, CEO*	*12:40-12:50 PM*	*10 min*
Q&A		*12:50-1:15 PM*	*25 min*

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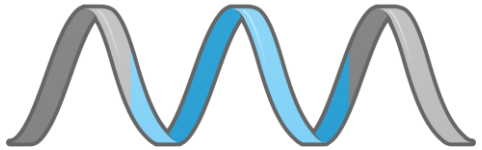
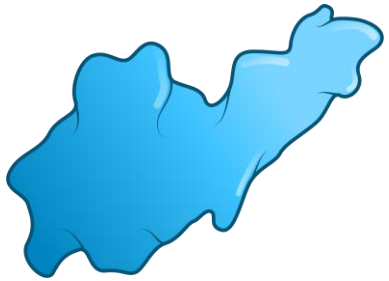
Central dogma of molecular biology

DNA → **messenger RNA** → **Protein**





Storage

DNA stores instructions for proteins in the nucleus

Software

mRNA is a temporary set of instructions for cells to make a protein; mRNA is made using DNA

Applications

Proteins form the basis of life by performing the functions required by every cell; proteins are made using mRNA

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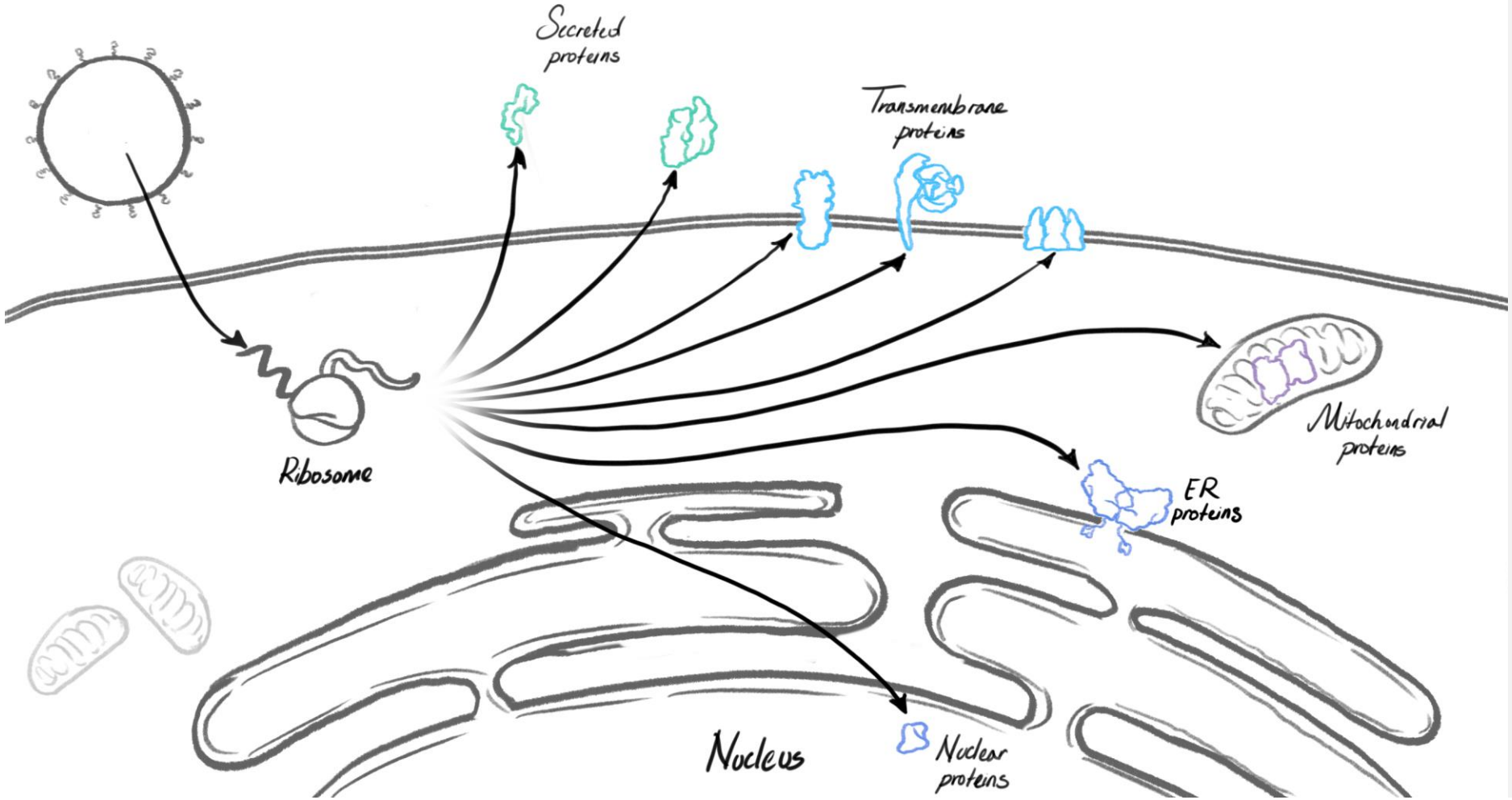
mRNA as a potential new class of medicines



1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology

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We have focused on managing risk since inception

With a focus on…

1. **Technology risk**
2. **Biology risk**
3. **Execution risk**
4. **Financing risk**

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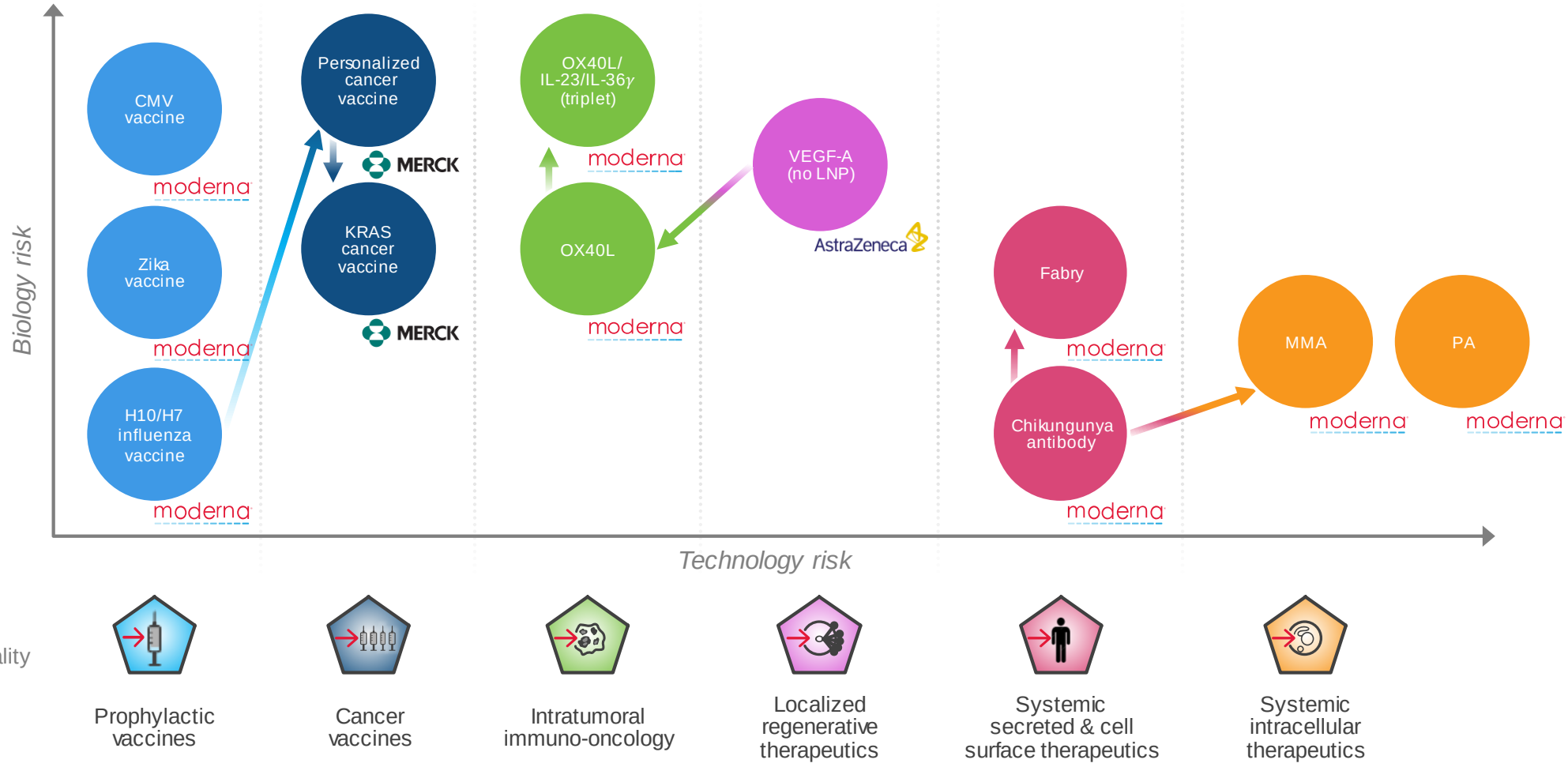
Risk management is essential to building a new class of medicines



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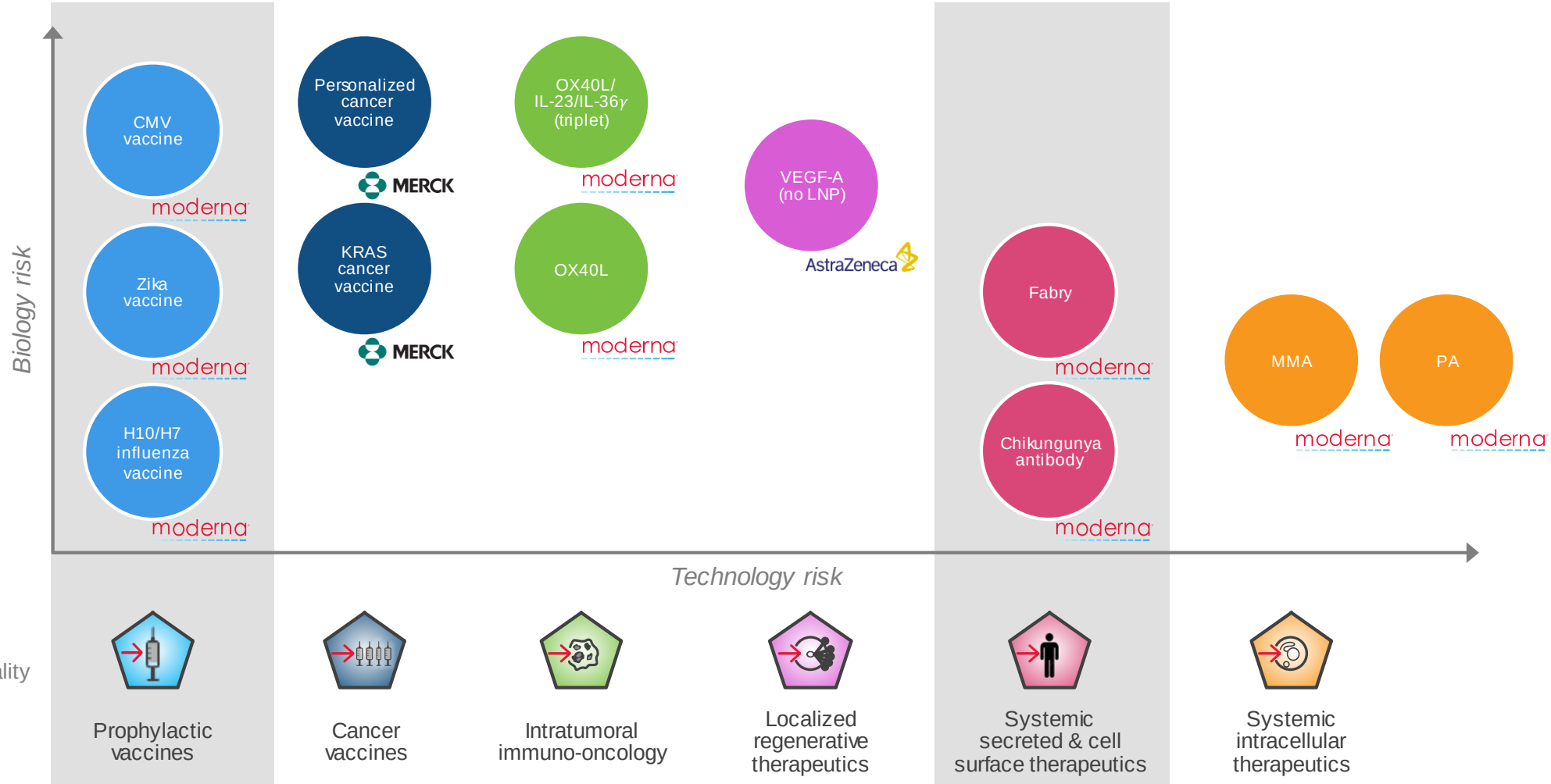
2019 was an inflection year in Moderna's history

Our modality strategy



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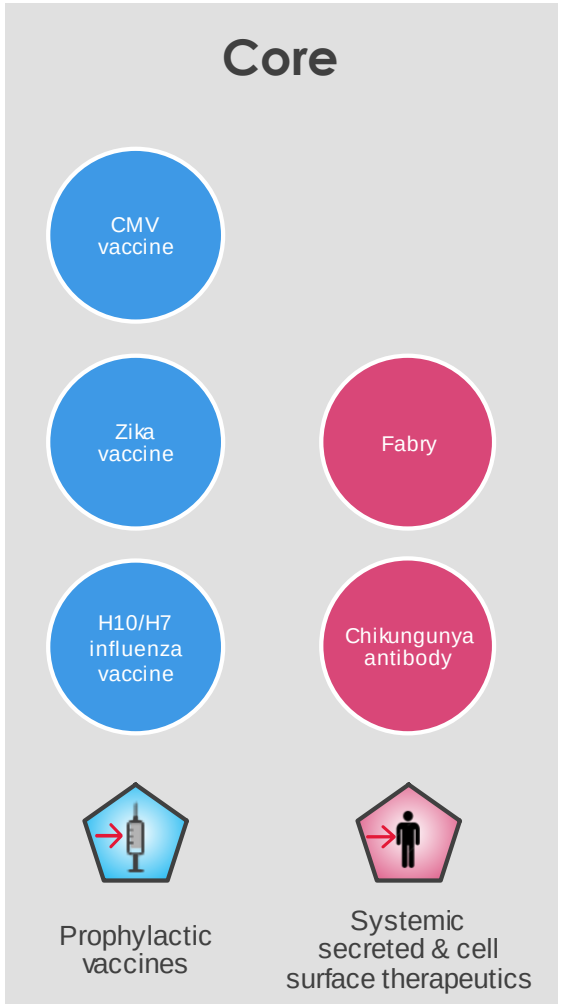

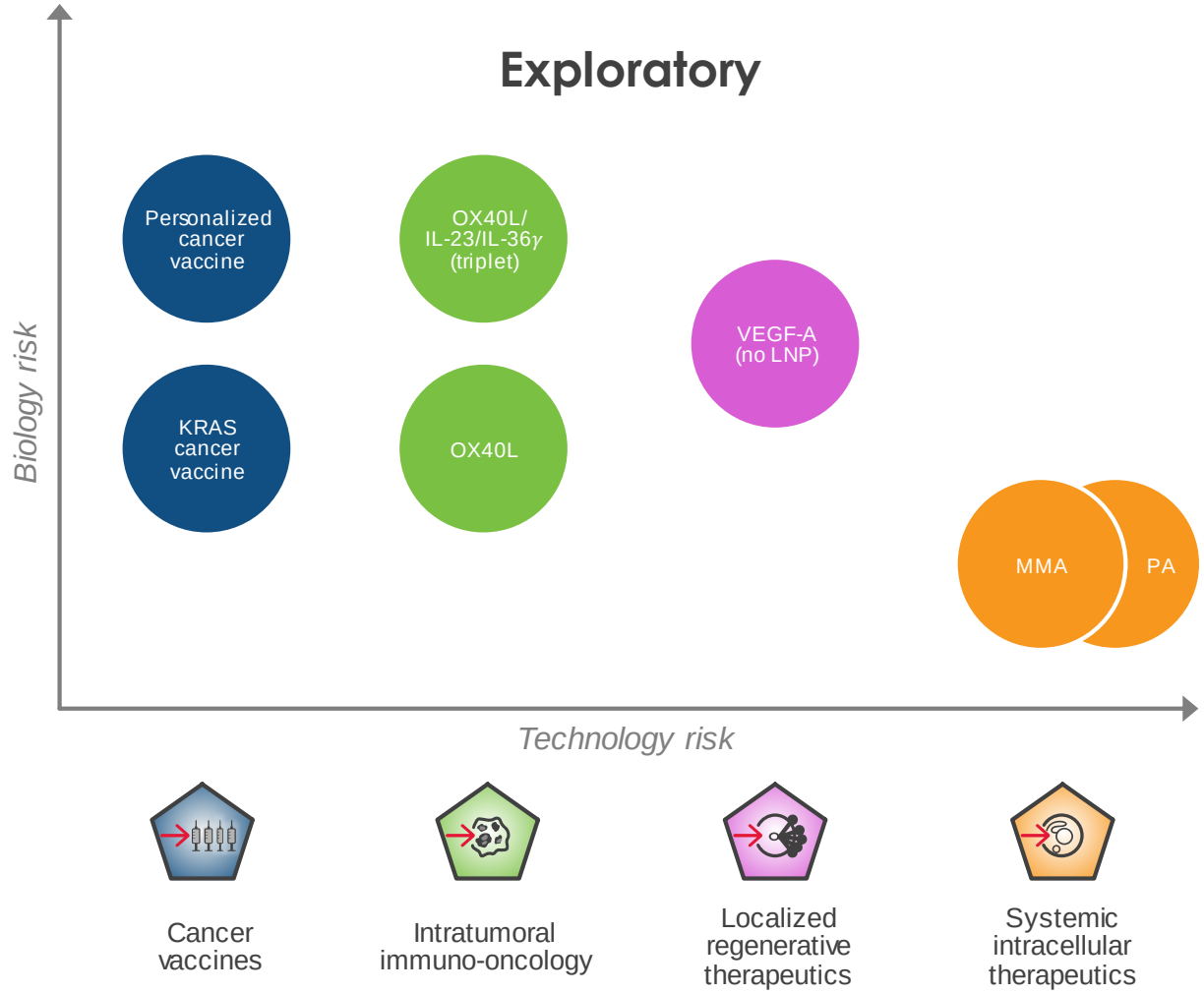

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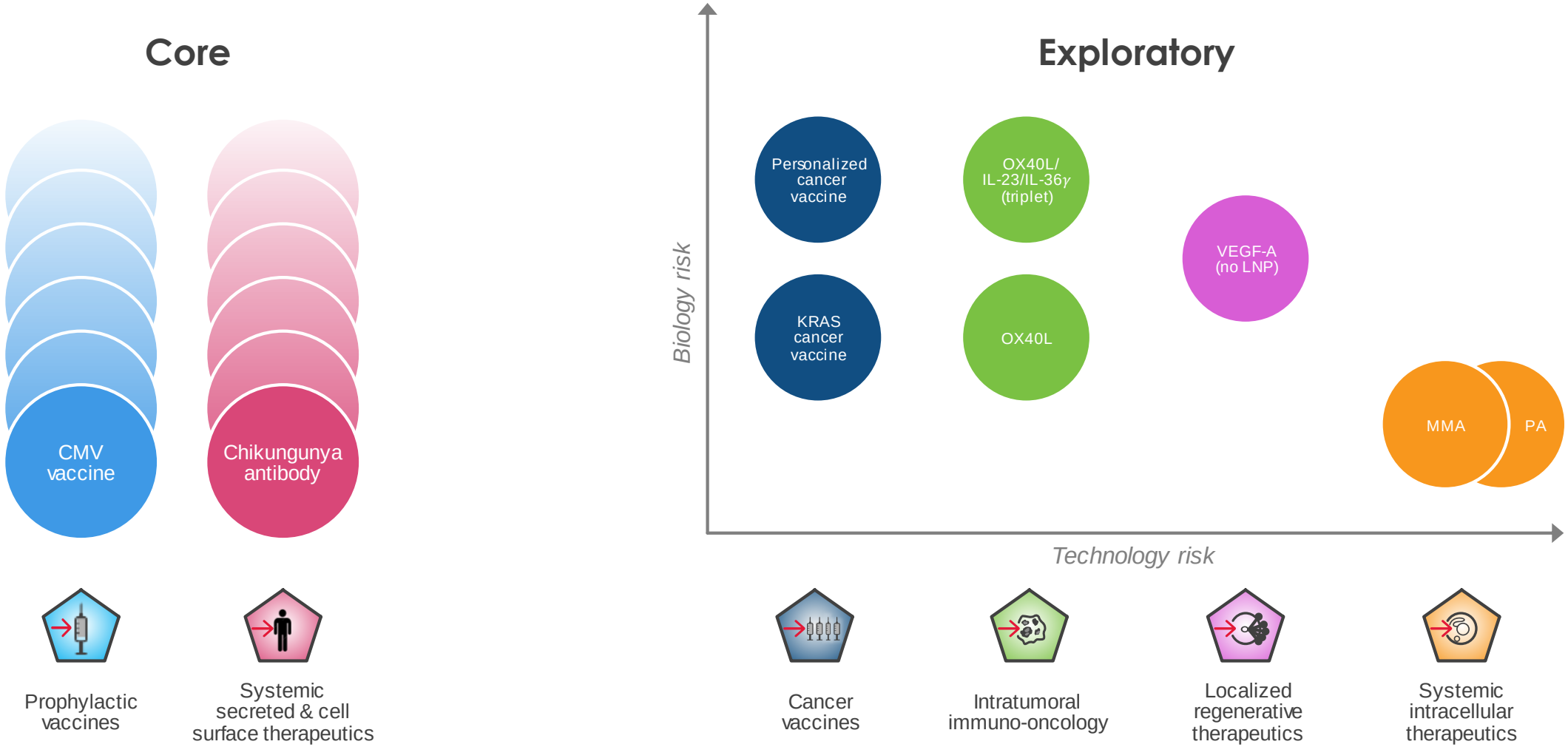
Expanding core modalities with additional development candidates



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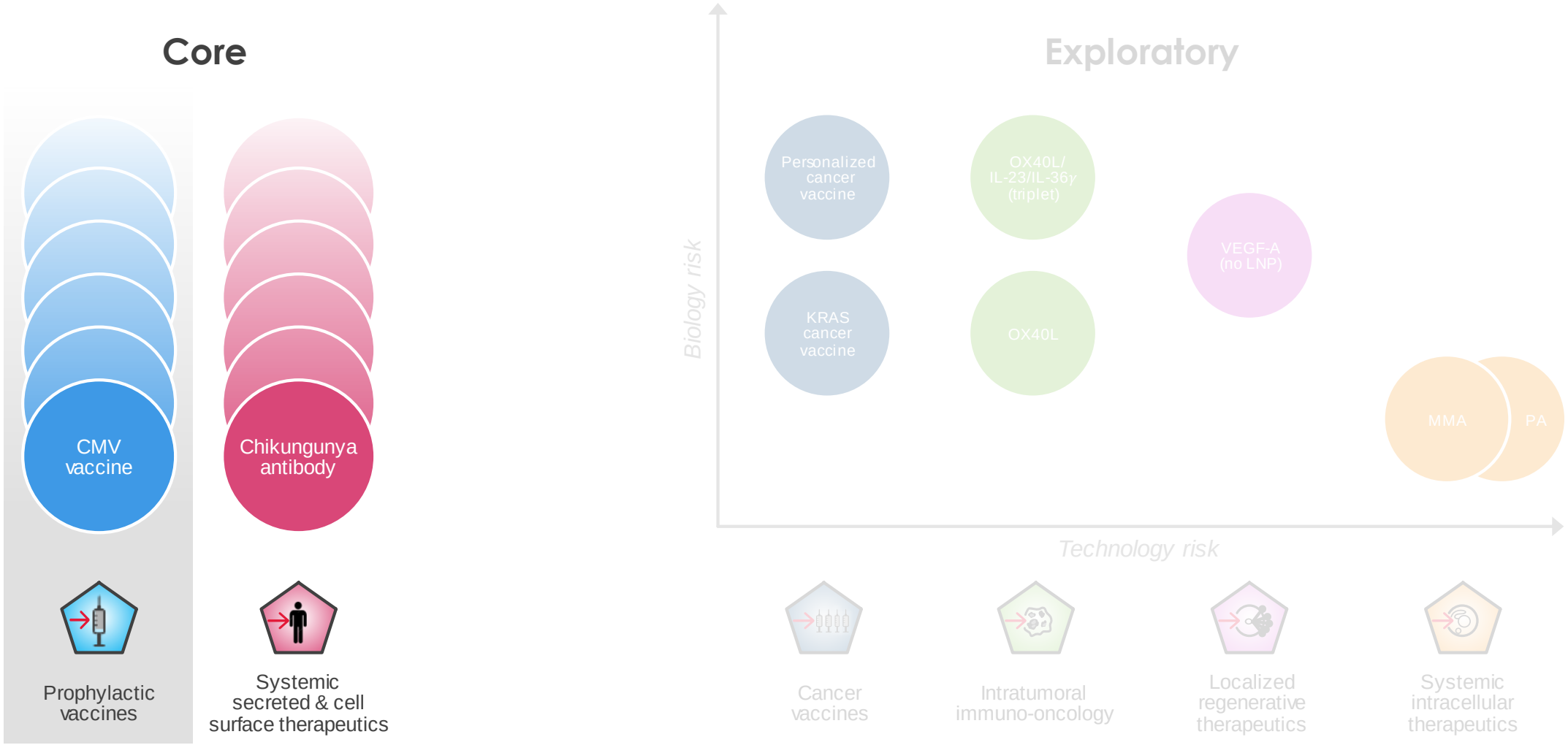
Vaccines Day

Deep dive into opportunities ahead



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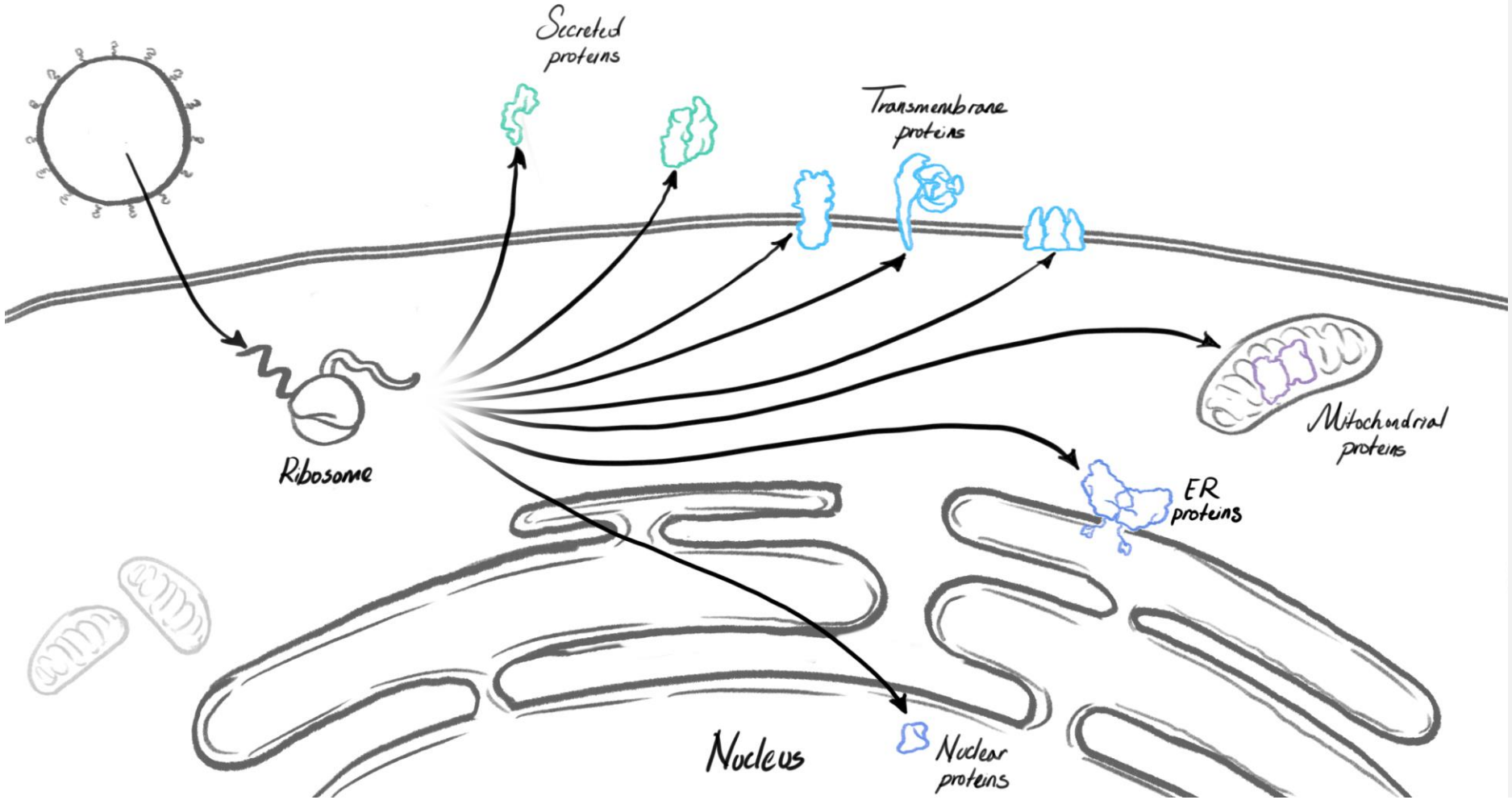
mRNA as a potential new class of vaccines



1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology

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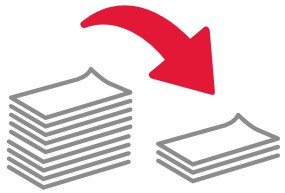
Evidence that the platform is delivering in vaccines

Large product opportunity	Higher probability of technical success	Accelerated research and development timelines	Greater capital efficiency over time (vs. recombinant)
			
Market opportunity	**Probability of success**	**Time requirements**	**Power of the platform**

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Evidence that the platform is delivering in vaccines

Large product opportunity

Market opportunity

Worldwide vaccine market was $35 billion, growing 9% a year[1]

Higher probability of technical success

Probability of success

Accelerated research and development timelines

Time requirements

Greater capital efficiency over time (vs. recombinant)

Power of the platform

1. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020)

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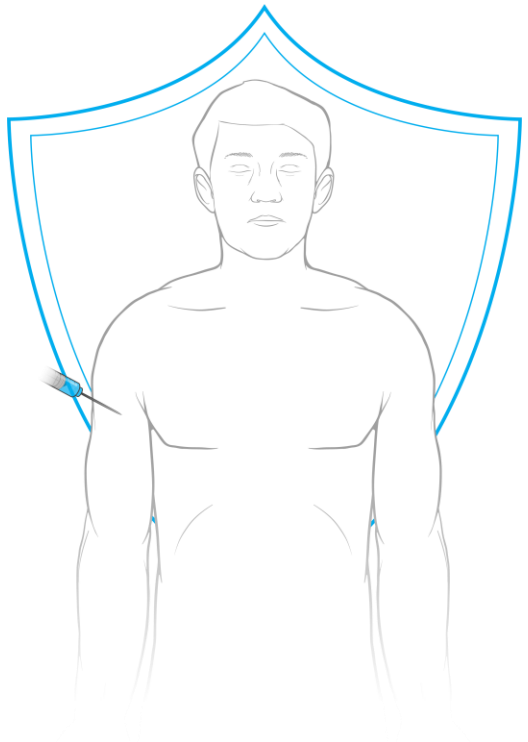
Best return on each healthcare dollar invested

CDC estimates of vaccination impact on children born between 1994-2013 (US) in the Vaccines for Children (VFC) program[1]



- $1.3 trillion saved in total societal costs
- 322 million illnesses prevented
- 732,000 deaths prevented

Every dollar invested in vaccination between 2011-2020 resulted in a return of **44 times the cost** in ninety-four low-and middle-income countries across ten antigens[2]

1. Whitney, Cynthia G, Zhou, Fangjun, Singleton, James, Schuchat, Anne. Benefits from Immunization During the Vaccines for Children Program Era – United States, 1994-2013. CDC, 2014 April.
2. Ozawa S, Clark S, Portnoy A, Grewal S, Brenzel L, Walker D.G. Return on investment from childhood immunization in low- and middle-income countries, 2011-20. Health Affairs. 2016 Feb;35(2): 199–20. Antigens include Haemophilus influenzae type b, Hepatitis B, Human papillomavirus, Japanese encephalitis, Measles, Neisseria meningitidis serogroup A, Rotavirus, Rubella, Streptococcus pneumoniae, Yellow fever

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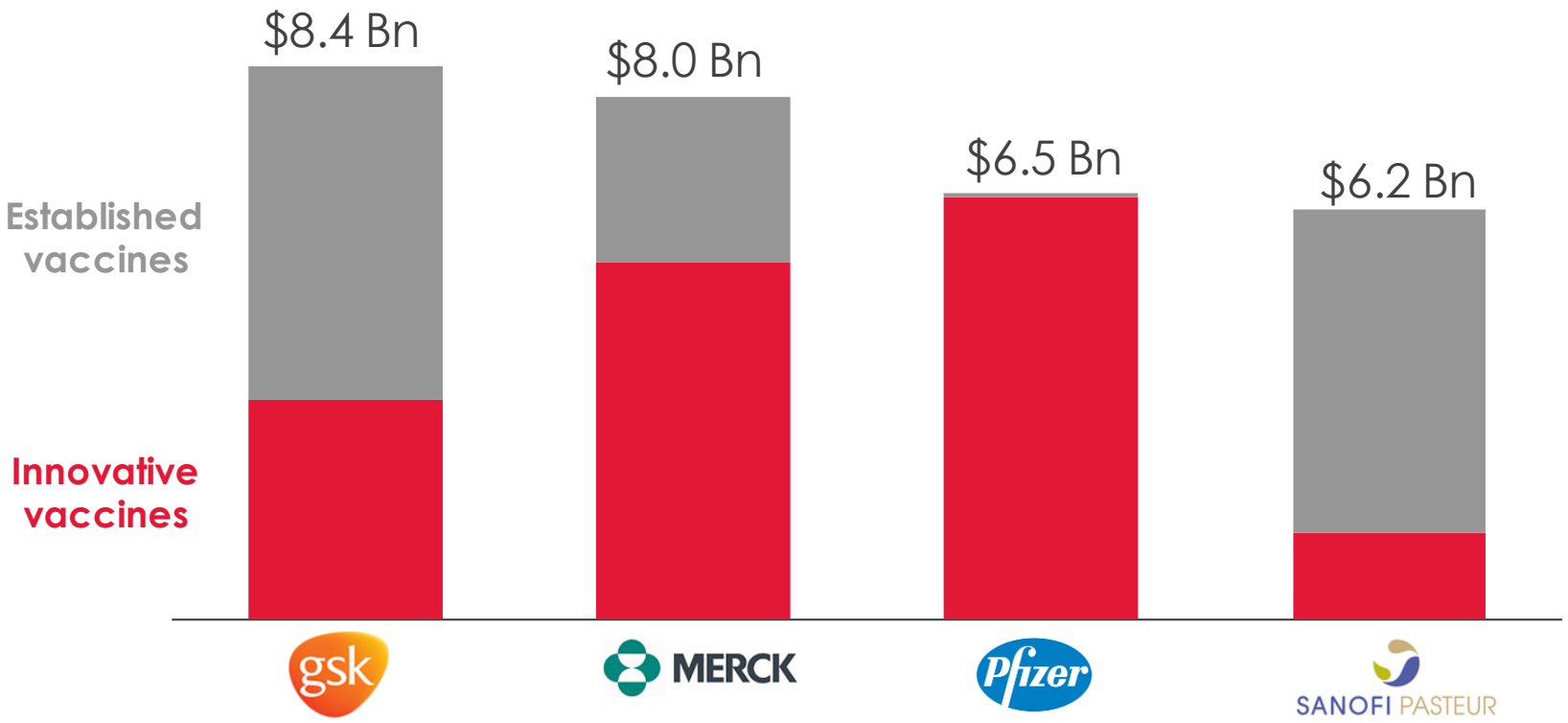
Key players in the global vaccine market

WW Vaccines Sales for Key Players[1]
(2019)



Assumes an exchange rate of 1 Pound Sterling : 1.18 USD, and 1 Euro : 1.09 USD

Accounts for **$29 billion of a $35 billion** vaccine market (>80% of WW vaccine sales)

Growing **9%** a year[2]

1. GSK Annual Report; Merck 4Q19 Financial Disclosures; Pfizer annual report; Sanofi 20-F
2. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020).

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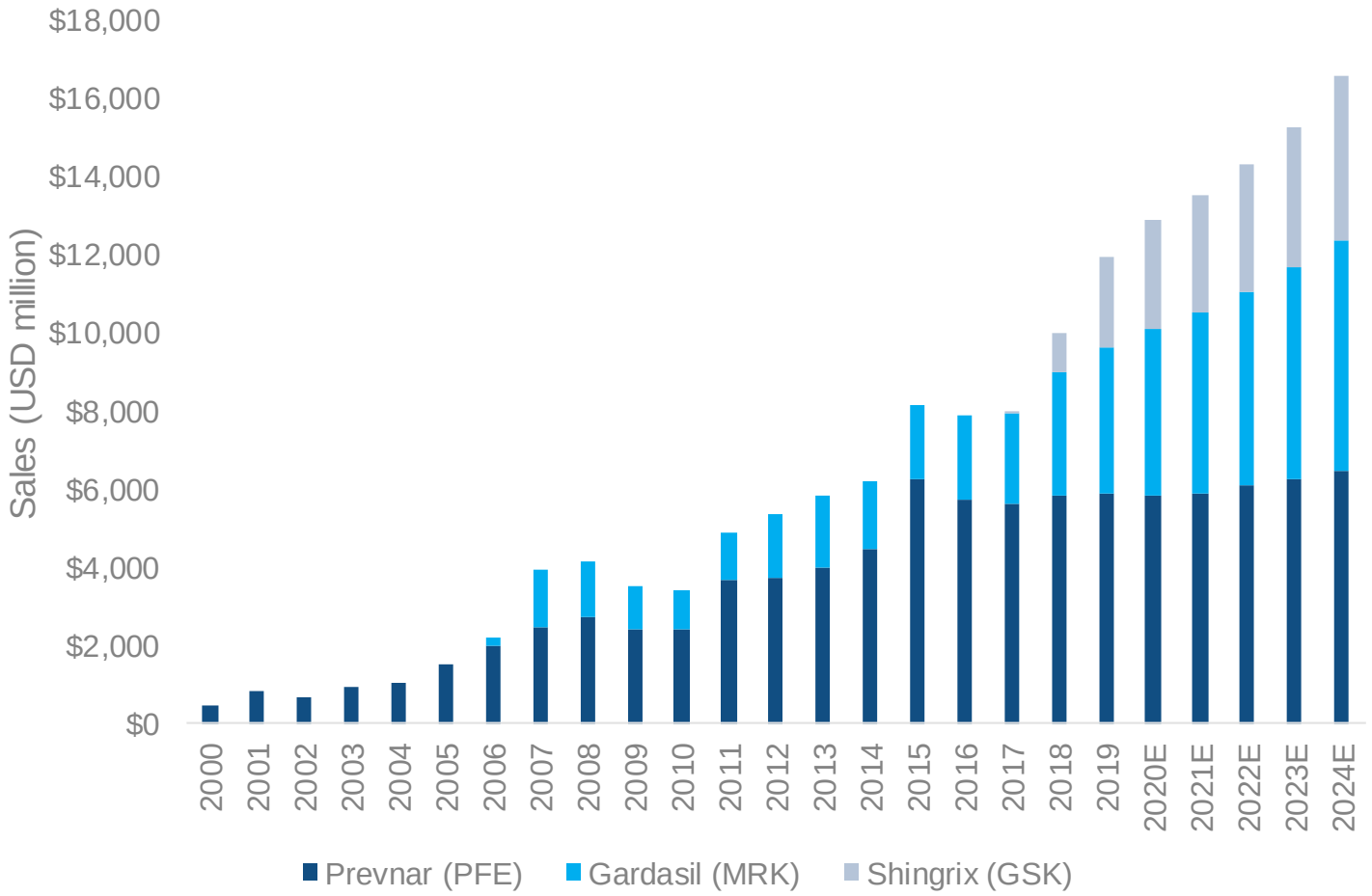
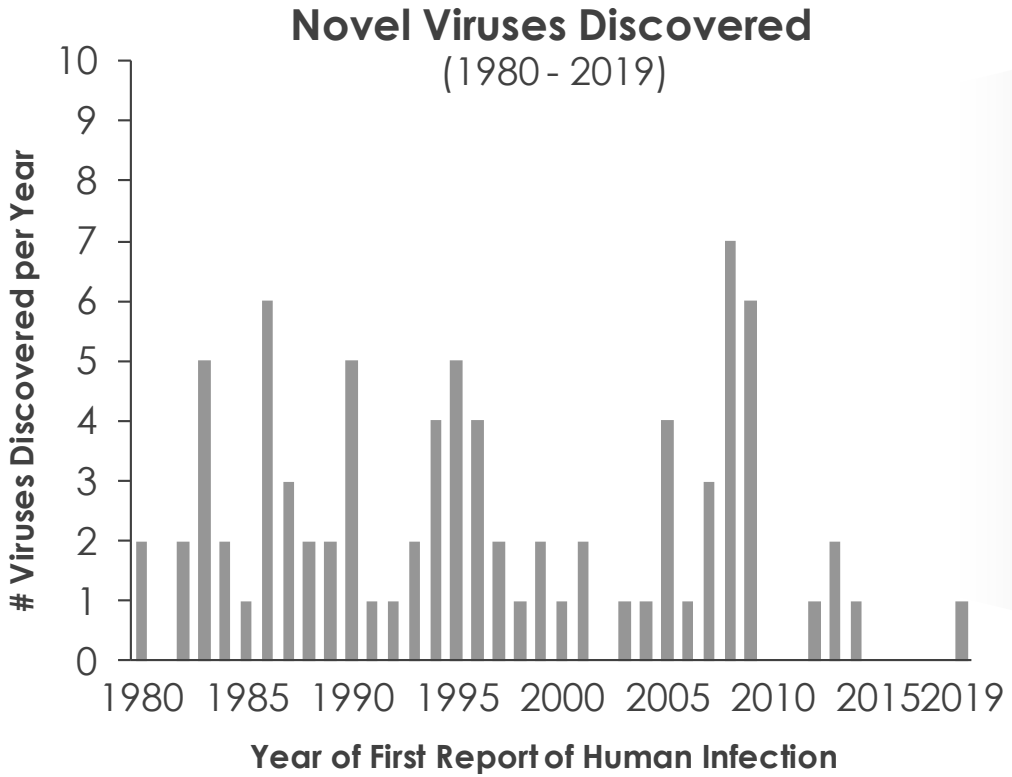
Innovative vaccines are a great opportunity



- Vaccines blockbusters by 2024 sales (examples)[1]
  - #1 product for Pfizer
  - #2 product for Merck
  - #2 product for GSK
- Strong sales ramp
- Annuity-like long tail of 25+ years sales
- Substantial pricing power due to value proposition for patients and payors (EBIT margins of ~50%)

1. EvaluatePharma estimates

More than 80 new viruses discovered since 1980



Average of **2** novel viruses discovered per year from 1980-2019

Sources: Institute of Medicine (US) Forum on Microbial Threats (2009); Medscape Medical News (2008); Lederburg, J. *Emerging Infectious Diseases from the Global to the Local Perspective: A Summary of a Workshop of the Forum on Emerging Infections* (2001); National Institutes of Health (US) Biological Sciences Curriculum Study (2007); Holshue, M. *et al NEJM* (2020); Bush, L. *Emerging...and Re-emerging Infectious Diseases* (2015); Gibbs, AJ. *Virology* (2009); CDC Zika Overview; CDC Ebola About; Platkin, S.A. *Clinical Infectious Diseases* (2006); Woolhouse, M. *et al. Phil Trans R Soc* (2012); WHO H7N9 China Update (2018); Tapparel, C. *et al. Virology* (2013); Hepatitis B Foundation. History Page; Ho, M. *Med Microbiol Immunol.* (2008); Nature. Dengue Viruses Page; Brauberger, K. *et al. Viruses* (2012); FDA approved vaccine list; CDC RSV Overview; Hendrickson, K.J. *Clinical Microbiology Reviews* (2003); Andersson, J. *Herpes* (2000); WHO Chikungunya Overview; CDC Varicella Overview; Xu, Y. *et al. Infect Genet Evol.* (2015); CDC Lassa Fever Overview;

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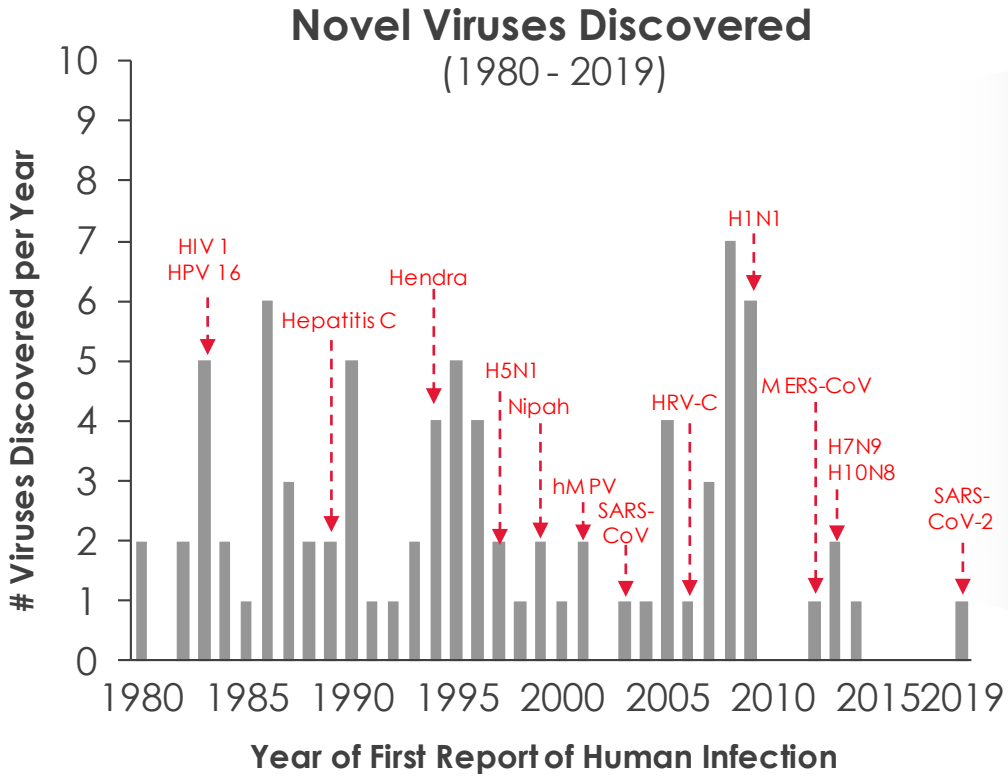

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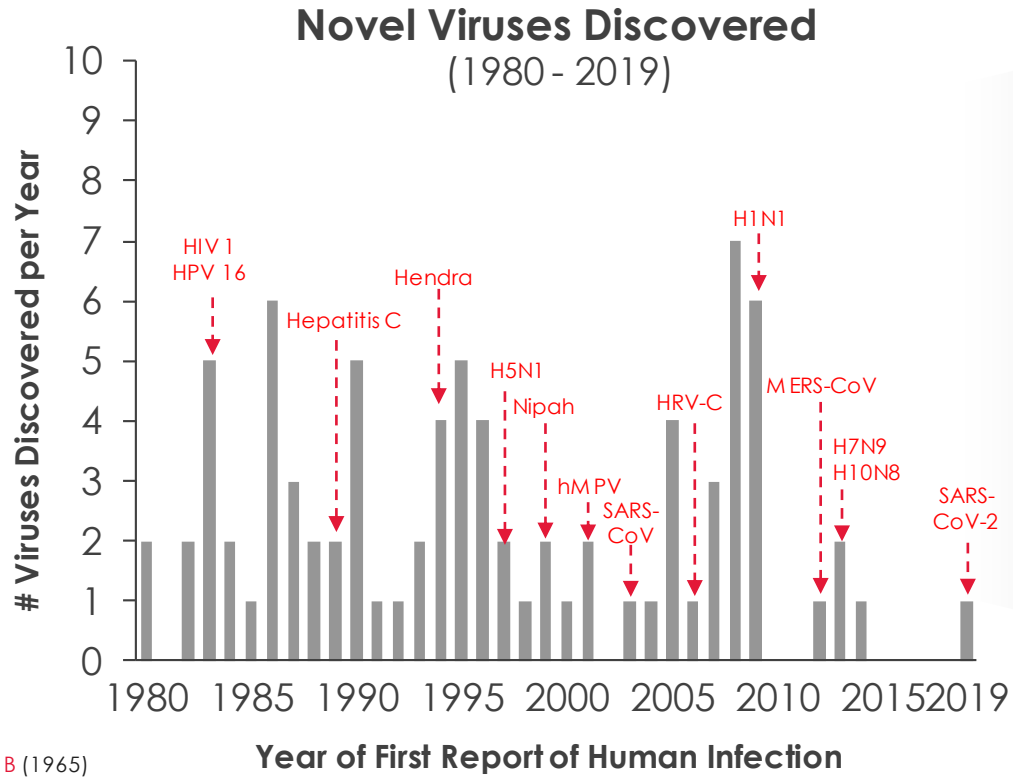

Average of **2** novel viruses discovered per year from 1980-2019

Discovered before 1980

Select viruses:

- Yellow fever (1901)
- Rubella (1941)
- Dengue (1943)
- PIV3 (1950s)
- Chikungunya (1952)
- Zika (1952)
- VZV (1954)
- RSV (1956)
- CMV (1956-1957)
- EBV (1964)
- Hepatitis B (1965)
- Marburg (1967)
- Lassa (1969)
- Ebola (1976)

Sources: Institute of Medicine (US) Forum on Microbial Threats (2009); Medscape Medical News (2008); Lederburg, J. *Emerging Infectious Diseases from the Global to the Local Perspective: A Summary of a Workshop of the Forum on Emerging Infections* (2001); National Institutes of Health (US) Biological Sciences Curriculum Study (2007); Holshue, M. *et al NEJM* (2020); Bush, L. *Emerging...and Re-emerging Infectious Diseases* (2015); Gibbs, AJ. *Virology* (2009); CDC Zika Overview; CDC Ebola About; Platkin, S.A. *Clinical Infectious Diseases* (2006); Woolhouse, M. *et al. Phil Trans R Soc* (2012); WHO H7N9 China Update (2018); Tapparel, C. *et al. Virology* (2013); Hepatitis B Foundation. History Page; Ho, M. *Med Microbiol Immunol.* (2008); Nature. Dengue Viruses Page; Brauberger, K. *et al. Viruses* (2012); FDA approved vaccine list; CDC RSV Overview; Hendrickson, K.J. *Clinical Microbiology Reviews* (2003); Andersson, J. *Herpes* (2000); WHO Chikungunya Overview; CDC Varicella Overview; Xu, Y. *et al. Infect Genet Evol.* (2015); CDC Lassa Fever Overview;

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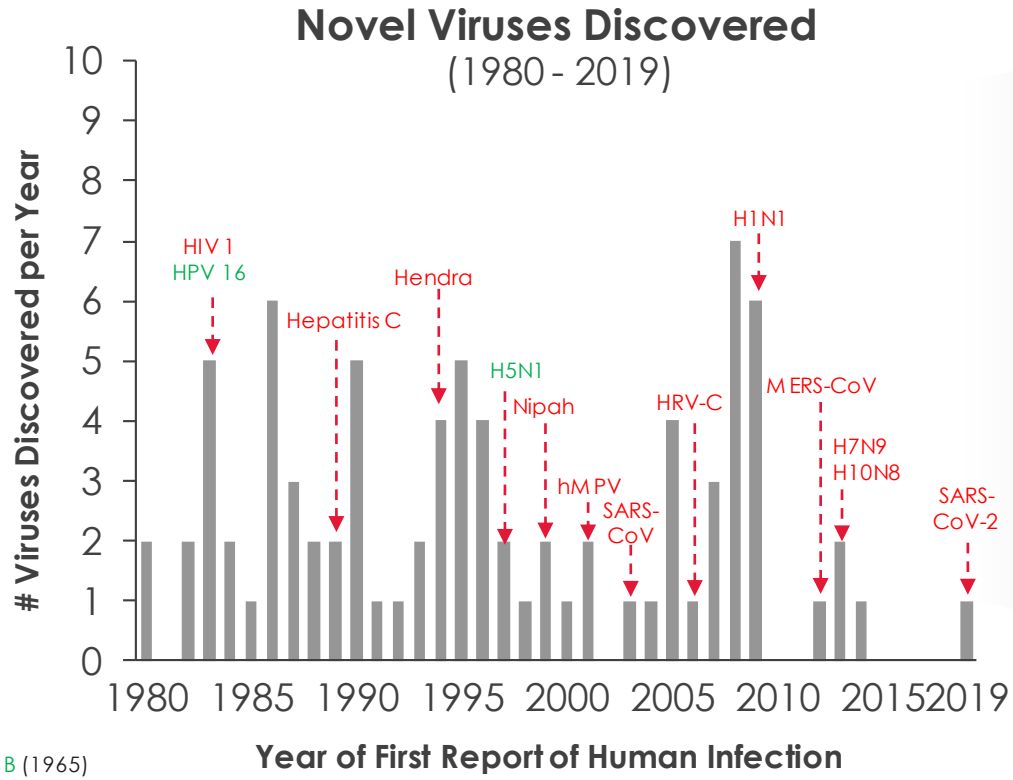

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Only **4%** have a vaccine commercially available in the US

Discovered before 1980

Select viruses:

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We believe our vaccines have a large peak sales potential

Wholly-owned vaccines

hMPV/PIV3 + RSV
hMPV/PIV3 (mRNA-1653)
Pediatric RSV (mRNA-1345)
CMV (mRNA-1647)
EBV (mRNA-1189)
Zika (mRNA-1893)
SARS-CoV-2 (mRNA-1273)

$6.5-$12 billion
peak sales potential with current portfolio of vaccine candidates[1,2]

1. All figures are estimates and subject to change
2. Does not include potential royalty revenue from mRNA-1172/mRNA-1777 targeting RSV

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Evidence that the platform is delivering in vaccines

Large product opportunity

Market opportunity

Worldwide vaccine market was $35 billion in 2019, growing 9% a year[1]

Total addressable market for Moderna's vaccine platform potentially much larger

Higher probability of technical success

Probability of success

Accelerated research and development timelines

Time requirements

Greater capital efficiency over time (vs. recombinant)

Power of the platform

1. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020)

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Evidence that the platform is delivering in vaccines

Large product opportunity	Higher probability of technical success	Accelerated research and development timelines	Lower capex and COGS (de-risking capex)
			
Market opportunity	**Probability of success**	**Time requirements**	**Power of the platform**
Worldwide vaccine market was $35 billion in 2019, growing 9% a year[1] Total addressable market for Moderna's vaccine platform potentially much larger	**Vaccines have highest overall POS to approval** **42% from Phase 2 start to approval[2]**		

1. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020)
2. Chi Heem Wong, Kien Wei Siah, Andrew W Lo, Estimation of clinical trial success rates and related parameters, *Biostatistics*, Volume 20, Issue 2, April 2019, Pages 273–286

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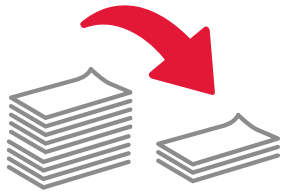
Evidence that the platform is delivering in vaccines

Large product opportunity	Higher probability of technical success	Accelerated research and development timelines	Greater capital efficiency over time (vs. recombinant)
			
Market opportunity	**Probability of success**	**Time requirements**	**Power of the platform**
Worldwide vaccine market was $35 billion in 2019, growing 9% a year[1] Total addressable market for Moderna's vaccine platform potentially much larger	Vaccines have highest overall POS to approval 42% from Phase 2 start to approval[2]	**SARS-CoV-2 vaccine (mRNA-1273)** **Sequence to Phase 1 clinical trial in 63 days**	

1. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020)
2. Chi Heem Wong, Kien Wei Siah, Andrew W Lo, Estimation of clinical trial success rates and related parameters, *Biostatistics*, Volume 20, Issue 2, April 2019, Pages 273–286

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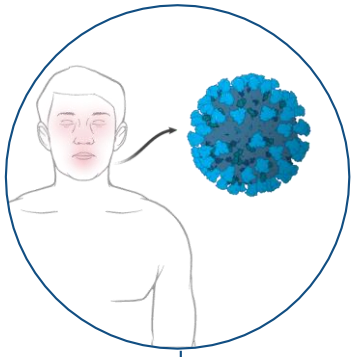
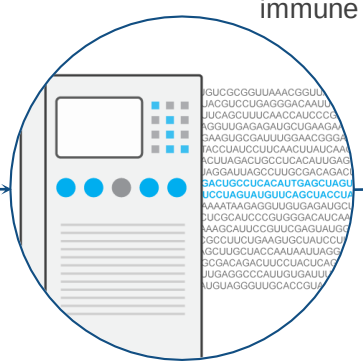
Accelerated research and development timeline

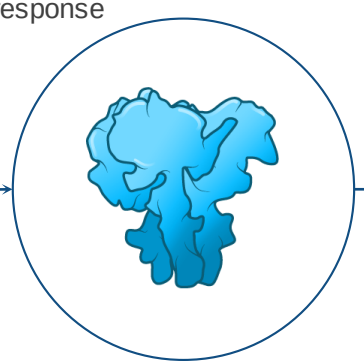
Example: SARS-CoV-2 (mRNA-1273)

Isolation/Sequencing
Viral sequence isolated from infected patient



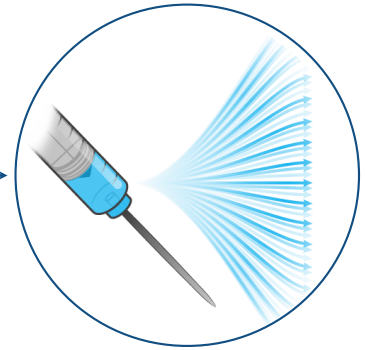
Antigen Design
Vaccine antigen designed to elicit robust immune response





Vaccine Manufacturing + Quality Testing

IND Review + Clinical Trial



2 DAYS

42 DAYS

21 DAYS

IN 63 DAYS

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Evidence that the platform is delivering in vaccines

Large product opportunity	Higher probability of technical success	Accelerated research and development timelines	Greater capital efficiency over time (vs. recombinant)
			
Market opportunity	**Probability of success**	**Time requirements**	**Power of the platform**
Worldwide vaccine market was $35 billion in 2019, growing 9% a year[1] Total addressable market for Moderna's vaccine platform potentially much larger	Vaccines have highest overall POS to approval 42% from Phase 2 start to approval[2]	SARS-CoV-2 vaccine (mRNA-1273) Sequence to Phase 1 clinical trial in 63 days	**Cell free drives lower capex (vs. recombinant proteins)** **Capex leverage across the value chain** **Ability to maximize sales at launch (flexible manufacturing to handle uncertainty in launch forecast)**

1. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020)
2. Chi Heem Wong, Kien Wei Siah, Andrew W Lo, Estimation of clinical trial success rates and related parameters, *Biostatistics*, Volume 20, Issue 2, April 2019, Pages 273–286

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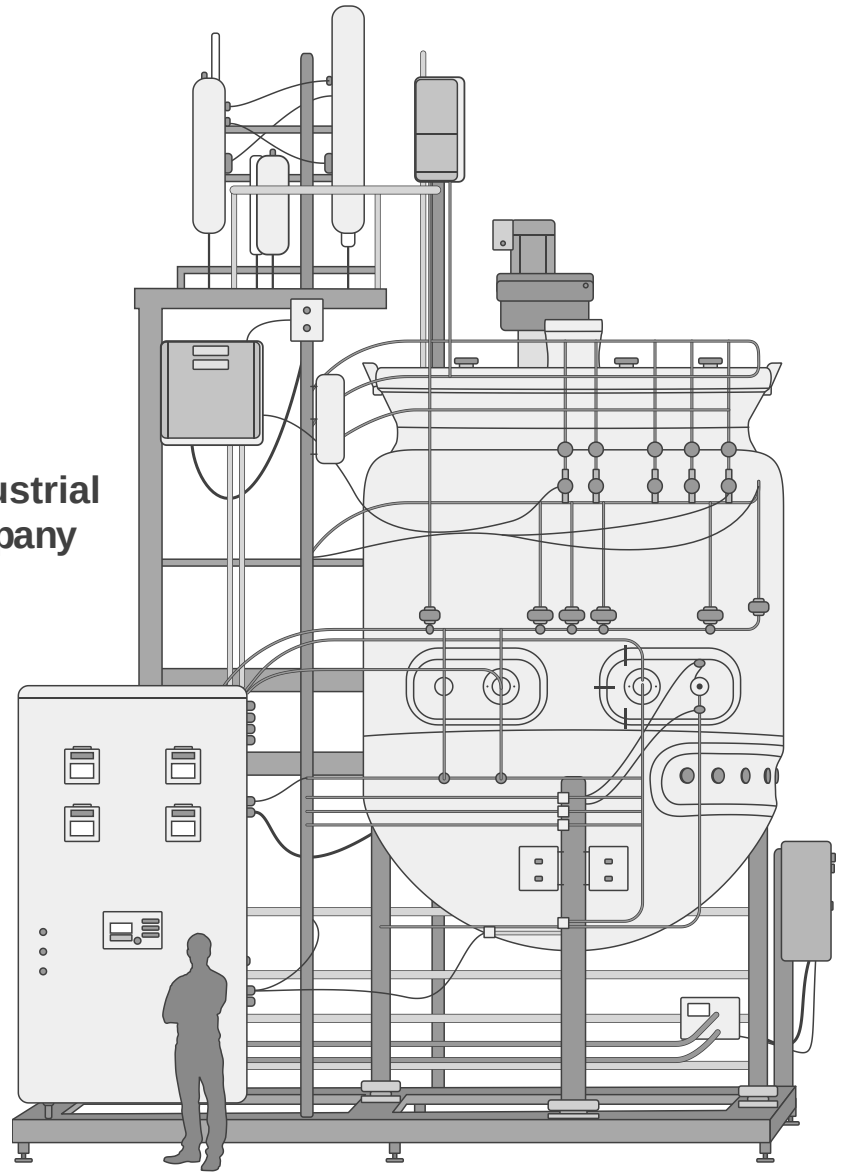
Not a traditional biotech



Standard Industrial Biotech Company

Cell free manufacturing

No dedicated plant to one product

Lower capex requirements

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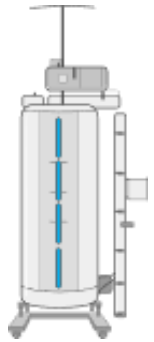
Clinical Manufacture

Commercial Manufacture



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Evidence that the platform is delivering in vaccines

Large product opportunity

Market opportunity

Worldwide vaccine market was $35 billion in 2019, growing 9% a year[1]

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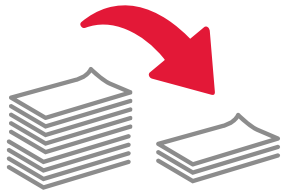

Time requirements

SARS-CoV-2 vaccine (mRNA-1273)

Sequence to Phase 1 clinical trial in 63 days

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Capex leverage across the value chain

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moderna

Andrew W. Lo, MIT Sloan School

Andrew W. Lo is the *Charles E. and Susan T. Harris Professor,* a Professor of Finance, the Director of the Laboratory for Financial Engineering at the MIT Sloan School of Management, and a Principal Investigator at the MIT Computer Science and Artificial Intelligence Laboratory.

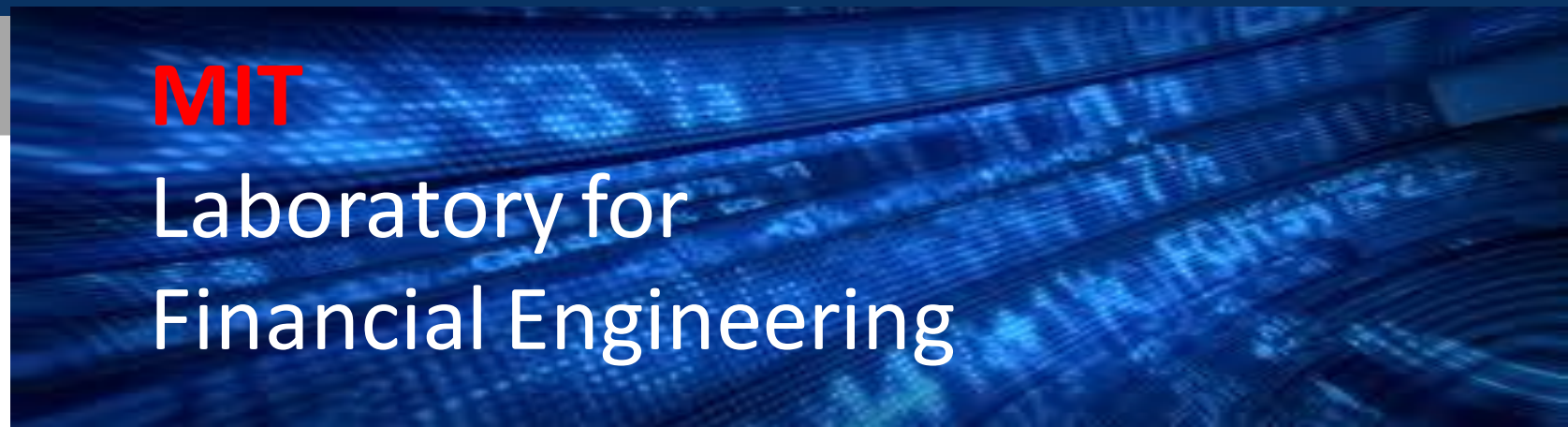
His research interests include the empirical validation and implementation of financial asset pricing models; the pricing of options and other derivative securities; financial engineering and risk management; and evolutionary and neurobiological models of individual risk preferences and financial market dynamics. His healthcare-related research interests include new financial and business models for drug and device development and healthcare delivery, statistical methods for incorporating patient preferences into the drug approval process, and predicting clinical trial outcomes via machine learning techniques. Dr. Lo received his B.A. in economics from Yale University and his A.M. and Ph.D. in economics from Harvard University.

Estimating the Probability of Success in Clinical Trials for Vaccines and Other Anti-Infectives

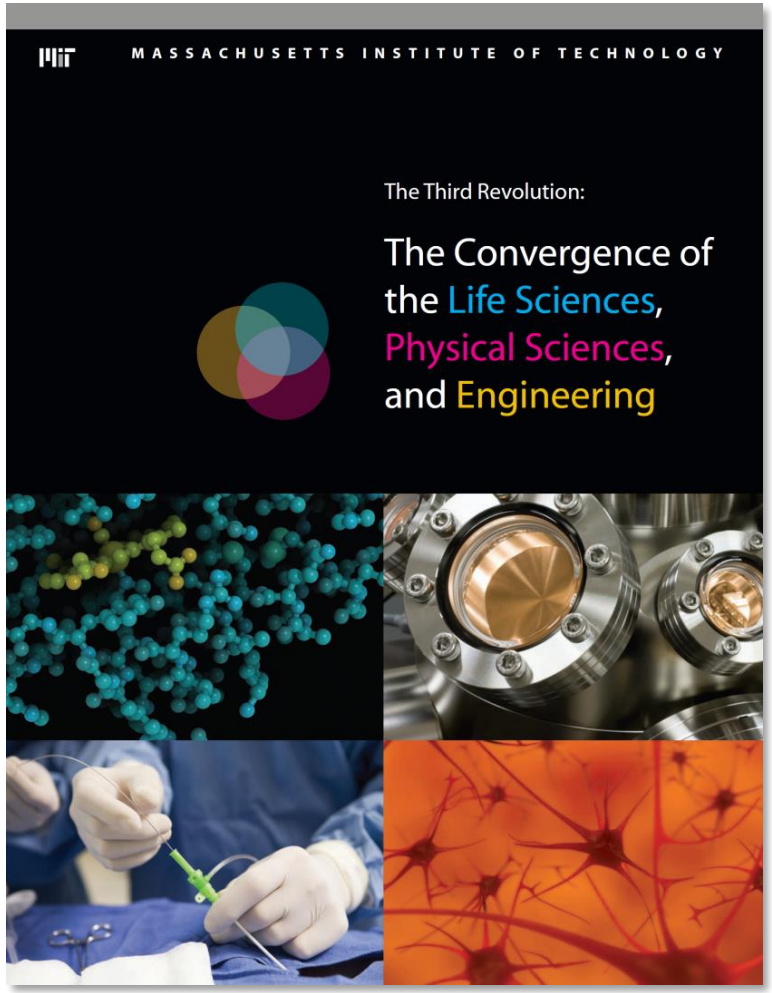
Andrew W. Lo, MIT

Moderna Therapeutics Presentation

14 April 2020



Biomedicine Is At An Inflection Point



The "omics" Revolution:

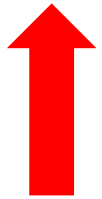
- Genomics
- Epigenomics
- Transcriptomics
- Proteomics
- Metabolomics
- Microbiomics

What About Economics??

Healthcare Finance

MIT LFE

$$\mathrm{E[NPV]} = \mathrm{PV[Revenues]} \times \mathrm{PoS} - \mathrm{Costs}$$



STATE OF THE ART

nature publishing group

Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs

JA DiMasi[1], L Feldman[1], A Seckler[1] and A Wilson[1]

This study utilizes both public and private data sources to estimate clinical phase transition and clinical approval probabilities for drugs in the development pipelines of the 50 largest pharmaceutical firms (by sales). The study examined the development histories of these investigational compounds from the time point at which they first entered clinical testing (1993–2004) through June 2009. The clinical approval success rate in the United States was 16% for self-originated drugs (originating from the pharmaceutical company itself) during both the 1993–1998 and the 1999–2004 subperiods. For all compounds (including licensed-in and licensed-out drugs in addition to self-originated drugs), the clinical approval success rate for the entire study period was 19%. The estimated clinical approval success rates and phase transition probabilities differed significantly by therapeutic class. The estimated clinical approval success rate for self-originated compounds over the entire study period was 32% for large molecules and 13% for small molecules. The estimated transition probabilities were higher for all clinical phases with respect to large molecules.

16.0%

INTRODUCTION

Numerous studies have found that the drug development process is highly expensive and that these costs have trended significantly upward for decades.[1–6] Many factors affect the cost of drug development, but two of the key basic elements are time and risk. Development times increased substantially from the 1960s through the 1980s but overall remained relatively stable during the 1990s.[7,8] Thus, development times did not directly contribute much to the rapid increase in pharmaceutical R&D costs in the past two decades. However, if clinical trials become larger and more complex, and the costs of inputs to the development process increase faster than inflation, the "time costs" associated with the investment of resources in new drug development will increase in absolute terms, even if development times remain the same. Indeed, there is evidence that the clinical trial process has become more extensive and complex in the past few decades.[4,9] The situation is similar for drug development risks. By development risk, we mean the likelihood that development of a drug will be terminated owing to efficacy, safety, or commercial concerns. High drug failure rates contribute substantially to R&D costs, whether or not these costs are otherwise increasing. Thus, the rate at which pharmaceutical firms successfully develop investigational compounds for marketing approval by regulatory agencies is an important indicator of the effectiveness of the drug development process. Successes and technological innovations that can improve the predictability of outcomes for new compounds can therefore significantly increase the productivity of new drug innovation.[10]

The historical literature focusing specifically on the quantification of drug development risks is fairly robust.[11–20] The aforementioned research on drug development costs includes estimates of drug development risks. Early research on development risks suggested that clinical approval rates for self-originated drugs in the 1960s were in the neighborhood of one in eight.[11] Subsequent studies indicated that development risks fell in the 1970s, with approval rates averaging approximately one in five; the risk levels pertaining to the 1970s remained fairly stable to the mid-1990s.[1,3,14,15]

This study provides updated clinical approval success rates and clinical phase transition analyses for the investigational compounds that entered clinical testing between the mid-1990s and the early 2000s from the 50 largest pharmaceutical firms (as determined by sales). We analyze approval success rates and phase transition rate trends within this period for new compounds as a whole and by therapeutic class. The data are also stratified by product type (large molecule vs. small molecule).

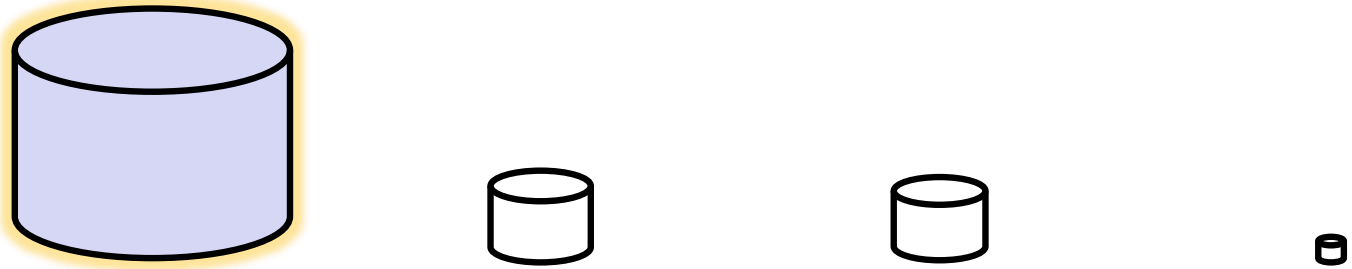
[1]Tufts Center for the Study of Drug Development, Tufts University, Boston, Massachusetts, USA. Correspondence: JA DiMasi (joseph.dimasi@tufts.edu)

Received 9 December 2009; accepted 9 December 2009; advance online publication 3 Febraury 2010. doi:10.1038/clpt.2009.295

With Big Data, We Can Do Better

MIT LFE

- Informa data



	Our study	Thomas et. al (2016)	Hay et. al (2016)	Dimasi et. al (2010)
Number of Drugs	15,102	?	5,820	1,316
Years of source data (time-span)	2000- 2015 (15 years)	2006-2015 (9 years)	2003-2011 (9 years)	1993-2009 (17 years)
Number of Companies	5,764	1,103	835	50
Phase Transitions	175,535	9,985	7,372	?
Analysis	Lead / All	Lead / All	Lead / All	Lead only
Methodology	"Path-by-path"	"Phase-by-phase"	"Phase-by-phase"	"Path-by-path"

Top 30 Drugs by World-Wide Sales

MIT LFE

2000

Rank	Marketer	Drug	Worldwide Sales ($M)	University/Hospital
1	AstraZeneca	Prilosec	6,260	
2	Merck	Zocor	5,280	
3	Pfizer	Lipitor	5,030	
4	Pfizer	Norvasc	3,361	
5	TAP Pharmaceuticals	Prevacid	2,740	
6	Johnson & Johnson	Procrit	2,709	University of Chicago
7	Pfizer; Pharmacia	Celebrex	2,614	Brigham Young University
8	Eli Lilly	Prozac	2,585	
9	Eli Lilly	Zyprexa	2,366	
10	GlaxoSmithKline	Paxil	2,349	
11	Schering Plough	Claritin	2,194	
12	Merck	Vioxx	2,160	
13	Pfizer	Zoloft	2,140	
14	Amgen	Epogen	1,963	University of Chicago
15	Wyeth	Premarin	1,870	
16	GlaxoSmithKline	Augmentin	1,847	
17	Merck	Vasotec	1,790	
18	Bristol-Myers Squibb	Pravachol	1,766	
19	Bristol-Myers Squibb	Glucophage	1,718	
20	Merck	Cozaar	1,715	
21	Johnson & Johnson	Tylenol	1,680	
22	Novo Nordisk	Novolin	1,671	
23	Bayer	Cipro; Ciprobay	1,648	
24	Johnson & Johnson	Risperdal	1,603	
25	Bristol-Myers Squibb	Taxol	1,561	Florida State University
26	Pfizer	Zithromax	1,382	
27	Schering Plough	Intron A	1,360	University of Zurich
28	Pfizer	Viagra	1,344	
29	Pfizer	Neurontin	1,334	
30	GlaxoSmithKline	Flixotide; Flovent	1,334	
		Total ($M)	**69,374**	**10,207**
		Percent of Total		**15%**

2015

Rank	Marketer	Drug	Worldwide Sales ($M)	University/Hospital
1	Abbvie; Eisai	Humira	14,359	Rockefeller University; Scripps
2	Gilead	Harvoni	13,864	University of Heidelberg; Rockefeller University
3	Amgen; Pfizer; Takeda	Enbrel	9,037	Massachusetts General Hospital; University of Texas
4	Johnson & Johnson; Merck;	Remicade	8,151	New York University
5	Pharmstandard; Roche	Rituxan	7,393	
6	Sanofi	Lantus	7,089	
7	Roche	Avastin	6,945	
8	Roche	Herceptin	6,794	University of California, Los Angeles
9	Daewoong Pharmaceutical;	Prevnar 13	6,328	
10	Celgene	Revlimid	5,801	Boston Children's Hospital
11	GlaxoSmithKline	Seretide; Advair	5,625	
12	AstraZeneca	Crestor	5,381	
13	Gilead	Sovaldi	5,276	
14	Pfizer	Lyrica	4,876	Northwestern University
15	Amgen	Neulasta	4,800	Memorial Sloan-Kettering Cancer Center
16	Novartis	Gleevec	4,658	Dana-Farber Cancer Institute; Oregon Health & Science
17	Bayer; Regeneron	Eylea	4,372	
18	Teva	Copaxone	4,029	Weizmann Institute of Science
19	Boehringer Ingelheim; Eli Lilly	Spiriva	3,942	
20	Bayer; Johnson & Johnson	Xarelto	3,930	
21	Merck	Januvia	3,870	Tufts University
22	Novartis; Roche	Lucentis	3,639	
23	Biogen	Tecfidera	3,638	
24	Gilead	Truvada	3,567	Emory University; Yale University
25	AstraZeneca	Symbicort	3,394	
26	AstraZeneca; Pfizer	Nexium	3,202	
27	Bristol-Myers Squibb; Gilead;	Atripla	3,134	Emory University; Yale University
28	Novo Nordisk	NovoRapid; NovoLog	3,082	
29	Bristol-Myers Squibb; Otsuka	Abilify	2,896	
30	Eli Lilly	Humalog	2,842	
		Total ($M)	**165,914**	**86,940**
		Percent of Total		**52%**

*Blue-shading indicates university/hospital origins.

Estimating Clinical Trials Success Rates

Biostatistics (2019) **20**, 2, *pp.* 273–286
doi:10.1093/biostatistics/kxx069
Advance Access publication on January 31, 2018

Estimation of clinical trial success rates and related parameters

CHI HEEM WONG, KIEN WEI SIAH

MIT Computer Science and Artificial Intelligence Laboratory & Department of Electrical Engineering and Computer Science, Cambridge, MA 02139, USA and MIT Sloan School of Management and Laboratory for Financial Engineering, Cambridge, MA 02142, USA

ANDREW W. LO*

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SUMMARY

Previous estimates of drug development success rates rely on relatively small samples from databases curated by the pharmaceutical industry and are subject to potential selection biases. Using a sample of 406 038 entries of clinical trial data for over 21 143 compounds from January 1, 2000 to October 31, 2015, we estimate aggregate clinical trial success rates and durations. We also compute disaggregated estimates across several trial features including disease type, clinical phase, industry or academic sponsor, biomarker presence, lead indication status, and time. In several cases, our results differ significantly in detail from widely cited statistics. For example, oncology has a 3.4% success rate in our sample vs. 5.1% in prior studies. However, after declining to 1.7% in 2012, this rate has improved to 2.5% and 8.3% in 2014 and 2015, respectively. In addition, trials that use biomarkers in patient-selection have higher overall success probabilities than trials without biomarkers.

Table 2. *The POS by therapeutic group, using data from January 1, 2000, to October 31, 2015. We computed this using the path-by-path method. SE denotes the standard error*

	All indications (industry)							
	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic group	Total paths	$POS_{1,2}$, % (SE, %)	Total paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	17 368	57.6 (0.4)	6533	32.7 (0.6)	6.7 (0.3)	1236	35.5 (1.4)	3.4 (0.2)
Metabolic/ Endocrinology	3589	76.2 (0.7)	2357	59.7 (1.0)	24.1 (0.9)	1101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2810	73.3 (0.8)	1858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4924	73.2 (0.6)	3037	51.9 (0.9)	19.5 (0.7)	1156	51.1 (1.5)	15.0 (0.6)
Autoimmune/ Inflammation	5086	69.8 (0.6)	2910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious disease	3963	70.1 (0.7)	2314	58.3 (1.0)	35.1 (1.0)	1078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (Infectious Disease)	1869	76.8 (1.0)	1235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41 040	66.4 (0.2)	21 180	58.3 (2.3)	35.1 (2.2)	7532	59.0 (0.6)	13.8 (0.2)
All without oncology	23 672	73.0 (0.3)	14 647	27.3 (0.4)	27.3 (0.4)	6296	63.6 (0.6)	20.9 (0.3)

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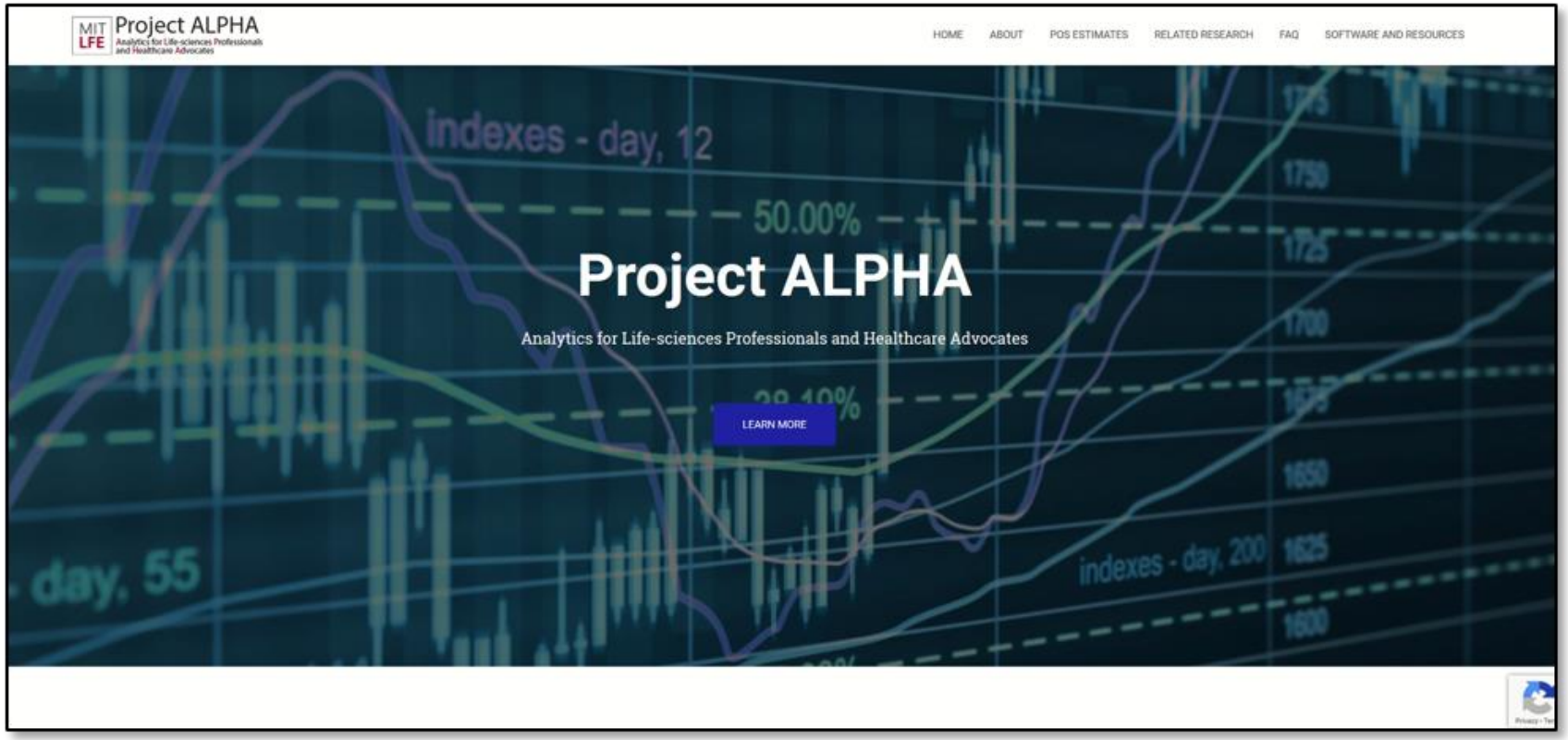
Project ALPHA

Analytics for Life Sciences Professionals and Healthcare Advocates



https://projectalpha.mit.edu/

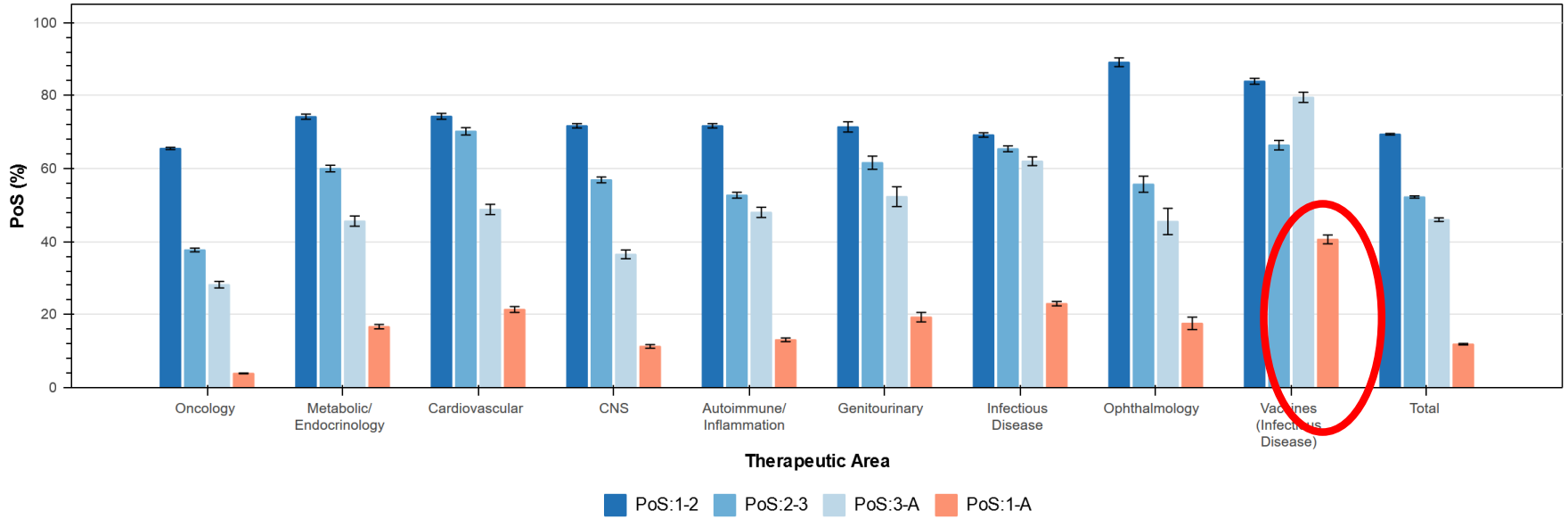
Project ALPHA

MIT LFE

Analytics for Life Sciences Professionals and Healthcare Advocates

Estimates of Clinical Trial Probabilities of Success (PoS)

Overall Estimates of PoS by Therapeutic Area – 2019Q4 Update



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Current Research

MIT LFE

Estimating Probabilities of Success of Clinical Trials for Vaccines and Other Anti-Infective Therapeutics[1]

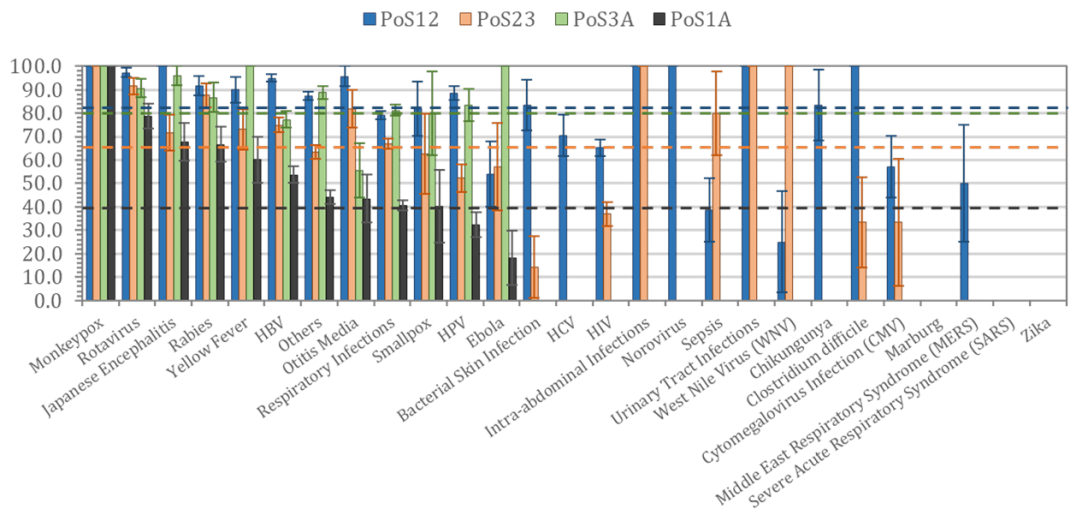
Chi Heem Wong[2], Kien Wei Siah[2], Andrew W. Lo[2,3]*

This Version: April 8, 2020

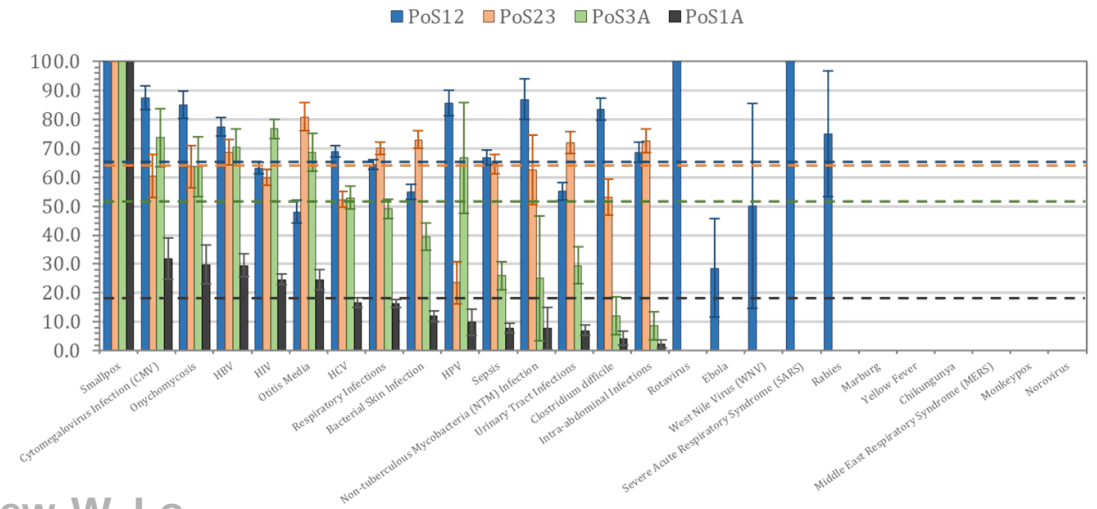
Abstract

A key driver in biopharmaceutical investment decisions is the probability of success of a drug development program. We estimate the probabilities of success (PoS) of clinical trials for vaccines and other anti-infective therapeutics using 43,414 unique triplets of clinical trial, drug, and disease between January 1, 2000, and January 7, 2020, yielding 2,544 vaccine programs and 6,829 non-vaccine programs targeting infectious diseases. The overall estimated PoS for an industry-sponsored vaccine program is 39.6%, and 16.3% for an industry-sponsored anti-infective therapeutic. Among industry-sponsored vaccines programs, only 12 out of 27 disease categories have seen at least one approval, with the most successful being against monkeypox (100%), rotavirus (78.7%), and Japanese encephalitis (67.6%). The three infectious diseases with the highest PoS for industry-sponsored non-vaccine therapeutics are smallpox (100%), CMV (31.8%), and onychomycosis (29.8%). Non-industry-sponsored vaccine and non-vaccine development programs have lower overall PoSs: 6.8% and 8.2%, respectively. Viruses involved in recent outbreaks—MERS, SARS, Ebola, Zika—have had a combined total of only 45 non-vaccine development programs initiated over the past two decades, and no approved therapy to date (Note: our data was obtained just before the COVID-19 outbreak and do not contain information about the programs targeting this disease.) These estimates offer guidance both to biopharma investors as well as to policymakers seeking to identify areas most likely to be undeserved by private-sector engagement and in need of public-sector support.

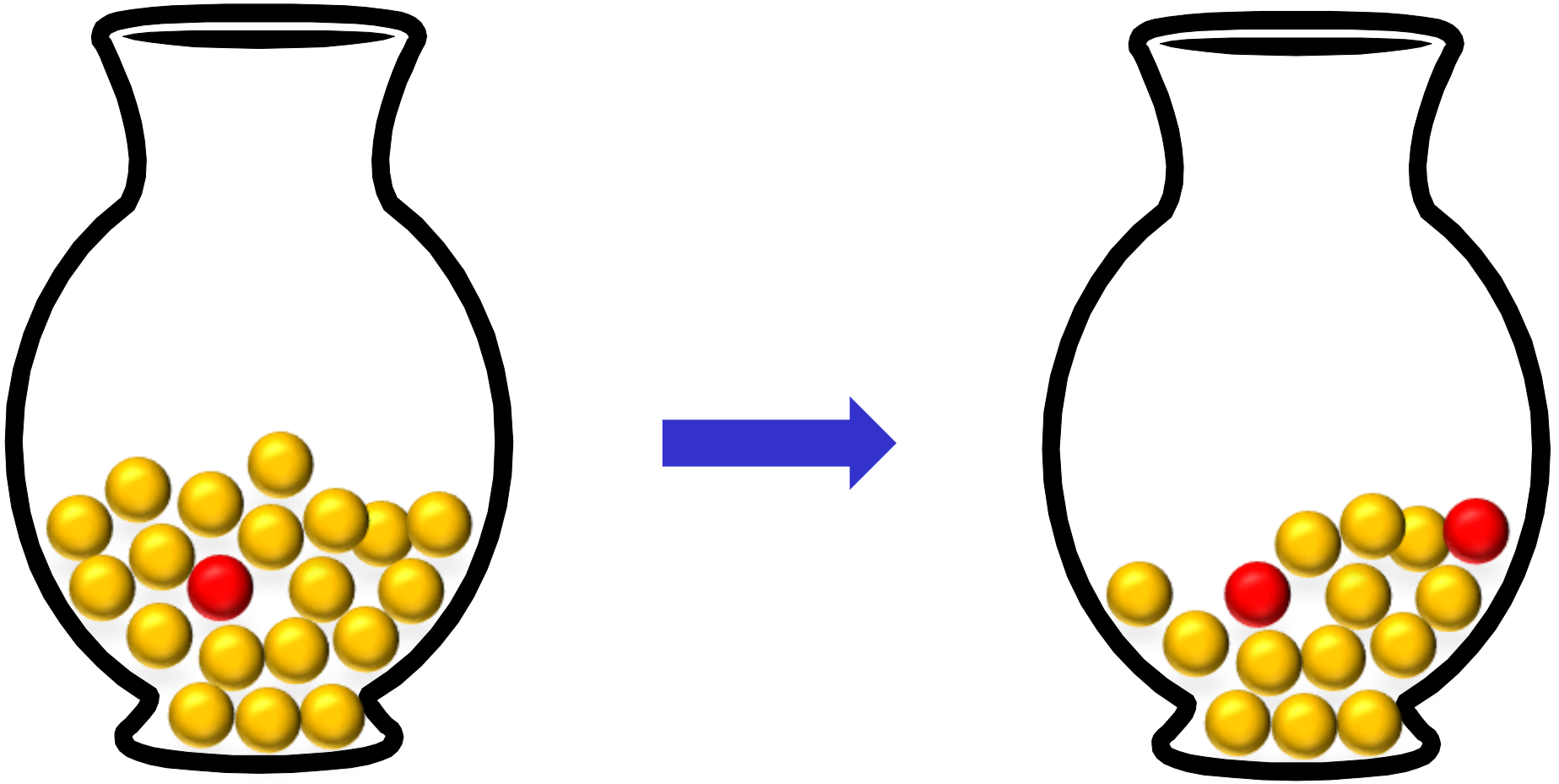
Vaccines



Non-Vaccine Anti-Infectives



More Ambitious Goal



With Machine Learning, We Can Do Better

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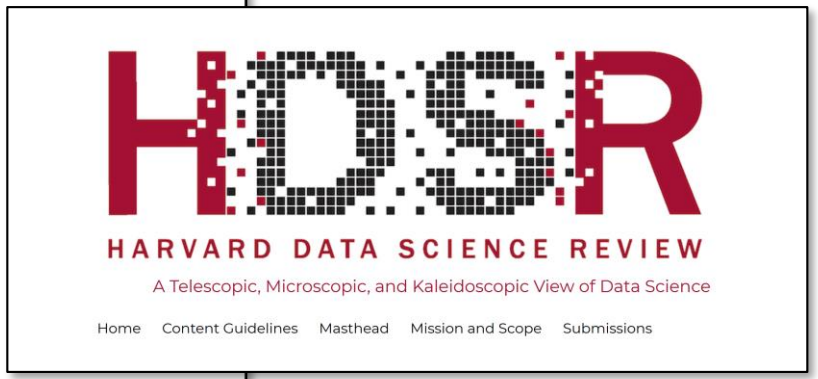
Andrew W. Lo, Kien Wei Siah, and Chi Heem Wong

Machine Learning with Statistical Imputation for Predicting Drug Approvals



We apply machine-learning techniques to predict drug approvals using drug-development and clinical-trial data from 2003 to 2015 involving several thousand drug-indication pairs with over 140 features across 15 disease groups. To deal with missing data, we use imputation methods that allow us to fully exploit the entire dataset, the largest of its kind. We show that our approach outperforms complete-case analysis, which typically yields biased inferences. We achieve predictive measures of 0.78, and 0.81 AUC ("area under the receiver operating characteristic curve," the estimated probability that a classifier will rank a positive outcome higher than a negative outcome) for predicting transitions from phase 2 to approval and phase 3 to approval, respectively. Using five-year rolling windows, we document an increasing trend in the predictive power of these models, a consequence of improving data quality and quantity. The most important features for predicting success are trial outcomes, trial status, trial accrual rates, duration, prior approval for another indication, and sponsor track records. We provide estimates of the probability of success for all drugs in the current pipeline.

Top and Bottom 10 Forecasts

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Machine Learning Forecasts of Vaccines and Anti-Infectives $PoS_{2,A}$, January 2020

					Route			Origin				Medium				Target Family		Parent Pharm	
Drug	Indication	Group	Type	ML Prediction	oral	injectable	inhaled	biological, virus particles	biological, protein, recombinant	biological, nucleic acid, viral vector	chemical, synthetic	capsule, hard	tablet	suspension	solution	enzyme	receptor	immunostimulant	viral replication inhibitor
seasonal influenza nanoparticle vaccine	infection, influenza virus prophylaxis	respiratory infections	vaccine	0.99	0	1	0	1	0	0	0							1	0
omadacycline	infection, urinary tract, uncomplicated	urinary tract infections	treatment	0.75	1	1	0	0	0	0	0	0	1	0	1			0	0
rsv vaccine	infection, respiratory syncytial virus prophylaxis	respiratory infections	vaccine	0.71	0	1	1	0	1	0	0	0	0	1	0			1	0
pneumococcal conjugate vaccine	infection, pneumococcal prophylaxis	respiratory infections	vaccine	0.69	0	1	0	0	0	0	0							1	0
hbv mabs	infection, hepatitis-b virus	HBV	treatment	0.68	0	1	0	0	0	0	0					1	0	1	0
ep-023938	infection, respiratory syncytial virus	respiratory infections	treatment	0.66	1	0	0	0	0	0	1	0	1	1	0				
ub-421	infection, hiv/aids	HIV	treatment	0.61	0	1	0	0	0	0	0					0	1	0	0
cabotegravir	infection, hiv/aids	HIV	treatment	0.59	1	1	0	0	0	0	1	1	1	1	1	1	0	0	1
rsv vaccine	infection, respiratory syncytial virus prophylaxis	respiratory infections	vaccine	0.56	0	1	0	0	1	0	0							1	0
syn-023	infection, rabies prophylaxis	rabies	vaccine	0.56	0	1	0	0	0	0	0							1	0
⋮	⋮	⋮	⋮	⋮				⋮							⋮				
terbinafine hydrochloride	infection, onychomycosis	onychomycosis	treatment	0.03	0	0	0	0	0	0	1					1	0	0	0
vtp-100	infection, influenza virus prophylaxis	respiratory infections	vaccine	0.03	0	1	0	1	0	0	0							1	0
ziresovir	infection, respiratory syncytial virus	respiratory infections	treatment	0.03	1	0	0	0	0	0	1	1	0	0	0			0	0
lys-228	infection, urinary tract, complicated	urinary tract infections	treatment	0.03	0	1	0	0	0	0	1								
vorinostat	infection, hiv/aids	HIV	treatment	0.03	1	1	0	0	0	0	1	0	0	0	0	1	0	0	0
bivalent subtype c gp120/as01b	infection, hiv prophylaxis	HIV	vaccine	0.02	0	1	0	0	0	0	0							1	0
ad26.mos4.hiv	infection, hiv prophylaxis	HIV	vaccine	0.02	0	1	0	0	0	1	0							1	0
dapivirine	infection, hiv/aids	HIV	treatment	0.02	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0
hiv vaccine	infection, hiv prophylaxis	HIV	vaccine	0.02	0	1	0	0	0	0	0							1	0
lys-228	infection, intra-abdominal, complicated	intra-abdominal infections	treatment	0.02	0	1	0	0	0	0	1								

Next Steps

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Imagine If We Had:

- Detailed chemical, biological properties
- PubMed citations, electronic medical records
- New business and pricing models
- Better and faster ways of making vaccines
- Government engagement and will

Conclusion

Don’t Just Declare War On COVID-19…

Conclusion

Don’t Just Declare War On COVID-19…

Also Put A Price Tag On Its Head!

Conclusion

Don't Just Declare War On COVID-19…

Also Put A Price Tag On Its Head!

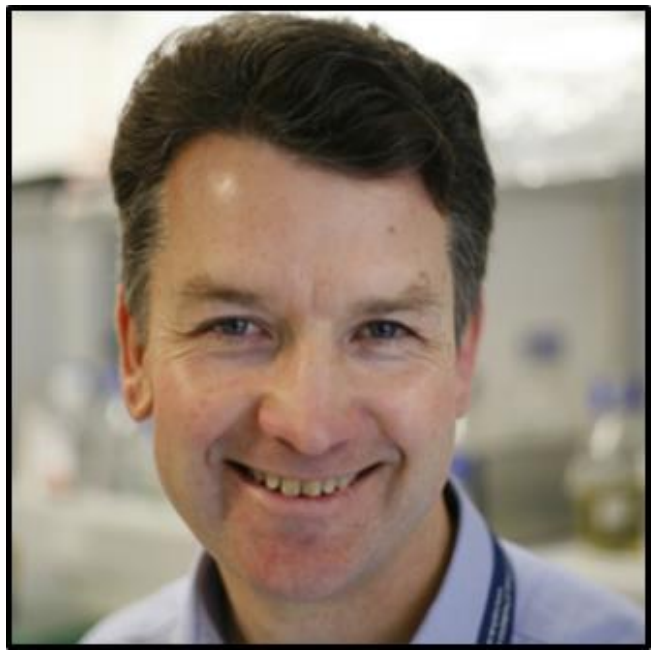
Using Data Science, We Can Do Well By Doing Good

- Finance doesn't always have to be a zero-sum game

Thank You!

Professor Paul Heath

Professor of Paediatric Infectious Diseases, St George's University of London & St George's University Hospitals NHS Trust, London



Paul Heath is a Professor and Honorary Consultant in Paediatric Infectious Diseases at St George's University Hospitals NHS Foundation Trust and St George's, University of London, where he co-leads the Paediatric Infectious Diseases Research Group and is the Director of the Vaccine Institute. His training in paediatrics and infectious diseases was at the Royal Children's Hospital, Melbourne, Australia, the John Radcliffe Hospital, Oxford and St George's Hospital, London.

His particular research interests are in the epidemiology of vaccine preventable diseases, in clinical vaccine trials, particularly in at-risk groups and in perinatal infections, and he has over 240 publications in these areas. He coordinates a European neonatal infection surveillance network (neonIN: https://www.neonin.org.uk) and the UK Paediatric Vaccine Group (UKPVG), and other recent work includes national surveillance on neonatal meningitis, neonatal GBS and Listeria infections, maternal immunisation trials and studies of different vaccine schedules in preterm infants.

He sits on national UK committees concerned with meningitis, Group B streptococcus prevention and immunisation policies in children. He was a member of the Global Alignment of Immunisation safety Assessment in pregnancy (GAIA) Executive Committee, is Chair of the Research Committee of the European Society of Paediatric Infectious Diseases, Associate Chief Editor of the Pediatric Infectious Diseases Journal, a member of the WHO WHO GBS Surveillance Technical Working Group and Clinical Lead for Children's research for the South London Clinical Research Network.

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Vaccines Day

Tuesday, April 14, 2020

Immunisation: an overview

Paul T. Heath

Professor of Paediatric Infectious Diseases

Vaccine Institute,

St George's, University of London

The importance of immunisation

immunisation vs. vaccination

- Over 100 million children are vaccinated every year before their first birthday
- Vaccination saves up to 3 million children each year
- Almost 20% of the children born each year do not complete routine vaccines scheduled in their first year of life (UNICEF)
- 1.5 million children are still dying every year from diseases that could have been prevented by vaccinations **One child every 20 seconds**

Key components of the immune system

- NON-ANTIGEN SPECIFIC
- ANTIGEN SPECIFIC

NON-ANTIGEN SPECIFIC

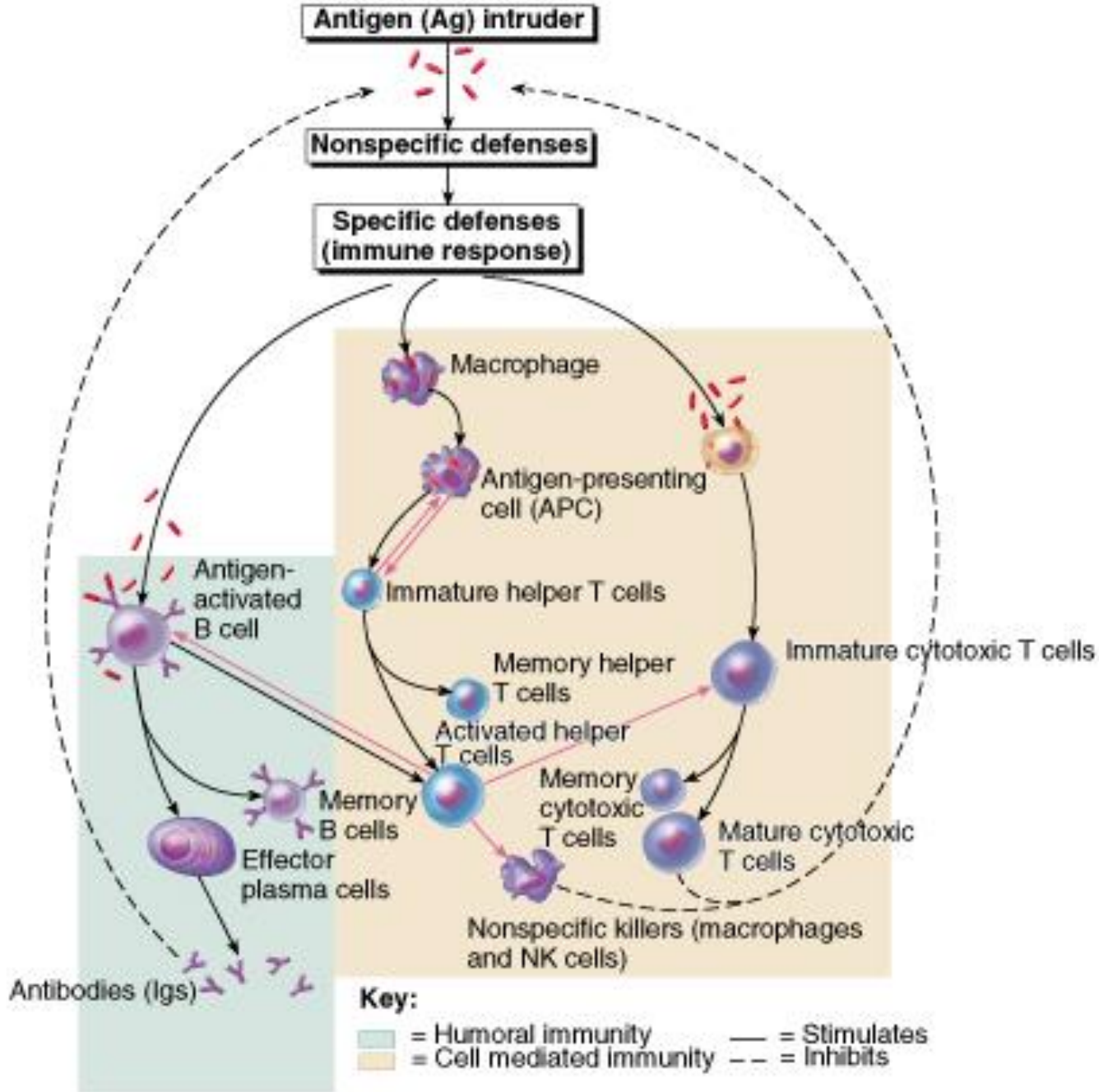
- Less sophisticated, more primitive components
  - Barriers: skin and mucosal surfaces
  - Cellular component: neutrophils, monocytes and macrophages
  - Soluble components: complement, cytokines

No memory persists afterwards

ANTIGEN-SPECIFIC

- More sophisticated
- Immune mechanisms are distinguished by ability to respond to **SPECIFIC antigens** so as to potentiate the immune response - are then committed to **immune MEMORY** resulting in more rapid and enhanced responses on subsequent exposure to antigen
  - T lymphocytes (cellular responses)
  - B lymphocytes (antibody responses)

usually acquired from exposure to natural infection or to a vaccine

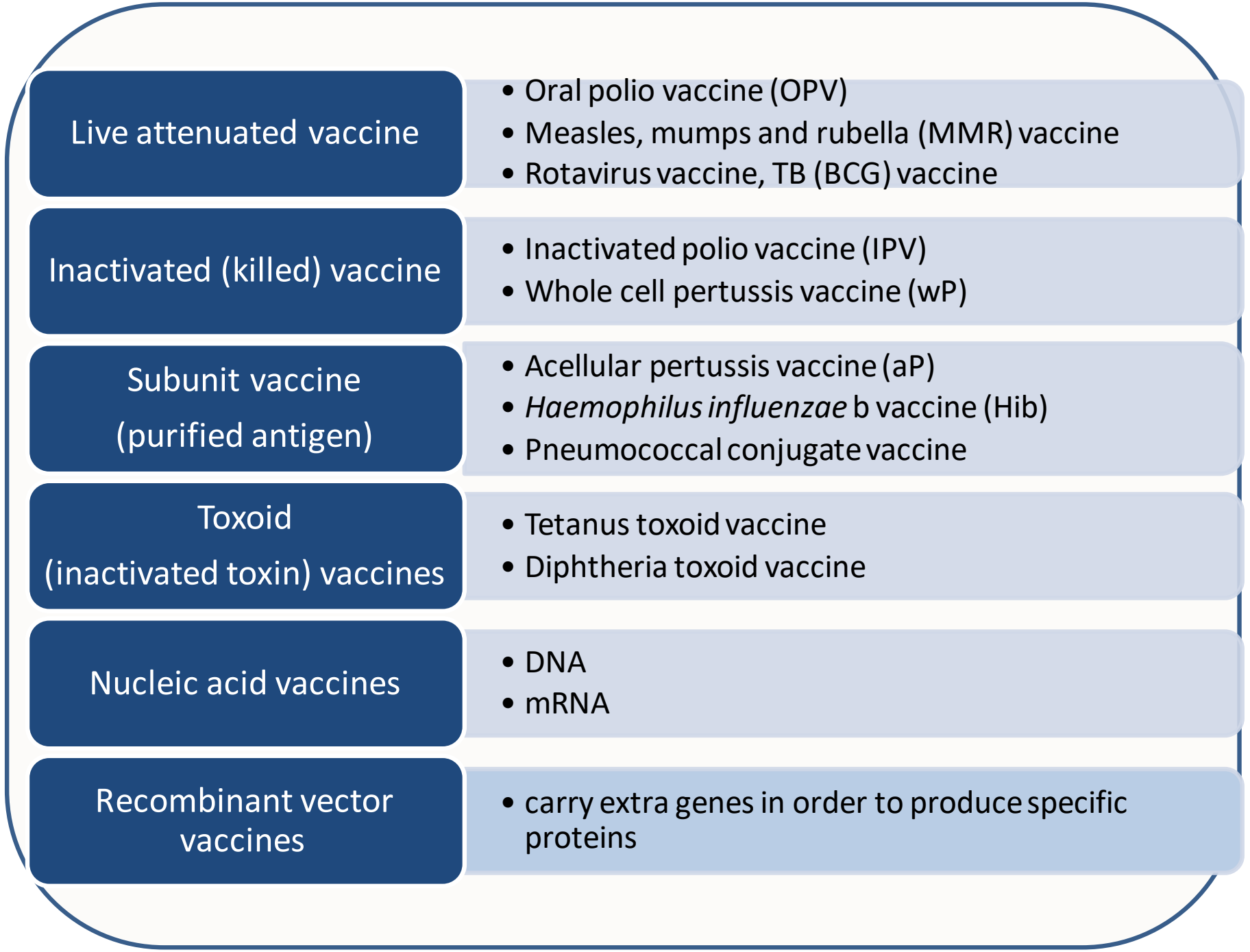


Immunisation:
passive vs. active

Passive immunisation

- temporary protection through the transfer of antibodies from immune individuals
  - **across the placenta**
    - e.g. tetanus, pertussis, influenza, measles
  - **through the use of specific antibodies**
    - animal source eg diphtheria anti-toxin
    - human source – pooled blood
      - human normal immunoglobulin
        - varicella zoster, hepatitis B, rabies, tetanus

Aim to provide protection after exposure in those in whom immune response is compromised and/or at high risk from disease or who are in contact with such people


Live attenuated vaccine
• Oral polio vaccine (OPV)
• Measles, mumps and rubella (MMR) vaccine
• Rotavirus vaccine, TB (BCG) vaccine
Inactivated (killed) vaccine
• Inactivated polio vaccine (IPV)
• Whole cell pertussis vaccine (wP)
Subunit vaccine (purified antigen)
• Acellular pertussis vaccine (aP)
• *Haemophilus influenzae* b vaccine (Hib)
• Pneumococcal conjugate vaccine
Toxoid (inactivated toxin) vaccines
• Tetanus toxoid vaccine
• Diphtheria toxoid vaccine
Nucleic acid vaccines
• DNA
• mRNA
Recombinant vector vaccines
• carry extra genes in order to produce specific proteins

Source: WHO

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Live attenuated vaccines

- attenuated strains which replicate in host
- the virus or bacterium has been weakened to reduce virulence to cause no or very mild disease in healthy people
- acts like “natural” infection
- live vaccines are the closest to actual infection and therefore elicit good, strong, long-lasting immune responses

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Live attenuated vaccines

Advantages

- Replicate in host
- Capacity to present multiple antigens across the viral life cycle in their native conformations
- Single dose often sufficient to induce long-lasting immunity
- Where cell-mediated immunity is required, attenuated pathogens are capable of replicating within host cells.
- Local and systemic immunity produced

Disadvantages

- Require complex containment and biosafety measures
- Potential to (rarely) revert to virulence
- Contraindicated in immunosuppressed patients
- Stability – requires strict storage
- Potential for contamination (contaminated tissue culture)

Non-live vaccines

Inactivated (killed) vaccine	suspensions of whole intact killed organisms
Subunit vaccine (purified antigen)	contain one or a few components of the organism that are important in protection
Toxoid (inactivated toxin) vaccines	based on the toxin produced by bacteria which causes most of the disease symptoms

Non-live vaccines

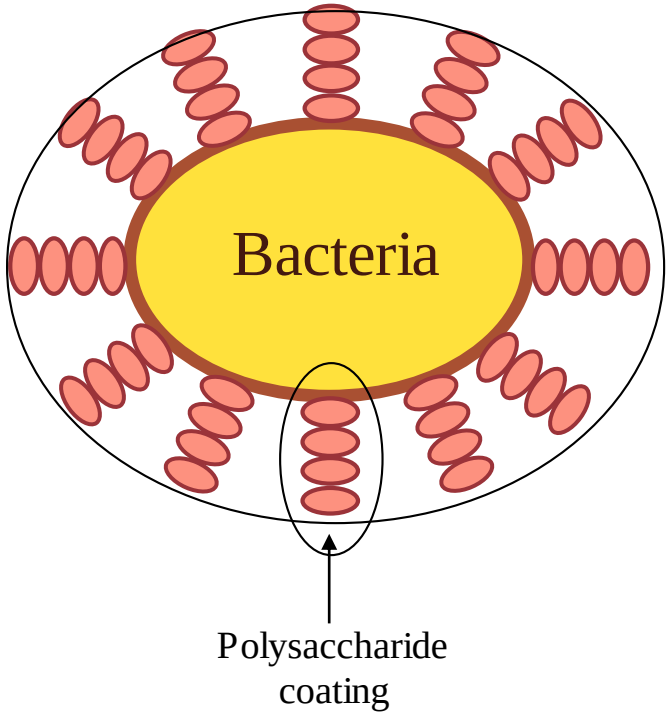
- Cannot cause disease
- Often safer and more stable than live vaccines (increased local reactions)
- Poorer immune response and a response that may not be long lived
- Adjuvant required
- Several doses may be required to evoke a sufficient immune response

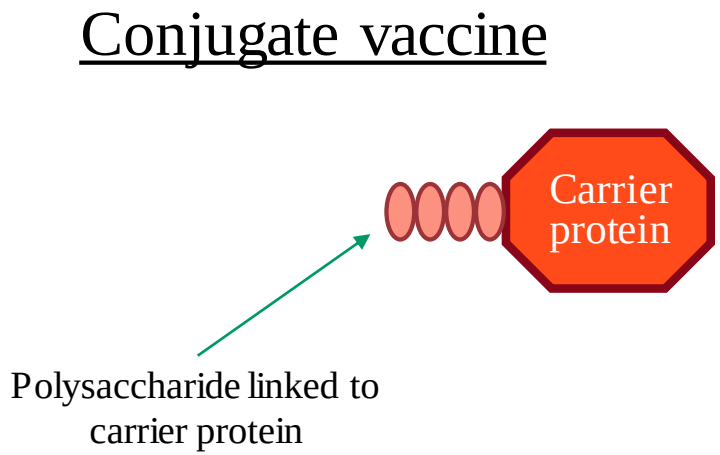
subunit vaccine: conjugate vaccines

- Some bacteria (e.g. *Haemophilus influenzae type b, Neisseria meningitidis, Streptococcus pneumoniae*) have an outer coating of sugar molecules (polysaccharides)
- A polysaccharide is a T cell independent antigen. *The human immune system does not develop the capacity to respond to such antigens until around 2 years of age*
- Polysaccharide vaccines are poorly immunogenic in children under 2 years old and do not stimulate long term immunological memory

Conjugation is the process of attaching the polysaccharide antigen to a protein carrier (e.g. diphtheria or tetanus), that the infant's immune system already recognises, in order to provoke an immune response

subunit vaccine: conjugate vaccines





Conjugation is the process of attaching the polysaccharide antigen to a protein carrier (e.g. diphtheria or tetanus), that the infant's immune system already recognises, in order to provoke an immune response

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Nucleic acid vaccines

natural antigen expression, production that is faster and more standardised than traditional vaccines

DNA VACCINES

- none licensed
- key challenges for DNA vaccines:
  - must pass through three phospholipid bilayer membranes
  - DNA must be transcribed into mRNA & translated into a protein antigen
  - require large doses and special delivery device
  - must prove that they have not integrated with DNA

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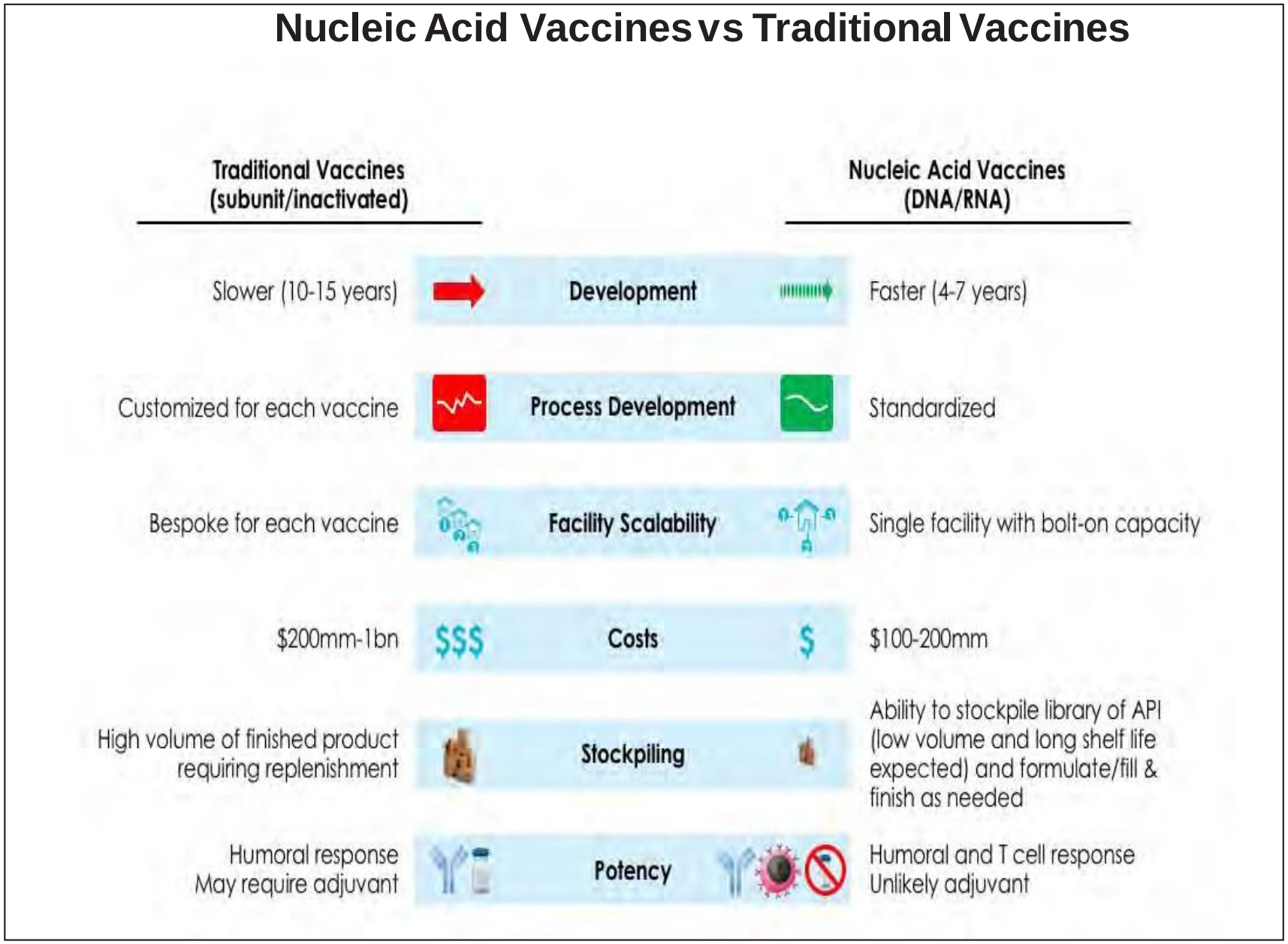
Nucleic acid vaccines

natural antigen expression, production that is faster and more standardised than traditional vaccines

mRNA VACCINES

- none licensed
- mRNA vaccines only need to get into the cytoplasm
- integration with DNA is not a risk
- require smaller doses and do not need special delivery devices

Nucleic Acid Vaccines vs Traditional Vaccines



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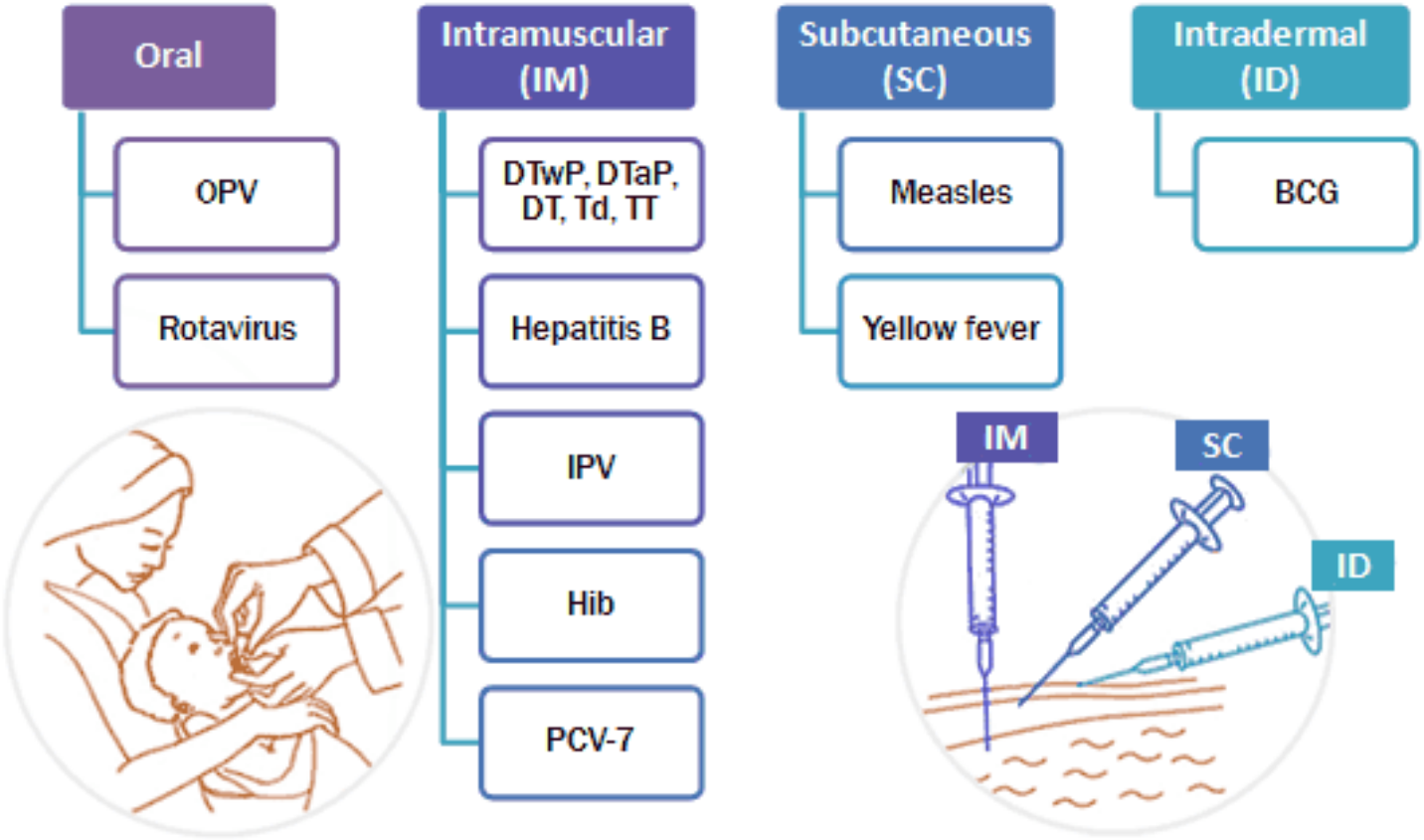
Routes of administration of vaccines



Routes of administration vary to maximize effectiveness of vaccine

Stages of Vaccine Trials

- Vaccine research and development is a carefully controlled and *often* very lengthy process

First Steps: Laboratory and Animal Studies

Exploratory Stage

- *Basic laboratory research*

Pre-Clinical Stage

- *Tissue-culture or cell-culture systems.*
- *Animal testing*

Clinical studies

- Before trials begin in humans: regulatory & ethical approval
- Vaccines then pass through 4 phases of vaccine evaluation

Stages of Vaccine Trials

Phase I studies

healthy adult volunteers, n = 20-30

aim: to assess safety and obtain limited immunogenicity data

Phase II studies

subjects in target age group for vaccine e.g. infants, n =100-200

aim: to assess common reactions and obtain immunogenicity data

- -assess dose response
- -compare with current vaccine

Stages of Vaccine Trials

Phase III studies

subjects in target population, number depends on incidence/risk of disease

aim: to assess protective efficacy & rarer reactions

Typically required for vaccine licensure

Stages of Vaccine Trials

Phase IV studies (post licensure)

- Studies of new vaccines do not stop at point of licensure
  - **The number of subjects in Phase I-III is still too small to detect rare events**
- Even once a vaccine is in use, ongoing studies are needed to detect rarer adverse events because in 'real life' there will be:
  - variability in preparation
  - variability in stability and storage
  - variability in people!
    - will be used in different groups than in pre-license studies

Vaccine effectiveness

Following licensure, effectiveness of vaccines is monitored through:

surveillance of disease incidence
monitoring of vaccine coverage
ascertaining vaccination status of individuals with disease

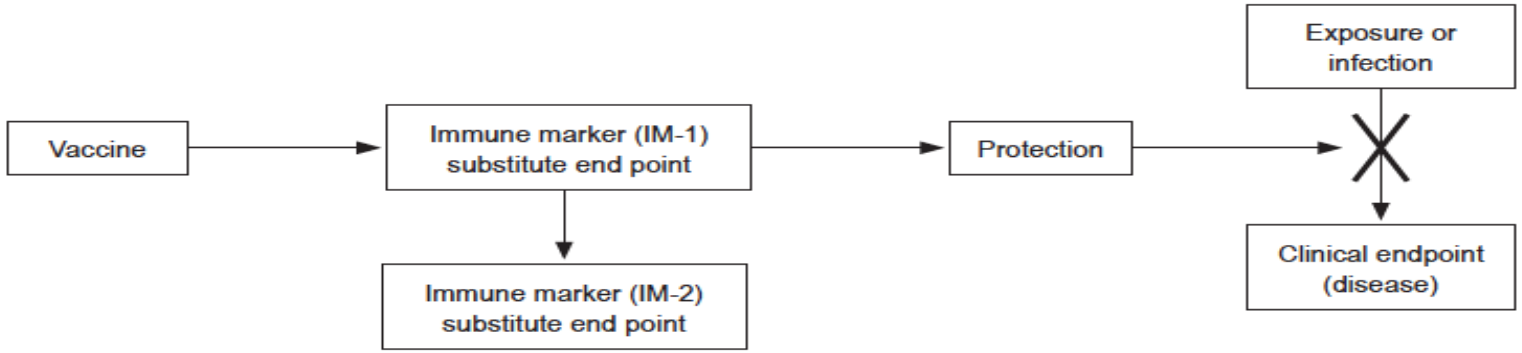
No vaccine is 100% effective and the effectiveness of each vaccine varies

For this reason, more than one dose and booster doses of vaccine are (often) recommended

Alternative pathways to licensure:
serological correlates of protection

The ability to assess the protective efficacy of a vaccine by measuring the proportion of vaccinees who generate a particular immune response, without having to measure clinical outcomes, has significant advantages… The availability of such **substitute endpoints** are important for vaccine development, licensure and effectiveness monitoring.

Figure 1. Simple illustration of the induction of protective immunity by a vaccine



Arrows imply direct causal relationships

WHO/IVB/13.01

IM-1 & IM-2 are two sorts of **immune markers** involved in, or influenced by the relationship between vaccination and protection

Protection implies an immunological mechanism to prevent or to reduce severity of infection or disease - this mechanism can involve both humoral and cellular arms of the immune system

Alternative pathways to licensure:
serological correlates of protection

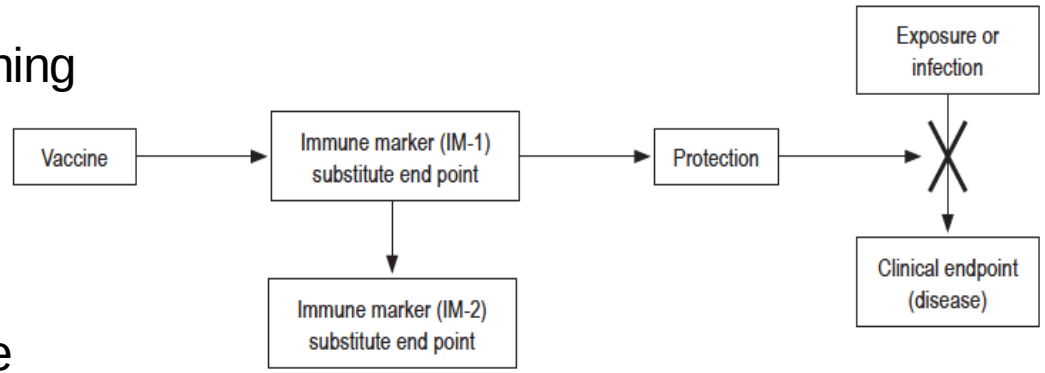
IM-1 and IM-2 are *correlates* of protection as they are statistically associated with vaccine-induced protection

IM-1 is on the direct arrow line between vaccine and protection, indicating that it is on the direct causal pathway: the vaccine induces protection via a mechanism involving IM-1. Hence it is a *surrogate.*

IM-2 is not on the causal pathway – it represents something that happens as a consequence of being vaccinated.

It is a *correlate*, not a surrogate

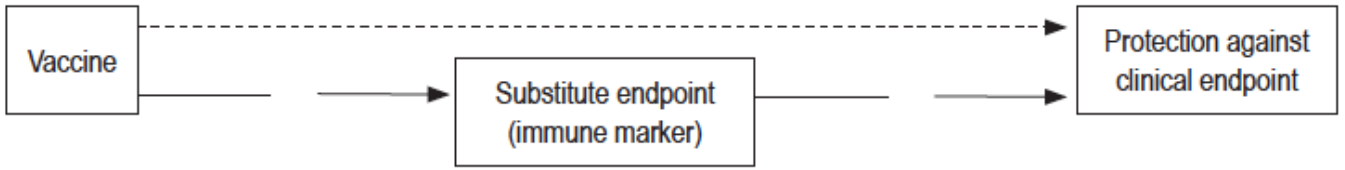
Figure 1. Simple illustration of the induction of protective immunity by a vaccine



Arrows imply direct causal relationships

Alternative pathways to licensure:
serological correlates of protection

Figure 8. Simplest possible relationship between vaccine, substitute endpoint and clinical endpoint



Variety of approaches can be used to identify, confirm and evaluate immunological markers as indicators of vaccine-induced protection

Randomised controlled trials with clinical endpoints
Immunogenicity studies
Passive immunisation studies
Challenge studies
Cohort studies
Natural history studies

Alternative pathways to licensure:
serological correlates of protection

Various ways to relate immune markers to vaccine protection
One example:

- antibody titres transformed into a dichotomous variable − a *threshold* level above which subjects are assumed to be protected and below which they are not

- simplest way to estimate a threshold level is to relate pre-exposure immune marker titres to disease incidence in a cohort study and the titre above which no individual develops the clinical endpoint is the protective threshold

e.g. surrogate of protection against measles (PRN titre >120 mIU/mL) was derived by finding that nobody with an antibody titre above that threshold developed typical clinical measles during an outbreak

Alternative pathways to licensure:
serological correlates of protection

Type of immune markers

most regulatory bodies prefer to measure functional antibodies instead of total antibody levels (which might include inactive antibodies)

- provides biological plausibility for any association found between immunological markers and clinical protection

Virus neutralisation:

an antibody response is crucial for preventing many viral infections

antibodies can be produced against many antigens on multiple virus proteins

some of these antibodies can block virus infection by a process called *neutralisation:*

- **antibodies interfere with virus binding to receptors, block uptake into cells, prevent uncoating of the virus, cause aggregation of virus particles…**

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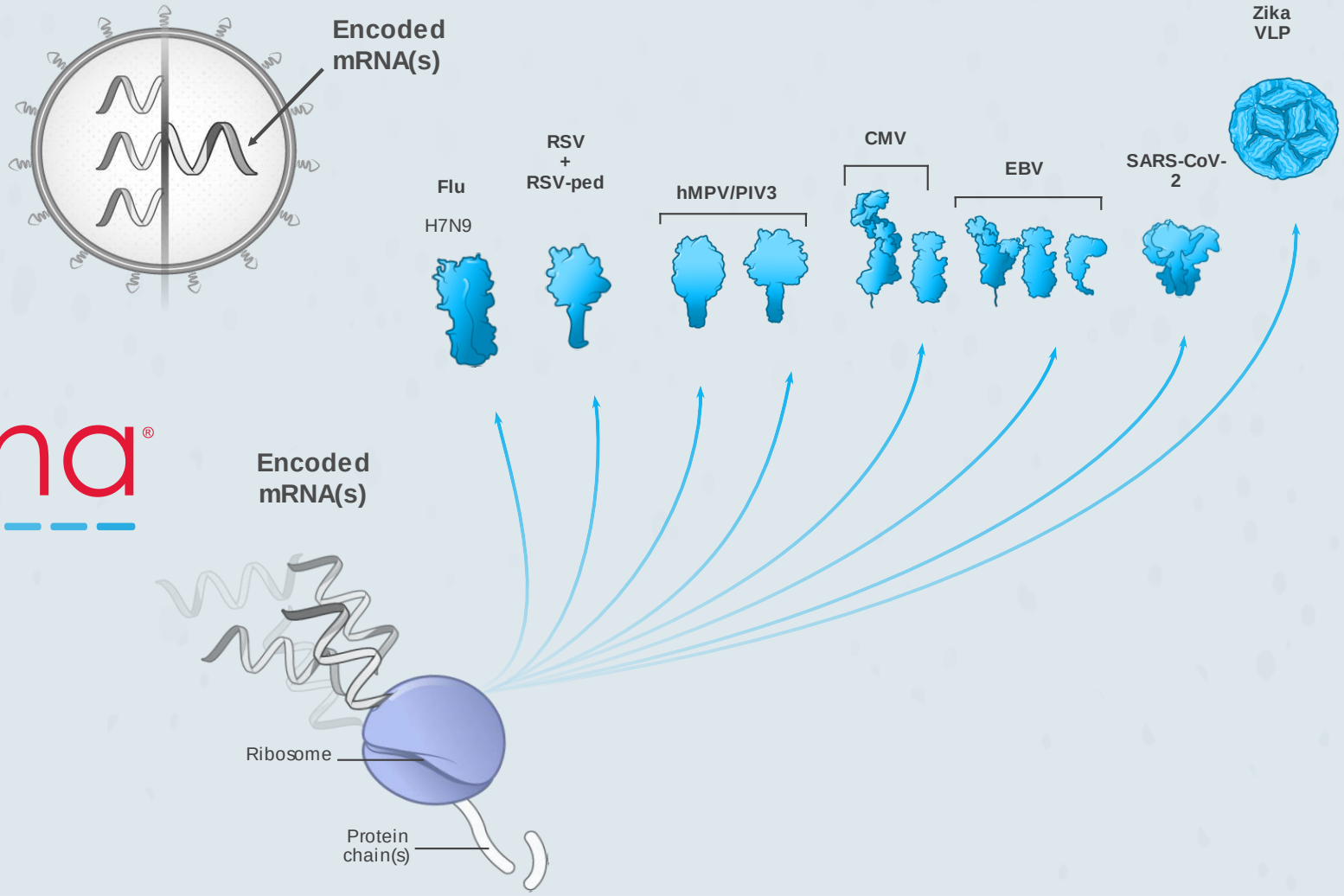
Immunisation: an overview

"With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction worldwide…"



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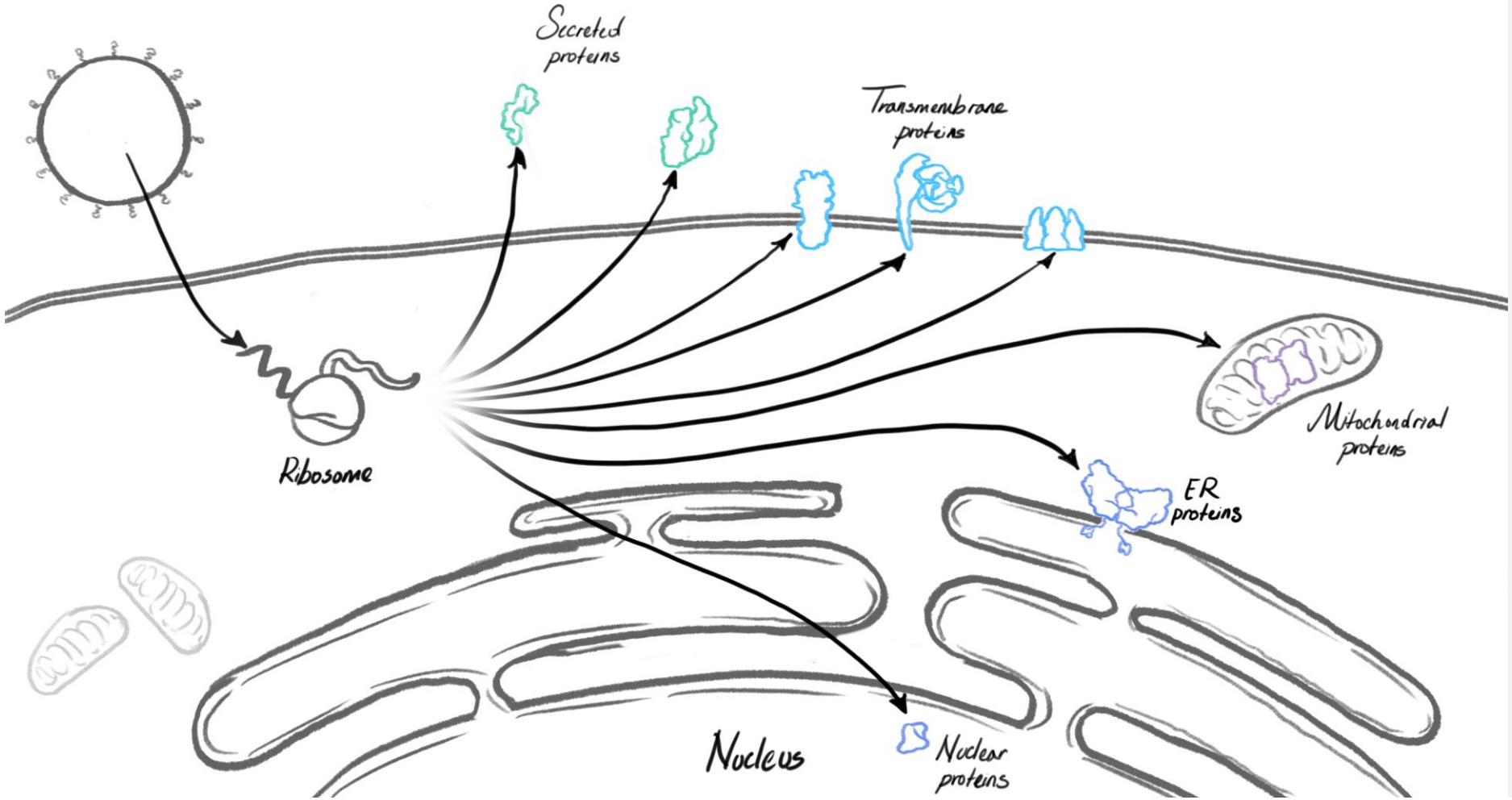
mRNA Vaccines Differentiation

Stephen Hoge, M.D., President

April 14, 2020

mRNA as a potential new class of medicines



1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology

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mRNA vaccines

Key characteristics and differentiation

1. **Large product opportunity**

- Ability to do complex antigens
- Ability to do combination vaccines

2. **Higher probability of technical success**

3. **Accelerated research and development timelines**

4. **Greater capital efficiency over time vs. recombinant technology**

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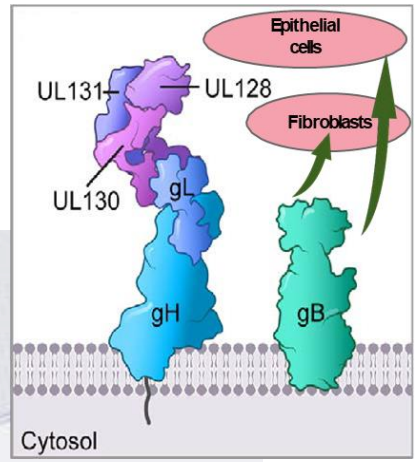
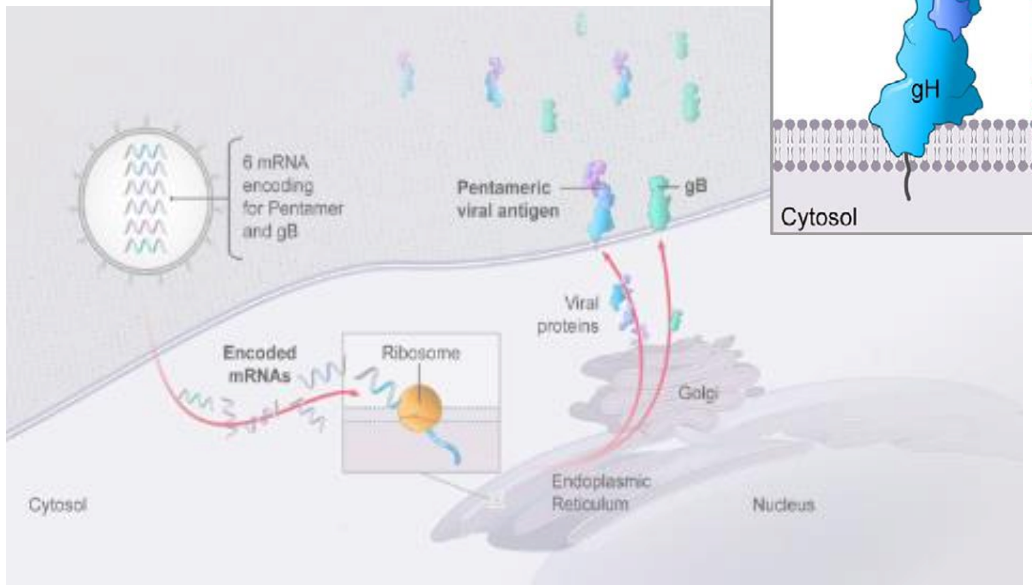
Ability to do complex antigens

Multi-protein complexes

CMV vaccine (mRNA-1647) includes six mRNAs

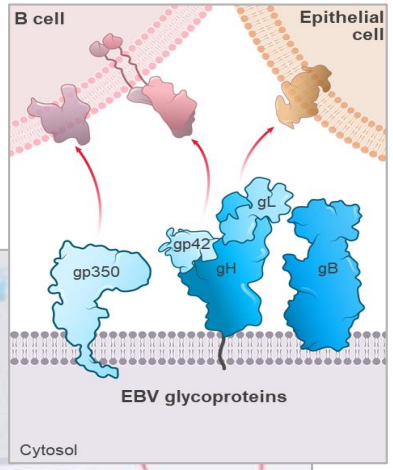
*5 encode the **Pentamer**, 6th encodes **gB antigen***

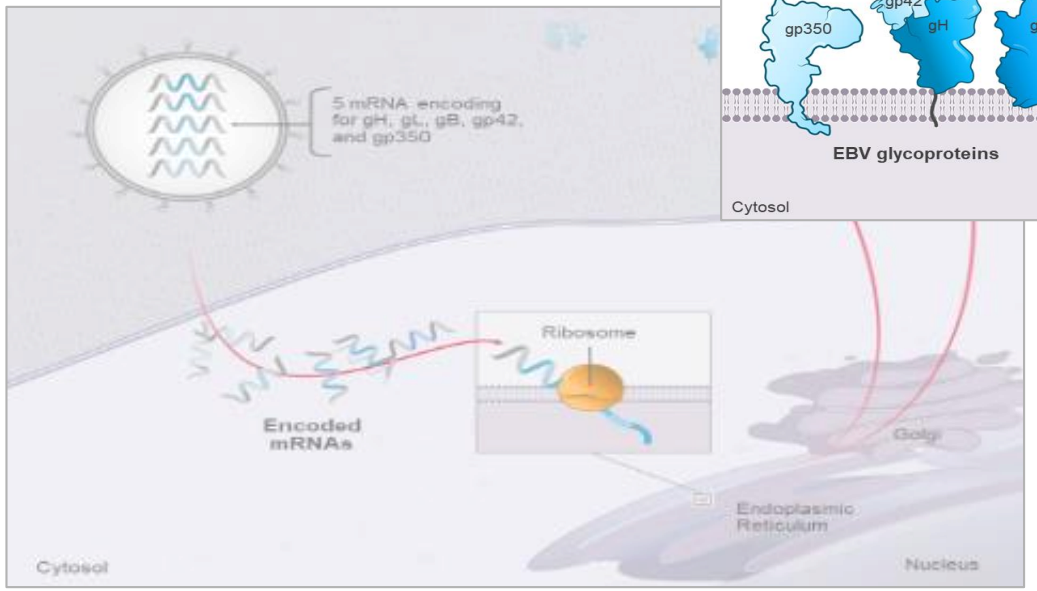




EBV vaccine (mRNA-1189) includes five mRNAs

*Inhibits both mechanisms for viral entry into **B cells** (**gp350** plus **gH/gL/gp42**), adds protection for **epithelial cells** (**gH/gL**), and includes **gB** for protection of all cells*





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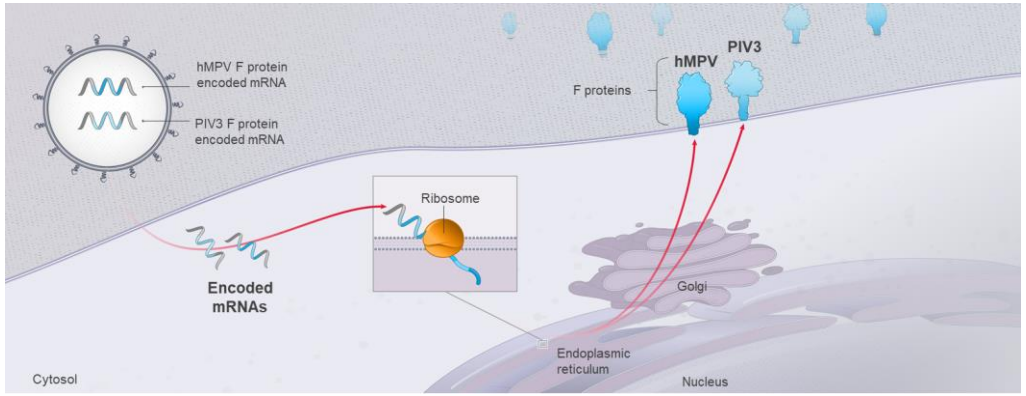
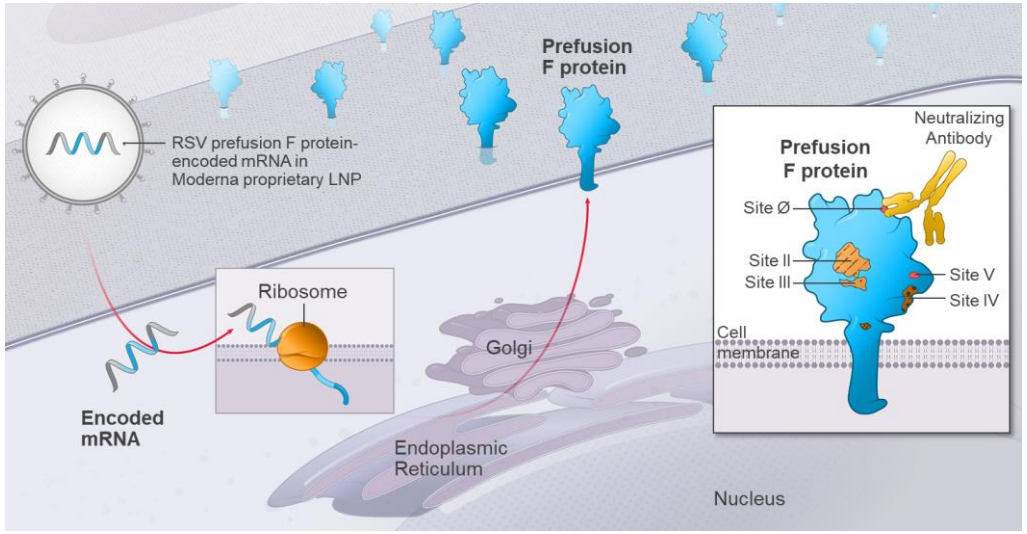
Ability to do combination vaccines

Create a pediatric respiratory vaccine

Intend to combine our pediatric RSV vaccine (mRNA-1345) with mRNA-1653, our vaccine against hMPV and PIV3. **Combination vaccine would address three leading causes of medically attended respiratory disease in young children,** accounting for 3 million visits annually in the US alone





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mRNA vaccines

Key characteristics and differentiation

1. Large product opportunity

- Ability to do complex antigens
- Ability to do combination vaccines

2. Higher probability of technical success

- Vaccine mechanism of action (MOA)
- T-cell response

3. Accelerated research and development timelines

4. Greater capital efficiency over time vs. recombinant technology

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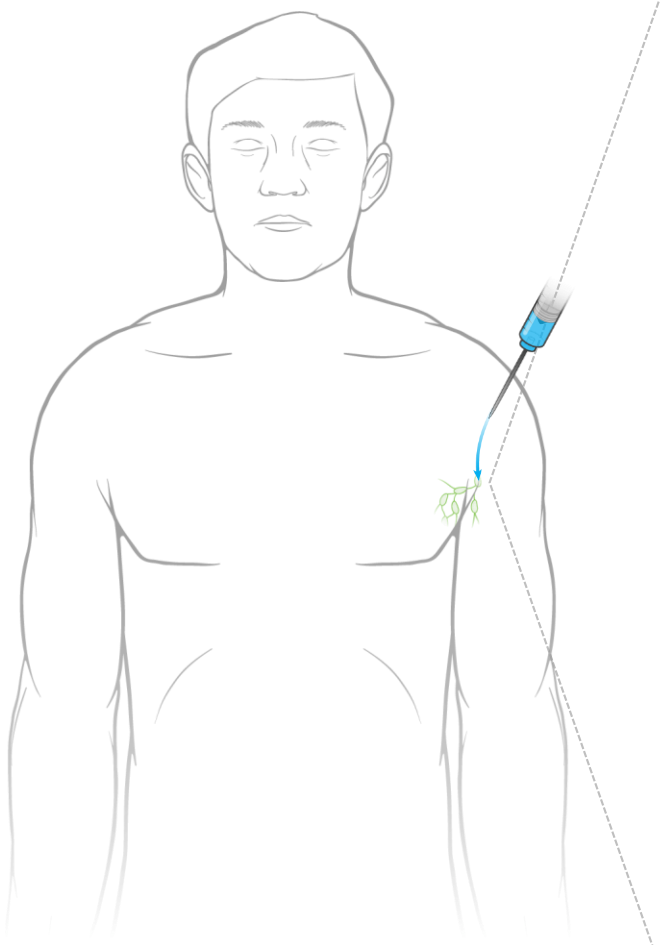
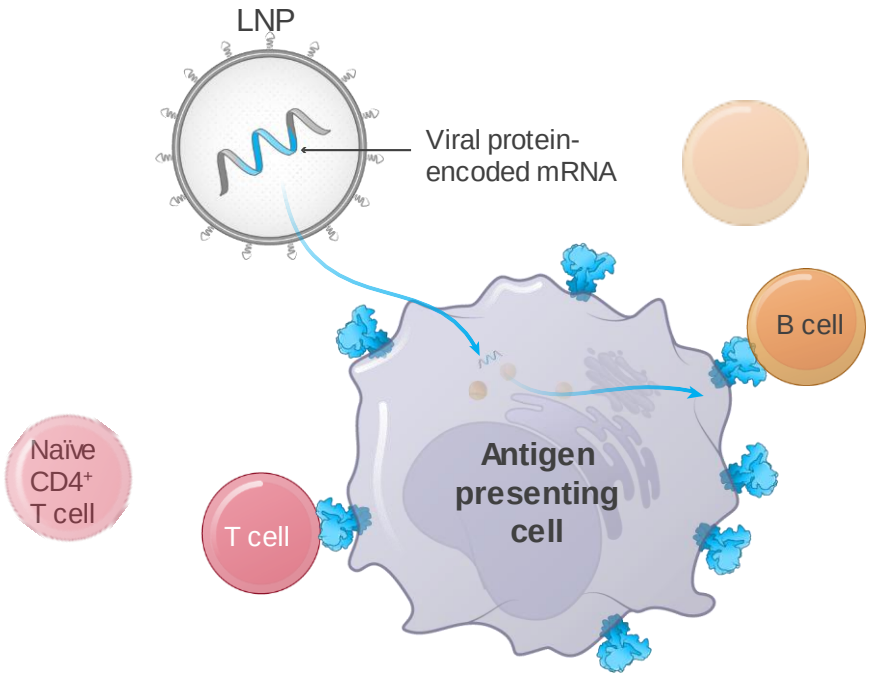
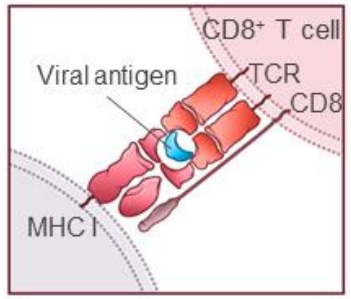
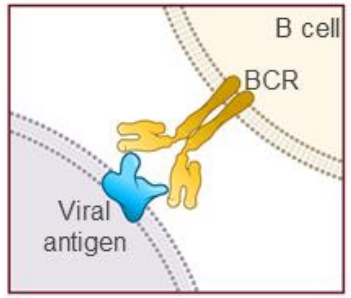
mRNA vaccines

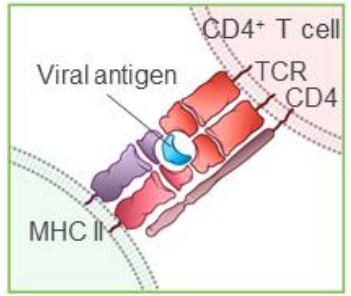
Unique platform mechanism of action (MOA)











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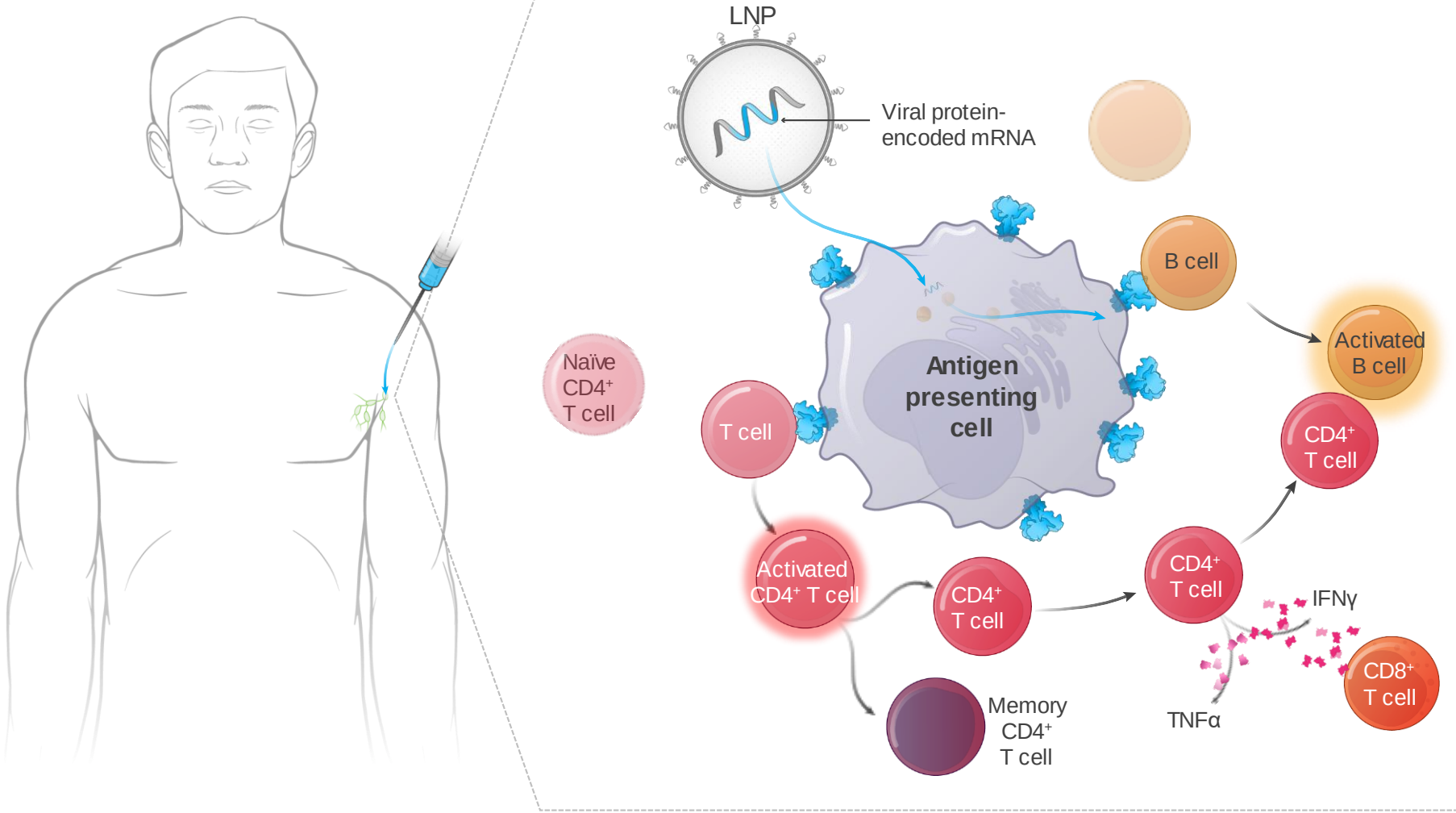
mRNA vaccines

Unique platform mechanism of action (MOA)



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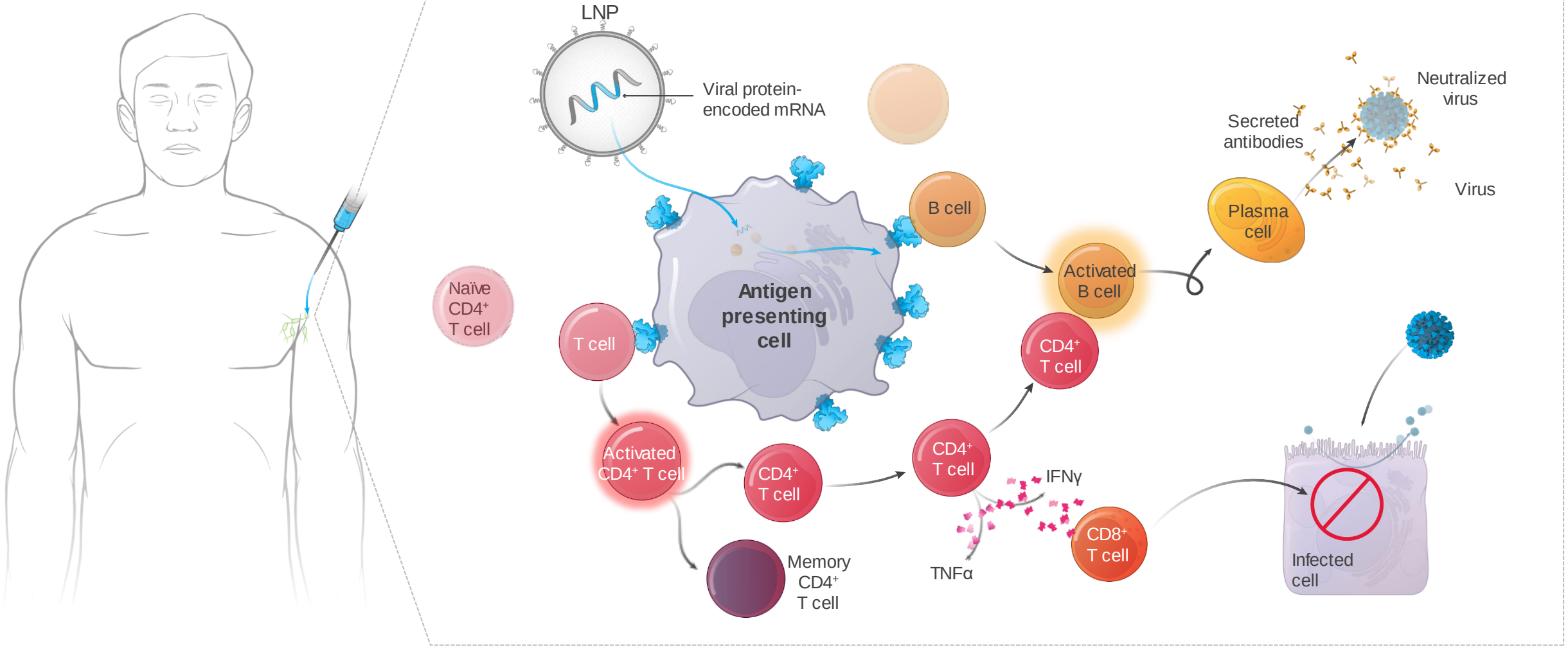
mRNA vaccines

Unique platform mechanism of action (MOA)



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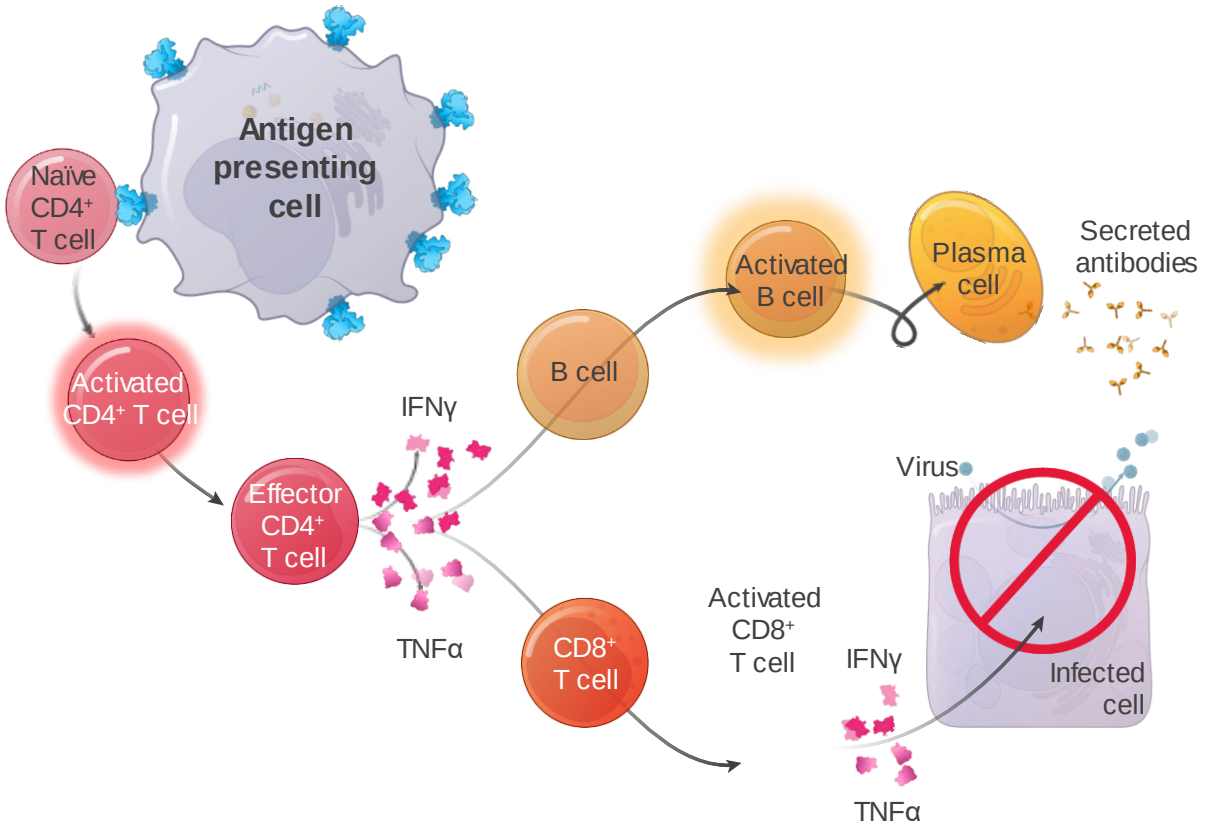
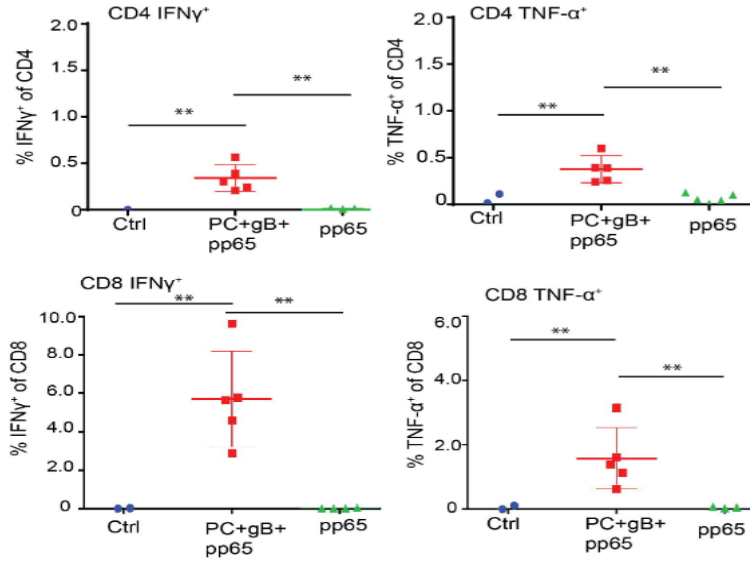
mRNA vaccines

T cell responses

- Evidence of CD4 and CD8 T-cell responses has been seen after vaccination with our mRNA vaccines in preclinical models and in humans (e.g., Personalized Cancer Vaccine, mRNA-4157)
- mRNA vaccines can elicit CD4+ Th1-type immune responses to CMV (CD4+ IFN***γ***+ and CD4+ TNF***α***+ cells)



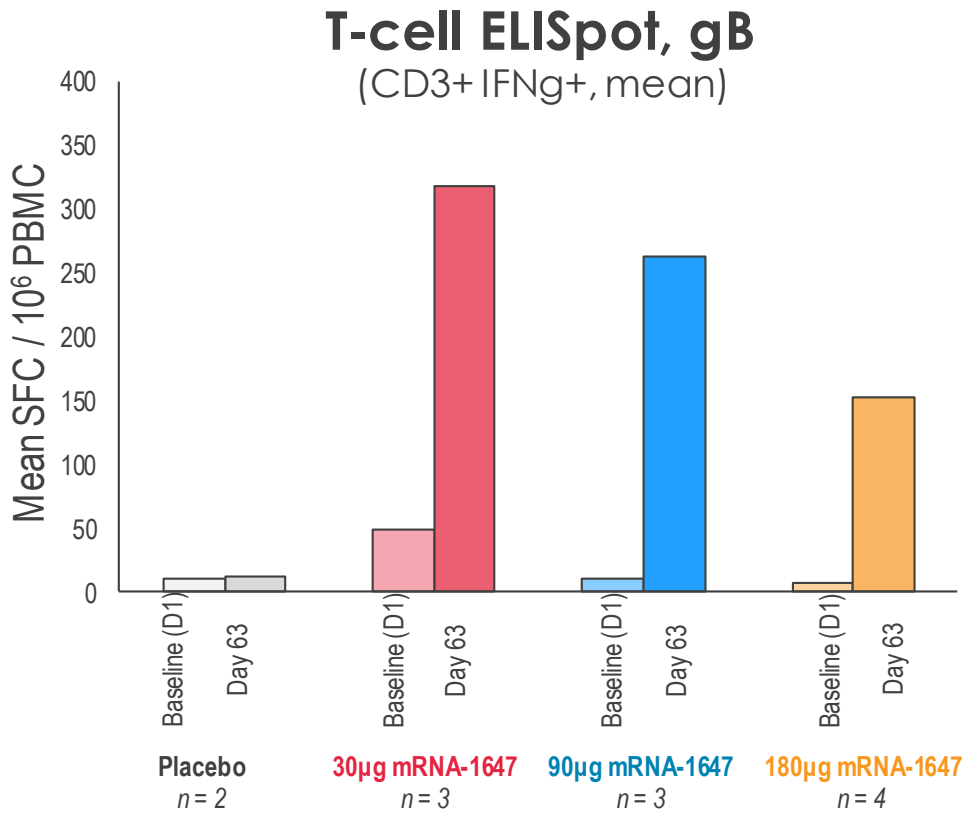
Pentameric complex (PC)-specific CD4 and CD8 T cell responses[1]



[1] S. John et al. Multi-antigenic human cytomegalovirus mRNA vaccines that elicit potent humoral and cell-mediated immunity. Vaccine 36 (2018) 1689–1699

mRNA vaccines

T cell responses



Neutralizing antibody (Fibroblast GMT, Day 84)	**8**	**139**	**405**	**542**

- Exploratory analysis of T-cell response in **mRNA-1647 Phase 1** (low n)
- All subjects showed **T-cell responses** after the 2nd vaccination primed by the 1st vaccination
- Subjects also seroconverted and boosted **neutralizing antibody responses** in fibroblast assay by day 84

Of data available, one subject in the 90µg treatment group was excluded due to titer at Baseline > LLOQ (presumed sero+); this subject still demonstrated significant boosting by ELISpot after vaccination

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mRNA vaccines overview

Key characteristics and differentiation

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- Ability to do combination vaccines

2. Higher probability of technical success

- Vaccine mechanism of action (MOA)
- T-cell response

3. Accelerated research and development timelines

- Time to clinical study/market
- Uniform process allows for fast scale up

4. Greater capital efficiency over time vs. recombinant technology

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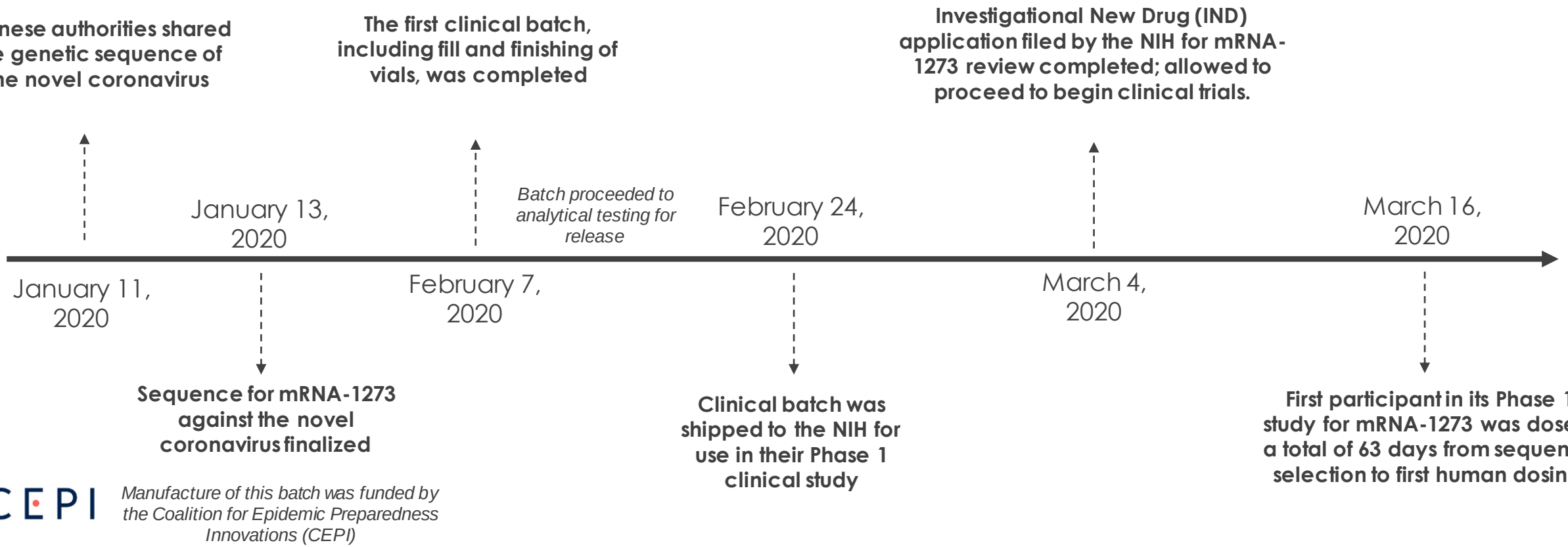
Accelerated research and development

SARS-CoV-2 vaccine (mRNA-1273)



CEPI

Manufacture of this batch was funded by the Coalition for Epidemic Preparedness Innovations (CEPI)

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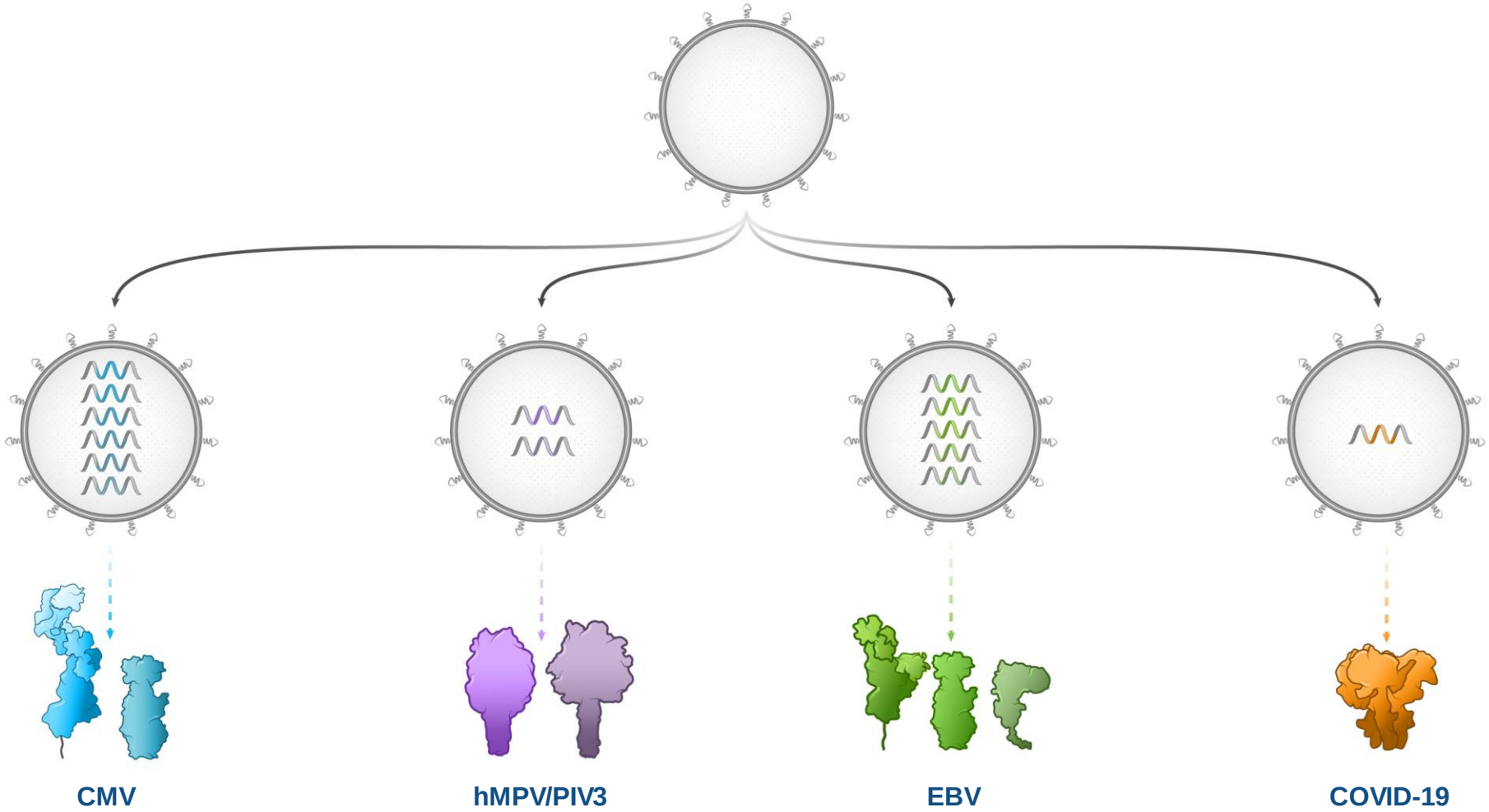
Uniform process allows for fast scale-up

High degree of flexibility



- Same **LNP** formulation
- Same **mRNA** nucleotides
- Same mRNA & LNP **manufacturing** processes

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mRNA vaccines overview

Key characteristics and differentiation

1. Large product opportunity	✓ Ability to do complex antigens ✓ Ability to do combination vaccines
2. Higher probability of technical success	✓ Vaccine mechanism of action (MOA) ✓ T-cell response
3. Accelerated research and development timelines	✓ Time to clinical study/market ✓ Uniform process allows for fast scale up
4. Greater capital efficiency over time vs. recombinant technology	✓ Lower capex ✓ Greater flexibility

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Agenda

Introduction of mRNA Vaccine Platform	*Stéphane Bancel, CEO*	*8:00-8:20 AM*	*20 min*
Clinical Trial POS	*Andrew W. Lo, MIT Sloan School of Management*	*8:20-8:40 AM*	*20 min*
Traditional Vaccines Overview	*Paul T. Heath, Vaccine Institute, St George's, University of London*	*8:40-9:20 AM*	*40 min*
mRNA Vaccines Differentiation	*Stephen Hoge, M.D., President*	*9:20-9:50 AM*	*30 min*
Coffee Break		*9:50-10:00 AM*	*10 min*
Vaccines Against Infections From Mother to Baby	*Tal Zaks, M.D., Ph.D., Chief Medical Officer*	*10:00-10:30 AM*	*30 min*
Vaccines Against Respiratory Diseases	*Tal Zaks, M.D., Ph.D., Chief Medical Officer* *Flor Munoz-Rivas, M.D., Baylor College of Medicine* *Mark R. Denison, MD, Vanderbilt University Medical Center* *Tal Zaks, M.D., Ph.D., Chief Medical Officer* *Juan Andres, Chief Technical Operations and Quality Officer*	*10:30-12:10 PM*	*100 min*
ACIP Overview/Framework	*Kathryn M. Edwards, M.D., Sarah H. Sell and Cornelius Vanderbilt Professor of Pediatrics*	*12:10-12:40 PM*	*30 min*
Conclusion	*Stéphane Bancel, CEO*	*12:40-12:50 PM*	*10 min*
Q&A		*12:50-1:15 PM*	*25 min*

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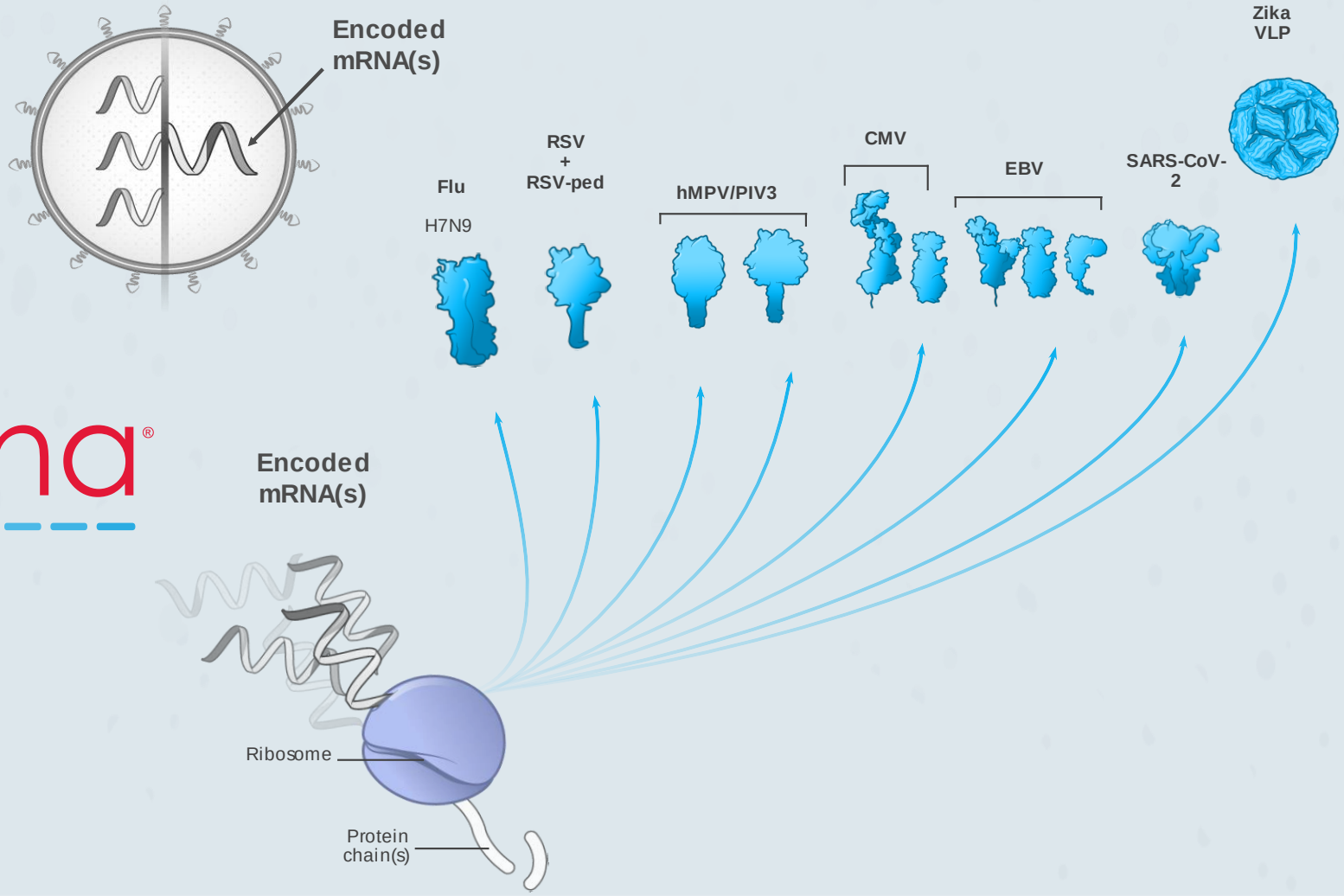

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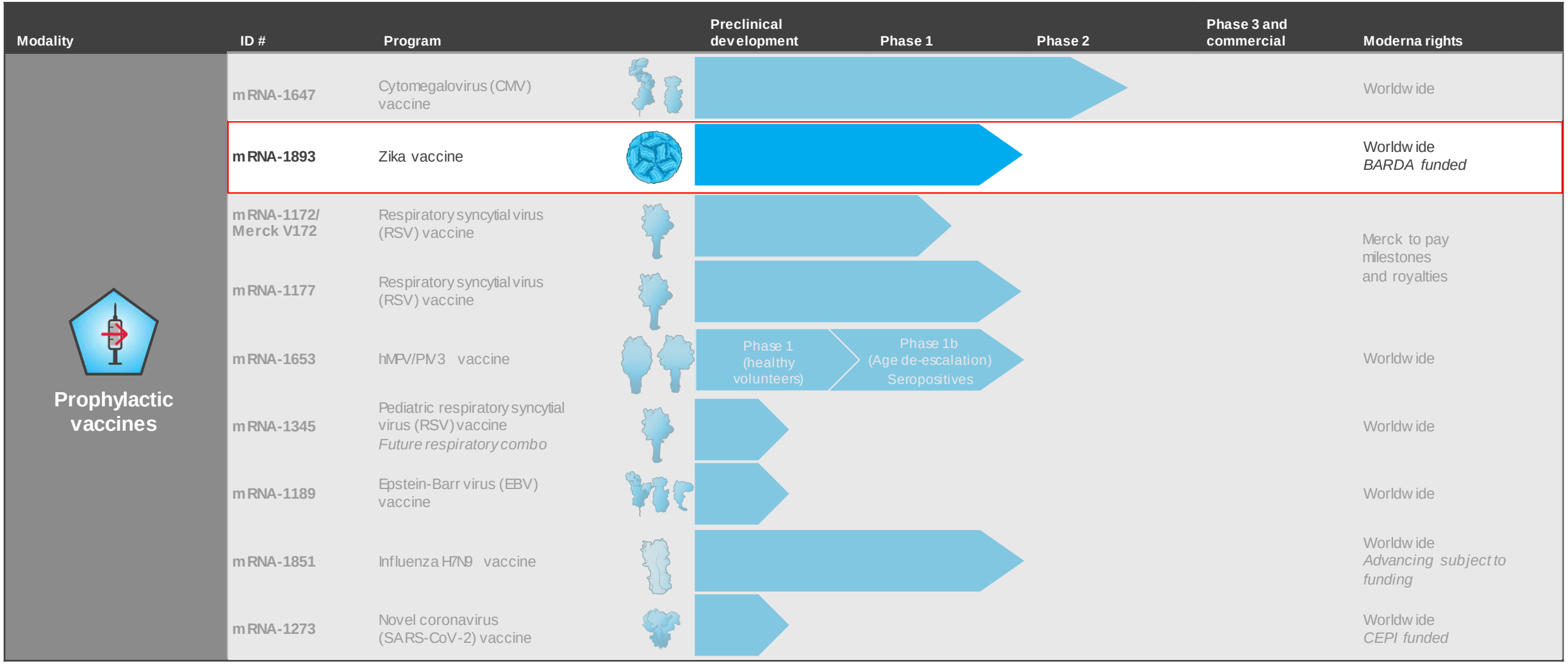
Vaccines Against Infections Transmitted From Mother to Baby

Tal Zaks, M.D., Ph.D., Chief Medical Officer

April 14, 2020

Prophylactic vaccines modality

Zika vaccine (mRNA-1893)



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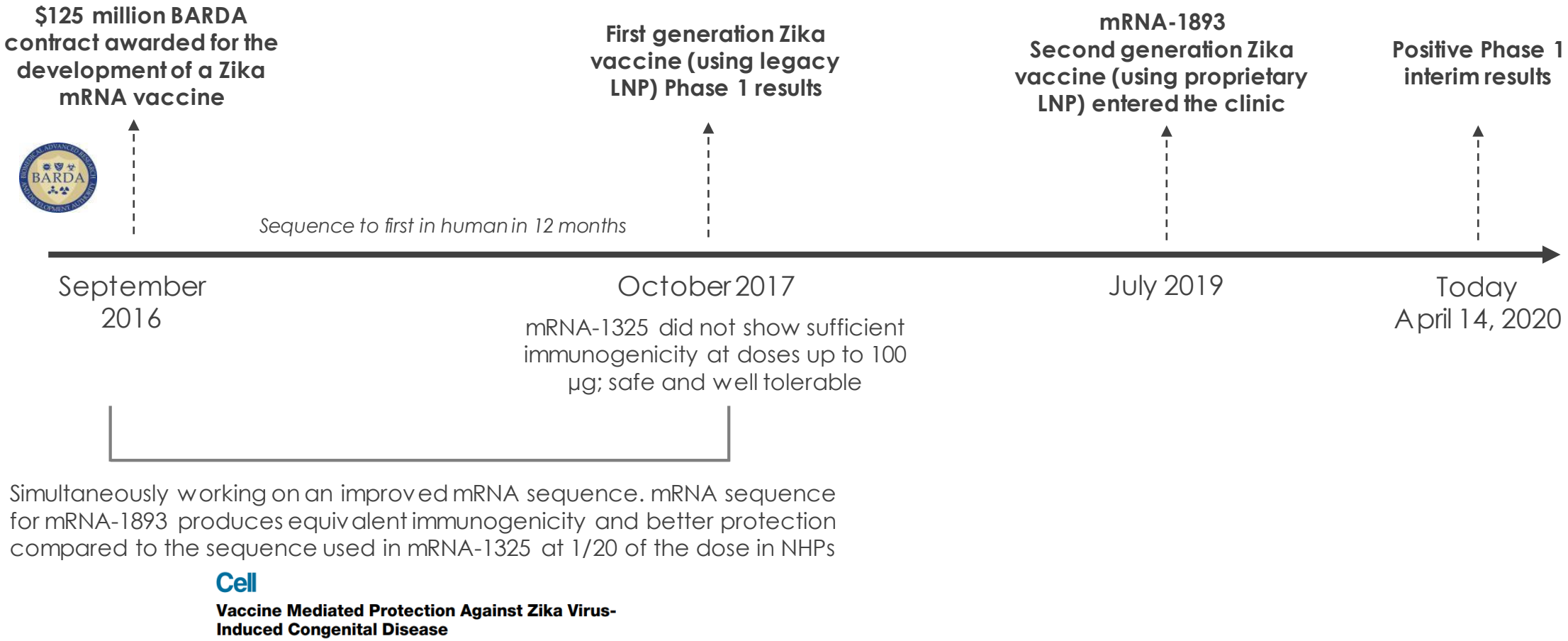
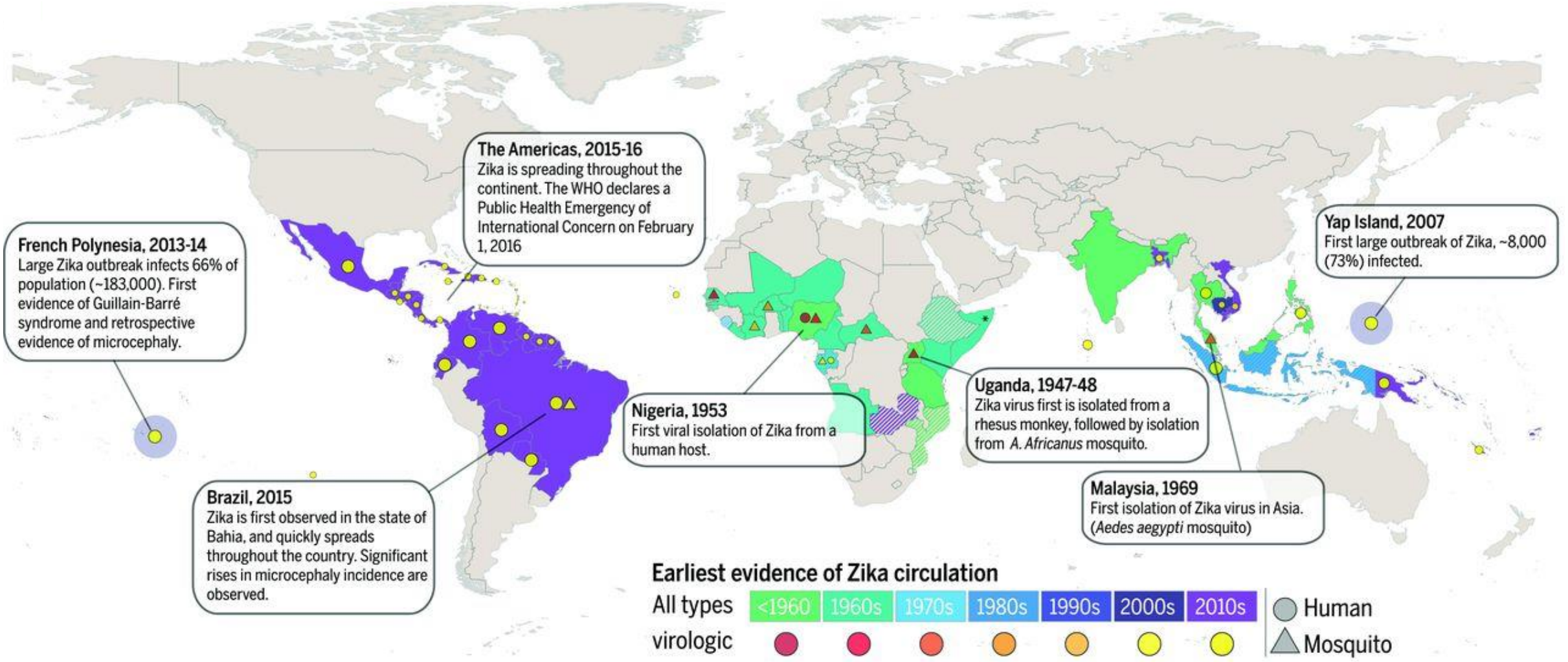
Responsiveness of the vaccines platform

Zika virus development history



This project has been funded in whole or in part with Federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201600029C.

Zika is an arbovirus and member of the Flaviviridae family



Assessing the global threat from Zika virus. Science. 12 Aug 2016: Vol. 353, Issue 6300

Zika virus overview

- Zika virus (ZIKV): The primary source of ZIKV infection in humans is from bites of infected mosquitoes
  - There have also been cases of sexual, perinatal, and suspected blood-transfusion transmission

- In 2015 and 2016, large outbreaks of Zika virus occurred in the Americas
  - Travel-associated cases in US states, widespread transmission in Puerto Rico and the US Virgin Islands, and limited local transmission in Florida and Texas

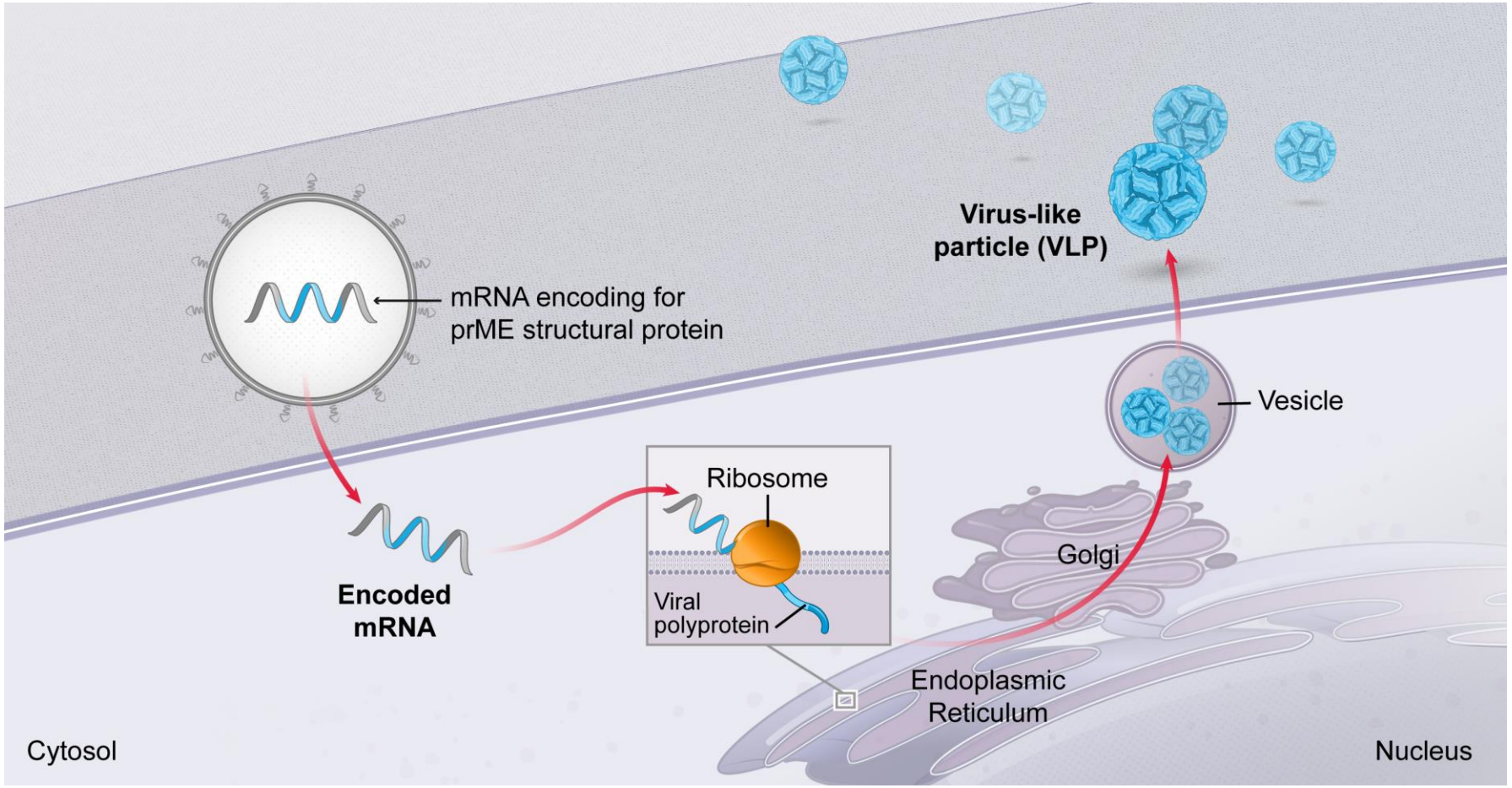
- **Disease burden:** Zika can be passed from a pregnant woman to her fetus
  - Increased risk of Guillain-Barré syndrome
  - Microcephaly was the first fetal abnormality to be recognized
  - Increasing evidence that ZIKV may be responsible for other fetal sequelae, such as intracranial calcifications, ventriculomegaly, ocular impairment, brainstem, hypoplasia, intrauterine growth restriction (IUGR),and fetal demise

- **Unmet need:** No approved Zika vaccine

Zika infection sequelae	
Neonatal period	Microcephaly Other severe brain defects
Infancy, childhood, adulthood	Fever Rash Headache Joint pain Red eyes Muscle pain

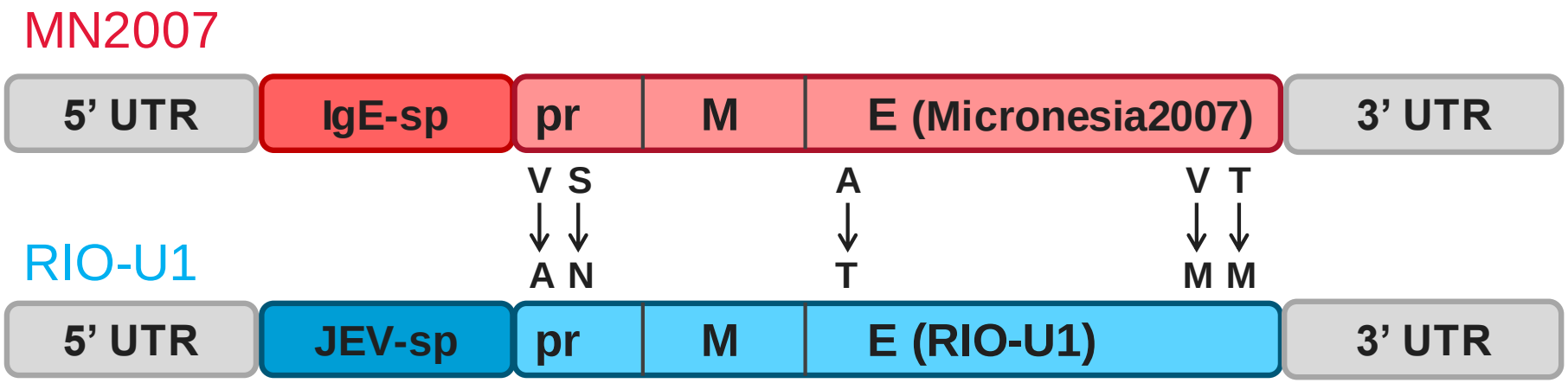
Zika vaccine (mRNA-1893)

Expression of prME can give rise to non-infectious, virus-like particles



Signal peptide and amino acid difference in the prME ORF

Between the mRNA-1325 (MN2007) and mRNA-1893 (RIO-U1) mRNA constructs



- Rio strain sequence was not available at the time of initial sequence selection
- Once additional sequences became available, the RIO-U1 strain was used for **RIO-U1** mRNA as it reflected the most current circulating strain
- Five amino acid differences in the pr and E sequences between **MN2007** and **RIO-U1**
- JEV-sp was selected for **RIO-U1** based upon the potential for improved processing of flavivirus VLPs[1]

1. Zhang *et al*. *Nature* 2016. A CRISPR screen defines a signal peptide processing pathway required by flaviviruses.

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Zika vaccine (mRNA-1893)

Phase 1 trial design – 4 dose levels tested: 10, 30, 100 and 250 µg

Key objective:

- To assess safety, reactogenicity, and immunogenicity of several dose levels of mRNA-1893 given with a 2-dose regimen at 28-day interval

Primary endpoint: Safety

Secondary endpoints:

- ZIKV-specific neutralizing antibodies as measured by Plaque Reduction Neutralization Test (PRNT50) at D29, D57, 7 months and 13 months post-last vaccine administration

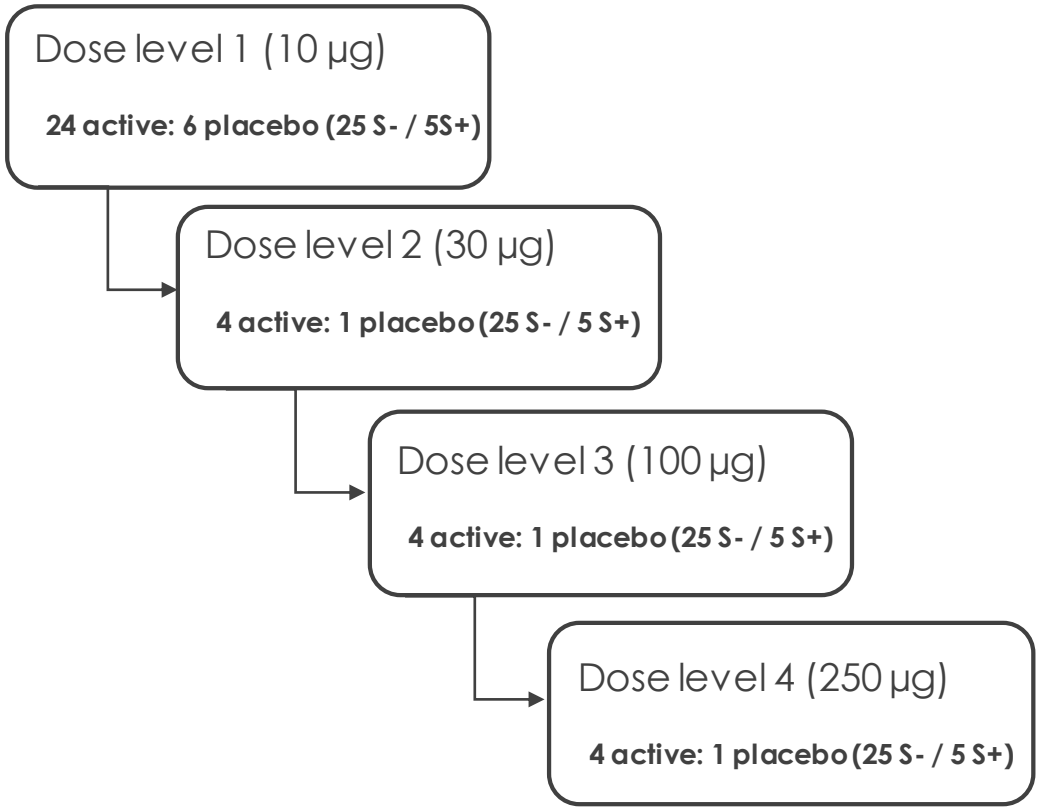
Exploratory endpoints:

- ZIKV-specific neutralizing antibodies as measured by Microneutralization (MN), Reporter Virus Particle neutralization (RVP) at D29, D57, 7 Months and 13 Months

Trial progress:

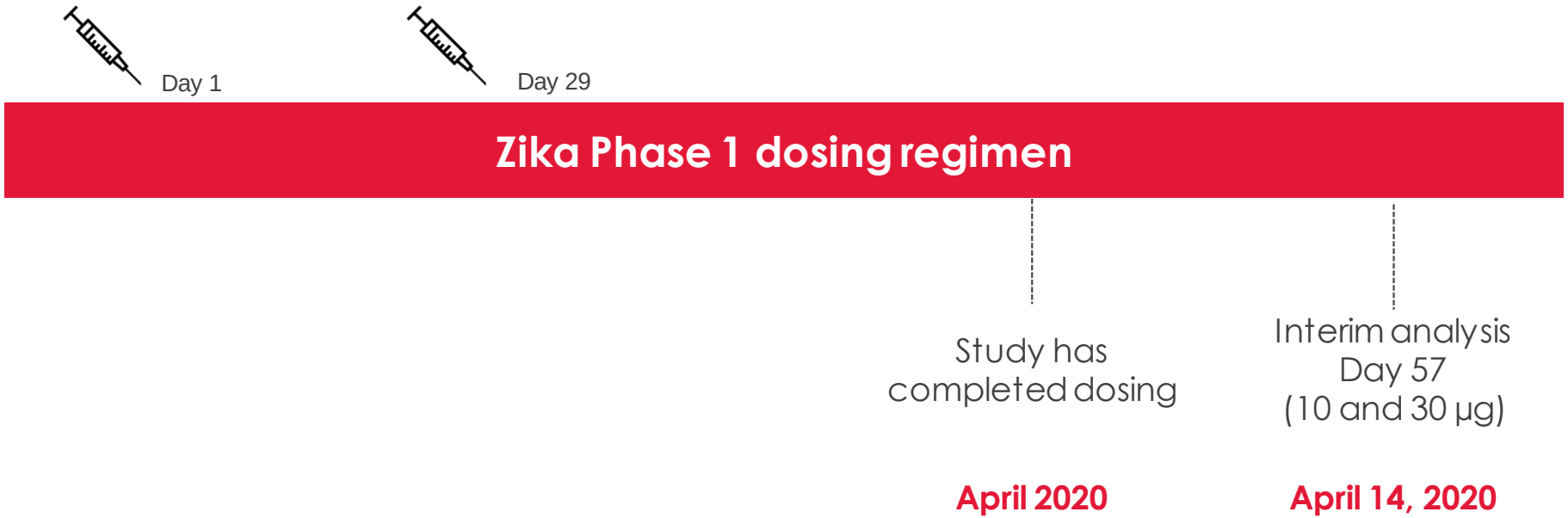
- Study has completed dosing
- **Interim analysis Day 57 10µg and 30µg – April 14th, 2020**

mRNA-1893-P101 Study Design



Zika vaccine (mRNA-1893)

Dosing regimen



Zika vaccine (mRNA-1893) Phase 1 interim analysis

Safety profile (10 and 30 µg cohorts)

		Solicited ARs post-Dose 1 (solicited safety set)			Solicited ARs post-Dose 2 (solicited safety set)			
		Placebo N=12 N(%)	10µg N=24 N(%)	30µg N=24 N(%)		Placebo N=12 N(%)	10µg N=23 N(%)	30µg N=23 N(%)
Local reactions	Pain	1/12 (8.3%) –	12/24 (50%) –	12/23 (52.2%) –	Pain	1 /12 (8.3%) –	8/23 (34.8%) –	11/22 (50%) –
	Redness	–	–	–	Redness	–	–	1/20 (5) 1 (5.0)*
	Swelling	–	–	–	Swelling	–	–	2/20 (10) 1 (5.0)*
Systemic reactions	Fever	–	1/24 (4.2) –	–	Fever	–	1/23 (4.3) –	3/22 (13.6) –
	Headache	3/12 (25) –	7/24 (29.2) –	5/23 (21.7) 1 (4.3)*	Headache	3/12 (25) –	5/23 (21.7) –	8/22 (36.4) –
	Fatigue	2/12 (16.7) –	8/24 (33.3) –	5/23 (21.7) –	Fatigue	1/12 (8.3) –	6/23 (26.1) –	10/22 (45.5) –
	Myalgia	1/12 (8.3) –	5/24 (20.8) –	3/23 (13) –	Myalgia	1/12 (8.3) –	7/23 (30.4) –	4/22 (18.2) –
	Arthalgia	–	2/24 (8.3) –	2/23 (8.7) –	Arthalgia	2/12 (16.7) –	4/23 (17.4) –	4/22 (18.2) –
	Nausea	–	4/24 (16.7) –	2/23 (8.7) –	Nausea	1/12 (8.3) –	2/23 (8.7) –	1/22 (4.5) –
	Chills	–	1/24 (4.2) –	–	Chills	2/12 (16.7) –	1/23 (4.3) –	5/22 (22.7) –
	Rash	–	1/24 (4.2) –	–	Rash	–	–	–

- Both 10 and 30 µg dose levels were generally well tolerated
- No grade 3 adverse reactions (ARs) were reported
- No serious adverse events (SAEs) related to mRNA-1893 were reported at either dose levels

N: number of participants in solicited safety set. The denominator of the rate is the number of participants who submitted any data for the respective event
Red text = grade 3 ARs
One participant experienced a Grade 4 Prothrombin Test increase at Day 29 with no clinical manifestations, this was considered not related to mRNA-1893 administration
* Updated on August 5, 2020

Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity in flavivirus baseline seronegative participants

Immunogenicity in Flavivirus Baseline Seronegative Participants (Per-Protocol Set)			
	$PRNT_{50}$		
	Placebo	**10µg**	**30µg**
Baseline	8.0	9.5	8.0
GMT post-dose 1	8.0	8.5	14.4*
GMT post-dose 2	8.0	195.6	303.4
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	5%; 94.4%	42.1%*; 100%
	MN		
	Placebo	**10µg**	**30µg**
Baseline	14.0	14.0	14.0
GMT post-dose 1	14.0	58.9	129.7
GMT post-dose 2	14.0	1,195.3	1,478.0
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	75%; 100%	85%; 100%

Reporter Virus Particle neutralization (RVP) data are pending
Seroconversion is defined as a change in $PRNT_{50}$ from below the lower limit of quantification to a $PRNT_{50}$ equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing $PRNT_{50}$ titers; Seroconversion is defined as a change in MN from below the lower limit of quantification to a MN equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing MN titers.
* Updated on August 5, 2020

Zika vaccine (mRNA-1893) Phase 1 interim analysis

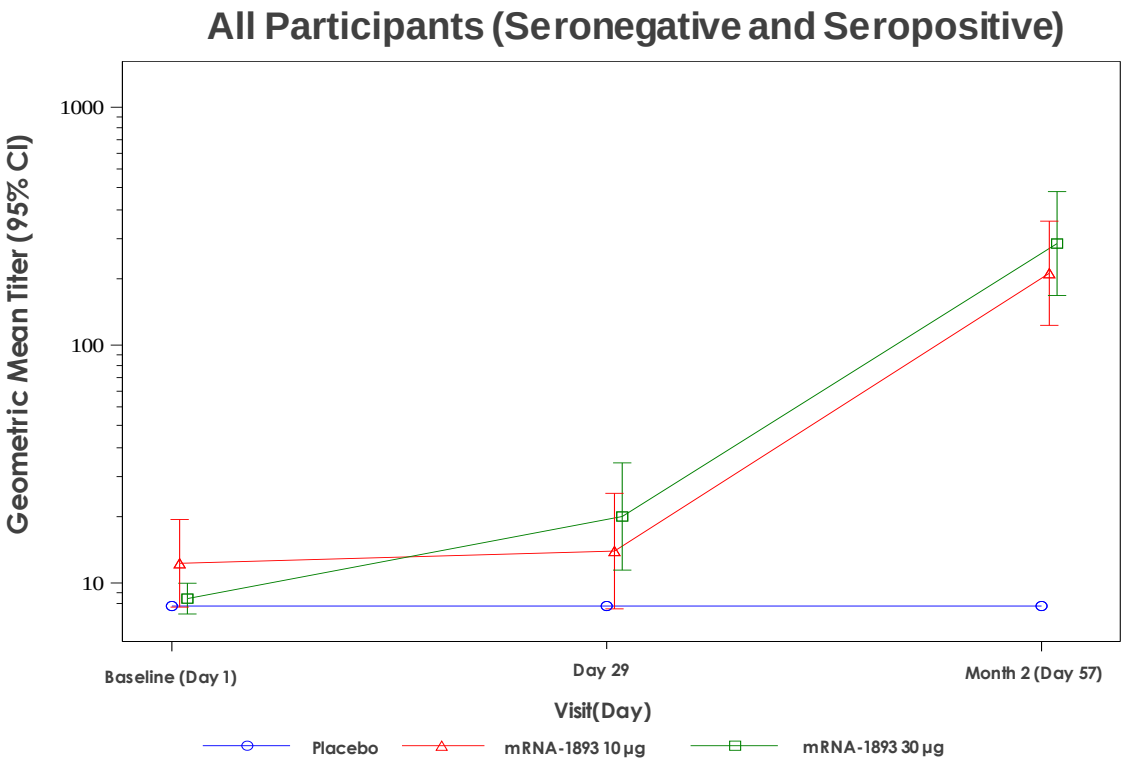
Immunogenicity in flavivirus baseline seropositive participants

Immunogenicity in Flavivirus Baseline Seropositive Participants (Per-Protocol set)			
	$PRNT_{50}$		
	Placebo	**10µg**	**30µg**
Baseline	8.0	41.5	12.3
GMT post-dose 1	8.0	147.9	88.1
GMT post-dose 2	8.0	224.1	150.9
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	50%; 50%	75%; 75%
	MN		
	Placebo	**10µg**	**30µg**
Baseline	14.0	54.0	39.4
GMT post-dose 1	14.0	375.0	226.7
GMT post-dose 2	14.0	645.9	578.5
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	100%; 75%	75%; 75%

Seroconversion is defined as a change in $PRNT_{50}$ from below the lower limit of quantification to a $PRNT_{50}$ equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing $PRNT_{50}$ titers; Seroconversion is defined as a change in MN from below the lower limit of quantification to a MN equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing MN titers.

Zika vaccine (mRNA-1893) Phase 1 interim analysis

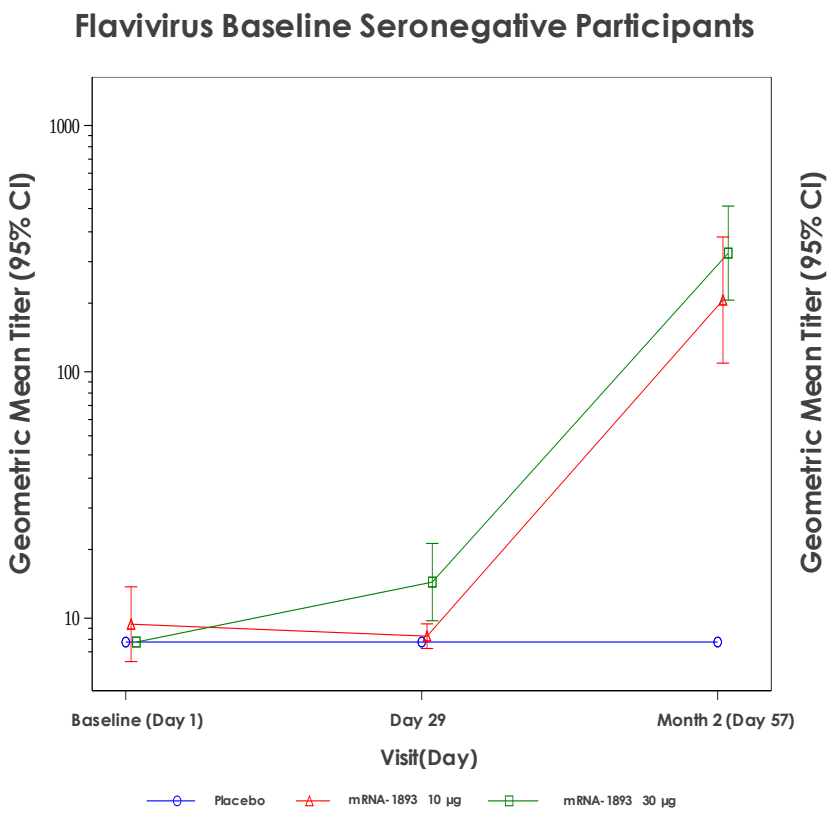
Immunogenicity ($PRNT_{50}$) at Day 57 – all participants (per-protocol set)

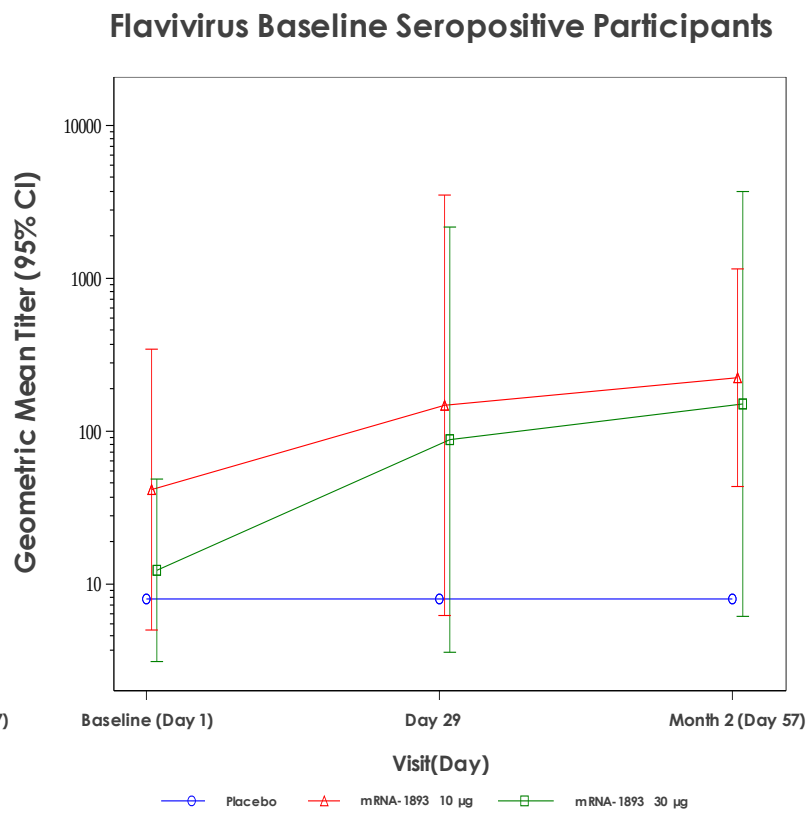


- Both 10 µg and 30 µg dose levels induce a strong ZIKV- specific neutralizing antibody response
- There is a clear benefit of a two-dose series given at 28-day interval

Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity ($PRNT_{50}$) at Day 57 by baseline flavivirus serostatus (per-protocol set)



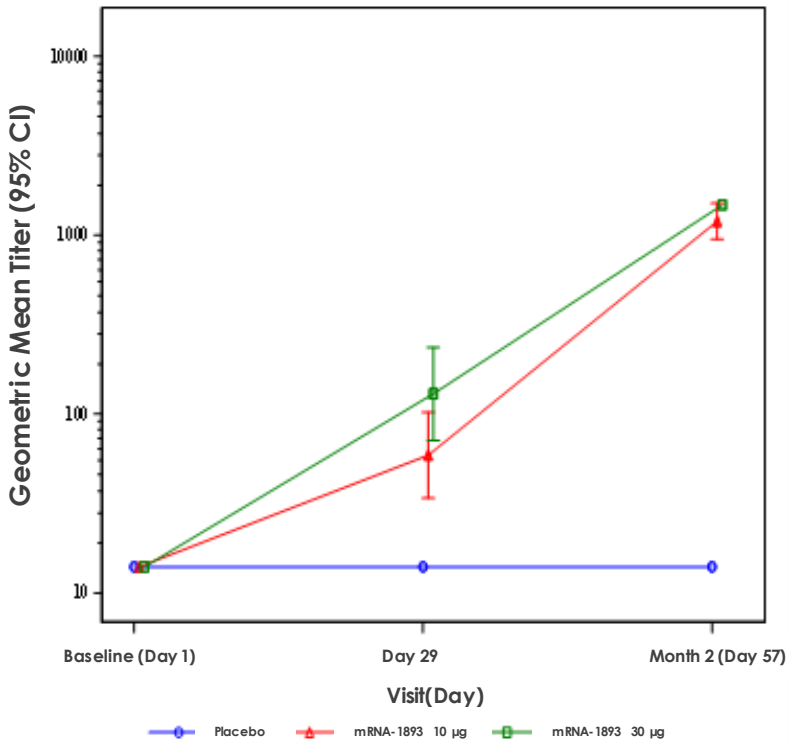


- In seronegative participants, there was a clear advantage of a second vaccine administration in terms of ZIKV-specific neutralizing antibody response
- In seronegative participants, a dose response observed after first vaccine administration
- In seropositive participants, mRNA-1893 was able to mount a ZIKV-specific neutralizing antibody response; compatible with a specific booster response

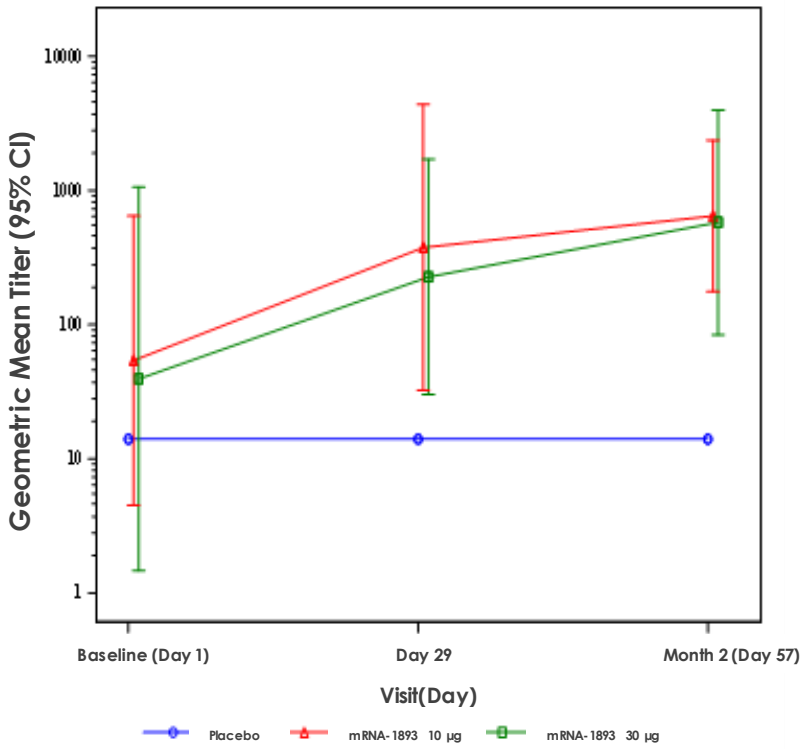
Zika vaccine (mRNA-1893) Phase 1 interim analysis

Immunogenicity (MN) at Day 57 by baseline flavivirus serostatus (per-protocol set)

Flavivirus Baseline Seronegative Participants



Flavivirus Baseline Seropositive Participants



- MN data are consistent with the $PRNT_{50}$ data
- MN titers are higher compared to those reported by $PRNT_{50}$; consistent with the known differences between the assays

Zika vaccine (mRNA-1893) Phase 1 interim analysis

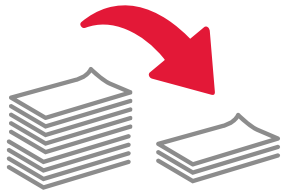
Immunogenicity at Day 57 – conclusions

- The 10 µg and 30 µg dose levels induce a strong neutralizing ZIKV-specific antibody response in both flavivirus infection naive participants and in participants with pre-existing flavivirus antibodies as shown by the GMTs and the seroconversion rates

- Notably, the 30 µg dose level is sufficient to seroconvert baseline flavivirus seronegative subjects following only a single vaccine administration

- Both MN and $PRNT_{50}$ assays provide equivalent guidance for data interpretation in terms of ZIKV-specific neutralizing immune response

Zika vaccine (mRNA-1893) conclusions

Large product opportunity	Higher probability of technical success	Accelerated research and development timelines	Greater capital efficiency over time (vs. recombinant)
			
Market opportunity	**Probability of success**	**Time requirements**	**Power of the platform**
We believe Zika (mRNA-1893) is a multi-hundred million dollar opportunity	Improved sequence for mRNA-1893 is based on Rio strain	IND to Phase 1 in 12 months	Same manufacturing facility, same process

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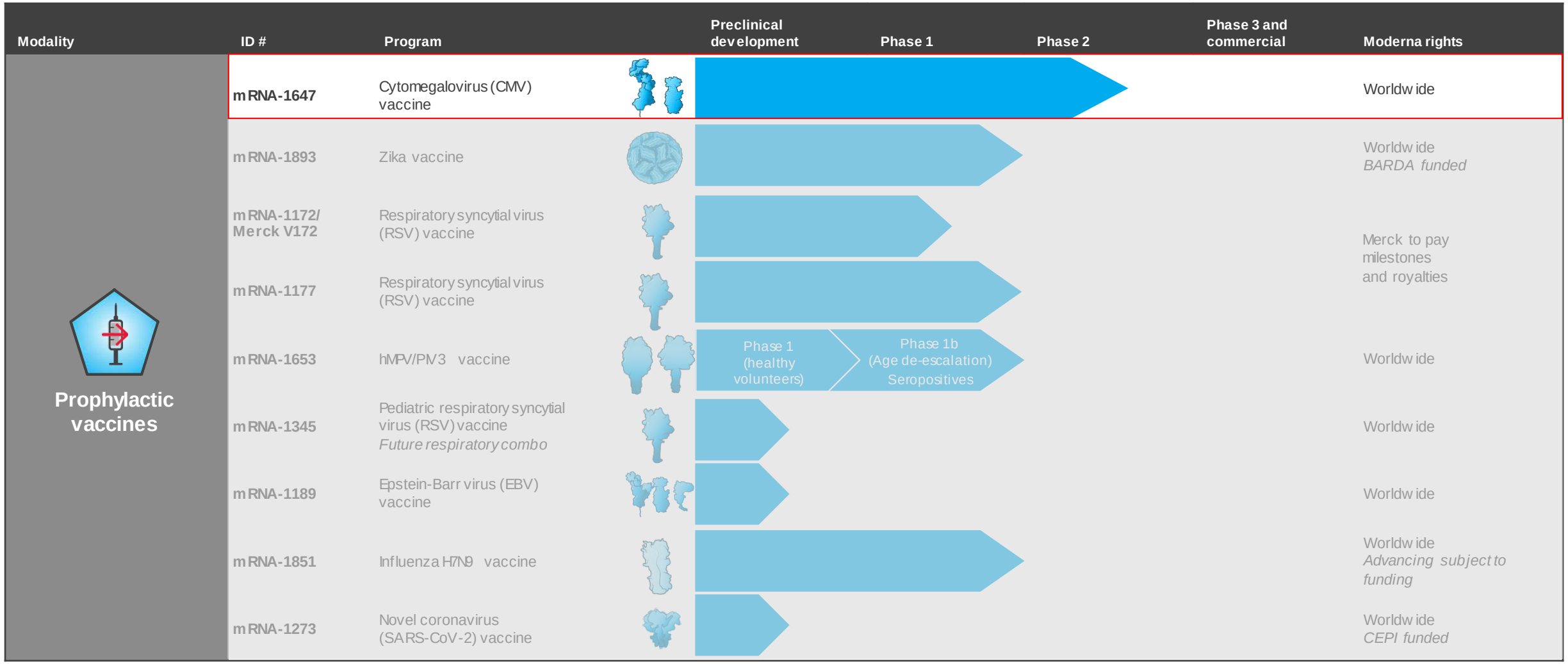
Prophylactic vaccines modality

CMV vaccine (mRNA-1647)



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Congenital cytomegalovirus overview

- Cytomegalovirus: CMV is a common infection and is the leading cause of birth defects in the US
  - 0.65% of US newborns infected annually (~25,000 US newborns)

- **Disease burden:** Significant impact on survivors, families, caregivers and health systems
  - 20% of newborns with CMV infection have permanent neurodevelopmental disability
  - 10-30% of infants with severe CMV disease will die in their first year of life

- **Unmet need:** No approved CMV vaccine

CMV infection sequelae	
Neonatal period	Jaundice Microcephaly Hearing loss Vision loss Seizures Low birth weight
Infancy, childhood, adulthood	Deafness/Hearing loss Neurodevelopmental delay Seizures

mRNA vaccine, IM-administered, designed to make gB and Pentamer antigens in their natural conformations to prevent or control CMV infection

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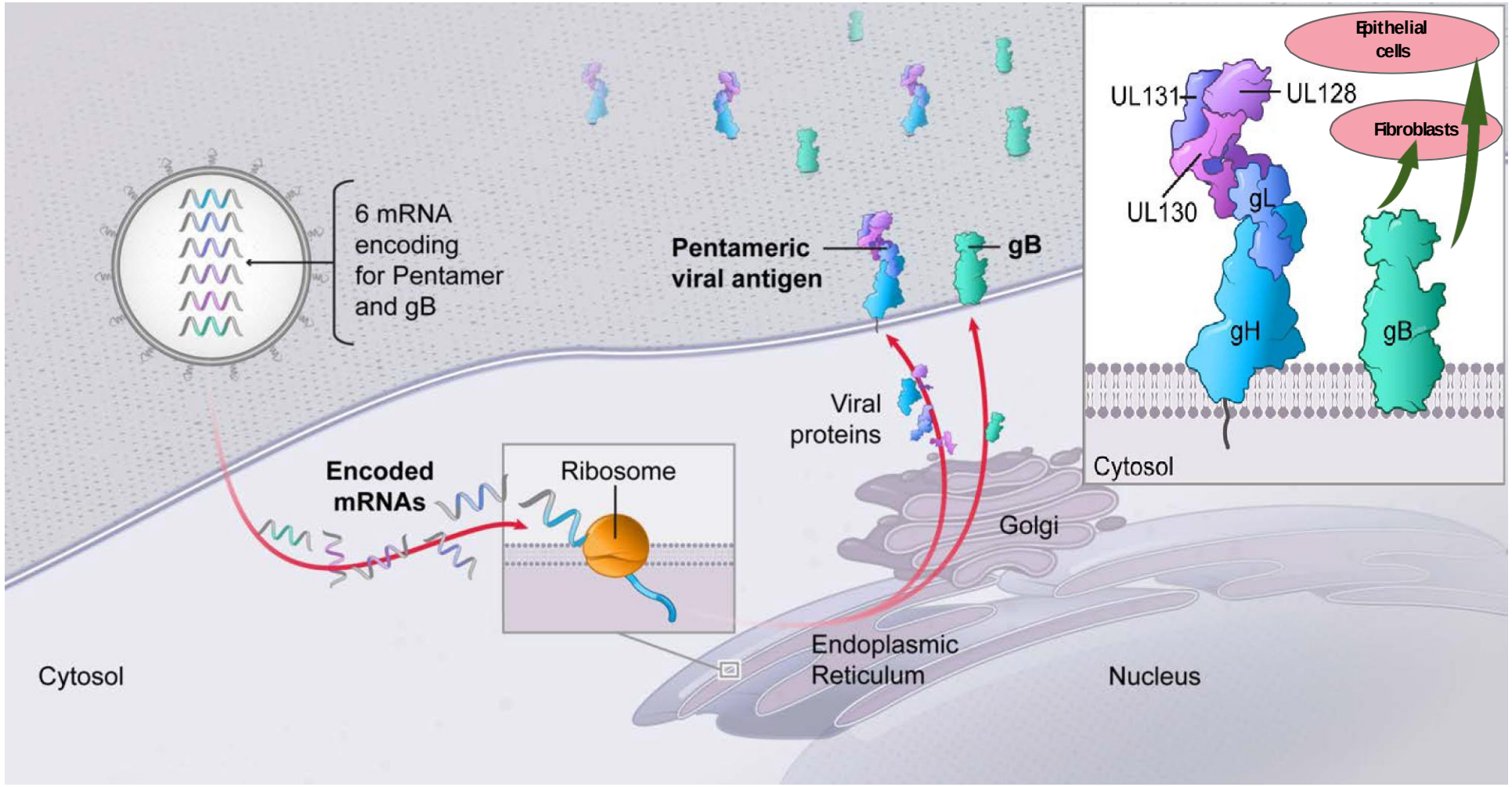
Congenital CMV vaccine includes 6 mRNAs

5 encode the Pentamer, 6th encodes gB antigen



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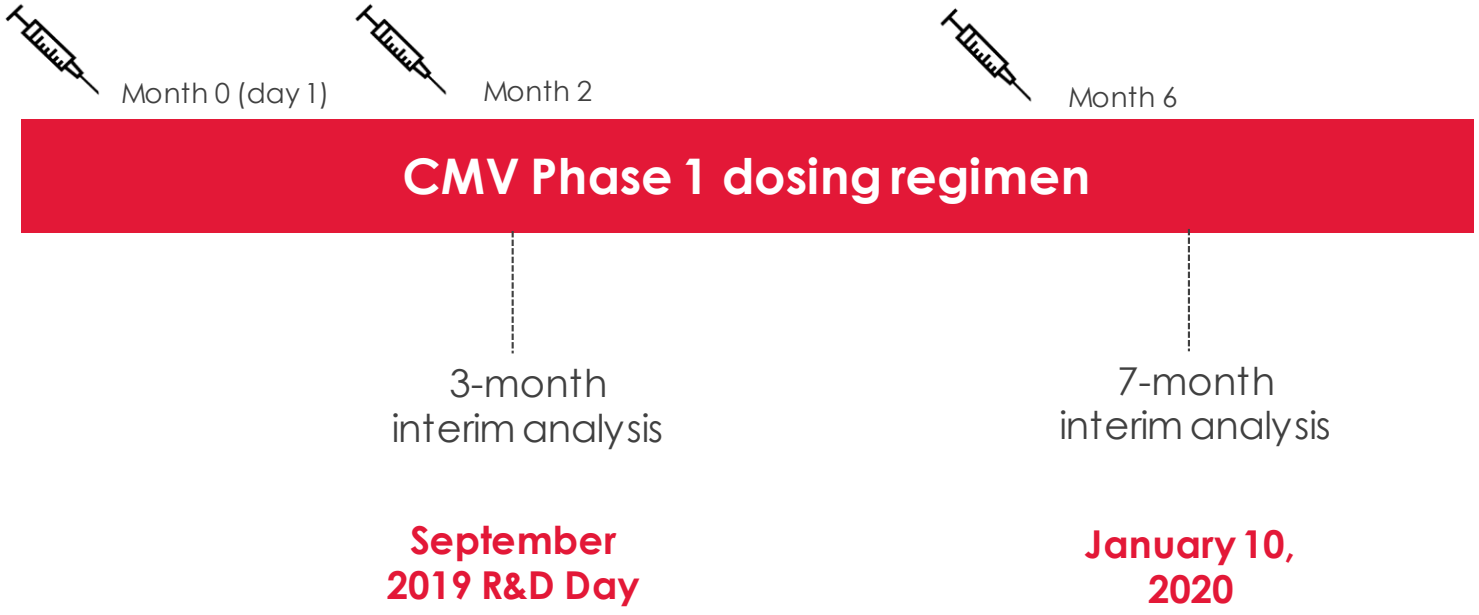
CMV data generation to date



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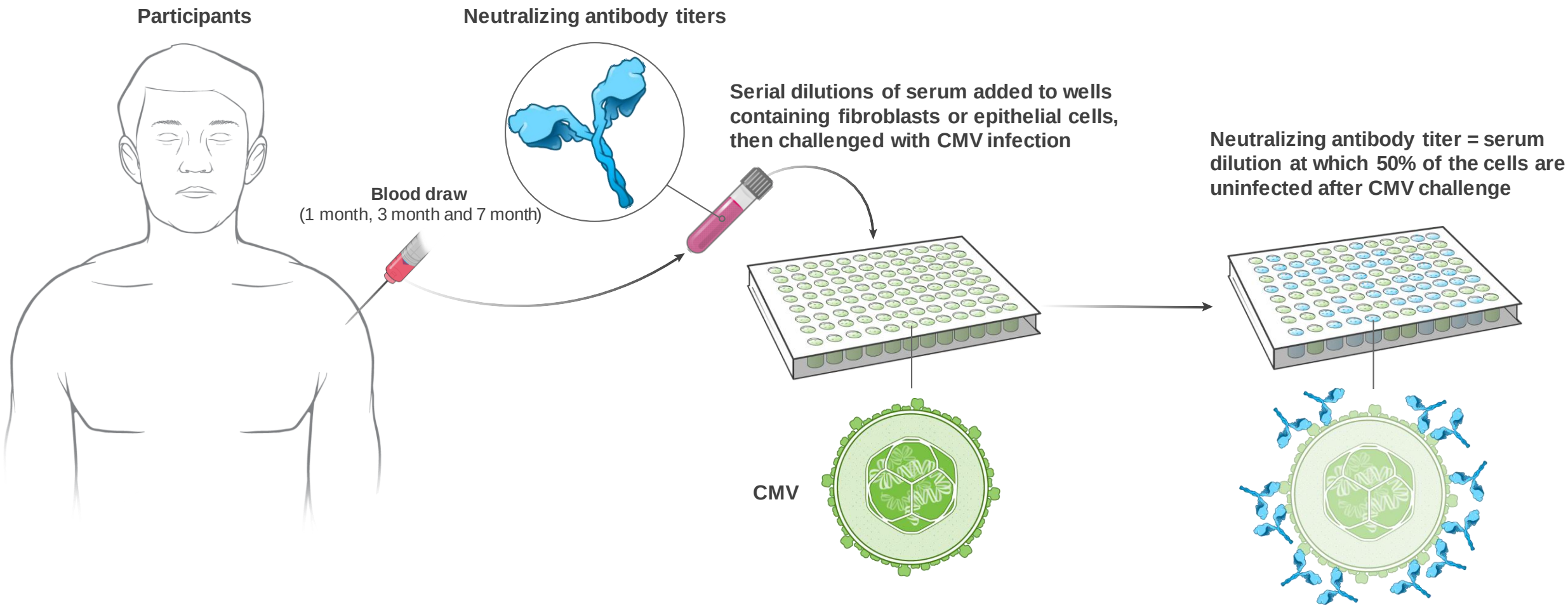
Neutralizing antibody titers



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Immunogenicity in CMV-seronegative participants, per-protocol set

Neutralizing Antibodies Against Epithelial Cell Infection CMV-seropositive GMT benchmark = 5,917[1]						
		Phase B			Phase C	
	Placebo	30 µg	90 µg	180 µg	Placebo	**300 µg**
GMT baseline	8	8	8	8	8	**8**
GMT post 1st vaccination (month 1)	8	37	708	1,387	8	**1,481**
GMT post 2nd vaccination (month 3)	12	3,263	15,305	30,743	8	**43,564**
GMT post 3rd vaccination (month 7)	**18**	**16,587**	**63,929**	**62,118**	**NA**	**NA**
GMT/benchmark post 2nd vaccination	---	0.6	2.6	5.2	---	**7.4**
GMT/benchmark post 3rd vaccination	---	**2.8**	**10.8**	**10.5**	**--**	**NA**

Neutralizing Antibodies Against Fibroblast Infection CMV-seropositive GMT benchmark = 1,449[1]						
		Phase B			Phase C	
	Placebo	30 µg	90 µg	180 µg	Placebo	**300 µg**
GMT baseline	8	8	8	8	8	**8**
GMT post 1st vaccination (month 1)	8	8	24	10	8	**18**
GMT post 2nd vaccination (month 3)	10	305	1,141	1,264	8	**1,091**
GMT post 3rd vaccination (month 7)	**17**	**1,131**	**1,890**	**2,029**	**NA**	**NA**
GMT/benchmark post 2nd vaccination	---	0.2	0.8	0.9	---	**0.8**
GMT/benchmark post 3rd vaccination	---	**0.8**	**1.3**	**1.4**	**NA**	**NA**

Bold face = new data as of January 2020

GMT = geometric mean titer; CMV-seropositive benchmark values derived from baseline values of all CMV seropositive participants; NA= not available

[1] The seropositive benchmark at the 3-month interim analysis as disclosed in September was 5,588 and 1,295 for epithelial cell and fibroblast infection respectively, with an n=38. With the enrollment of an additional 30 seropositive subjects in connection with the phase C 300 µg dose level, the seropositive benchmark is now 5,917 and 1,449 for epithelial and fibroblast respectively, with an n=68.

- Neutralizing antibody titers against both epithelial cell and fibroblast infection continued to increase after the third vaccination
- Neutralizing titers against epithelial cell infection were 10-fold higher than CMV seropositive GMT benchmark after the third vaccination
- Neutralizing antibody titers against fibroblasts were 1.4-fold higher after the third vaccination

Subject n at each timepoint, epithelial cell and fibroblast infection

	Pla	30 µg	90 µg	180 µg	Pla	300 µg
Baseline	13	17	14	15	3	13
Month 1	12	17	10	15	3	12
Month 3	11	14	12	12	3	11
Month 7	10	11	12	11	NA	NA

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Immunogenicity in CMV-seropositive participants, per-protocol set

Neutralizing Antibodies Against Epithelial Cell Infection CMV-seropositive GMT benchmark = 5,917[1]						
	Phase B				Phase C	
	Placebo	30 µg	90 µg	180 µg	Placebo	**300 µg**
GMT baseline	8,169	3,614	5,634	5,700	6,900	**7,179**
GMT post 1st vaccination (month 1)	7,891	24,752	39,020	52,775	6,673	**84,628**
GMT post 2nd vaccination (month 3)	7,490	49,390	62,400	119,829	5,974	**156,583**
GMT post 3rd vaccination (month 7)	**7,647**	**76,914**	**141,020**	**211,503**	**NA**	**NA**
GMR post 2nd vaccination	0.9	14.4	9.9	19.4	0.9	**17.3**
GMR post 3rd vaccination	**1.0**	**26.2**	**22.4**	**40.8**	**NA**	**NA**

Neutralizing Antibodies Against Fibroblast Infection CMV-seropositive GMT benchmark = 1,449[1]						
	Phase B				Phase C	
	Placebo	30 µg	90 µg	180 µg	Placebo	**300 µg**
GMT baseline	1,298	1,094	1,458	1,371	3,631	**1,836**
GMT post 1st vaccination (month 1)	1,278	2,654	3,885	3,879	3,382	**5,419**
GMT post 2nd vaccination (month 3)	1,451	2,517	3,891	5,578	2,797	**7,788**
GMT post 3rd vaccination (month 7)	**2,673**	**3,412**	**8,433**	**6,098**	**NA**	**NA**
GMR post 2nd vaccination	1.1	2.5	3.0	4.1	0.8	**3.8**
GMR post 3rd vaccination	**2.2**	**4.0**	**6.5**	**3.9**	**NA**	**NA**

- In seropositive subjects, the third vaccination boosted neutralizing antibody titers by 22-fold and 40-fold over baseline levels
- Neutralizing antibody titers against fibroblast infection were boosted 4-fold to 6-fold over baseline levels

Subject n at each timepoint epithelial cell infection

	Pla	30 µg	90 µg	180 µg	Pla	300 µg
Baseline	14	13	12	13	3	13
Month 1	14	13	12	13	3	13
Month 3	12	11	9	9	3	9
Month 7	12	10	9	6	NA	NA

Subject n at each timepoint fibroblast infection

	Pla	30 µg	90 µg	180 µg	Pla	300 µg
Baseline	14	13	12	13	3	13
Month 1	14	13	12	13	3	13
Month 3	12	11	9	9	3	9
Month 7	12	10	9	5	NA	NA

Bold face = new data as of January 2020
GMT = geometric mean titer; GMR=geometric mean ratio, defined as the average of the ratio between Baseline/post 2nd or 3rd vaccination for each participant
CMV-seropositive benchmark values derived from baseline values of all CMV seropositive participants; NA= not available
GMT values at 30µg dose post 2nd vaccination for the 3-month IA September disclosure is based on n=10, and for the 7-month IA January disclosure is based on n=11
[1] The seropositive benchmark at the 3-month interim analysis as disclosed in September was 5,588 and 1,295 for epithelial cell and fibroblast infection respectively, with an n=38. With the enrollment of an additional 30 seropositive subjects in connection with the phase C 300 µg dose level, the seropositive benchmark is now 5,917 and 1,449 for epithelial and fibroblast respectively, with an n=68.

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Solicited adverse reactions (AR) post 2nd vaccination, solicited safety set

		CMV Serostatus at Baseline											
		CMV-seronegative						CMV-seropositive					
		Phase B				Phase C		Phase B				Phase C	
		Placebo	30 µg	90 µg	180 µg	Placebo	300 µg	Placebo	30 µg	90 µg	180 µg	Placebo	300 µg
Local ARs	**Pain**	-	11 (73%) -	11 (79%) 2 (14)	12 (80%) 2 (13)	-	**10 (91%)** **2 (18)**	-	9 (75%) 1 (8)	10 (77%) -	10 (91%) 3 (27)	-	**9 (100%)** **3 (33)**
	Redness	-	-	-	3 (21) -	-	**2 (22)** **1 (11)**	-	-	-	2 (18) 1 (9)	-	**-**
	Swelling	-	-	-	-	-	**2 (25)** **1 (13)**	-	-	-	1 (9) -	-	**1 (14)** **-**
Most common systemic ARs	**Headache**	3 (25) -	5 (33) -	8 (57) -	9 (60) 2 (13)	-	**9 (82)** **-**	2 (14) -	4 (33) 1 (8)	6 (46) -	9 (82) 2 (18)	-	**8 (89)** **2 (22)**
	Fatigue	2 (17) -	5 (33) 1 (7)	6 (43) 1 (7)	11 (73) 1 (7)	-	**9 (82)** **-**	1 (7) -	7 (58) 3 (25)	9 (69) 1 (8)	8 (73) 3 (27)	-	**7 (78)** **2 (22)**
	Myalgia	1 (8) -	5 (33) 1 (7)	6 (43) 3 (21)	11 (73) 2 (13)	1 (33) -	**7 (70)** **1 (10)**	-	5 (42) 4 (33)	9 (69) 1 (8)	7 (64) 2 (18)	-	**7 (78)** **1 (11)**
	Arthralgia	-	4 (27) -	5 (36) -	9 (60) 2 (13)	1 (33) -	**4 (40)** **1 (10)**	-	5 (42) 3 (25)	6 (46) -	5 (46) 2 (18)	-	**8 (89)** **1 (11)**
	Nausea	1 (8) -	4 (27) -	4 (29) -	7 (47) 1 (7)	-	**4 (40)** **1 (10)**	-	2 (17) 1 (8)	7 (54) 1 (8)	7 (64) 2 (18)	-	**6 (67)** **1 (11)**
	Chills	1 (8) -	3 (20) 1 (7)	6 (43) 1 (7)	11 (73) 3 (20)	1 (33) -	**8 (80)** **1 (10)**	-	6 (50) 1 (8)	8 (62) 1 (8)	9 (82) 3 (27)	-	**7 (78)** **2 (22)**
	Fever	-	3 (20) -	3 (21) 1 (7)	5 (33) -	1 (33) -	**6 (55)** **1 (9)**	-	2 (17) -	6 (46) 3 (23)	6 (55) 2 (18)	-	**6 (67)** **3 (33)**

Values represent n (%) participants reporting each AR, red text=grade 3 ARs

- One asymptomatic Grade 4 elevation in partial thromboplastin time (PTT), Grade 1 at baseline, deemed related to study product, normal value on retesting (180 µg treatment group)
- No vaccine-related serious adverse events (SAEs)

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Solicited adverse reactions (AR) post 3rd vaccination, solicited safety set

		CMV Serostatus at Baseline							
		CMV-seronegative				CMV-seropositive			
		Placebo	30 µg	90 µg	180 µg	Placebo	30 µg	90 µg	180 µg
Local ARs	**Pain**	1 (9%) -	8 (73%) -	7 (54%) 1 (8)	9 (75%) 1 (8)	-	8 (73%) -	6 (60%) -	6 (100%) -
	Redness	-	-	2 (15) -	1 (8) -	-	-	2 (20) -	1 (17) -
	Swelling	-	-	1 (8) -	1 (8) -	-	-	1 (10) -	-
Most common systemic ARs	**Headache**	1 (9) -	4 (36) -	4 (31) -	6 (50) 2 (17)	3 (23) -	5 (46) 1 (9)	6 (60) -	5 (83) 1 (17)
	Fatigue	1 (9) -	4 (36) -	5 (39) 1 (8)	7 (58) 2 (17)	1 (8) -	5 (46) -	7 (70) -	4 (67) 1 (17)
	Myalgia	-	3 (27) -	6 (46) 1 (8)	6 (50) 2 (17)	-	5 (46) 1 (9)	6 (60) -	3 (50) -
	Arthralgia	-	3 (27) -	5 (39) -	6 (50) -	-	4 (36) -	4 (40) -	2 (33) -
	Nausea	-	2 (18) -	3 (23) -	4 (33) -	1 (8) -	4 (36) 1 (9)	5 (50) -	1 (17) -
	Chills	-	2 (18) -	5 (39) -	4 (33) 1 (8)	-	3 (27) 1 (9)	6 (60) -	4 (67) 1 (17)
	Fever	-	1 (9) -	1 (8) -	3 (25) -	-	1 (9) -	4 (40) 1 (10)	3 (50) 1 (17)

Values represent n (%) participants reporting each AR, red text=grade 3 ARs

- No vaccine-related serious adverse events (SAEs)

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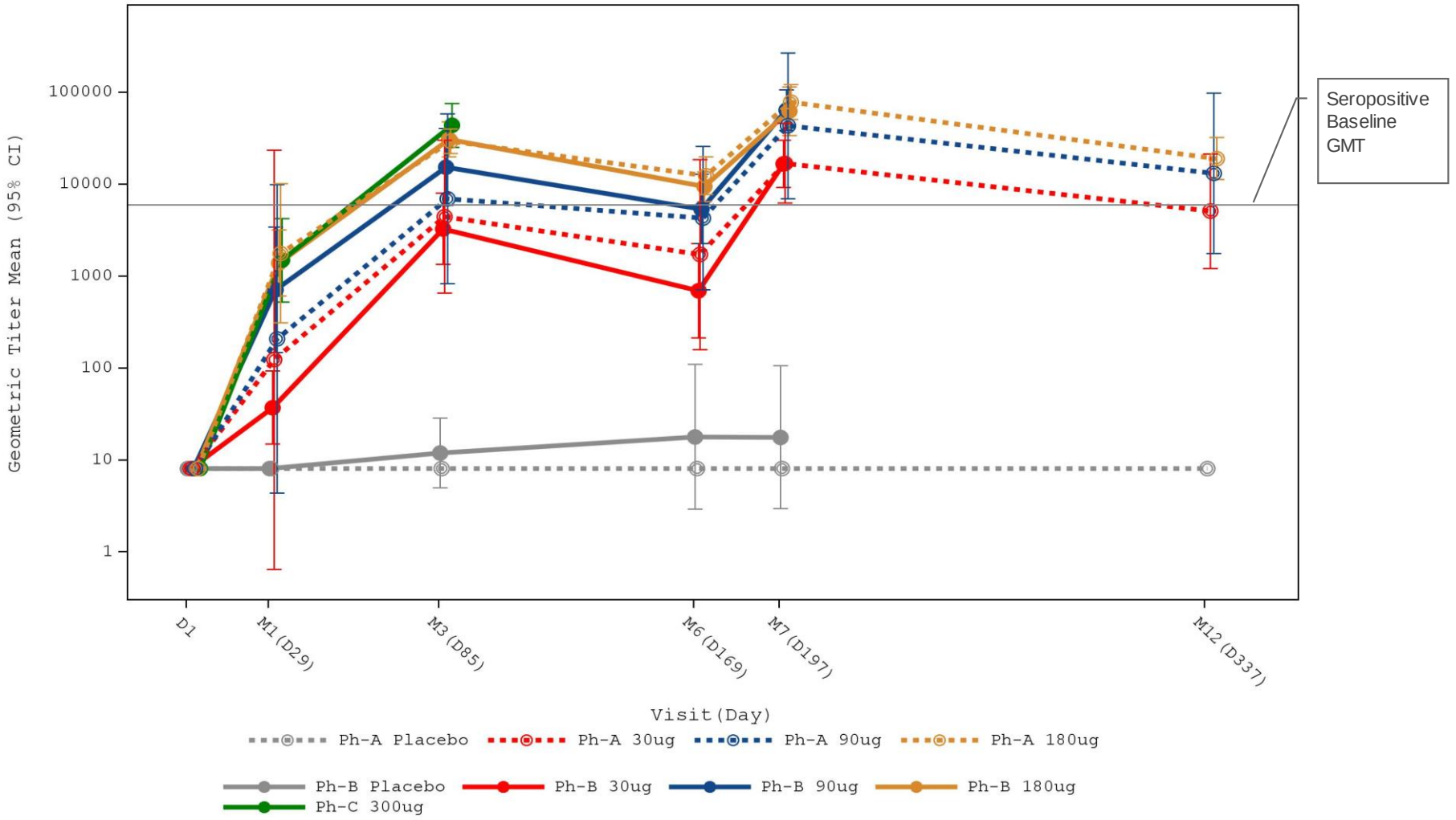
Durable immunogenicity demonstrated in seronegative initial cohort

Neutralizing antibodies against epithelial cell infection



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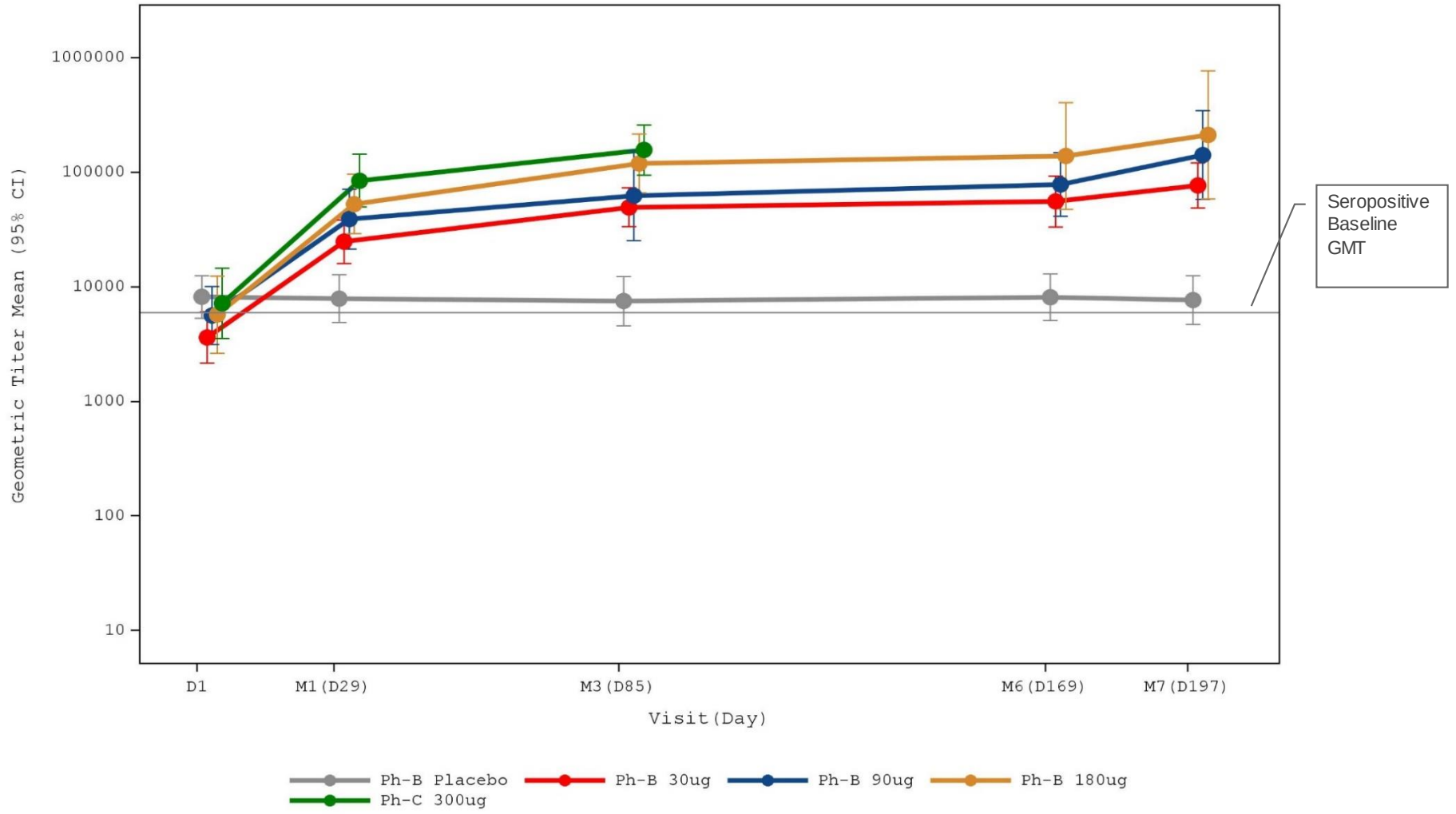
Additional boosting demonstrated in seropositive cohort

Neutralizing antibodies against epithelial cell infection



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CMV vaccine (mRNA-1647)

7-month interim analysis summary

- **Safety:** The vaccine was generally well-tolerated and there were no vaccine-related serious adverse events (SAEs). Safety and tolerability at the 300µg dose level was comparable to that observed at the 180µg dose level

- **In the CMV-seronegative group at seven months, neutralizing antibody titers:**
  - Continued to increase after the third vaccination in both epithelial cell and fibroblast assays
  - Against epithelial cell infection were greater than 10-fold higher than CMV-seropositive baseline titers at the 90 and 180 µg dose levels after the third vaccination, compared to 3-fold to 5-fold higher after the second vaccination
  - Against fibroblast infection were 1.4-fold higher than CMV-seropositive baseline titers at the 90 and 180 µg dose levels after the third vaccination, compared to titers that were comparable to CMV-seropositive baseline titers after the second vaccination

- **In the CMV-seropositive group, neutralizing antibody titers:**
  - Continued to increase in both epithelial cell and fibroblast assays
  - Boosted against epithelial cell infection to levels of 22-fold to 40-fold over baseline across treatment groups, compared to 10-fold to 19-fold over baseline after the second vaccination
  - Boosted neutralizing antibody titers against fibroblast infection to levels of 4-fold to 6-fold over baseline across treatment groups, compared to 2-fold to 4-fold over baseline after the second vaccination

- **Early evidence of durability out to 12 months**

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Late stage development for CMV vaccine (mRNA-1647)

Phase 2 dose confirmation study

- 3 dose levels; randomized, observer-blind, placebo-controlled, multicenter
- 252 seronegative & seropositive adults
- Utilizes intended Phase 3 formulation; same lipid nanoparticle (LNP) used in Phase 1
- Phase 2 study fully enrolled; Closely monitoring trial given COVID-19 impact
- Some participants have not yet received all scheduled doses of the vaccines. Some participants will not be able to receive their next vaccine dose on time or at all due to the disruptions from COVID-19
- Evaluating the impact on the integrity of the trial

Planned pivotal Phase 3 trial

- **Primary endpoint**: prevention of primary CMV infection in a population that includes women of childbearing age (WOCBA)
- Intended to begin in 2021 in USA and Europe; RFP sent to CROs
- Expect **<8,000 participants**
- Preparation and product manufacturing underway
- Phase 3 trial in WOCBA: costs currently estimated at $200-250 million[1]

1. Current estimates based on benchmarks; final trial design and costs remain to be determined

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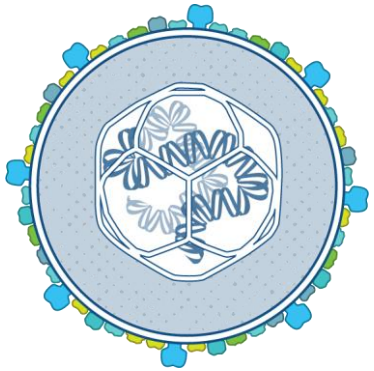
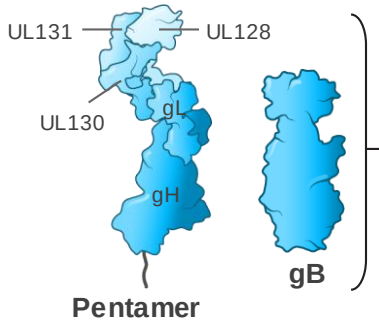
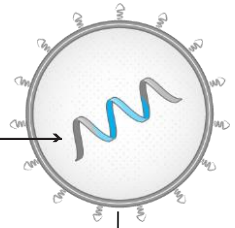
Determining prevention of infection in baseline seronegative vaccinated participants

Cytomegalovirus (CMV)





mRNA-1647



Vaccinated participant (baseline seronegative)

Antibodies against other CMV antigens not included in vaccine indicates infection

CMV surface antigens

Pentamer (UL131, UL128, UL130, gL, gH)
gB

} **Antigens included in mRNA-1647**

gM
gN
gO
PC

} Antigens not in mRNA-1647

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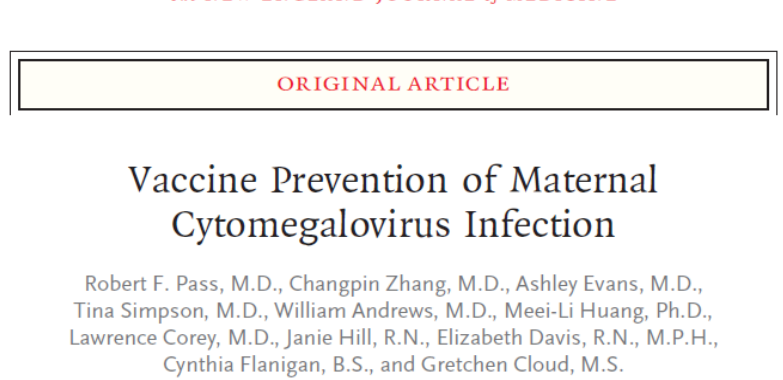
CMV is a blockbuster opportunity

- Estimated annual peak sales of $2-5 billion
- Assuming GARDASIL[2] like average selling price; GM estimated to be >90%[3] (EBIT margins estimated at approximately 50%)
- NEJM phase 2 publication by Pass et al. shows 50% vaccine efficacy with Sanofi's vaccine targeting only the gB antigen
- Moderna owns worldwide rights to mRNA-1647



1. Merck investor day, 2019
2. GARDASIL® is a registered trademark of Merck & Co., Inc
3. Gross margin at scale in the U.S.

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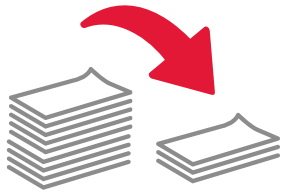
CMV vaccine (mRNA-1647) conclusion

Large product opportunity	Higher probability of technical success	Accelerated research and development timelines	Greater capital efficiency over time (vs. recombinant)
			
Market opportunity	**Probability of success**	**Time requirements**	**Power of the platform**
We believe CMV (mRNA-1647) is a multi-billion dollar opportunity	Sanofi test with gB only gets 50% efficacy	CMV Phase 3 preparations underway	CMV manufacturing scale (from 5g to 150g)

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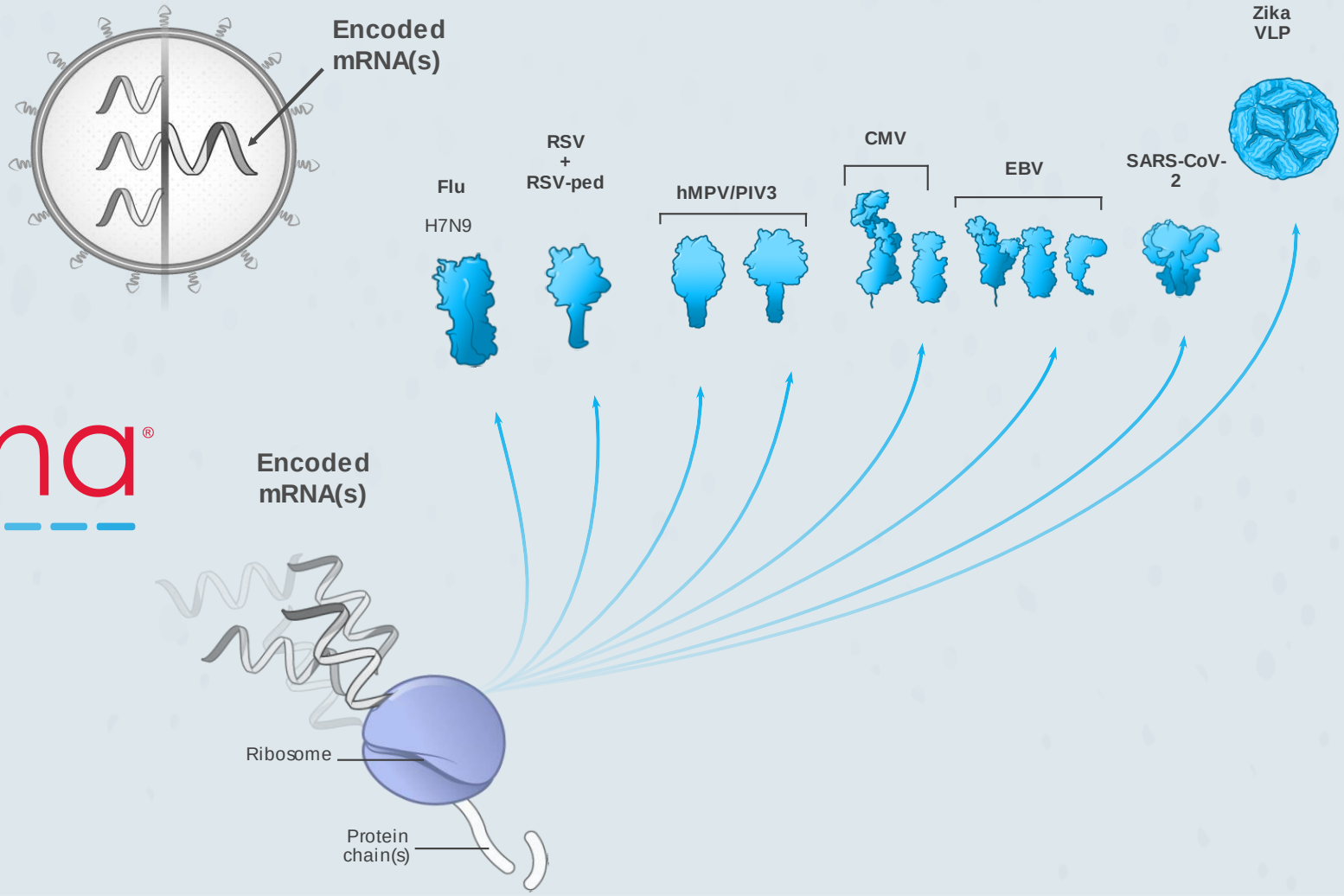

Vaccines Against Respiratory Diseases

Tal Zaks, M.D., Ph.D., Chief Medical Officer

April 14, 2020

Prophylactic vaccines modality

Modality	ID #	Program	Preclinical development / Phase 1 / Phase 2 / Phase 3 and commercial	Moderna rights
Prophylactic vaccines	mRNA-1647	Cytomegalovirus (CMV) vaccine		Worldwide
	mRNA-1893	Zika vaccine		Worldwide *BARDA funded*
	mRNA-1172/ Merck V172	Respiratory syncytial virus (RSV) vaccine		Merck to pay milestones and royalties
	mRNA-1177	Respiratory syncytial virus (RSV) vaccine		
	mRNA-1653	hMPV/PIV3 vaccine	Phase 1 (healthy volunteers) → Phase 1b (Age de-escalation) Seropositives	Worldwide
	mRNA-1345	Pediatric respiratory syncytial virus (RSV) vaccine *Future respiratory combo*		Worldwide
	mRNA-1189	Epstein-Barr virus (EBV) vaccine		Worldwide
	mRNA-1851	Influenza H7N9 vaccine		Worldwide *Advancing subject to funding*
	mRNA-1273	Novel coronavirus (SARS-CoV-2) vaccine		Worldwide *CEPI funded*

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Human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) overview

- hMPV and PIV3 are RNA viruses that are important causes of respiratory tract infections, particularly in children

- Increasing rates of diagnosis and association with hospitalization for respiratory illness

- **Disease burden:** Major cause of hospitalization due to respiratory infection
  - —Symptoms range from mild upper respiratory tract infection to life threatening severe bronchiolitis and pneumonia
  - —Both viruses cause clinically indistinguishable disease
- **Target population: infants**
  - —Most hMPV or PIV3-associated hospitalizations in children occur under 2 years old
  - —Hospitalization rates in children < 5 years old in the U.S.:
    - hMPV: 1.2 per 1,000
    - PIV3: 0.5 per 1,000
- **Unmet need:** No approved hMPV or PIV3 vaccine
  - —Other companies' previous attempts focused only on hMPV or PIV alone (no known attempts at a combination vaccine)

hMPV and PIV3 infection sequelae
High fever
Otitis media
Thick nasal discharge
Breathing difficulties, coughing
Croup
Pneumonia
Bronchiolitis

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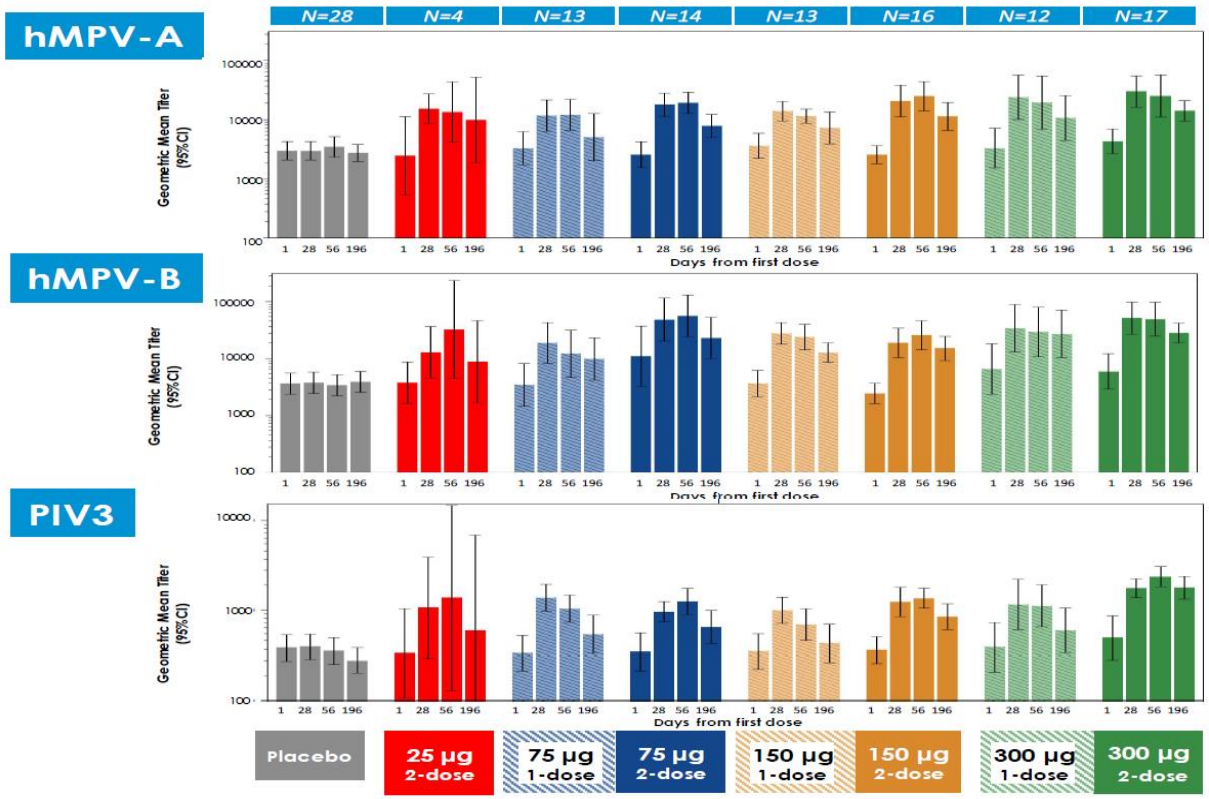
hMPV/PIV3 vaccine (mRNA-1653)

Phase 1 in healthy adults; Interim results, through 7 months

Neutralizing Antibody Titers Through Day 196 by Dose Level and Regimen



Immunogenicity

- Single vaccination boosted serum neutralization titers against hMPV and PIV3 at all dose levels tested
- Second vaccination did not further boost antibody titers, suggesting a single vaccination was sufficient to achieve a plateau in neutralizing antibodies in this pre-exposed population
- Second interim data show antibody titers remained above baseline at all dose levels at 7 months after vaccination

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hMPV/PIV3 vaccine (mRNA-1653)

Phase 1 in healthy adults; Summary interim results, through 7 months

Safety and tolerability

- mRNA-1653 was found to be generally well tolerated at all dose levels
- No serious adverse events (SAEs), adverse events of special interest, or adverse events leading to withdrawal were reported
- Injection site pain was the most commonly reported solicited adverse event and grade 3 adverse event

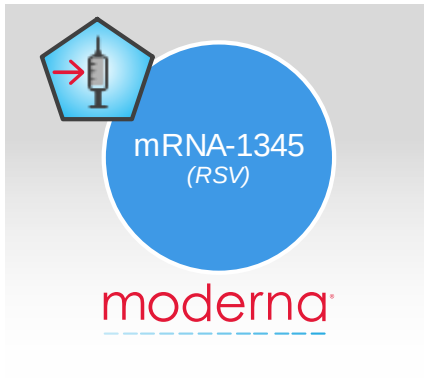
Immunogenicity

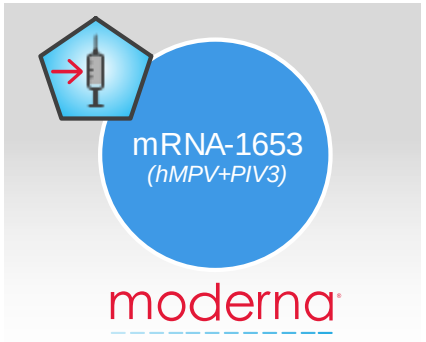
- Single vaccination boosted serum neutralization titers against hMPV and PIV3 at all dose levels testedmRNA-1653 was found to be generally well tolerated at all dose levels
- Neutralizing antibodies against hMPV and PIV3 present at baseline in all subjects, consistent with prior exposure to both viruses
- 1 month after a single vaccination, hMPV and PIV3 neutralization titers ~6x and ~3x baseline, respectively
- Second vaccination did not further boost antibody titers, suggesting a single vaccination was sufficient to achieve a plateau in neutralizing antibodies in this pre-exposed population
- Second interim data show antibody titers remained above baseline at all dose levels at 7 months after vaccination

Pediatric respiratory diseases

RSV, hMPV and PIV3 are leading causes of respiratory illness in young children

	RSV *Respiratory syncytial virus*	**hMPV** *Human metapneumovirus*	**PIV3** *Parainfluenza virus type 3*
Epidemiology	• **Hospitalization rate in children** < 5 years old in the U.S.:~**3:1000**[1] • Associated with estimated 2 million medically attended infections	• **Hospitalization rate in children** < 5 years old in the U.S.:**~1.2:1000**[1] • Associated with estimated 1 million outpatient clinic visits and > 250k ED visits annually among U.S. children < 5 years old[2]	• **Hospitalization rate in children** < 5 years old in the U.S.:**~0.5:1000**[1]
Clinical disease	Upper and lower respiratory tract infection		





1. Williams JV, Edwards KM, Weinberg GA, et al. Population-based incidence of human metapneumovirus infection among hospitalized children. *J Infect Dis*. 2010;201(12):1890-8.
2. Edwards KM, Y. Zhu, M.R. Griffin, G.A. Weinberg, C.B. Hall, P.G. Szilagyi, *et al.* Burden of human metapneumovirus infection in young children. *N. Engl. J. Med.*, 2013;368(7):633-643.

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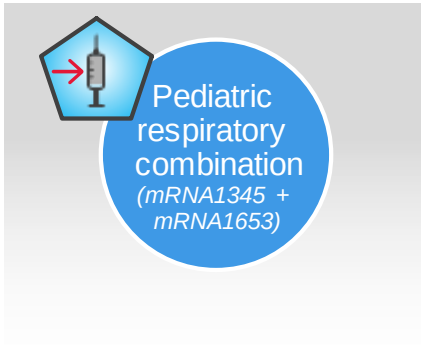
Pediatric respiratory diseases

RSV, hMPV and PIV3 are leading causes of respiratory illness in young children

	RSV *Respiratory syncytial virus*	**hMPV** *Human metapneumovirus*	**PIV3** *Parainfluenza virus type 3*
Epidemiology	• **Hospitalization rate in children** < 5 years old in the U.S.:~**3:1000**[1] • Associated with estimated 2 million medically attended infections	• **Hospitalization rate in children** < 5 years old in the U.S.:**~1.2:1000**[1] • Associated with estimated 1 million outpatient clinic visits and > 250k ED visits annually among U.S. children < 5 years old[2]	• **Hospitalization rate in children** < 5 years old in the U.S.:**~0.5:1000**[1]
Clinical disease	Upper and lower respiratory tract infection		



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Flor Munoz-Rivas, M.D.

Flor Muñoz, MD, is Associate Professor of Pediatrics and Infectious Diseases at Baylor College of Medicine, and Director of Transplant Infectious Diseases at Texas Children's Hospital in Houston, TX. She is a clinician-investigator with various projects supported by the US NIH, CDC, BMGF and industry, focusing on the epidemiology of respiratory infections in healthy and immunocompromised hosts, and the evaluation of vaccines in pregnant women, children, and special populations. She has published substantially on topics related to influenza, RSV, vaccines, and maternal immunization.

Dr. Muñoz is a member of the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID), the CDC's Advisory Committee on Immunization Practices (ACIP) influenza working group, and the American College of Obstetrics and Gynecology (ACOG) Immunization Expert Work Group. She is a member of various academic societies, including the Pediatric Infectious Diseases Society (PIDS), the Society for Pediatric Research (SPR), and the Research Committee of the European Society of Pediatric Infectious Diseases (ESPID). Dr. Munoz serves as chair of the Institutional Review Board (IRB) at Baylor College of Medicine.

RSV – HMPV – PIV
THE NEED FOR A PEDIATRIC RESPIRATORY VIRUS VACCINE

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Disclosures

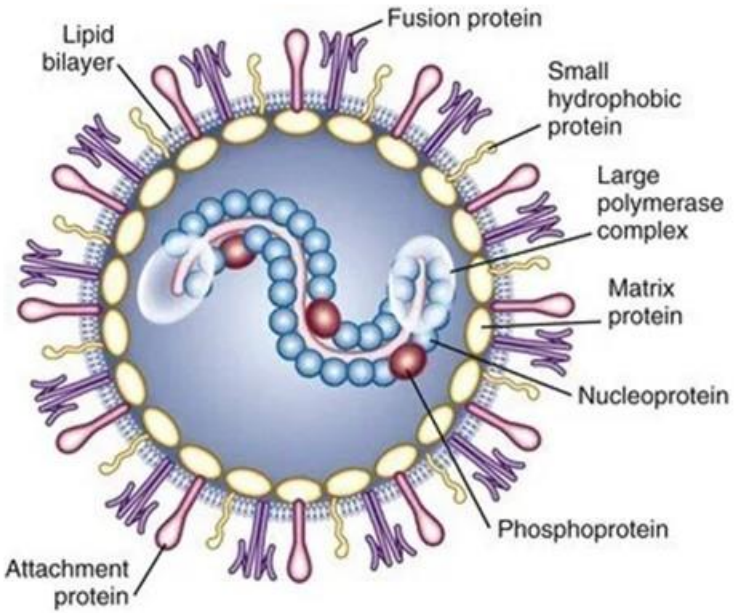
- Research
  - Novavax (RSV vaccine), Janssen (RSV epidemiology)
  - Regeneron (RSV mAb)
  - Biocryst (Peramivir)
  - NIH (epidemiology, surveillance, vaccines, therapeutics - VTEU)
  - CDC (viral surveillance and epidemiology)
- DSMB
  - Moderna (various vaccines)
  - Pfizer (RSV)
  - NIH (various projects)

Texas Children's Hospital

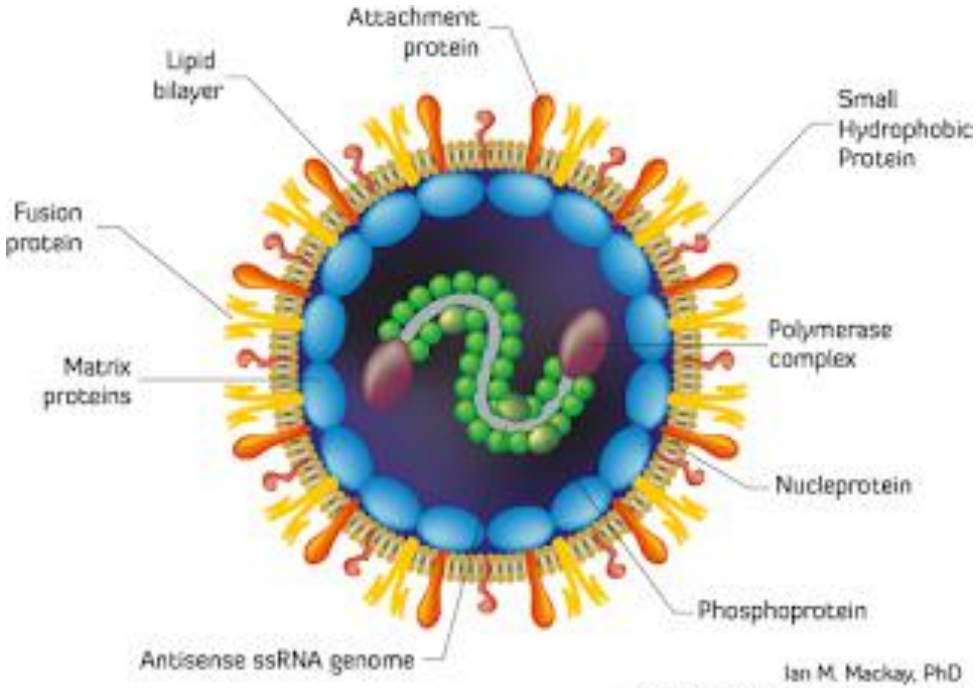
Baylor College of Medicine

Pneumoviruses and Paramyxoviruses Enveloped, Single Stranded RNA

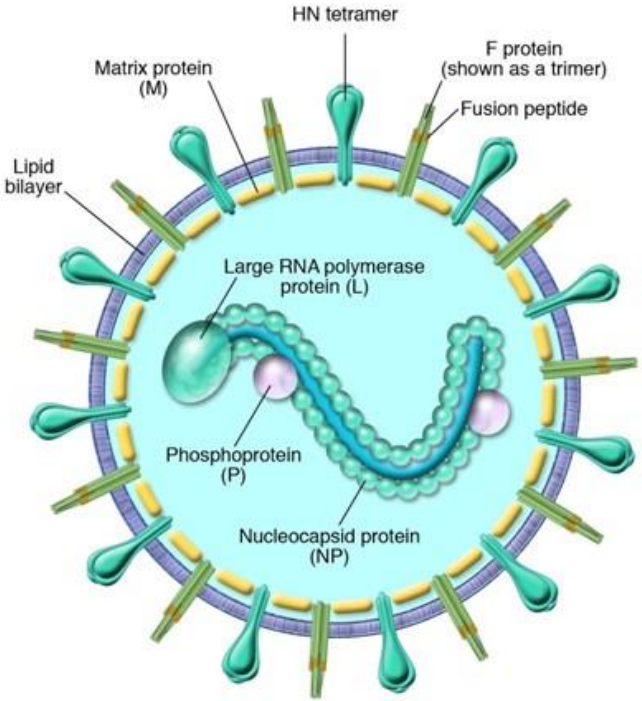
RSV

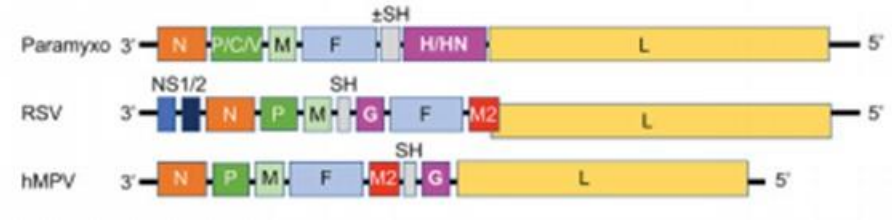


HMPV



PIV





https://oncohemakey.com/ Ruckwardt TJ. Immunity Review. 2019 https://www.jci.org/articles/view/25669/figure/1

Respiratory Syncytial Virus

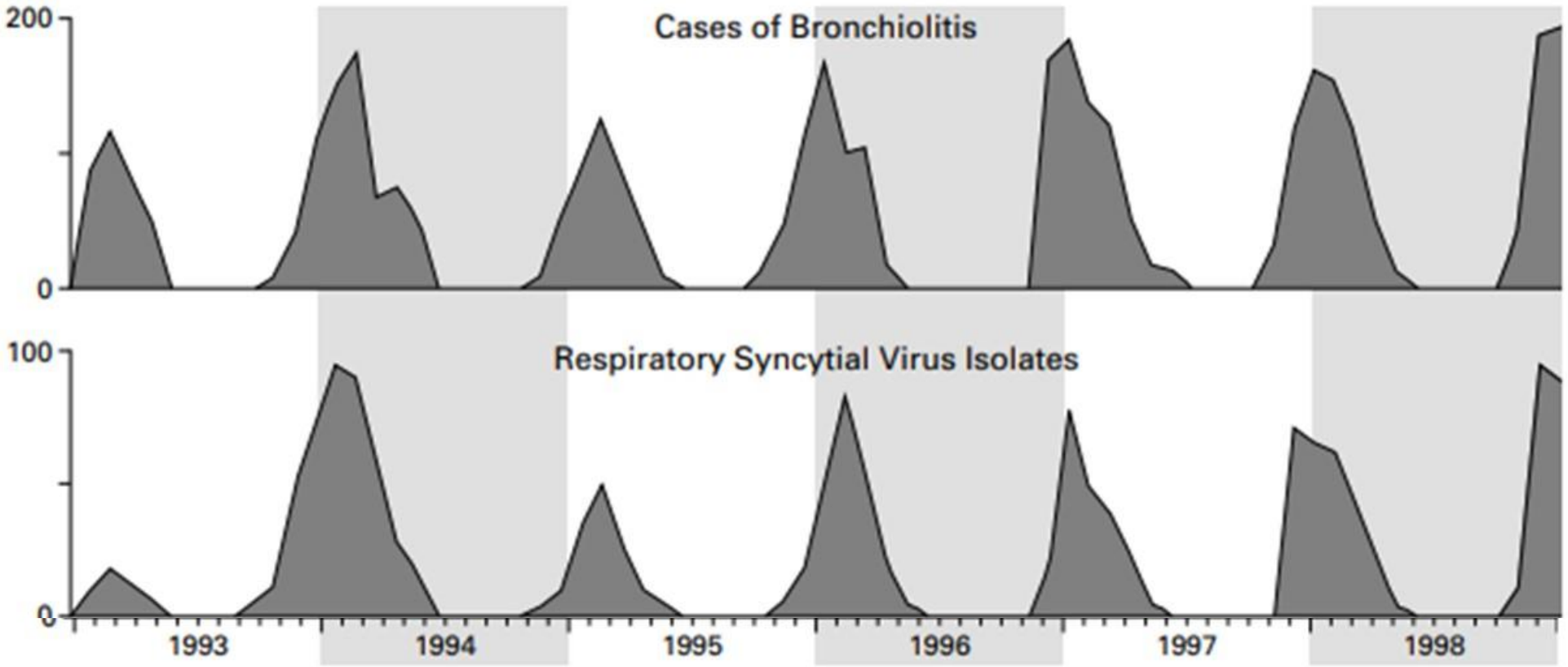
- RNA Pneumovirus
- First described in 1957 (Chimpanzee coryza agent)
- Causes **URI and LRTI – Bronchiolitis**
- **Co-circulating subgroups A and B - winter outbreaks**
- Illness burden and disease severity is greatest **in infants**, **young children** and **elderly adults**
- **Recurrent infections** occur throughout life and are milder except for people with chronic medical conditions
- **Virus-specific serum neutralizing antibody to F > G surface glycoproteins** protects against severe RSV LRTI
  - infection-induced
  - maternally derived
  - passively administered


BBC.com


Pediatricsafey.net


Nortonhealthcare

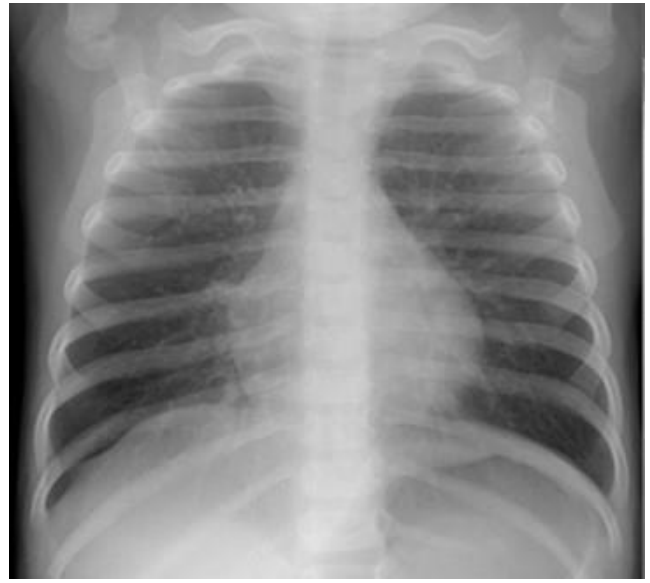
RSV is the most important cause of infant bronchiolitis

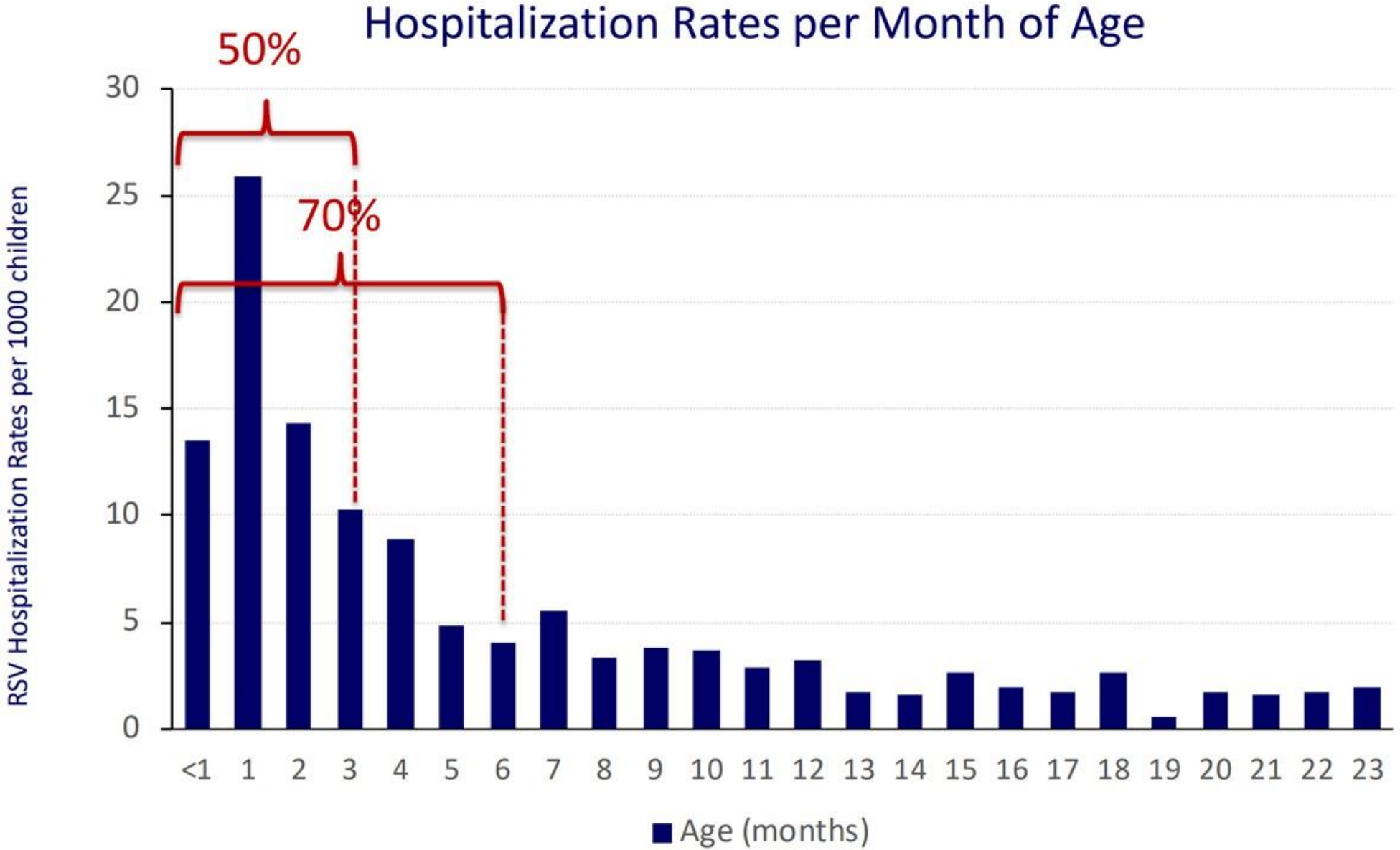


Caroline B. Hall. NEJM 2001

Impact of RSV Disease in Children

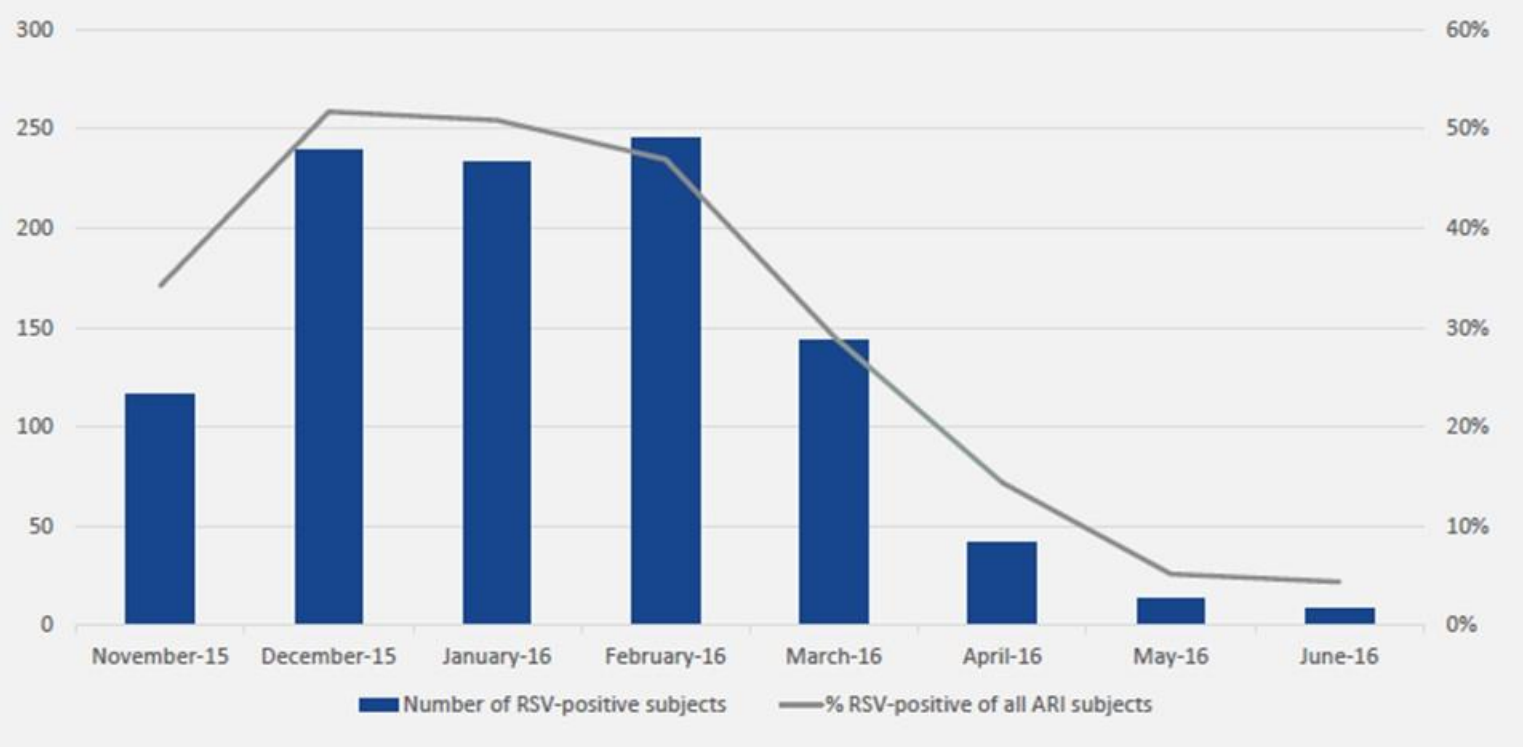
- Most important cause of LRTI in infants and young children
- Nearly all children are infected at least once by age 2
- **30% to 40% of primary infections result in LRTI**
- **2-3% of infected children require hospitalization**
- **> 75% of RSV disease hospitalization occurs in full term, healthy infants.**
- **Higher (2x) mortality than influenza in infants**
- Severe infection may be associated with subsequent reactive airways disease/asthma





Hall et al Pediatrics 2013

RSV Hospitalization – New Vaccine Surveillance Network* (NVSN) Data

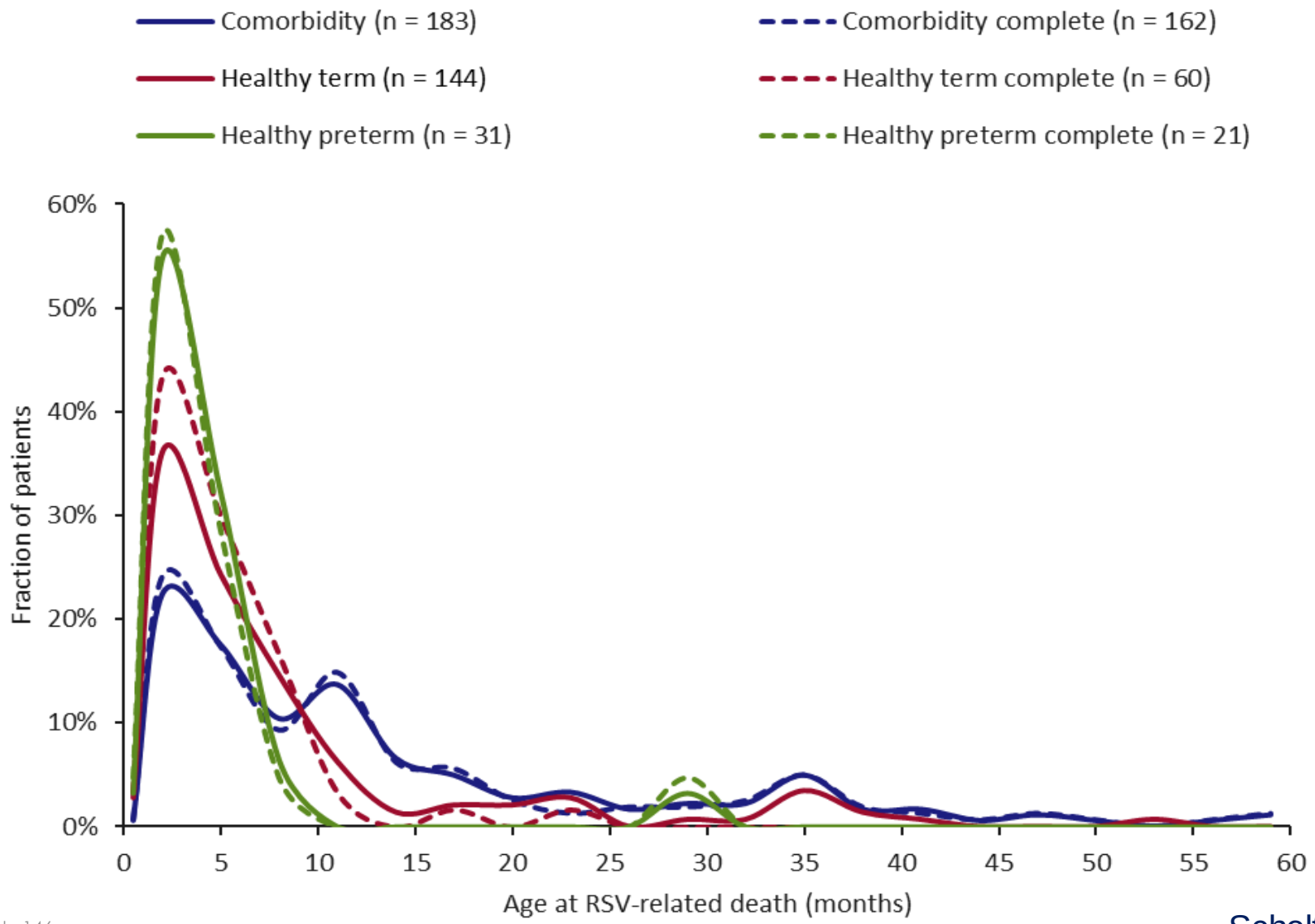


Variable	Rate per 1000 Children (95% CI)
Age group *(months)*	
0–2	19.0 (17.1–21.0)
3–5	11.0 (9.6–12.5)
6–11	4.9 (4.2–5.7)
12–23	2.9 (2.5–3.4)
24–59	0.6 (0.5–0.8)
<60	3.0 (2.8–3.2)

* Seven US medical centers participate with the CDC in active sentinel surveillance

Rha B. RSV hospitalization in young children.US, 2015-2016_Presented at RSV Symposium 2018

Very young infants are most at risk for RSV-related death



- Case series hospital data from 23 countries
- **Median age** for RSV-related deaths is **5 months**
- **> 40% deaths occur in under 3 months**

Scheltema NM et al. Lancet Glob Health 2017

RSV is a Major Global Pathogen In Children under 5 years

2005 Estimates:

- **RSV-ALRI: 33.8** (19.3-46.2) million cases/yr
- **Severe RSV-ALRI: 3.4** (2.8-4.3) million cases/yr (22% of all episodes)
- **Deaths: 55,000 to 199,000** annually attributed to RSV

2015 Estimates in 132 developing countries:

- **RSV-ALRI: 33.1** (21.6-50.3) million cases/yr
- **Hospitalizations: 3.2** (2.7-3.8) million **in children <5 yr** and **1.4 (1.2-1.7)** million **in <6 mo**
- **Hospital Deaths: ~60,000 (48-75K) in children <5 yr** and **27,000 (21-36K) in <6 mo** attributed to RSV

Mortality estimates suggest RSV is an important cause of death in children
Overall mortality: ~120,000 (95,000 to 150,000)
99% of the deaths occur in developing countries
45% of deaths occur in infants < 6 months

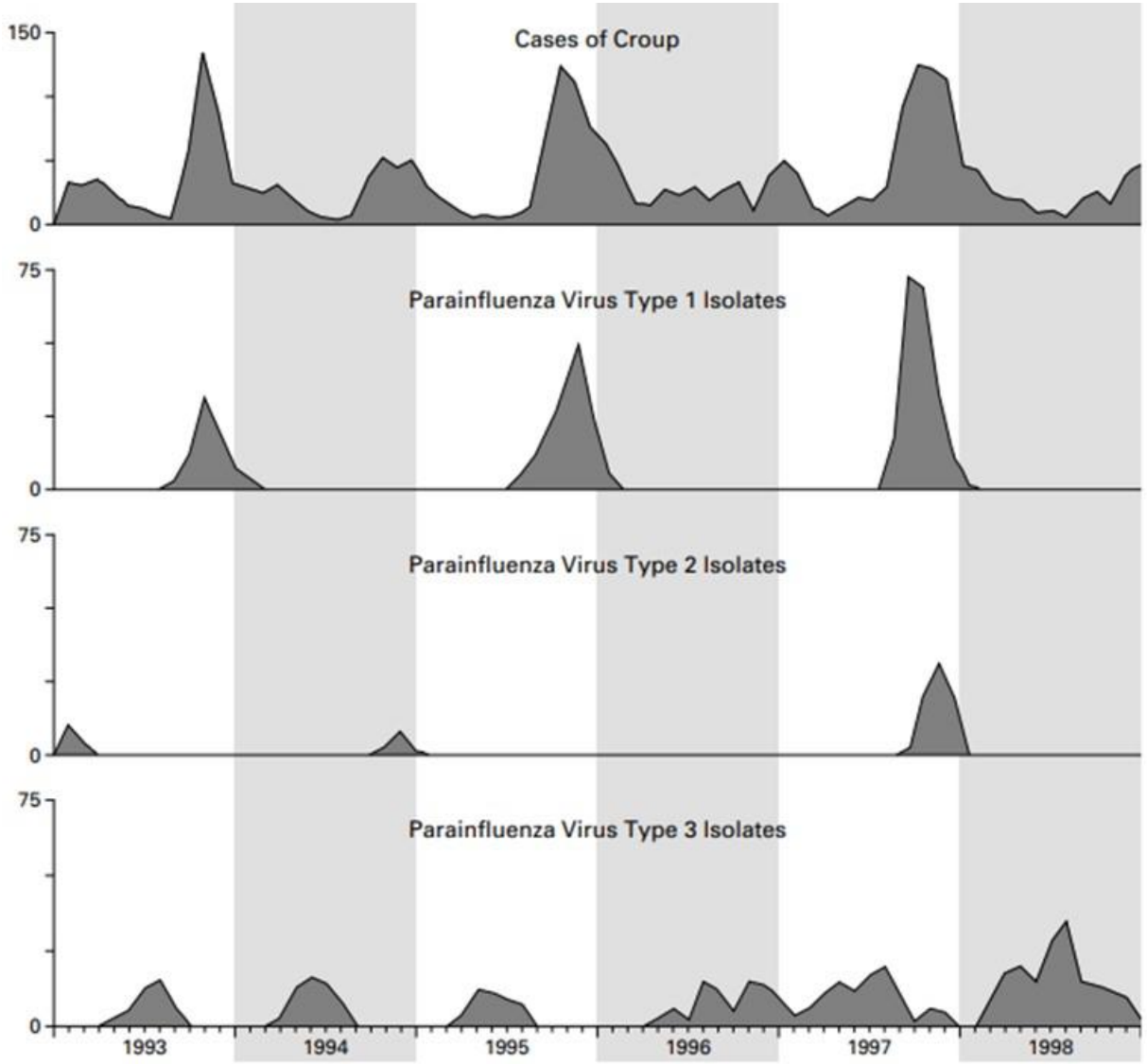
Nair H, et al., Lancet 2010;375:1545-55. and Shi T. et al. Lancet 2017;390:946-58

Parainfluenza Virus (PIV)

- Enveloped, single stranded negative sense RNA Paramyxoviruses
- Four antigenically distinct types: PIV 1-4, with 2 subtypes (4A and 4B)
- Sporadic infection and outbreaks
- PIV-1 – annual outbreaks in the FALL
- PIV-2 – annual outbreaks, also in the Fall
- PIV-3 – Endemic, mostly in SPRING and summer
- PIV-4 – Less clear seasonality
- Infection does *not* confer complete protective immunity, therefore reinfections can occur at any age

myDr.com.au

Parainfluenza Viruses



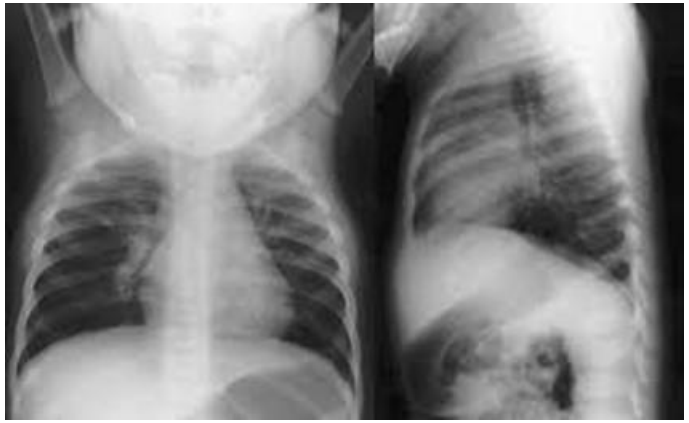
Caroline B. Hall. NEJM 2001

Parainfluenza Virus: Clinical Presentation

- PIV-1 and PIV-2 : Croup
- PIV-3: Bronchiolitis and pneumonia in infants and young children
- Exacerbation of asthma and Chronic lung disease
- Refractory infection (severe pneumonia with dissemination, persistent shedding, death) in immunodeficient patients, lung and HSCT recipients (PIV-3)
- Uncommon presentations: parotitis, aseptic meningitis, encephalitis, Guillain Barre Syndrome
- Most children infected by age 5, with any type
- Incubation period 2-6 days
- Shedding up to 1 week prior to onset of symptoms to 1-3 weeks after resolution. Longer in immunocompromised.

Human Metapneumovirus (HMPV)

- Discovered in 2001
- Enveloped, single negative stranded RNA Paramyxovirus
- Two antigenic subgroups: A and B, co-circulate
- Overlap with RSV: **Winter – early spring seasons**
- Most children infected by 5 years of age
- **Co-infection** with other viruses is common
- **Common symptoms**: **Cough**, fever, rhinorrhea, wheezing, dyspnea
- **Clinical Syndromes**: **Bronchiolitis, croup**, URI, OM, **pneumonia**, asthma exacerbation in children, COPD exacerbation in adults, LRTI that is potentially fatal in lung transplant and HSCT recipients
- Incubation period 3-5 days
- Viral shedding 1-2 weeks in healthy children, longer in immunocompromised



Source: Clin Virol 2009

Lefebvre et al. J Clin Virol, 2016

Human Metapneumovirus: Clinical Presentation

- Prevalence among hospitalized children with CAP: ~ 6.4%
  - Hospitalization rates are **highest in < 6 month olds**
- Prevalence among outpatient and emergency room cases of ARI:
  - in children < 5 years: 7%
  - in children > 5 years: 5%
- Significantly **more likely to be associated with pneumonia** when compared to HMPV-negative ARI (13% vs. 4%)
- **Outpatient visit rates from infants to first 5 years of age remain the same!** (different from RSV and CoV, which decrease after 1 yr)
- May be **more important for older children** than RSV

Lefebvre et al. J Clin Virol, 2016
Howard LM et al. JPIDS March 2017

What do RSV, HMPV and PIV have in common?

- Encapsulated, single stranded RNA viruses
- Viral diagnosis by RT-PCR
- Treatment is supportive
- No available antivirals
- **No available vaccine**

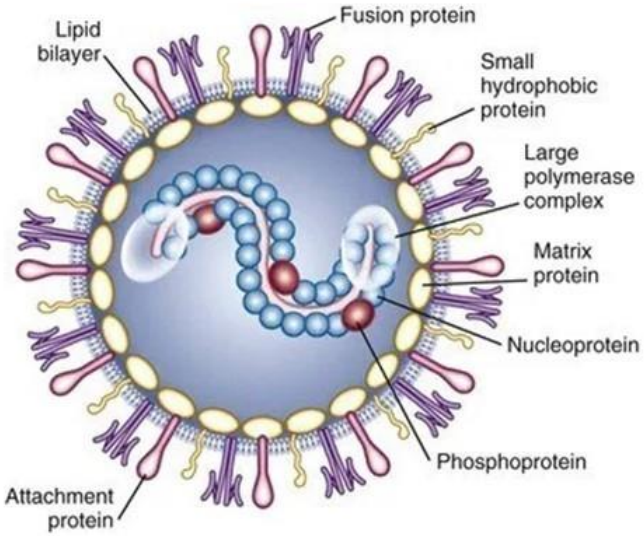


TABLE 2 Proteins of RSV, hMPV, and PIV[a]

RSV		hMPV		PIV	
Gene	Protein	Gene	Protein	Gene	Protein
F	Fusion	F	Fusion	F	Fusion
G	Attachment	G	Attachment	HN	Hemagglutinin-neuraminidase
M	Matrix	M	Matrix	M	Matrix
N	Nucleoprotein	N	Nucleoprotein	NP	Nucleoprotein
P	Phosphoprotein	P	Phosphoprotein	P+C	Polymerase complex
L	Large polymerase complex	L	Large (RNA polymerase)	L	Large polymerase complex
SH	Short hydrophobic	SH	Short hydrophobic		
M2-1	Nonstructural	M2-1	Nonstructural		
M2-2	Nonstructural	M2-2	Nonstructural		
NS1	Nonstructural				
NS2	Nonstructural				

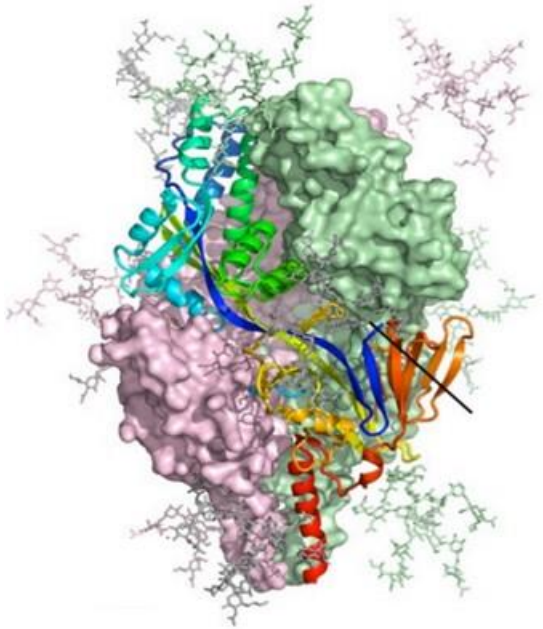
Source: Williams, Piedra, Englund. RSV, HMPC and PIV. Clin Virol 2009

THE MOST URGENT NEED IN RESPIRATORY VIRUS PREVENTION STRATEGIES IS TO PROTECT INFANTS AND YOUNG CHILDREN

Source: www.jcpportraits.com

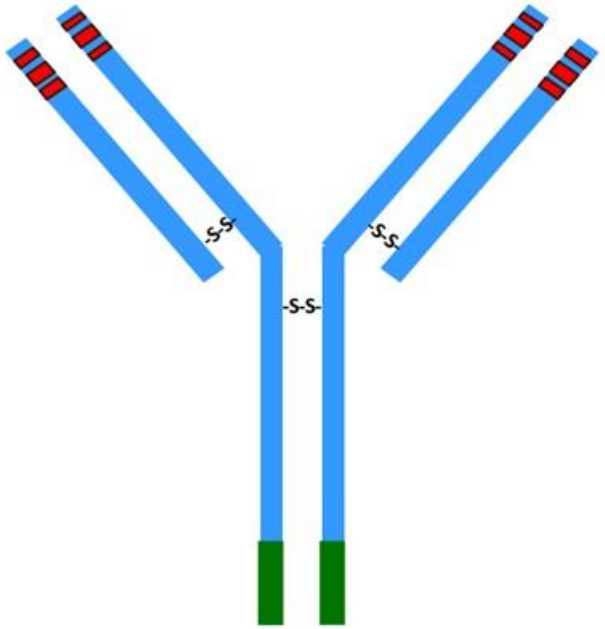
Source: cdc.gov

Options for RSV Prevention



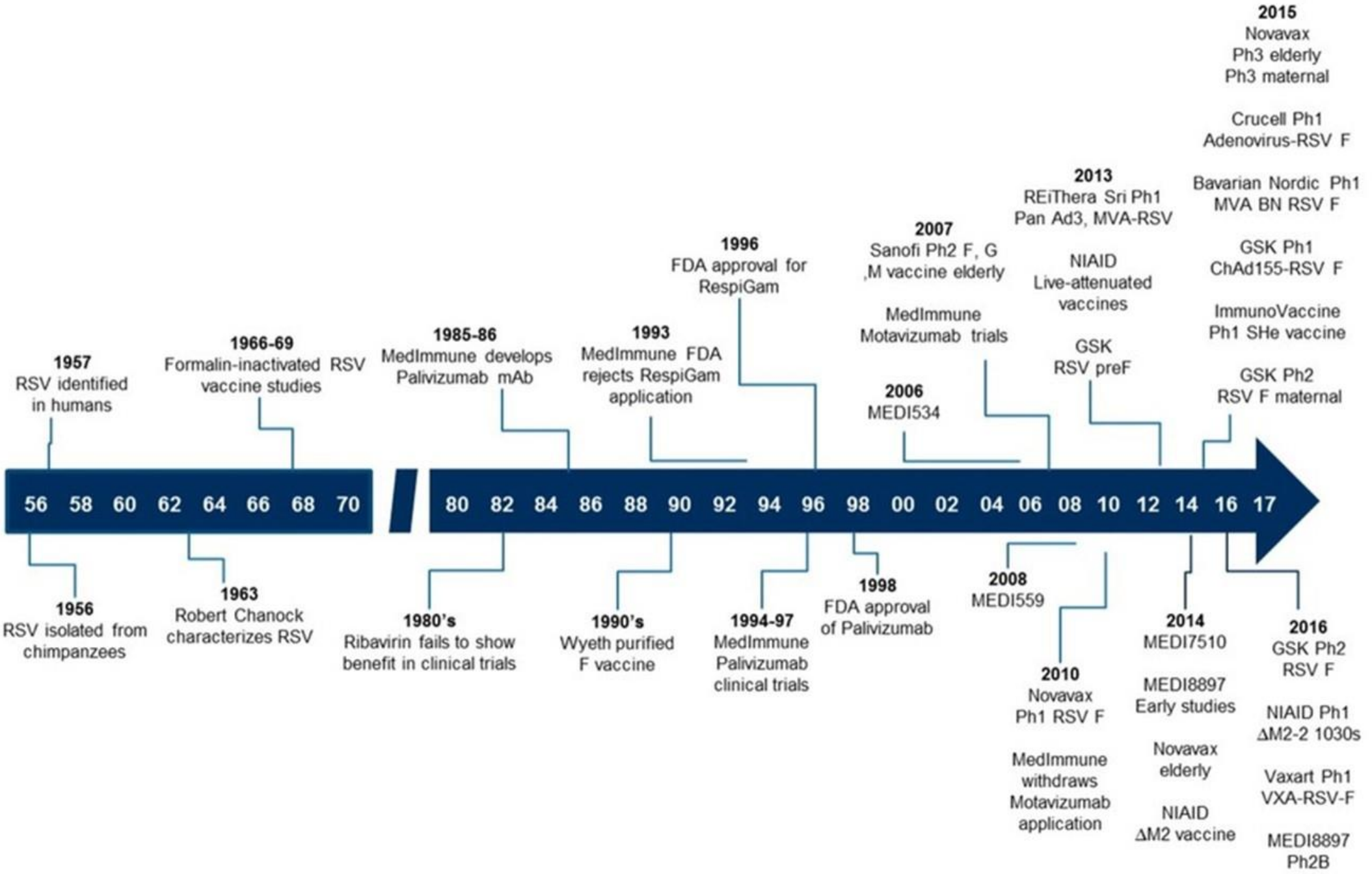
Prefusion F trimer

VS



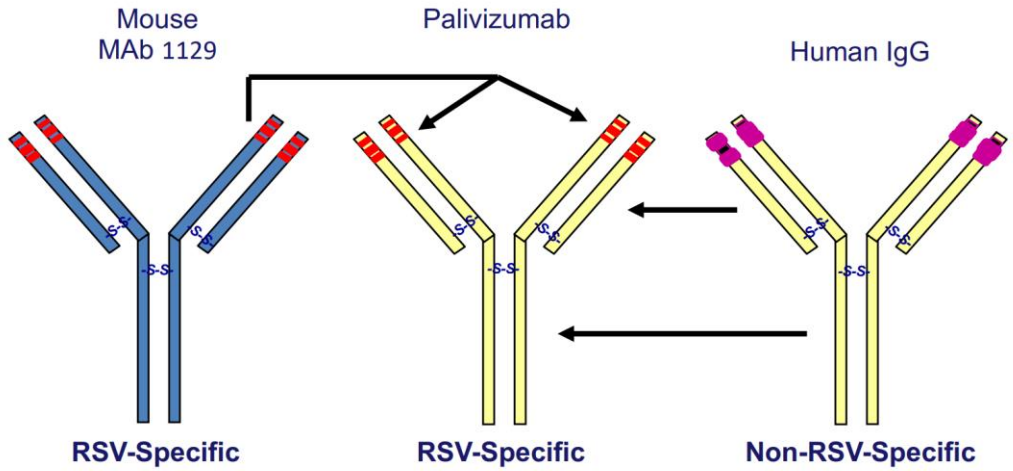
Vaccines

mAbs


1957
RSV identified in humans
1966-69
Formalin-inactivated RSV vaccine studies
1985-86
MedImmune develops Palivizumab mAb
1993
MedImmune FDA rejects RespiGam application
1996
FDA approval for RespiGam
2007
Sanofi Ph2 F, G ,M vaccine elderly
MedImmune Motavizumab trials
2006
MEDI534
2013
REiThera Sri Ph1 Pan Ad3, MVA-RSV
NIAID Live-attenuated vaccines
GSK RSV preF
2015
Novavax Ph3 elderly Ph3 maternal
Crucell Ph1 Adenovirus-RSV F
Bavarian Nordic Ph1 MVA BN RSV F
GSK Ph1 ChAd155-RSV F
ImmunoVaccine Ph1 SHe vaccine
GSK Ph2 RSV F maternal
56 58 60 62 64 66 68 70 80 82 84 86 88 90 92 94 96 98 00 02 04 06 08 10 12 14 16 17
1956
RSV isolated from chimpanzees
1963
Robert Chanock characterizes RSV
1980's
Ribavirin fails to show benefit in clinical trials
1990's
Wyeth purified F vaccine
1994-97
MedImmune Palivizumab clinical trials
1998
FDA approval of Palivizumab
2008
MEDI559
2010
Novavax Ph1 RSV F
MedImmune withdraws Motavizumab application
2014
MEDI7510
MEDI8897 Early studies
Novavax elderly
NIAID ΔM2 vaccine
2016
GSK Ph2 RSV F
NIAID Ph1 ΔM2-2 1030s
Vaxart Ph1 VXA-RSV-F
MEDI8897 Ph2B

RSV in Children
Current Prevention Strategies

- **No licensed vaccine for children or adults**
- **Passive Antibody**
  - **RSV-Specific IgG** (RSV-IG or Respigam®)
  - **Monoclonal antibody** (Palivizumab or Synagis®)
    - Licensed 1998 US
    - Binds F protein of RSV preventing infection of host cell
    - Effective: Reduces mortality and severity of RSV disease
  - **Restricted to**:
    - Preterm infants < 29 weeks of gestation
    - Preterm infants with chronic lung disease (O2 requirement > 28 days)
    - Infants with hemodynamically significant/cyanotic congenital heart disease
  - Requires monthly IM administration and is Costly
  - Protective levels need to be achieved *prior to* exposure
  - Most infants who are at risk for RSV (term) are excluded



Why don't we have a RSV vaccine for children?

- Primary target population, the very young infant (0-4 months of age), has a **suboptimal immune response to vaccination** in part due to presence of **maternal antibody**
- **Incomplete immunity to natural RSV infection**, especially in younger patients
- Enhanced pulmonary disease (pneumonia/death) in very young seronegative infants receiving **formalin-inactivated RSV vaccine in the 1960's**
- **Subunit vaccines** safe but not immunogenic enough
- **Live attenuated** vaccines administered intranasally pose challenges to balance between immunogenicity and reactogenicity

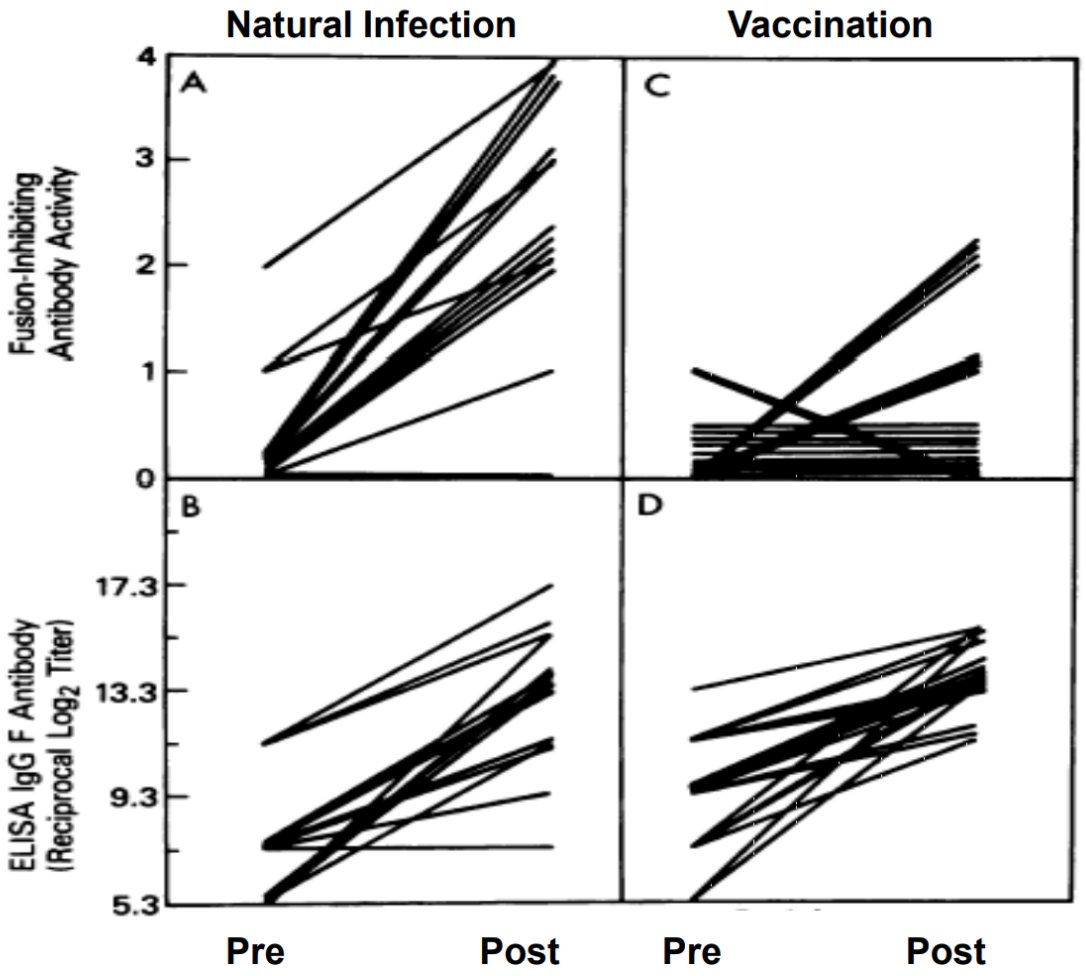
FI-RSV Experience (Pfizer vaccine)

1966-7: 4 independent studies using Pfizer lot 100 formalin-inactivated RSV did not protect and caused enhanced disease in children 2 to 23 months of age

RSV-outcome	Vaccinated group	Control group	Time between last dose and outcome	Reference
pneumonia	9/13 (69%)	4/47 (9%)	15 to 236 days	Kapikian
hospitalization	9 cases	2 cases	Not provided	Chin
hospitalization	16/31 (52%)	1/40 (2.5%)	23 d to 11 mo	Kim
hospitalization	10/111 (9%)	2/173 (1.2%)	Not provided	Fulginiti

Kapikian et al, AJE 1969;89:405-421
Chin et al,AJR 1969;89:449-463 (<1yr & 1-4 yrs: FI-RSV 43 & 99; FI-PIV 43 & 91)
Kim et al, AJE 1969;89:422-433 (2 infants died at 14 and 16 months; vaccination started at 2 and 5 months, respectively; both received 3 doses)
Fulginiti et al., AJE 1969;89:435-448

FI-RSV Immunization Resulted in a Discordance Between Functional and Binding Antibody



Fusion Inhibition

Dissociation between serum neutralizing and glycoprotein antibody responses of infants and children who received inactivated respiratory syncytial virus vaccine.
Murphy, Walsh et al JCM 1986; 24:197.

ELISA

Formalin-inactivated respiratory syncytial virus vaccine induces antibodies to the fusion glycoprotein that are deficient in fusion-inhibiting activity.
Murphy, Walsh et al JCM 1988; 26:1595

Aberrant Immune Responses and Enhanced Respiratory Disease

Antibody Mediated Responses

- Poor neutralizing or fusion-inhibiting activity results in high viral loads, immune complex deposition, complement fixation, and immunopathology
- Poorly functional antibodies related to conformational state of the F protein (heating – post-fusion)

GOAL: Eliciting highly neutralizing antibodies

T-Cell Responses

- FI-RSV resulted in CD4+ T-cell proliferation and lung eosinophils (Th2-bias – IL4, IL-5, IL-9, IL-13), in addition to neutrophils, lymphocytes and mononuclear infiltrates after RSV infection.
- Neonates are naturally Th2-biased
- Priming (primary vaccination) with vaccines that induce CD8+ and Th1 CD4+ T-cells prevents Th2 biased responses

GOAL: Establishing T-cell memory with the right phenotype and B-cell memory with the right specificity

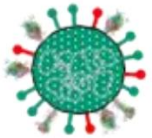
Ruckwardt TJ. Immunity Review. 2019

RSV Vaccines in Development

Poorly immunogenic F-subunit vaccines, modest neutralizing activity, not effective in preventing RSV LRTI in older adults and maternal immunization trials

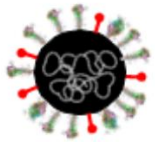
Historical

Recombinant or chimeric viruses

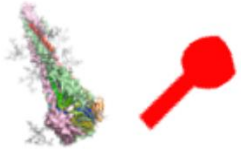


WT or attenuated virus

Whole-inactivated virus



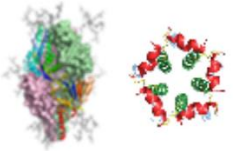
Postfusion F or G subunit



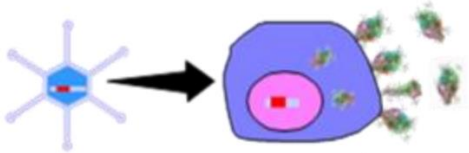
Subunit F (F+G+M, FG, F+G) and G (BBG2Na) given to adults and children with pre-existing immunity (2-3 fold rise in NT; >10-20 fold rise in ELISA titers)

New

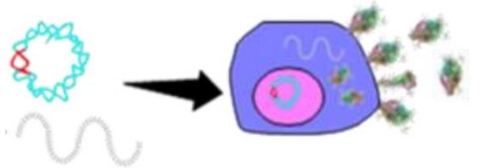
Prefusion F subunit or SH pentamer



Vectors

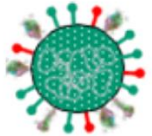


Naked DNA or mRNA



VLPs or virosomes

Genetically modified and recombinant chimeric viruses



Antigens stimulate innate immunity and boost the elicitation of CD8+ T cells and Th1 CD4+ T cells balanced with potently neutralizing antibodies.

Source: B. Graham lecture ADVAC
Ruckwardt TJ. Immunity Review. 2019

RSV Vaccines in Development

	Vaccine Type/Manufacturer	Viral Target	Target Population	Administration route	Clinical Development	Advantages	Challenges
PROTEIN VACCINES	**Particle based**						
	RSV F nanoparticle; *(Novavax)*	Prefusogenic	Maternal*** Elderly** Pediatric*	Systemic	Phase-3*** Phase-2** Phase-1*	- Safe - Immunogenic	- Post-F based? - Risk of ERD - Ab durability
	Subunit						
	DS-Cav1; *(NIH/NIAID)*	Pre-F	Maternal & Elderly	Systemic	Phase-1	- Induce high affinity neutralizing Ab - Facilitate cross-priming - Safe	- Factors affecting transplacental transfer - Instability of pre-F - Ab durability - No protection for premature infants
	GSK RSV F[¶]; *(GlaxoSmithKline)*	sPre-F	Maternal & Elderly	Systemic	Phase-1		
	DPX-RSV; *(Immunovaccine & VIB)*	SHe	Elderly	Systemic	Phase-1		
	RSV-F; *(Janssen)*	Pre-F	Elderly	Systemic	Phase-1		
	RSV-F; *(Pfizer)*	Pre-F	Maternal & Elderly	Systemic	Phase-2		
	RSV-G Beijin Advaccine Biotech	G	Pediatrics & Elderly	Systemic	Phase-1		
LIVE VACCINES	**Vector-based**						
	AdV26 RSV; *(Janssen)*	Pre-F	Pediatric & Elderly	Systemic	Phase-2	- Not attenuated - Low risk of ERD - No interference with maternal Abs	Potential for developing anti-vector immunity
	ChAdV155-RSV; *(GlaxoSmithKline)*	Pre-F, N, M2-1	Pediatrics	Systemic	Phase-2		
	VXA-RSV (AdV5); *(Vaxart)*	Post-F	Elderly	Mucosal & Systemic	Phase-1		
	MVA-BN RSV; *(Bavarian Nordic)*	Post-F, GA/GB, N, M2	Elderly	Systemic	Phase-2		
	Live-attenuated/chimeric						
	rBCG/N-hRSV; *(Universidad de Chile)*	N	Newborn	Systemic	Phase-1	Predominant Th1 immune responses	
	RSV/ΔG *(Intravac)*	Lacks G	Pediatric	Mucosal	Phase-1	- Low risk of ERD - Intranasal delivery - Replication in presence of maternal Ab - Broad stimulation of immune responses	- Balance of attenuation/ immunogenicity - Reverse to wild-type - Stability for mass production
	RSV ΔNS2 Δ1313/1314L RSV 276 RSV 6120/ΔNS2/1030$_S$ *(Sanofi-Pasteur &NIH)*	Pre-F/Post-F	Pediatric	Mucosal & Systemic	Phase-1		
	SeV/RSV; *(St Jude Hospital)*	F	Pediatric	Mucosal	Phase-1		

MVA: modified vaccinia Ankara virus; Adv: adenovirus. For VXA and MVA it appears that expression of post-F > pre-F. ERD: enhance RSV disease. ND: not disclosed.

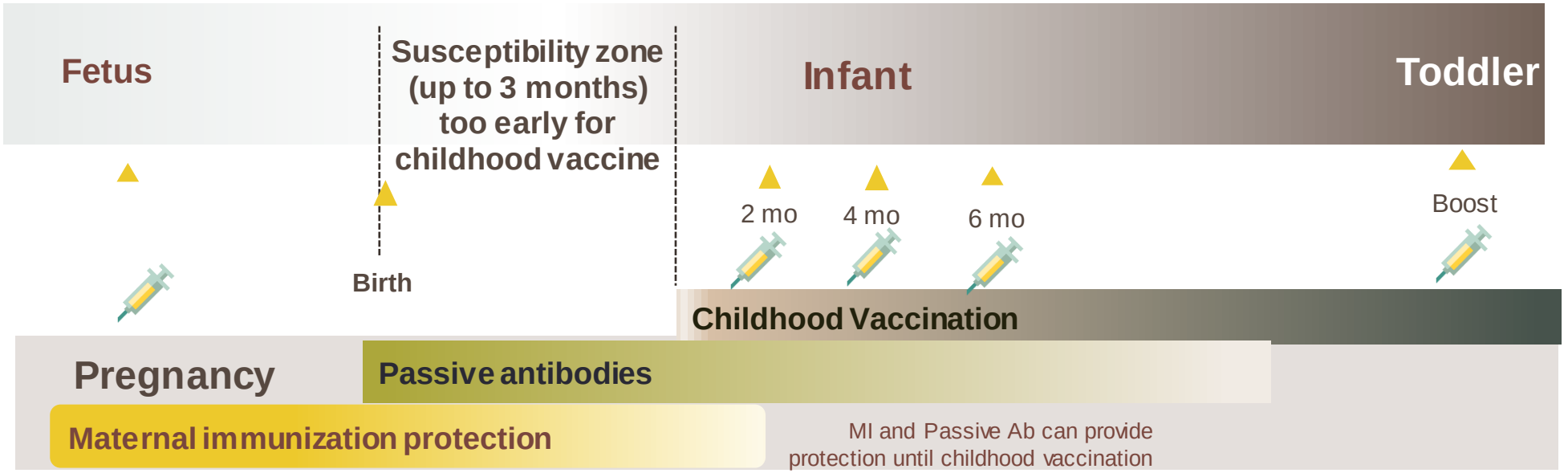
From: Mejias A. et al.
The Journey to an RSV vaccine
Ann All Asthma Immunol
March 2020 pre-print

RSV Vaccines for Children

	Vaccine Platform	Target population	Immunogenicity and Potential or Actual** Clinical Outcomes
FI-RSV			Disproportionate increase in binding antibody with poor neutralization capacity. **ERD following natural infection resulting in severe illness and two deaths**
F-specific mAb			No induction of adaptive immunity. **Transferred antibody provides passive protection from severe illness.**
Live-attenuated and Chimeric			Induction of mucosal antibody and T cell responses. Prevention of severe upper and lower respiratory tract disease, and potential for sterilizing immunity.
Nucleic Acid			Induction of both antibody and T cell responses and prevention of upper and lower respiratory tract disease.
Vector-based			Induction of both antibody and T cell responses and prevention of upper and lower respiratory tract disease.

Ruckwardt TJ. Immunity Review. 2019

RSV Prevention Strategies



1. Maternal + Infant vaccination
2. Passive antibody + Infant vaccination

Maternal Newborn Child Health; Source: Every Newborn: An action plan to end preventable deaths (2013)

RSV-HMPV-PIV Prevention Strategies

- mRNA technology allows the development of a **"Pediatric Respiratory Virus Combination Vaccine": RSV A, B + HMPV + PIV 3 (1-2)**
- Vaccines must elicit **highly neutralizing antibodies**, **supportive T-helper responses, and CD-8+ T-cells** to clear viral infection, reduce shedding, and provide long lasting RSV-specific memory (not poor neutralization or Th2-biased responses, to minimize risk of enhanced respiratory disease)
- **First administration 0-6 months of life** prior to first winter-viral respiratory season
- **Booster(s) in toddlers up to 5 years of age**
- <u>Potential impact:</u>
  - Substantial reduction of LRTI in first year to 5 years of life
  - Reduction in associated hospitalization and mortality globally
  - Reduction in secondary bacterial infections, antimicrobial use, antibiotic resistance
  - Reduction in transmission to vulnerable populations (elderly and immunocompromised)

Thank you

Baylor College of Medicine

Texas Children's Hospital®

Mark R. Denison, MD

Edward Stahlman Professor of Pediatrics, Professor of Pathology, Microbiology & Immunology, and Director of the Division of Pediatric Infectious Diseases at Vanderbilt University Medical Center

Mark R. Denison, MD, is the Edward Stahlman Professor of Pediatrics, Professor of Pathology, Microbiology & Immunology, and Director of the Division of Pediatric Infectious Diseases at Vanderbilt University Medical Center.

The Denison Lab has been NIH funded for investigation of coronavirus replication, pathogenesis, evolution, and countermeasures for over 30 years. Coronaviruses (CoVs) are a family of RNA viruses causing respiratory infections and also zoonotic infections of global importance as potential pandemic pathogens and agents of bioterrorism, including SARS-CoV, MERS-CoV, and the current SARS-CoV-2 (COVID-19) pandemic. Investigators in the Denison lab currently focus on: Discovery of antivirals broadly active against known and potential zoonotic CoVs, including remdesivir; testing of monoclonal antibodies and vaccines against MERS and SARS-CoV-2; and identification of novel determinants of replication as targets for inhibition or virus attenuation.

Dr. Denison has served on national and international forums and panels regarding development of policies for biosecurity and biosafety, including those of the National Academies and the NSABB.

SARS-CoV-2: What do we know, and where do we go from here?

Denison Lab 2019

Maria Agostini | Jim Chappell | Jennifer Gribble | Andrea Pruijssers | Laura Stevens | Tia Hughes | Mark Denison | Xiaotao Lu

Lab Alumni and new

Jordan Anderson-Daniels
Amelia George
Nicole Sexton

Collaborators

UNC- Chapel Hill

Ralph Baric

Amy Sims

Tim Sheahan

Rachel Graham

Emory University

George Painter
Mike Natchus
Greg Bleumling

Gilead Sciences

Joy Y. Feng
Danielle Porter
Thomas Cihlar

Funding

U19-AI109680 – UAB / UNC / VUMC

R01 AI132178

R01 AI108197

Vaccine Research Center- NIH / Leidos

NIH – Vaccine Treatment and Evaluation Units

Dolly Parton COVID-19 Research Fund – Vanderbilt University Medical Center

Questions to address

- Where did the virus come from – Recombination – Mutation?
- What are unique features of coronavirus replication and evolution?
- Is the virus mutating rapidly?
- Immune response and Protection – Cross Protection?
- Durability of Immunity?
- Seasonality and Endemicity?
- Approaches to Countermeasures?
- Can we predict if, when, and how the pandemic will evolve / resolve?

Mostly - *We don't know!*

- New human virus – no precedent in history
- 7.8 billion immune naïve - susceptible humans -
  Assume 20 million infected - 0.25%
- Seasonality and endemicity arguments are for highly established endemic viruses – Human CoVs, Flu, RSV, other
- SARS-CoV-2 appears ready to go. - Evidence for selection / adaptation – for better or worse – is not present
- Herd immunity is not established
- We must plan for it to NOT be seasonal or milder endemic virus

Public Health Response

- Limit transmission
- Limit genetic variation
- Assess mechanisms of transmission

Monoclonal Antibodies

- Prevent / treat infection
- Temporary immunity
- Interrupt transmission
- Prophylax populations

COVID-19 Response and counter-measures

Antivirals

- Treat acute infection
- Prevent disease progression
- Prophylax Vulnerable populations
- Locally limit transmission

Vaccines

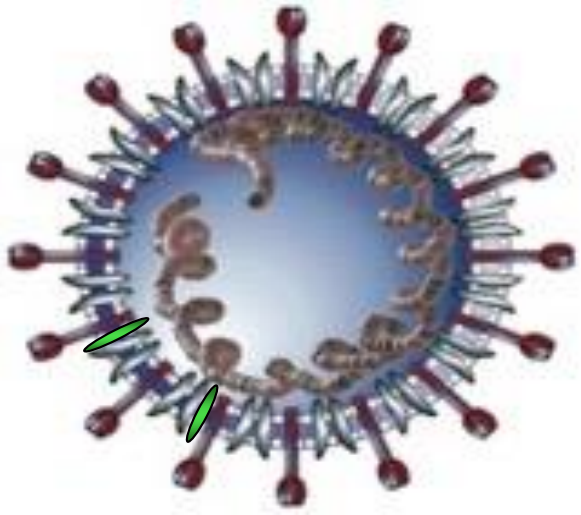
- Long Lasting Immunity
- Prevent Disease /Infection
- Interrupt Epidemic
- Limit Disease on subsequent exposure

Human Endemic Coronaviruses (HCoVs)

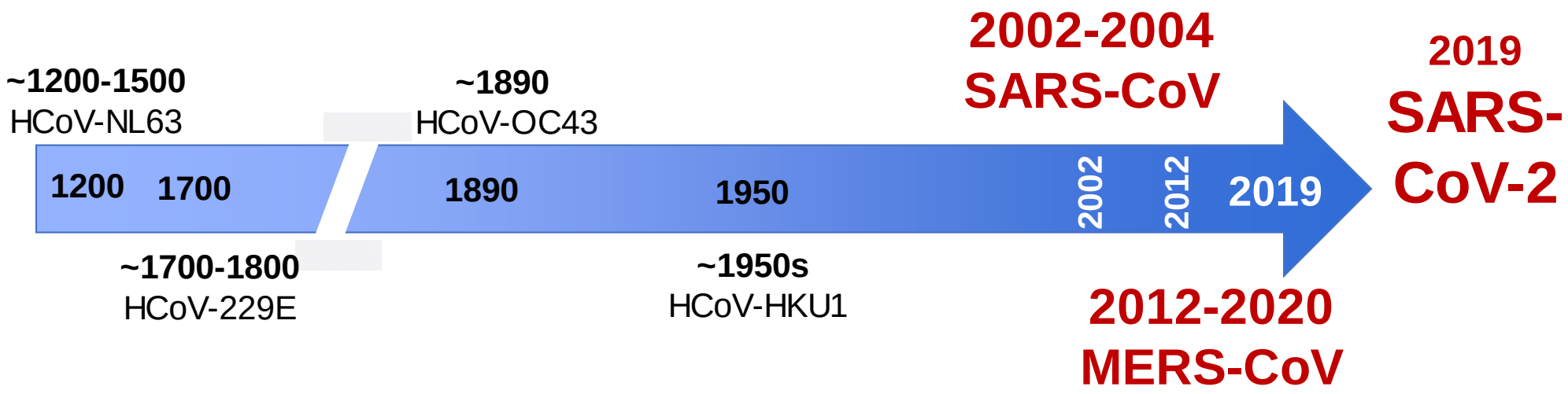
- 229E, HKU1, NL63, OC43
- Up to 15-30% of human colds – also lower respiratory tract – exacerbations of asthma, bronchiolitis, elderly
- Limited durable immunity vs genetic variation over time
- Reinfections in setting of existing antibodies and high seroprevalence – throughout life
- Seasonal, cyclic, persistent, alternating

Emerging Coronaviruses

- **SARS-CoV (2002-2004). – Severe Acute Respiratory Syndrome**
  - >8000 cases, 10% mortality, 32 countries in 3 months.
  - Bats –Civet Cats / Raccoon Dogs / Humans
- **MERS-CoV (2012-Present) (Middle East Respiratory Syndrome)**
  - > 2500 cases, ~35% mortality, 27 countries
  - Bats – Camels – Humans
- **COVID-19, SARS-CoV-2 (2019-present)**
  - ~2,000,000 confirmed, >120,000 deaths
  - Bat most likely

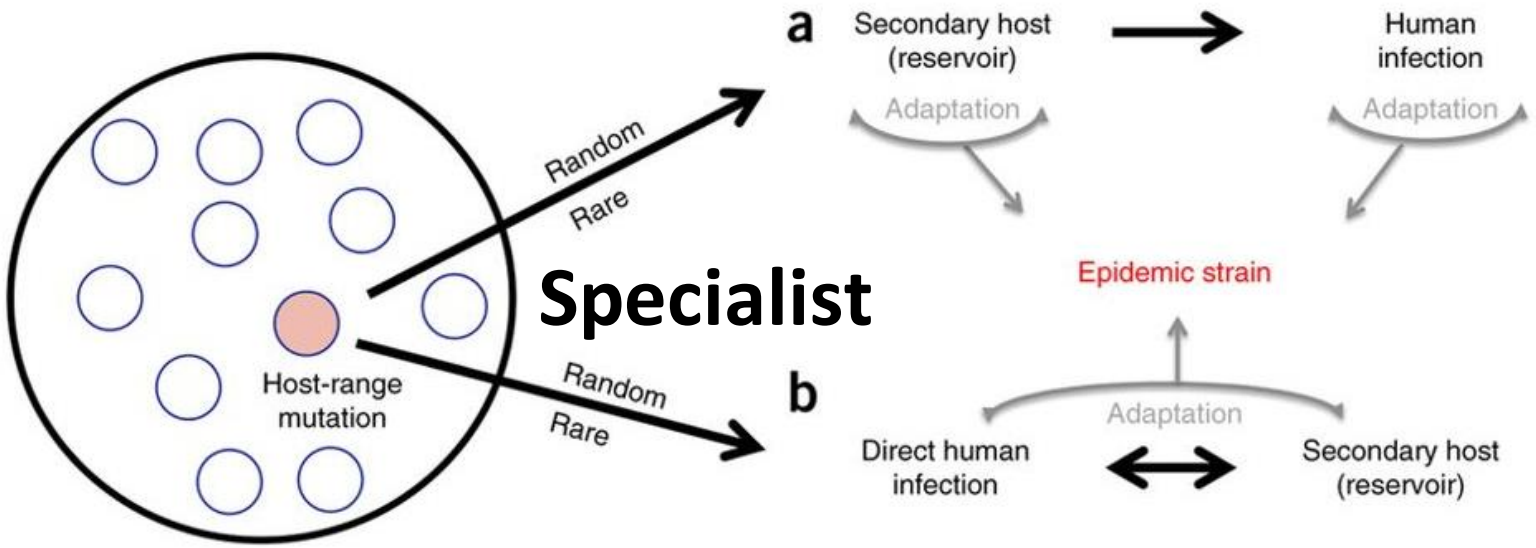


Accelerating Emergence of Zoonotic CoVs with Pandemic Potential



Models for CoV Zoonoses

Host Range Mutations



Menachery et al. Nature Medicine 2015

Models for CoV Zoonoses

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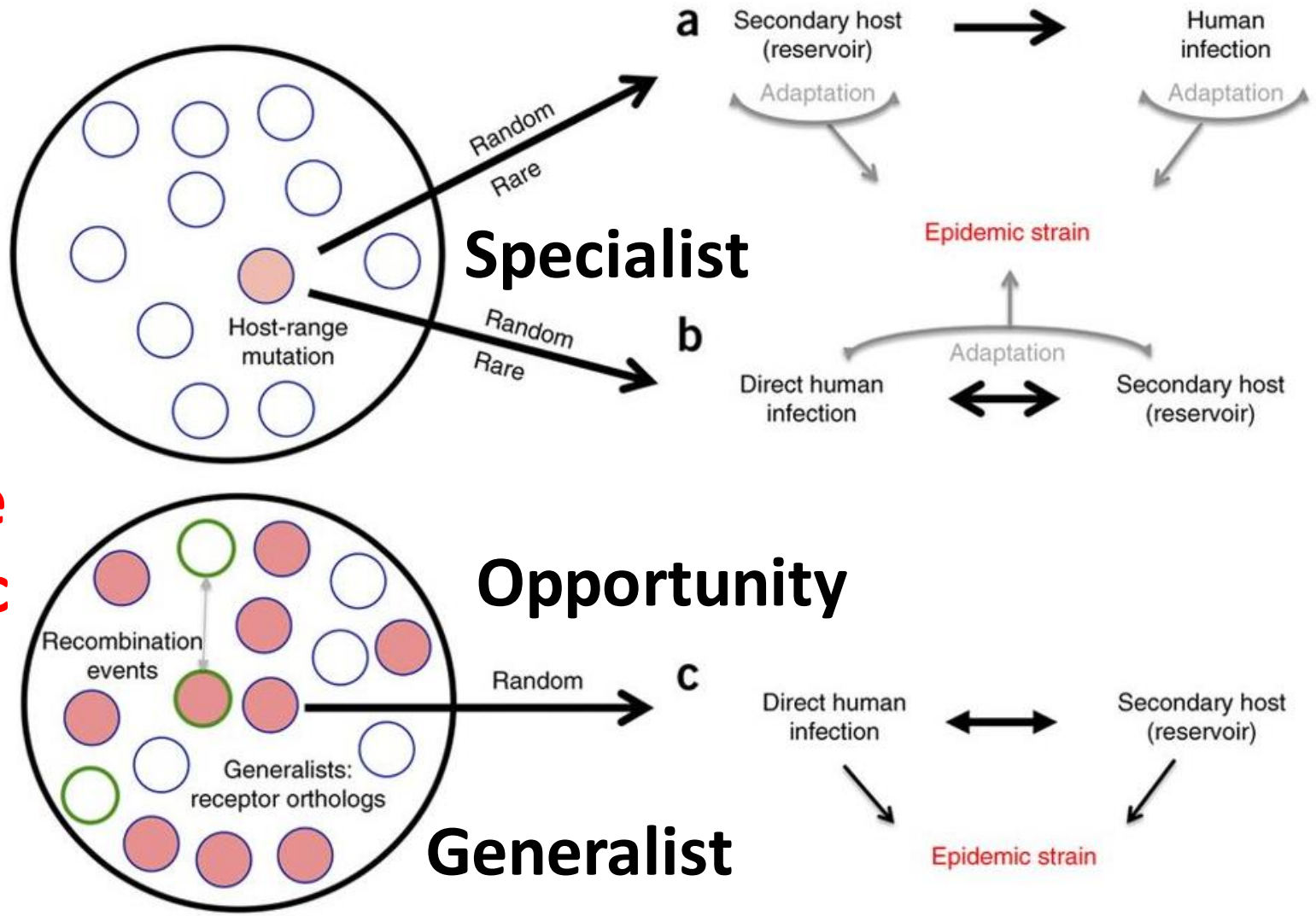


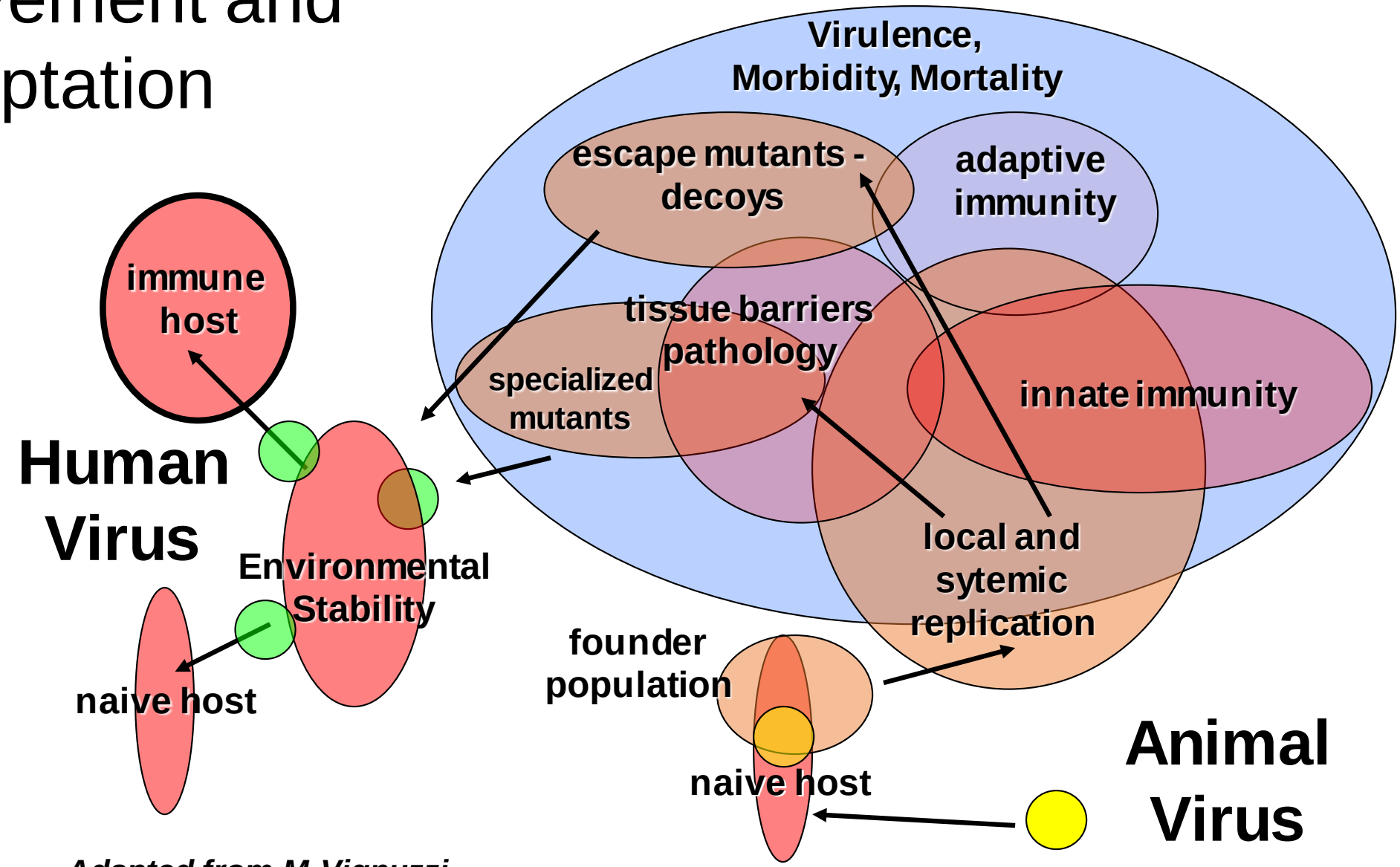
"Ready-Made Pre-Pandemic

Opportunity

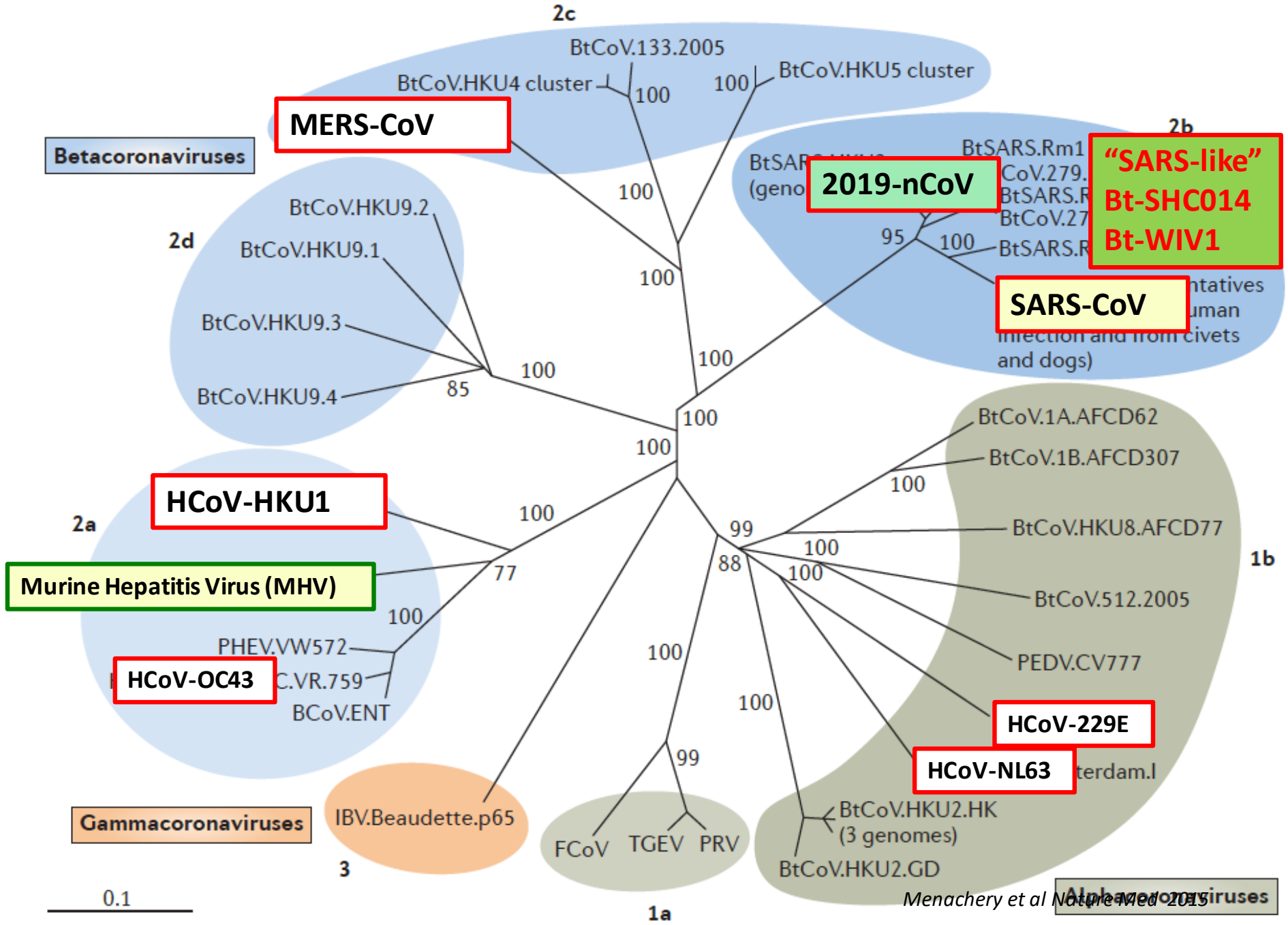
Generalist

Menachery et al. Nature Medicine 2015

Hurdles to Virus Movement and Adaptation



Adapted from M.Vignuzzi



Ready-made pre-pandemic

Menachery et al Nature Med 2015

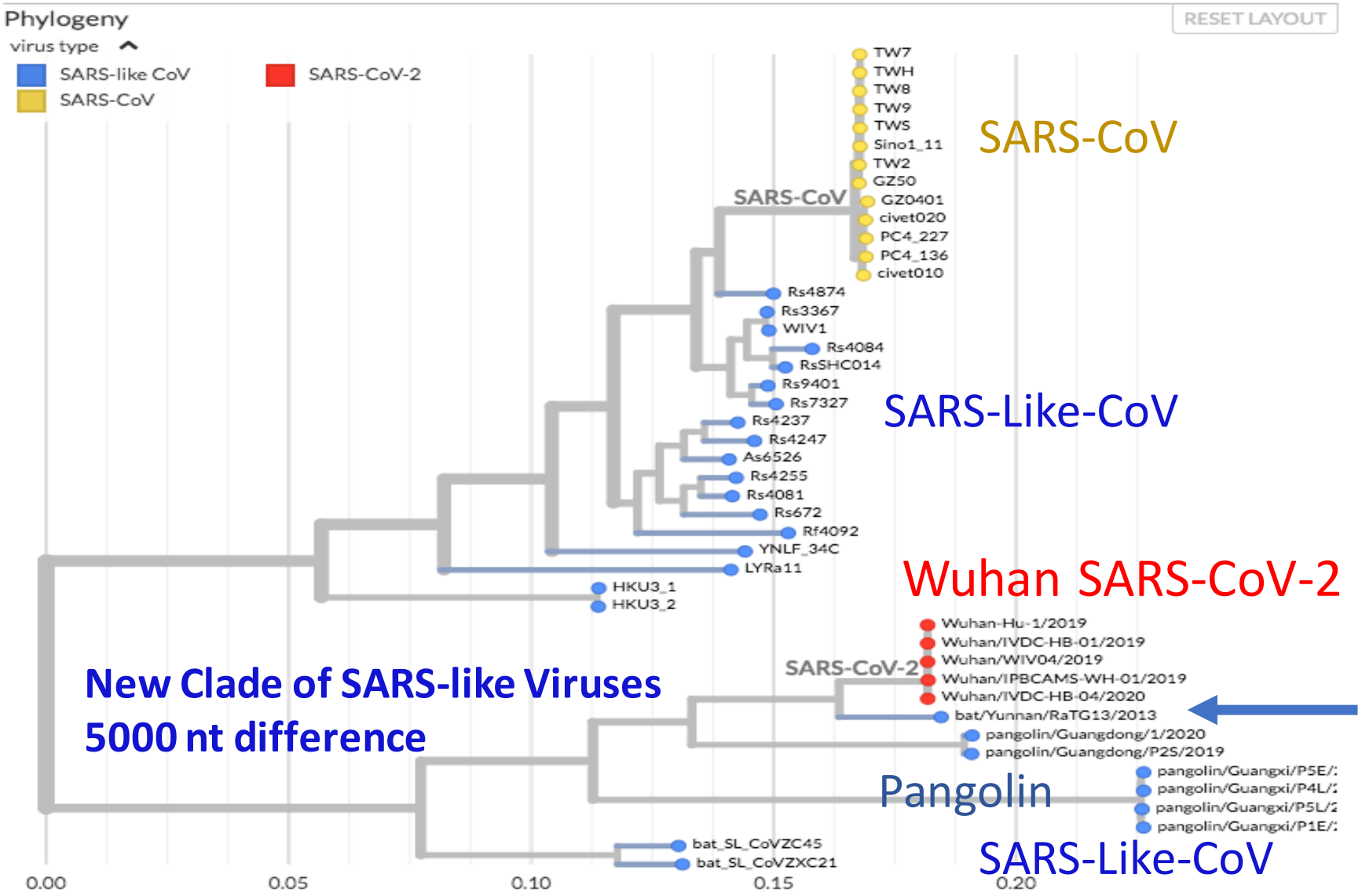
Phylogeny of SARS-like betacoronaviruses including novel coronavirus SARS-CoV-2

Built with github.com/blab/sars-like-cov. Maintained by Trevor Bedford.

Showing 45 of 45 genomes.

https://nextstrain.org/groups/blab/beta-cov

Feb 24, 2020



SARS-CoV

SARS-Like-CoV

Wuhan SARS-CoV-2

New Clade of SARS-like Viruses
5000 nt difference

BAT RaTG13 from Cave Bat in Yunnan Province
96% nt identity (1200 nt)

Pangolin SARS-Like-CoV

COVID19 Clinical Symptoms

- Fever (83-98%)
- Cough (46-82%)
- Myalgia or fatigue (11-44%)
- Shortness of breath (31%)
- Less common symptoms: diarrhea, productive sputum
- Potential for worsening clinical course during second week of symptoms
- Acute Respiratory Distress Syndrome
- Secondary infection uncommon

COVID-19 Disease Severity

- 36,160 cases (81%) reported mild symptoms
- 6,168 cases (13.8%) reported severe symptoms
- 2,087 cases (4.7%) were critically ill
- Case fatality higher among those with comorbid conditions (2-12%0 compared to those with no comorbidities (0.9%)

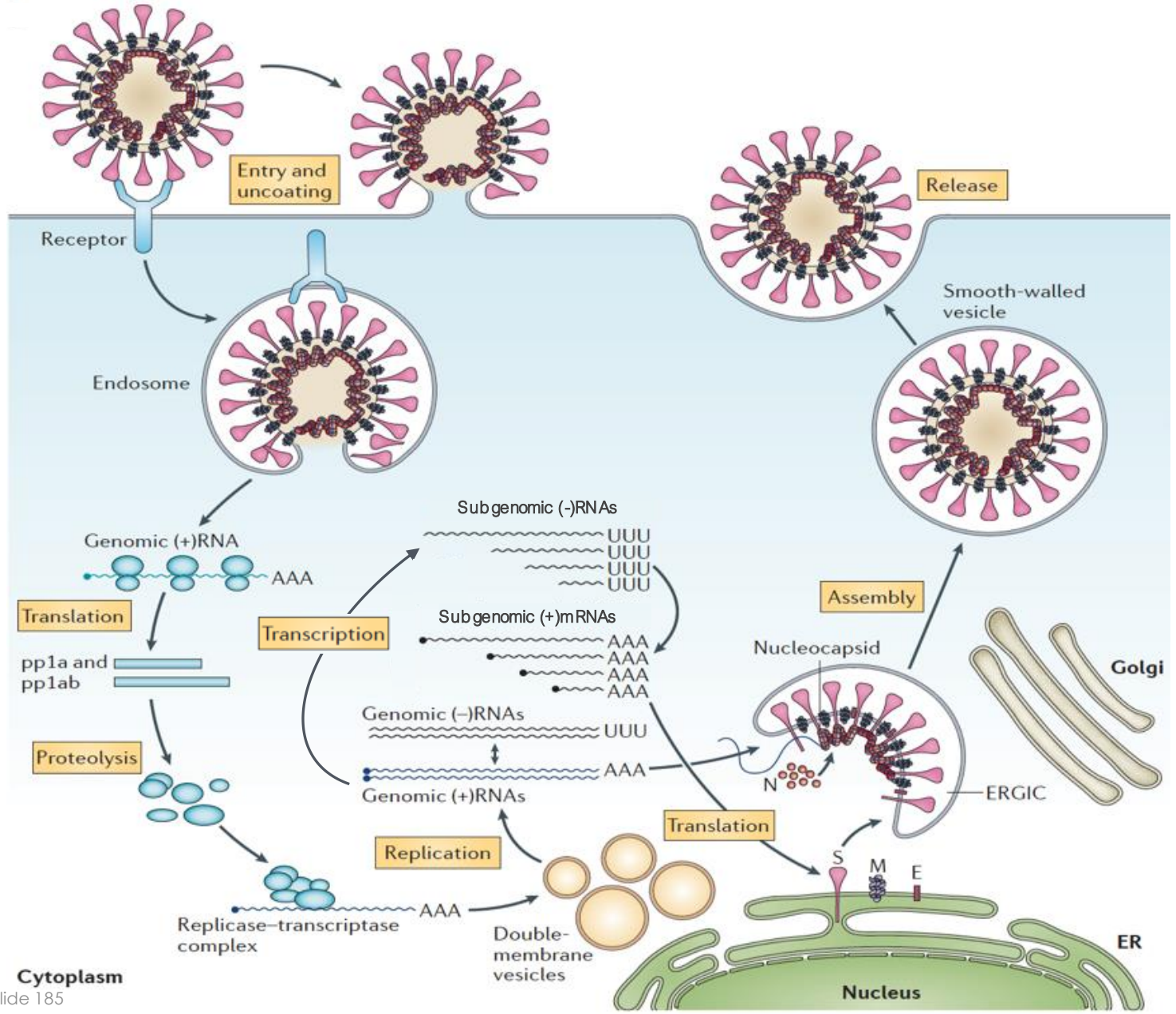
China CDC Weekly Report February 17, 2020

SARS-COV-2 Transmission

- Based on knowledge of other coronaviruses (SARS and MERS)
- Person to person via respiratory droplets among close contacts
  - Within 6 feet of a patient with SARS-COV-2 for a prolonged period of time
  - Having direct contact with infectious secretions from a patient with SARS-COV-2 (sputum, serum, blood, respiratory droplets)
  - SARS-COV-2 has been detected in stool but clinical significance is unknown
- Asymptomatic / pre-symptomatic, subacute – no question
- Superspreading Events – evidence says yes

https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html

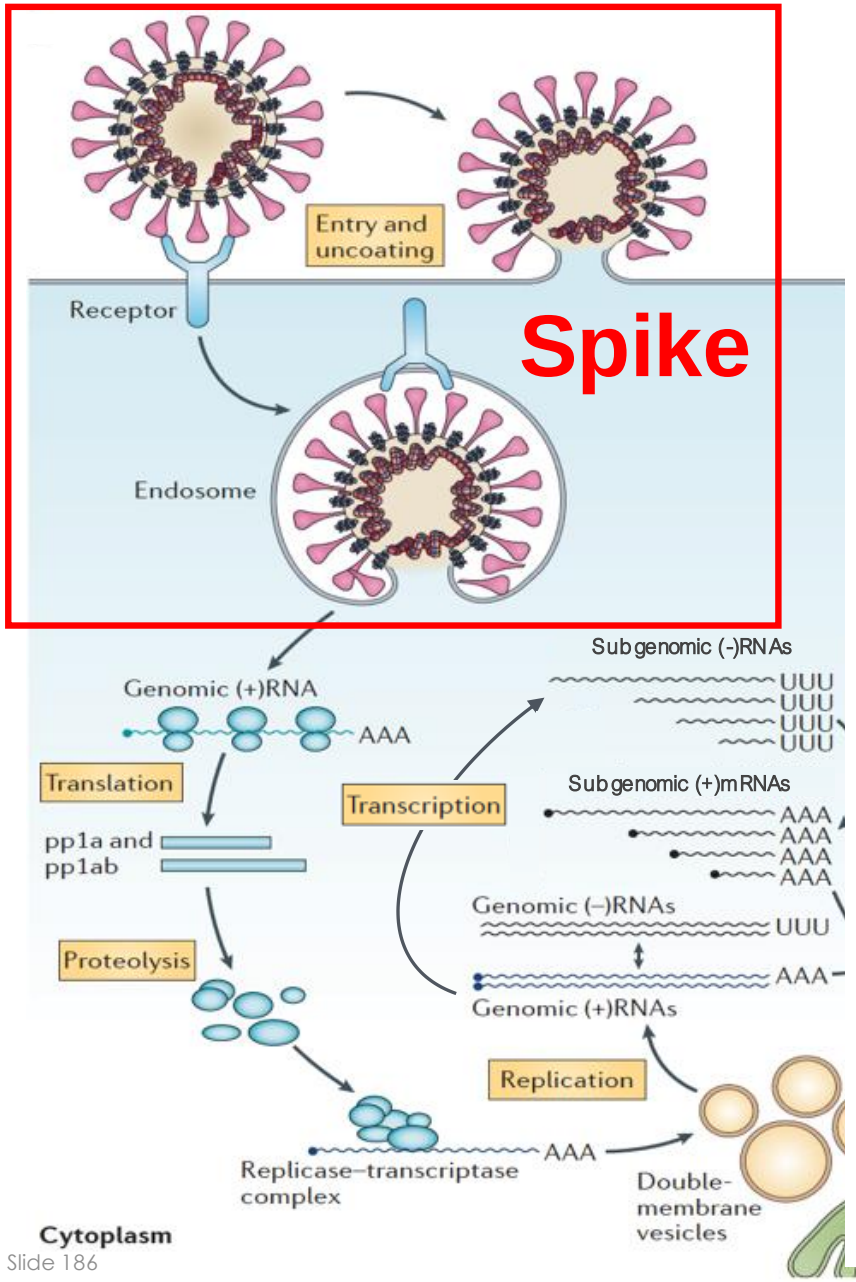
Coronavirus Replication



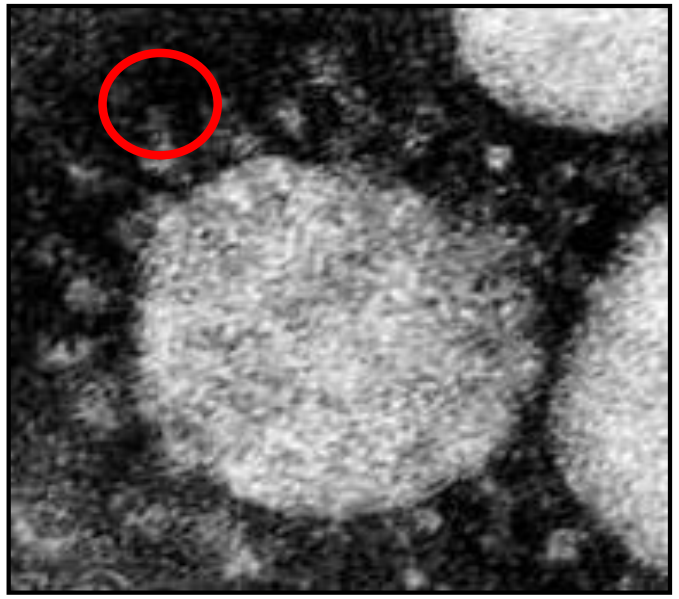
- Obligate Intracellular Replication
- Virus binding – ACE2
- RNA Genome uncoating
- Genome TRANSLATION and PROTEIN PROCESSING
- Replicase assembly and genome replication
- Virus assembly
- Virus egress - release

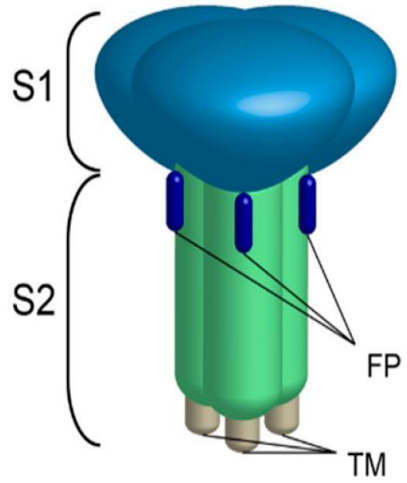
Adapted from de Wit et al. Nat. Rev. Micro. 2016.

Coronavirus Replication



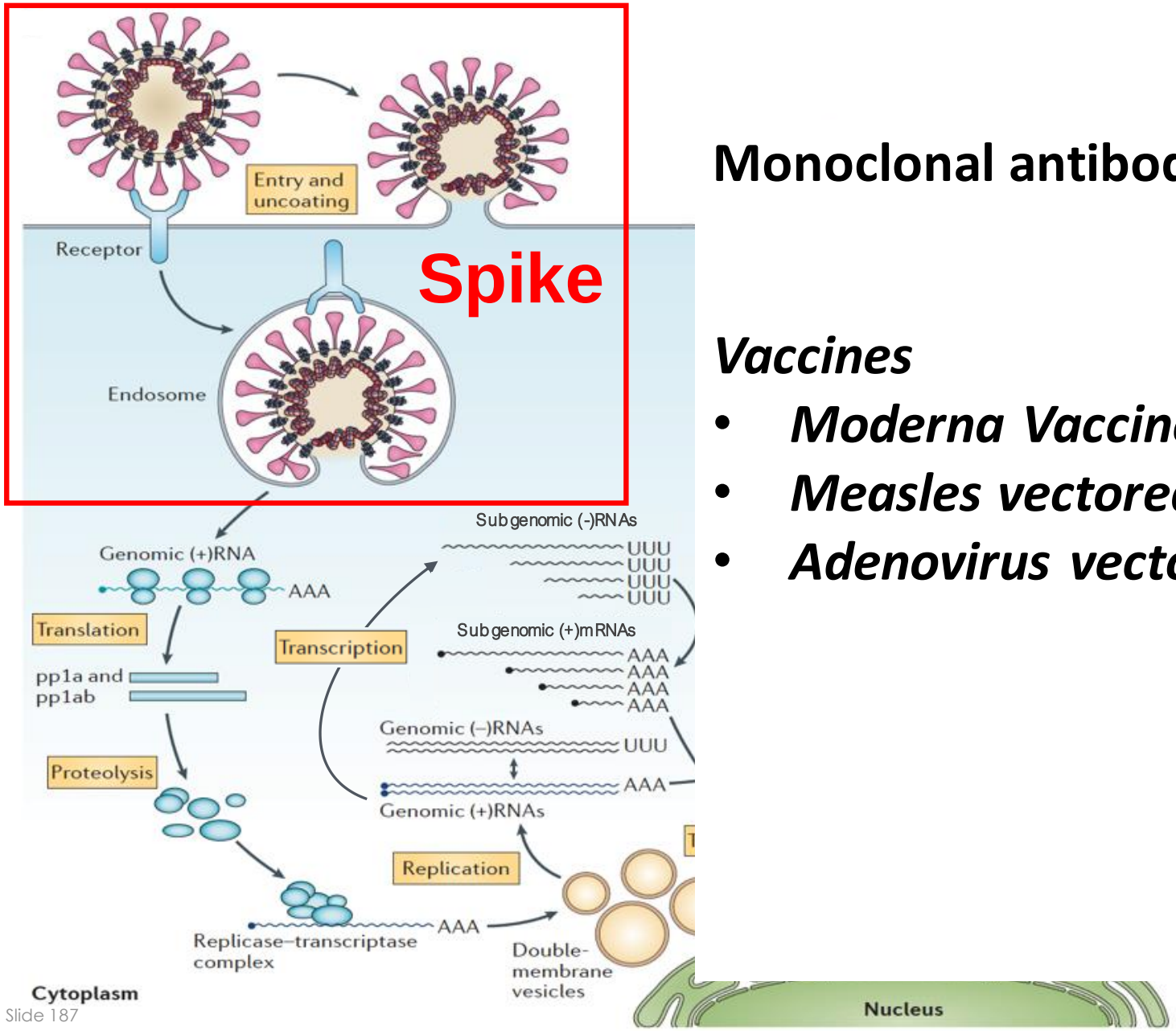
Spike protein





- Host cell receptor binding and virus entry
- Determinant of species specificity, tropism and immunity

Coronavirus Replication

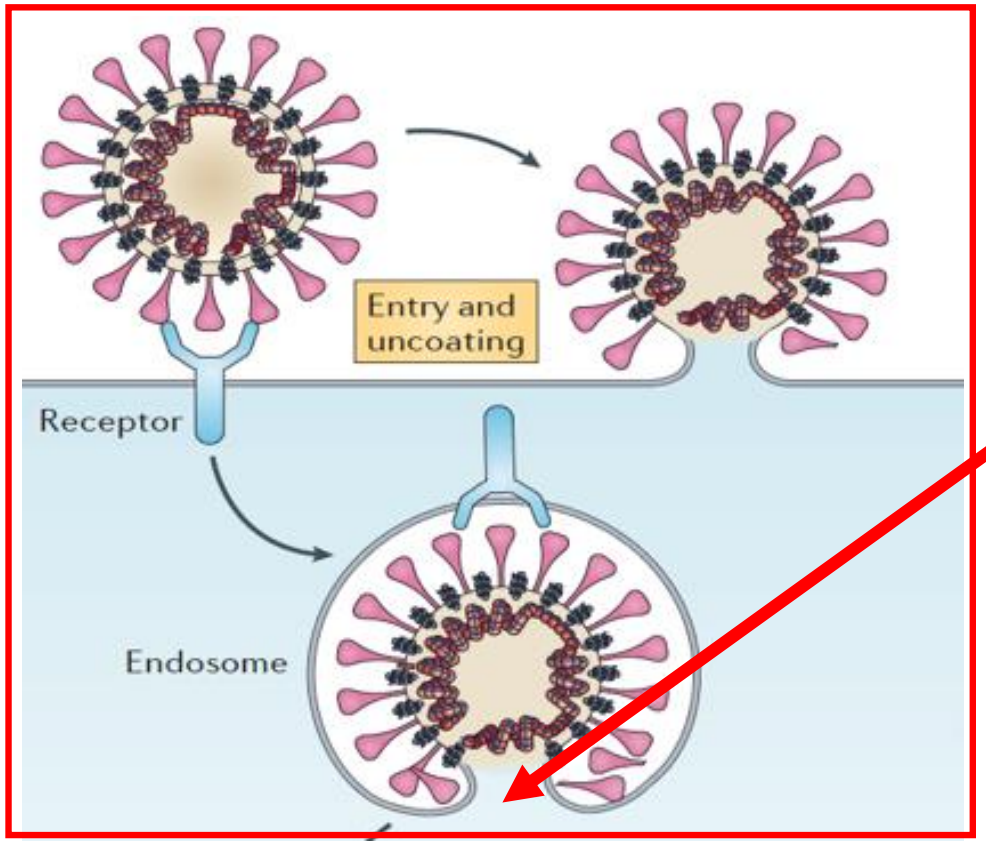


Monoclonal antibodies

Vaccines

- ***Moderna Vaccine***
- ***Measles vectored***
- ***Adenovirus vectored***

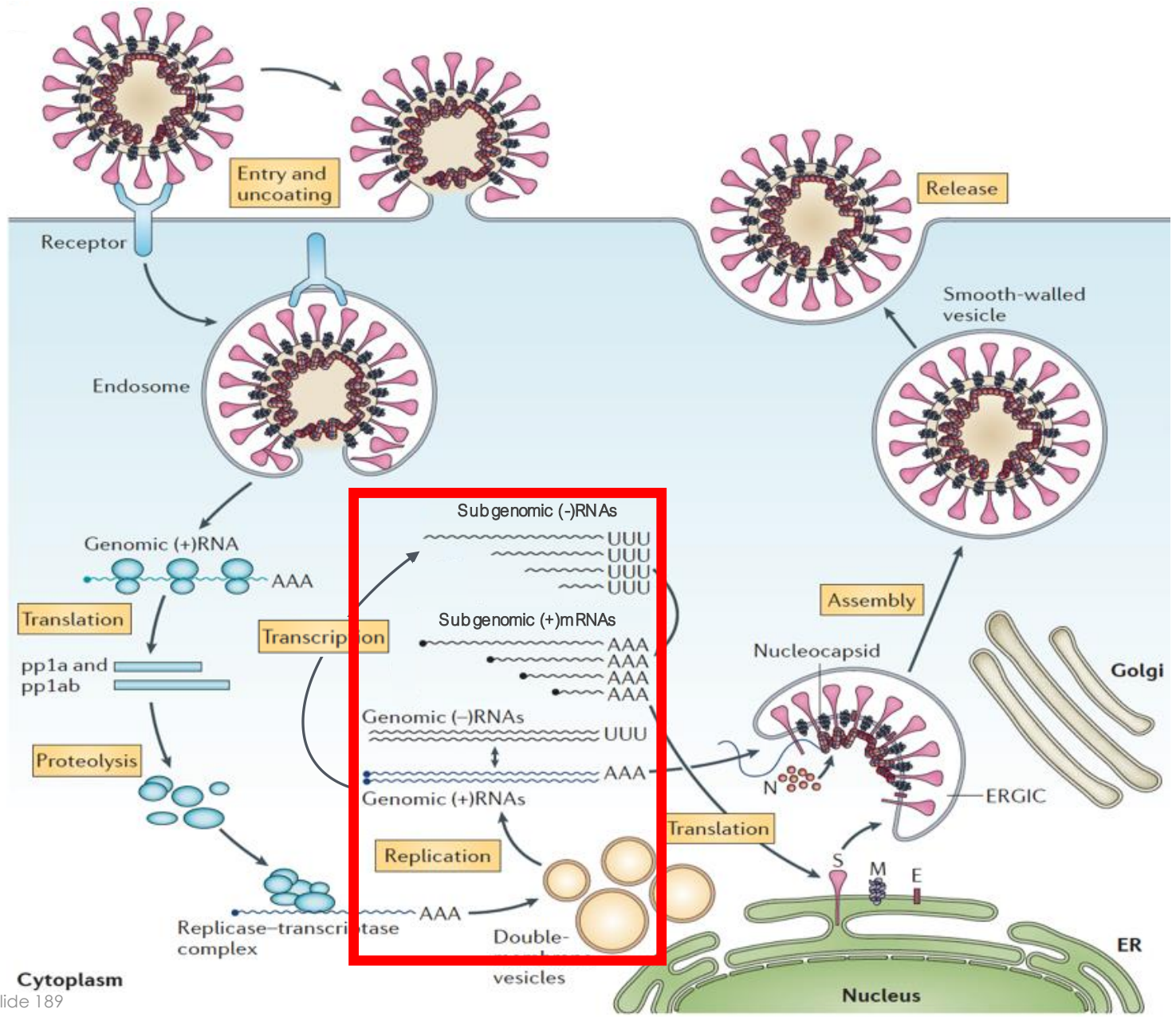
Adapted from de Wit et al. Nat. Rev. Micro. 2016.



Chloroquine

- **Blocks** acidification of endosome, lysosome, Golgi
- Block fusion / uncoating?
- *Paradoxical for ChickV – enhanced replication and decreased immune response*
- *Cardiac side effects*
- *Psychiatric side effects*

Coronavirus Replication

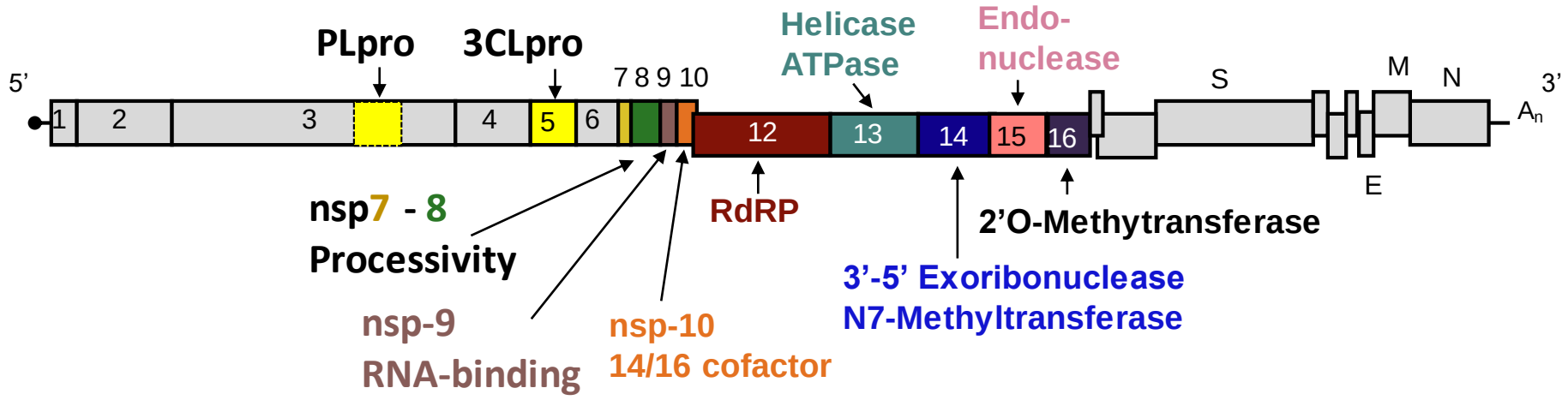


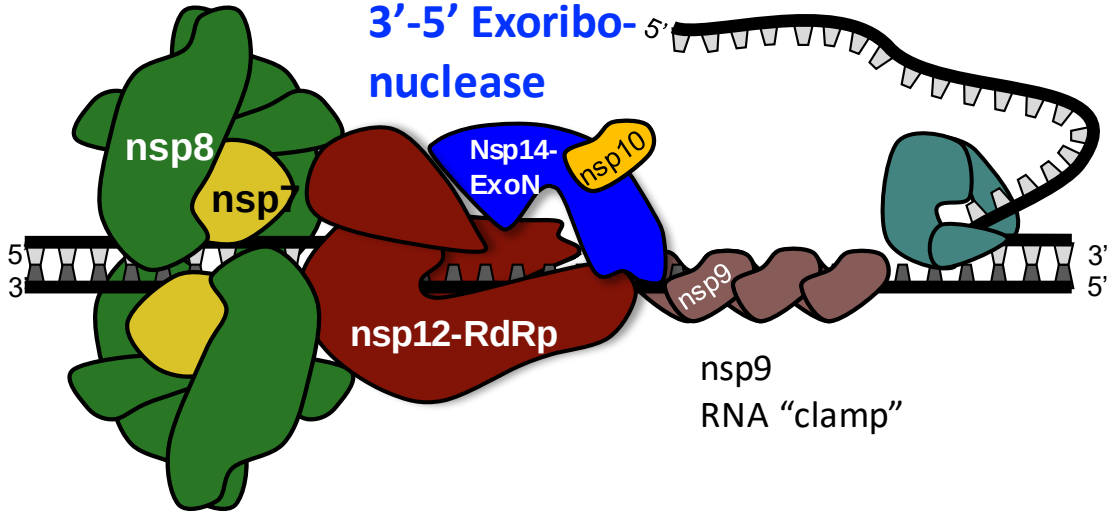
Virus RNA synthesis

- Replicase Proteins assemble and modify host membranes into replication factories
- RdRp- polymerase as critical protein
- Highly conserved across coronaviruses

Adapted from de Wit et al. Nat. Rev. Micro. 2016.

Coronaviruses assemble a multiprotein replicase complex



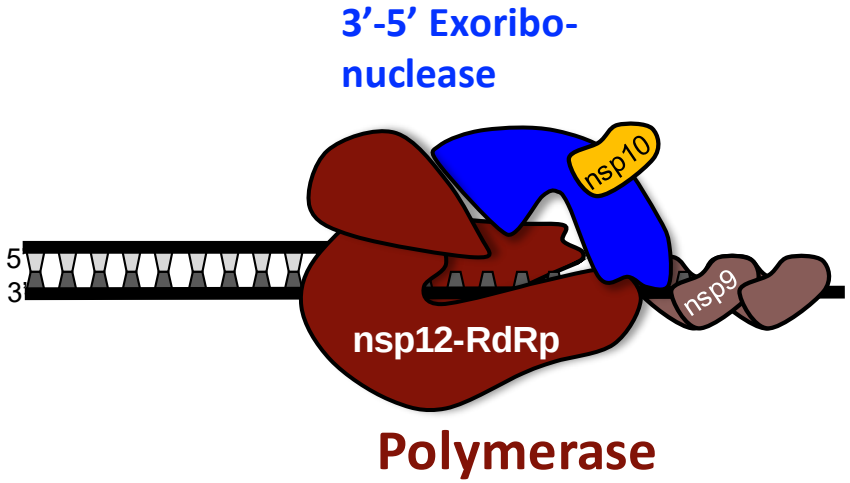


RNA proofreading – nsp14-ExoN

- High fidelity replication – >20 fold that of other RNA viruses
- Inactivation attenuates virus, mutator phenotype, impairs fitness

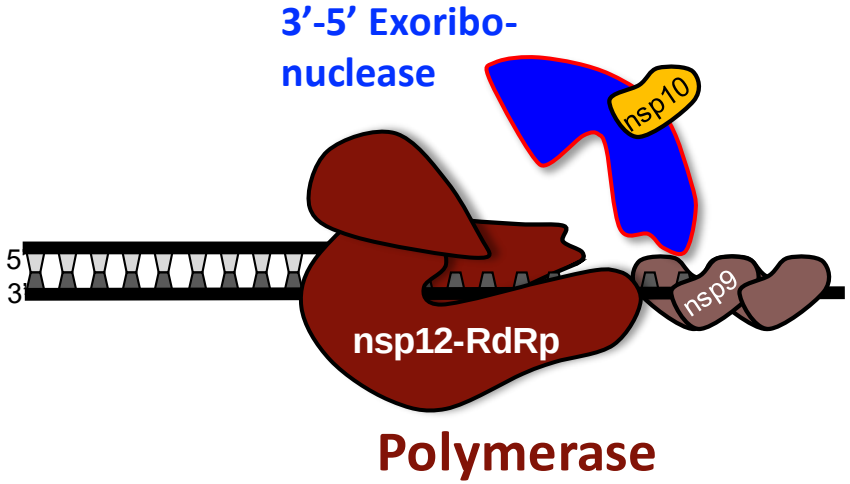
nsp12 RdRp- RNA-dependent RNA polymerase

Model for evolutionary role for RNA proofreading complex – Hypothesis based on experimental data



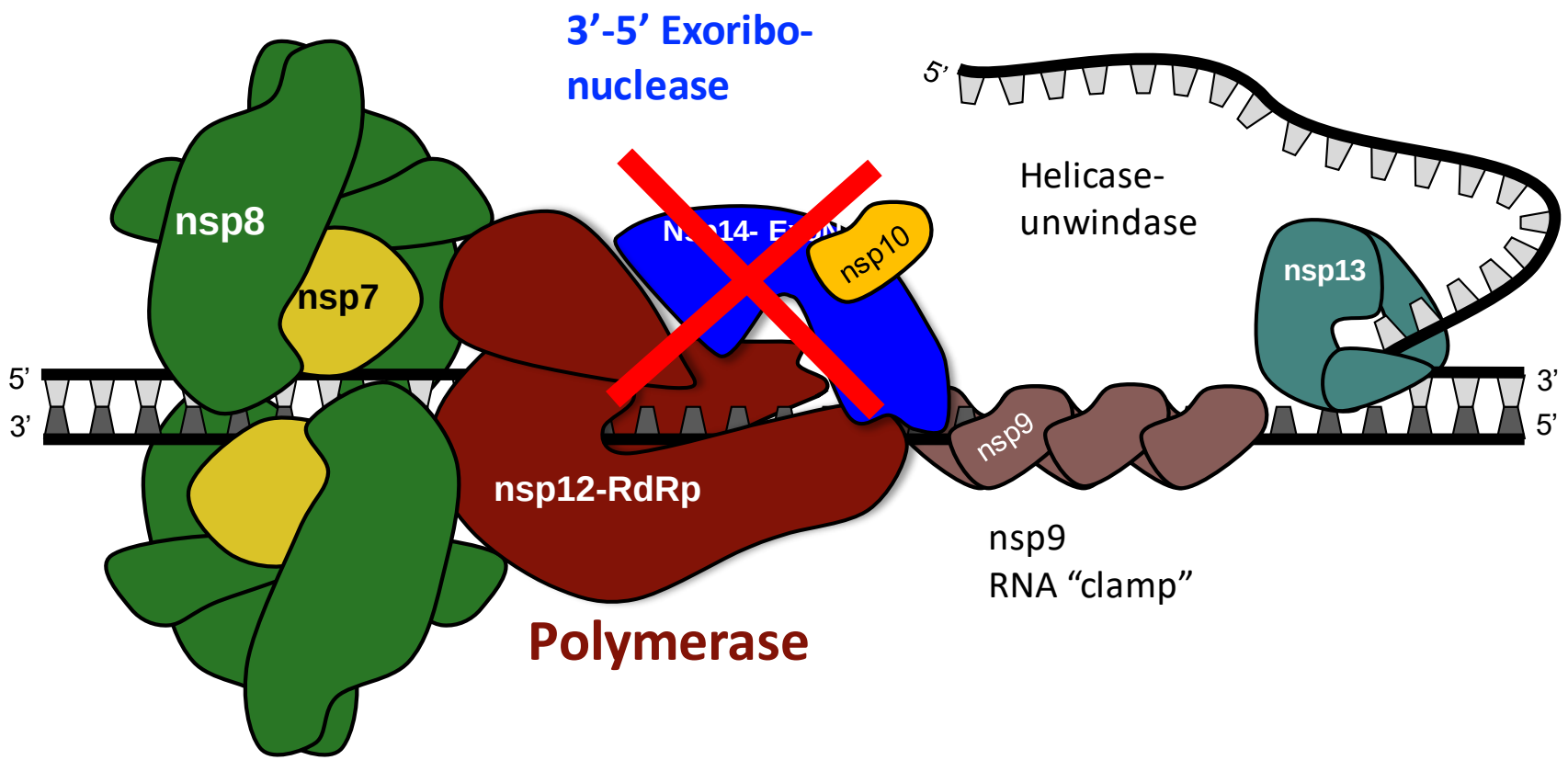
No selective pressure

- Complex intact
- High-fidelity – very few mutations
- Stable genome, limited variation



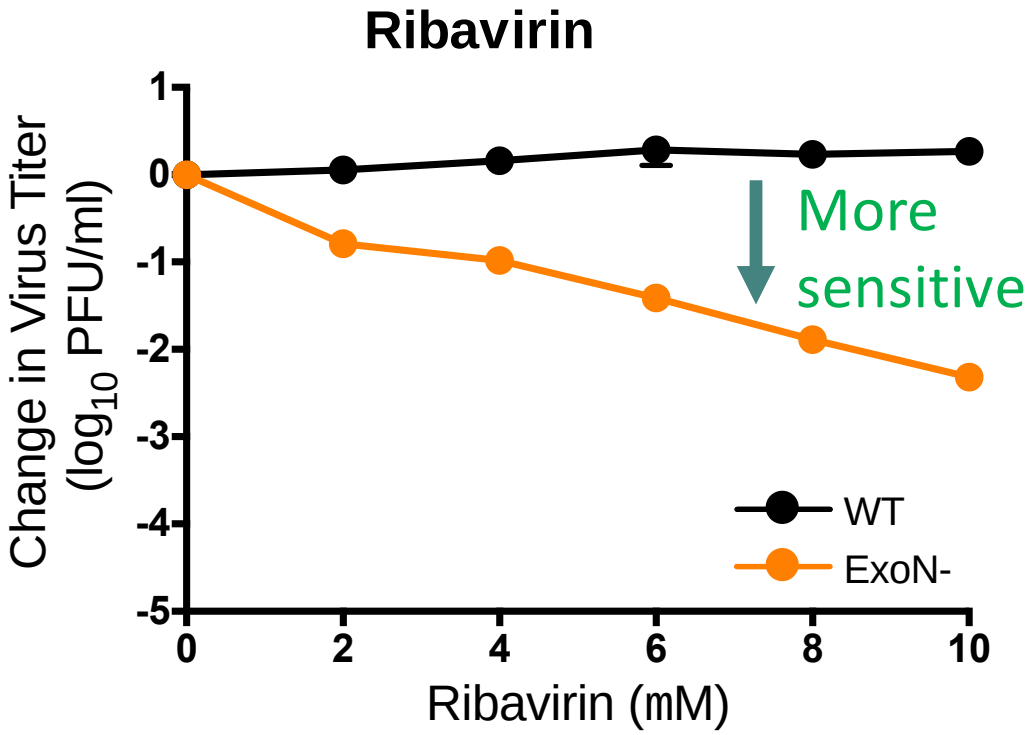
Selective pressure

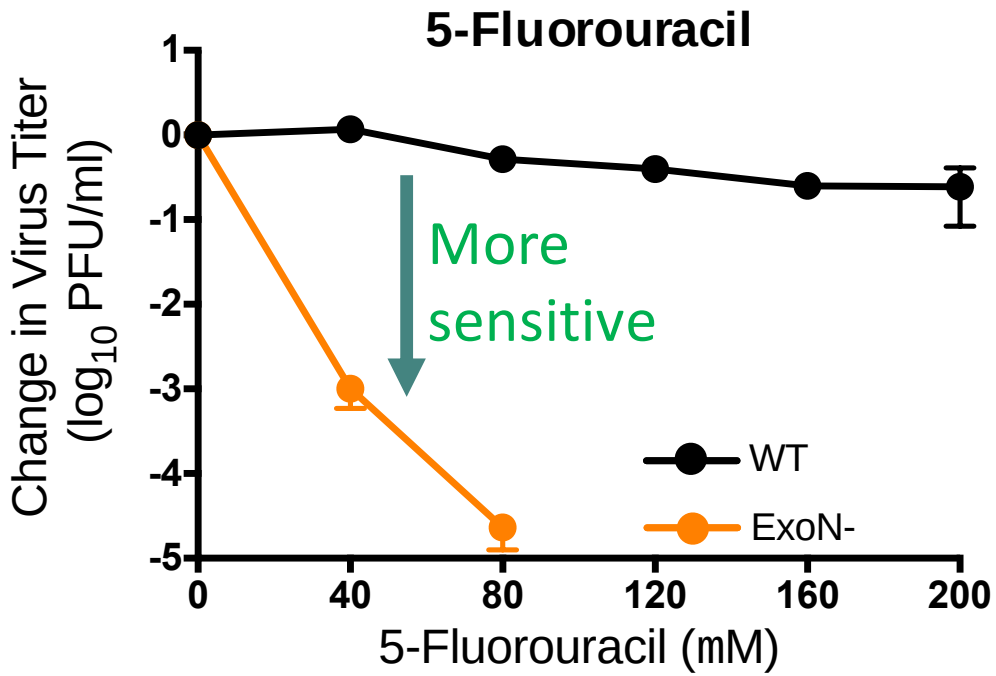
- Disrupted complex
- Low Fidelity – many mutation generated
- Rapid Adaptation – variation favored over stability



Inactivate Exonuclease Proofreading

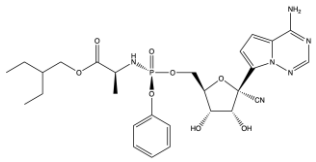
Proofreading nsp14-ExoN is responsible for CoV native resistance to nucleoside analogs

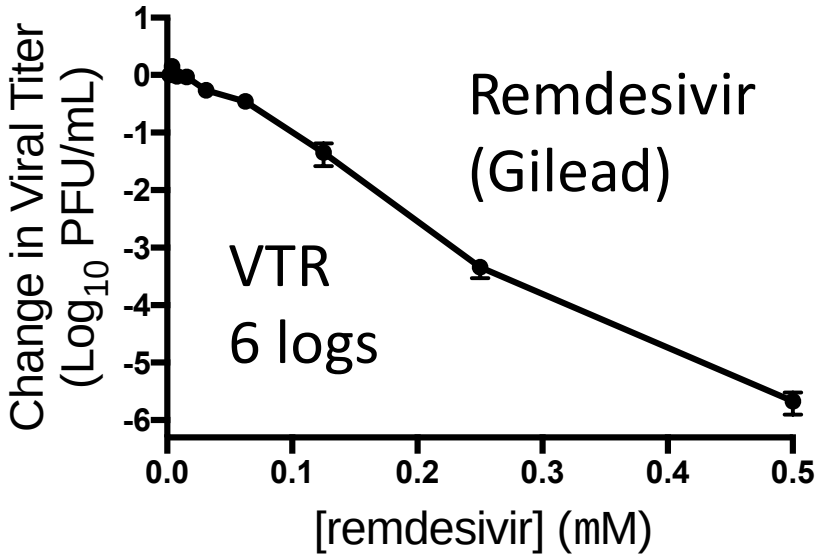


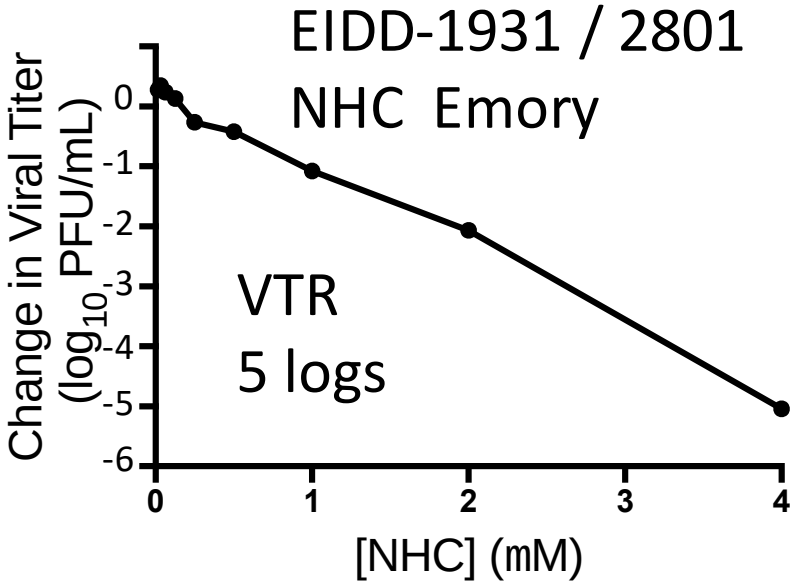


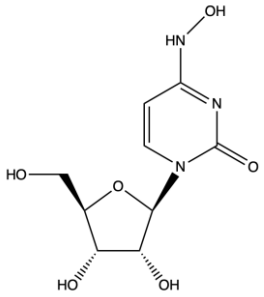
Adapted from Smith et al. *PLOS Path.* 2013.

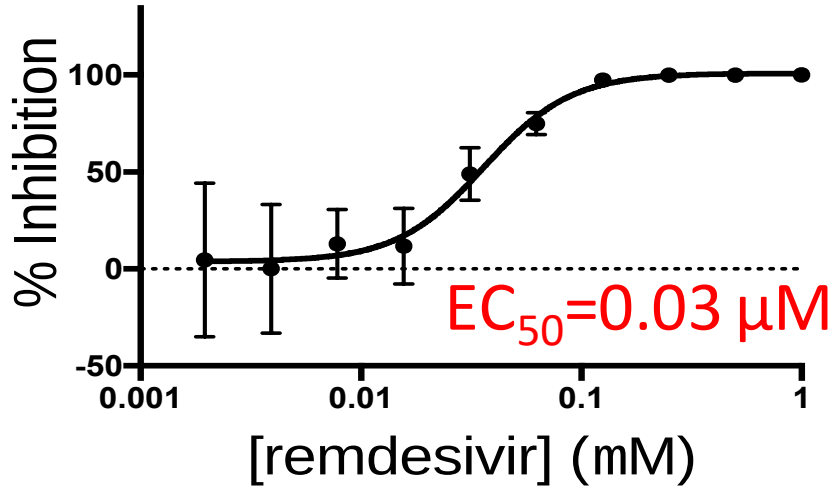
Remdesivir and β-D-N^4-Hydroxycytidine (EIDD-1931/2801, NHC) inhibit CoV replication

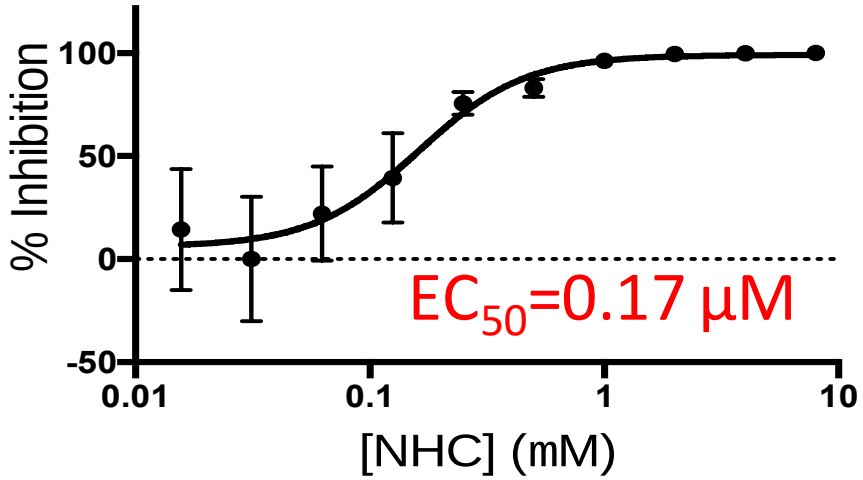












Agostini et al mBio 2017

Agostini et al J Virol 2019

Remdesivir - IV

EIDD-2801- NHC

oral

- Potently inhibits multiple divergent CoVs ✓
- Resistance has high barrier and detrimental to virus ✓
- Efficacious for prophylaxis in mouse model of lethal SARS-CoV ✓
- Decreases disease and virus titer when administered early in infection ✓
- Active against SARS-CoV-2 ✓
- Chain terminator

Mutagen

Implications for vaccines

- Many precedents for good responses in animals to multiple approaches for SARS-CoV and MERS-CoV
- Broadly neutralizing antibodies against SARS-CoV and MERS-CoV
- Evidence for human CoVs - that subsequent infections are milder even if protection is not sterilizing or absolute
- Capability of virus family to adapt and change it well known
- Vaccines are essential for control, changing dynamic of the virus
- Likelihood that this virus will persist, flare, recur, without seasonality

Public Health Response

- Limit transmission
- Limit genetic variation
- Assess mechanisms of transmission

Monoclonal Antibodies

- Prevent / treat infection
- Temporary immunity
- Interrupt transmission
- Prophylax populations

COVID-19 Response and counter-measures

Antivirals

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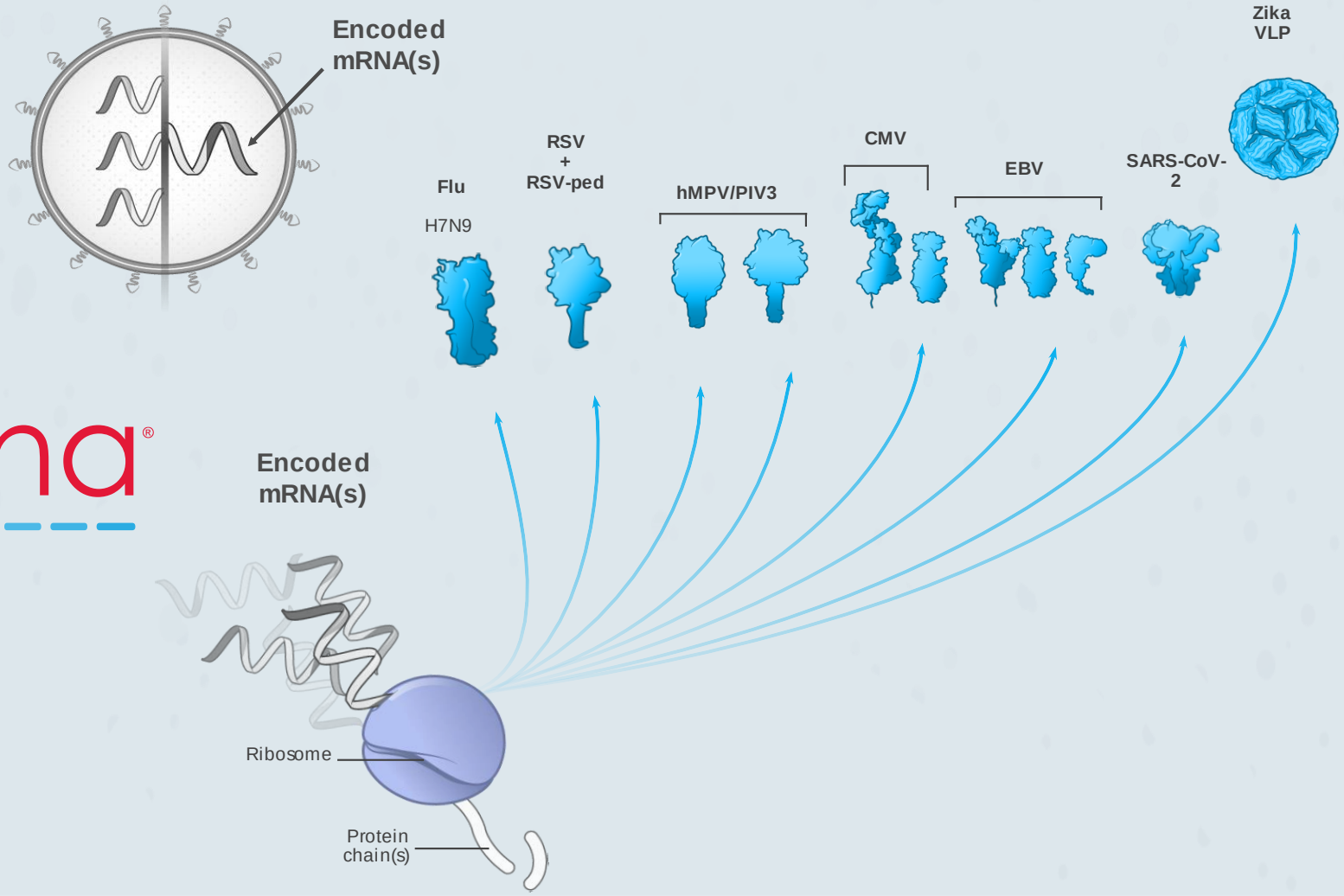
- Can we predict if, when, and how the pandemic will evolve / resolve?



moderna®

mRNA-1273 Overview

Tal Zaks, M.D., Ph.D., Chief Medical Officer

April 14, 2020

Coronavirus overview

Betacoronaviruses include:

- MERS
- SARS
- Human coronavirus HKU1
- WIV16
- SARS-CoV-2

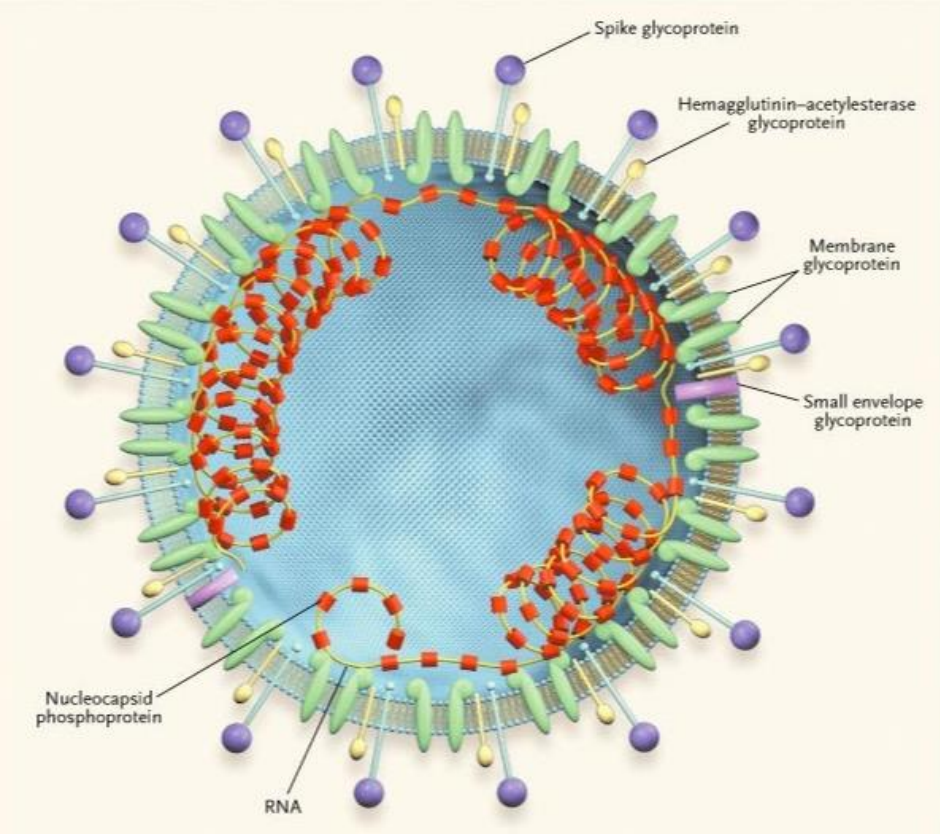
Sequence comparison between betacoronaviruses

- Spike S protein in SARS-CoV-2 is 80% homologous SARS coronavirus and
- 30% homologous with MERS coronavirus

Insights from pre-clinical research with our mRNA vaccines against MERS coronavirus

- Full length Spike S protein significantly more immunogenic than S-2 domain

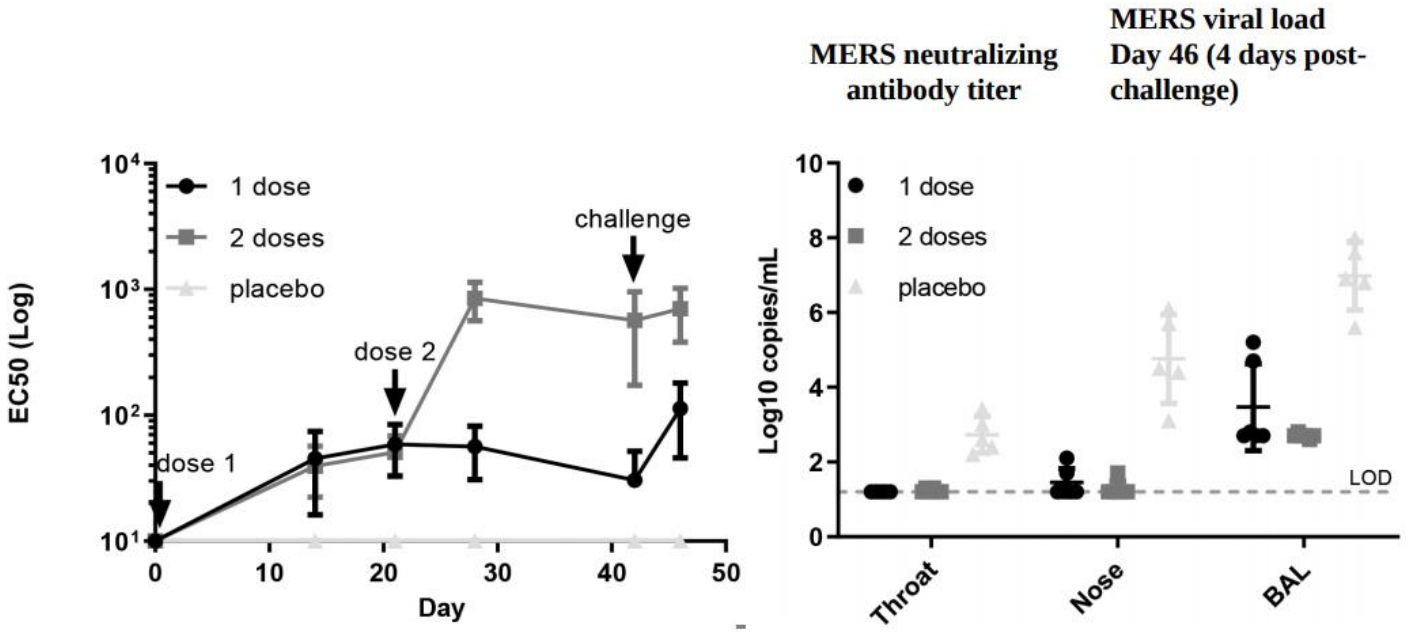
Structure of the Coronavirus Virion[1]



1. Holmes, Kathryn. N Engl J Med 2003; 348:1948-1951. SARS-Associated Coronavirus

Representative preclinical information regarding a related coronavirus, MERS

Rabbits were dosed with either one or two doses of vaccine (one dose plus a booster at day 21) and then challenged with MERS virus at day 42. At day 46, MERS viral load was measured in the throat and nose, and via bronchoalveolar lavage ("BAL")



We observed an induction of **neutralizing antibodies which were sufficient to affect a ~3-log reduction in viral titers in the nose, and ~4-log reduction in viral titers** detected from BAL. Viral titers in the throat were reduced to the lower limit of detection.

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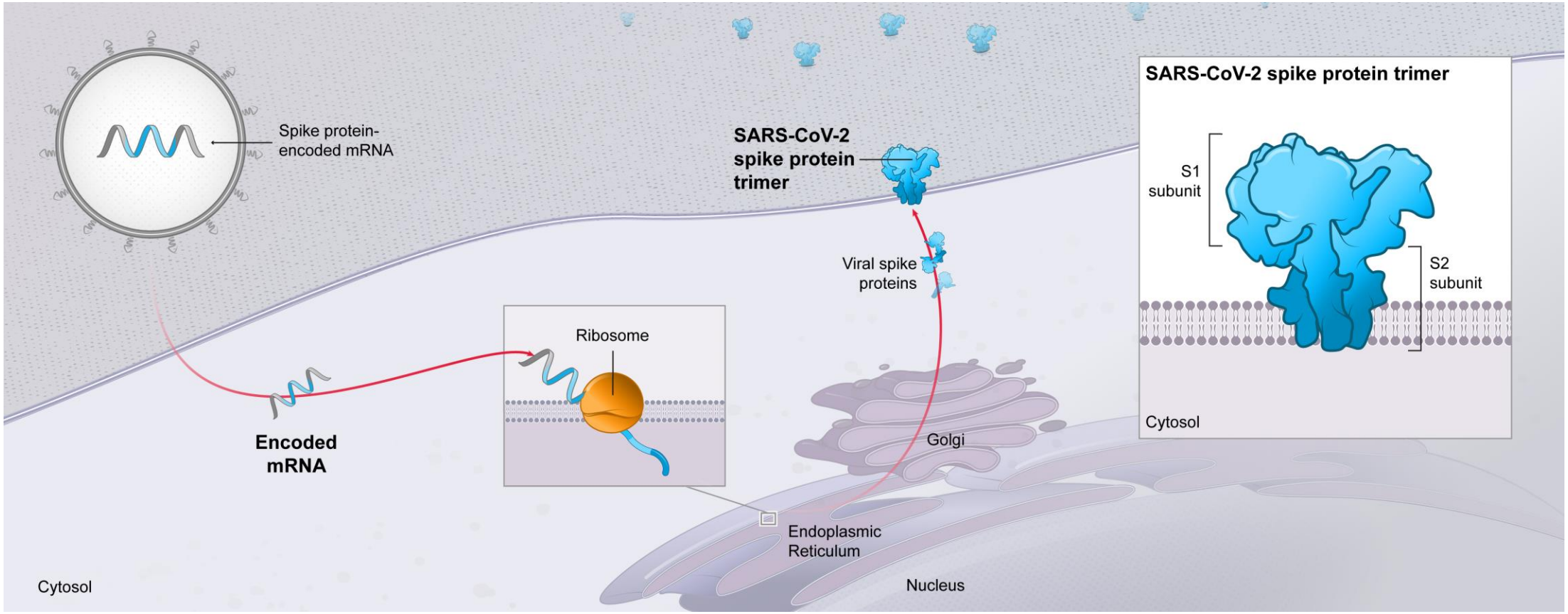
SARS-CoV-2 vaccine (mRNA-1273)

Encodes for the full spike S protein



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SARS-CoV-2 vaccine (mRNA-1273)

Phase 1 trial (run by the National Institutes of Health)

Key objective: To assess the safety, reactogenicity and immunogenicity of mRNA-1273

Study Design: Phase 1, open-label dose ranging clinical trial in males and non-pregnant females, 18 to 55 years of age

- Forty-five subjects will be enrolled into one of three cohorts (25, 100 and 250 µg
- Subjects will receive an intramuscular (IM) injection (0.5 milliliter [mL]) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394)

Primary endpoint:

- Safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart, across 3 dosages in healthy adults

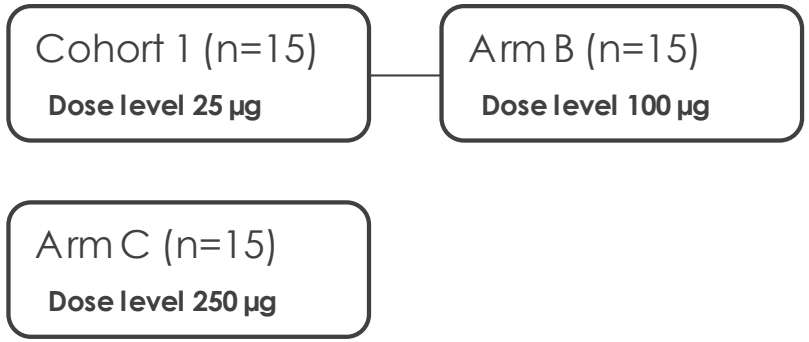
Secondary endpoint:

- Evaluate the immunogenicity as measured by IgG ELISA to the SARS-CoV-2 S protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57

Trial progress/details:

- Enrollment of 250ug Cohort initiated week of April 8

mRNA-1273-P101 Study Design



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All regulatory paths require a positive benefit/risk assessment

	Size	Endpoint	Risk
Phase 1	10s	Safety and tolerability Immunogenicity	Tolerability (predicted local and systemic vaccine adverse events)
Phase 2	100s	Dose confirmation (immunogenicity) Safety and tolerability	Safety (unpredicted)
Phase 3	1,000s	Less disease Less infection Safety and tolerability	Enhanced disease

Regular Approval

Clinical efficacy demonstrated

Accelerated Approval

a surrogate "reasonably likely" to predict benefit

Emergency Use Authorization

"May have benefit"

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Manufacturing introduction

Juan Andres, Chief Technical and Quality Officer

April 14, 2020

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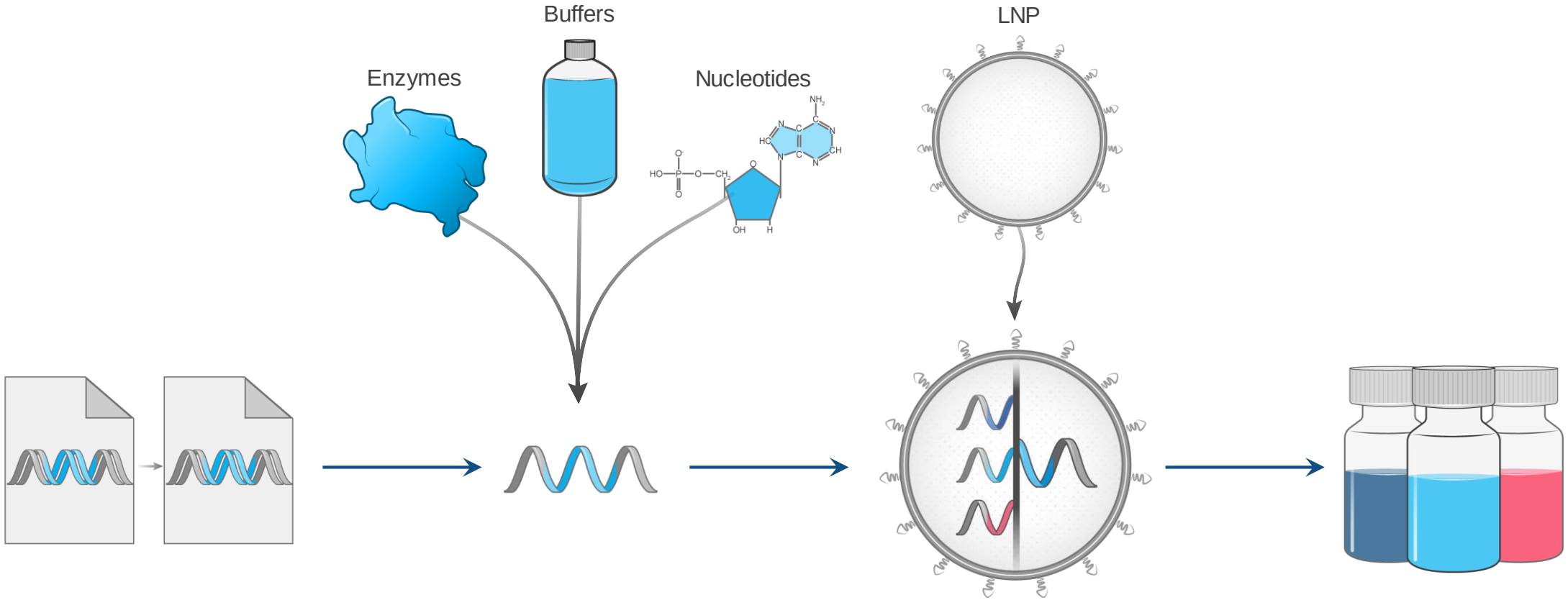
NEW

We are a platform…



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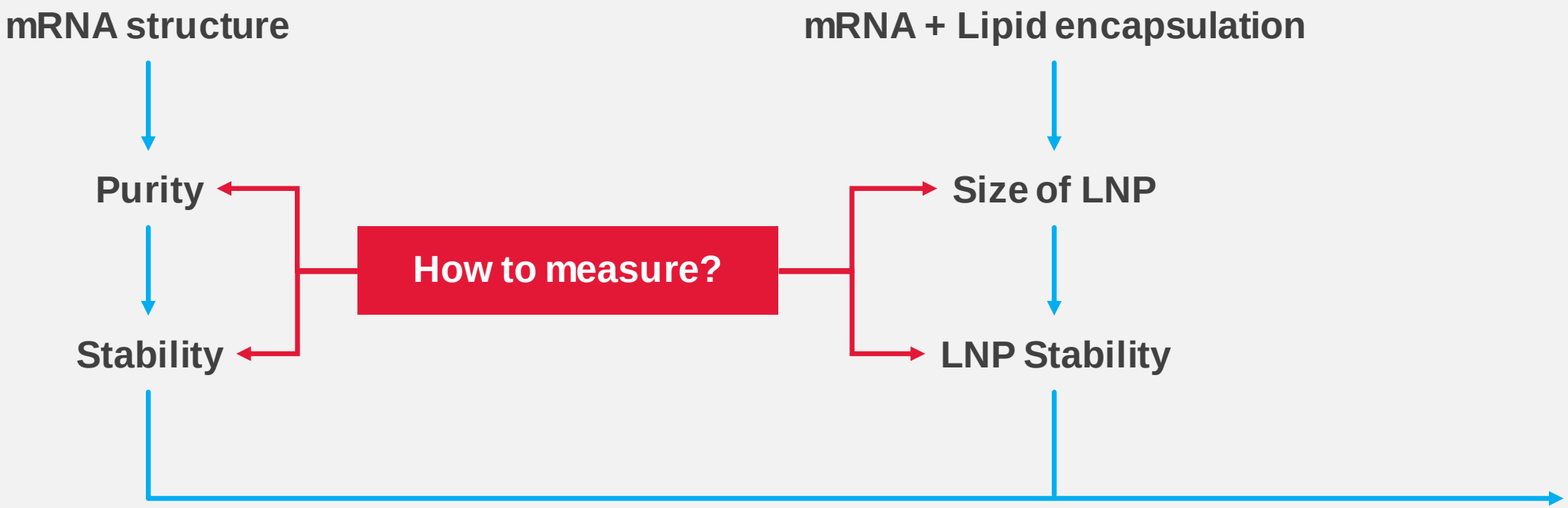
We have solved many questions



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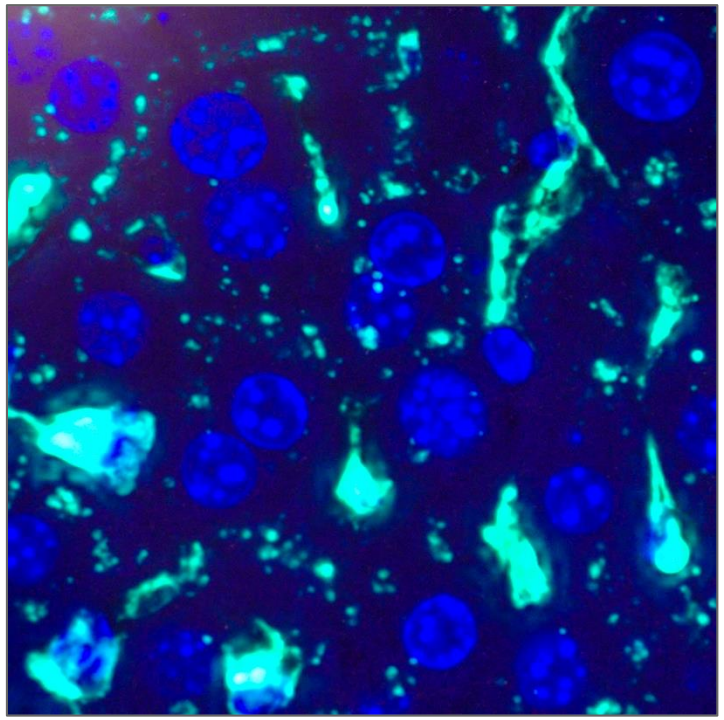
Platform research + technical development = “create”



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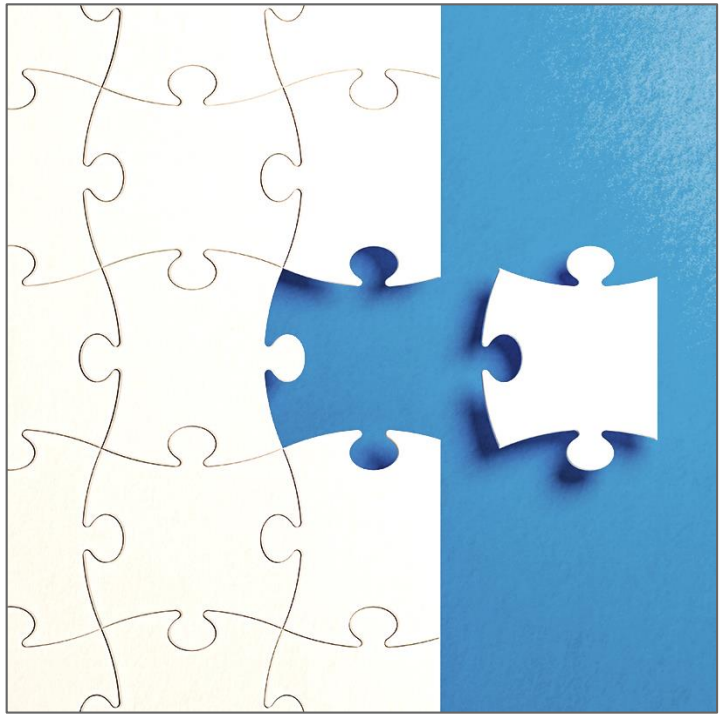

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Before having our own manufacturing site

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Our manufacturing site is scalable

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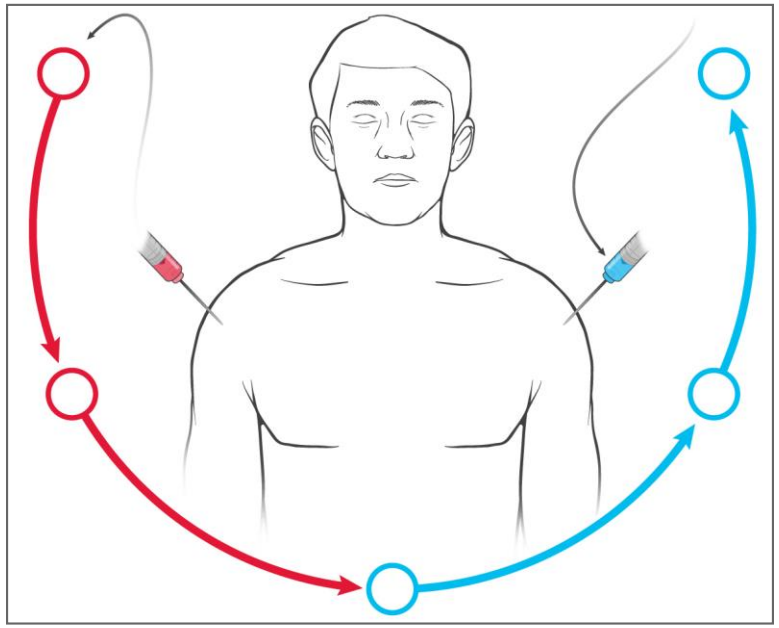
3 Engines

PRECLINICAL

PERSONALIZED VACCINE UNIT



CLINICAL

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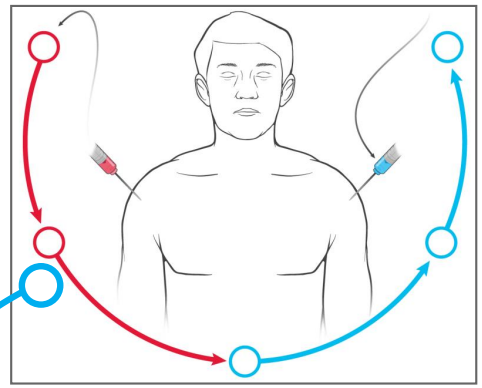
	PRECLINICAL	PERSONALIZED VACCINE UNIT	CLINICAL
Batches			
	23,500	1 batch/1 patient; 90 to date	1 batch/many patients
Scale			
	10mg	>100mg	5g-75g+

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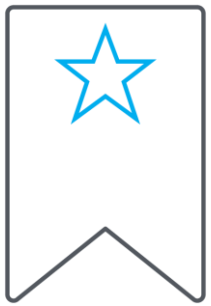
What we know now…. Platform technology

Similar processes

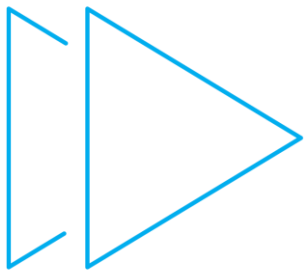
Fast process improvements

Cell-free

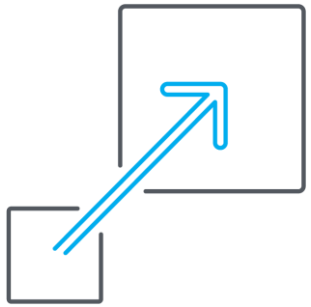
Less capital investment



Quality



Speed



Scale

Cost

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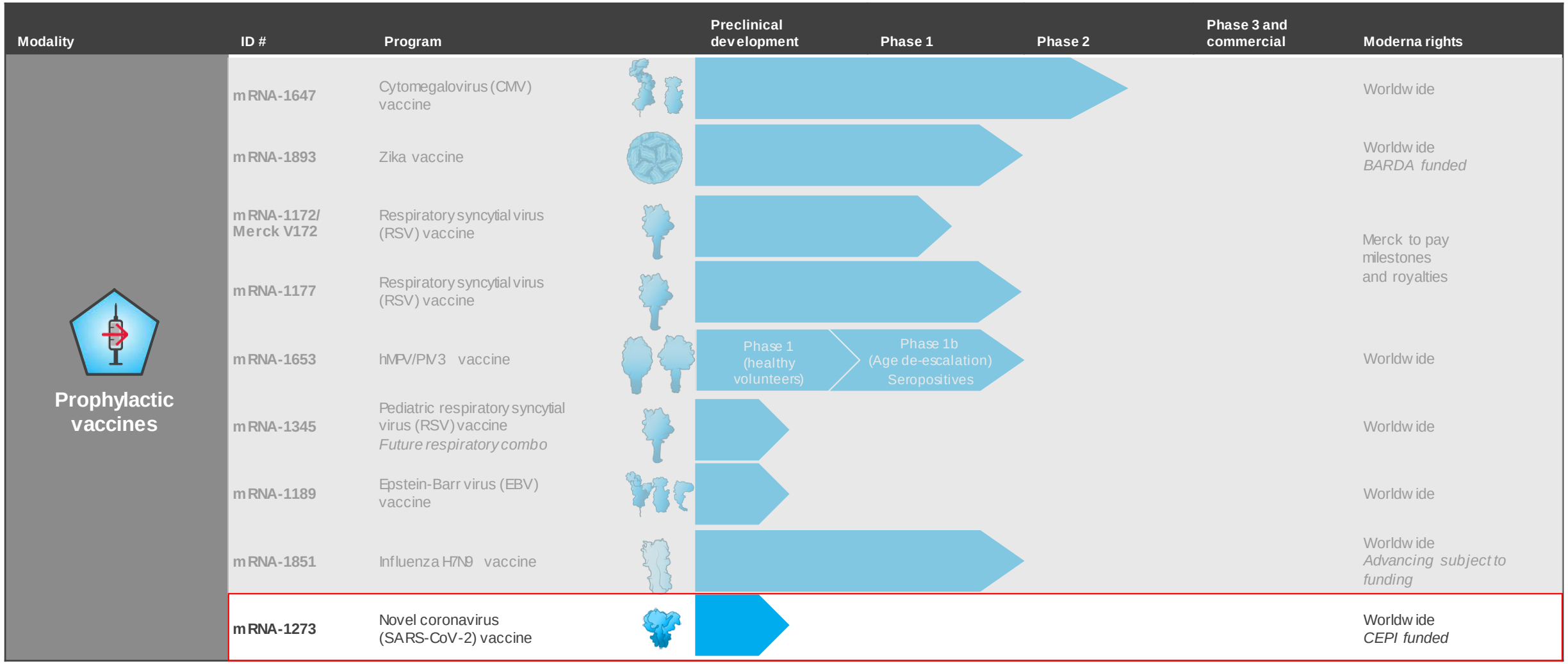
Prophylactic vaccines modality

SARS-CoV-2 vaccine (mRNA-1273)



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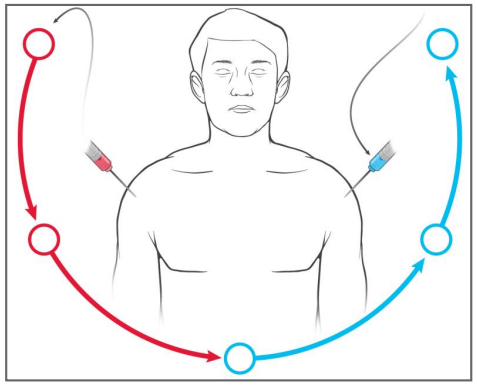
Firing up on all engines…

	PRECLINICAL	PERSONALIZED VACCINE UNIT	CLINICAL
Batches			
	23,500	1 batch/1 patient; 90 to date	1 batch/many patients
Scale			
	10mg	>100mg	5g-75g+

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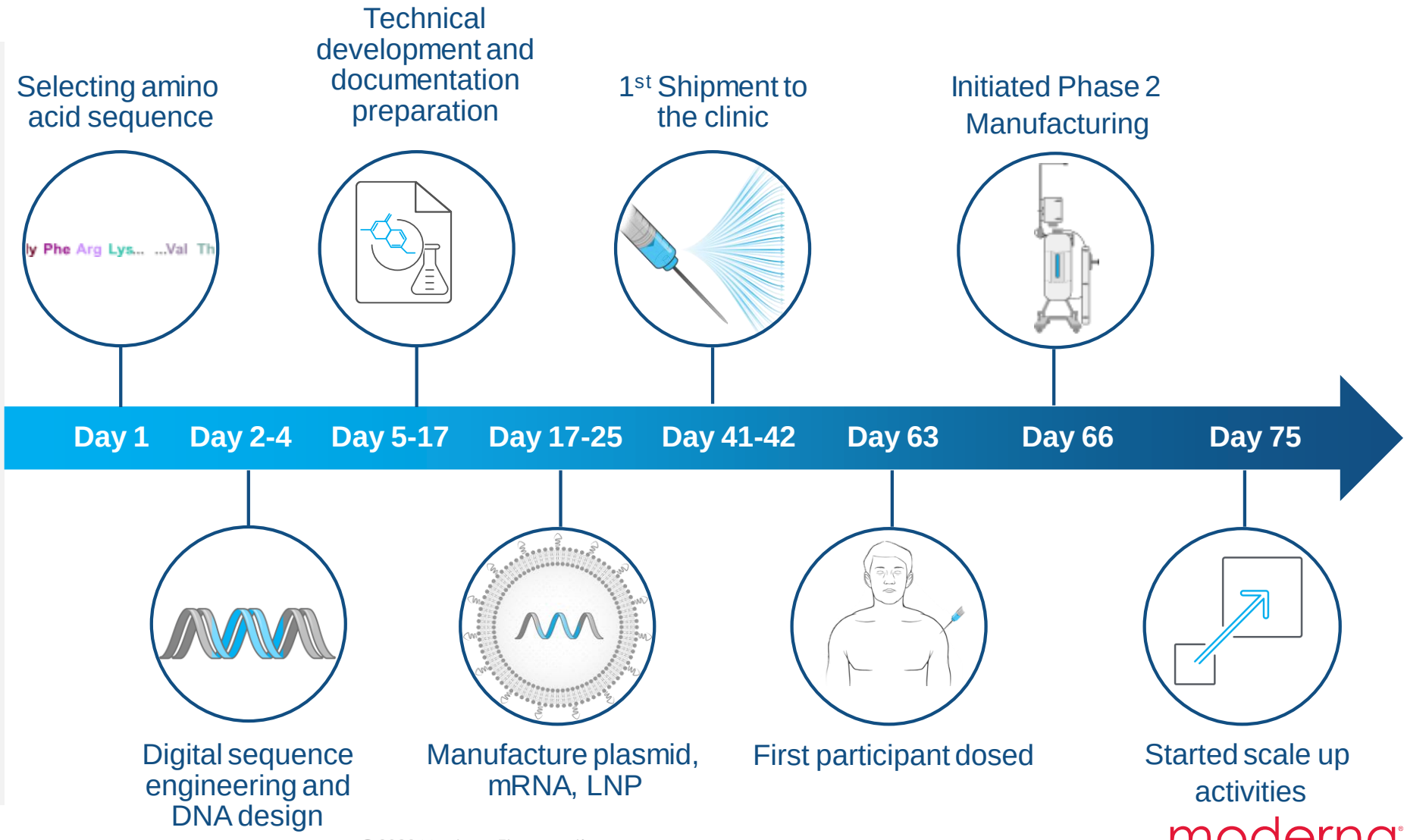
Concept to Phase 1 in 42 days

Speed

- Jan 13
- Feb 7
- Feb 23



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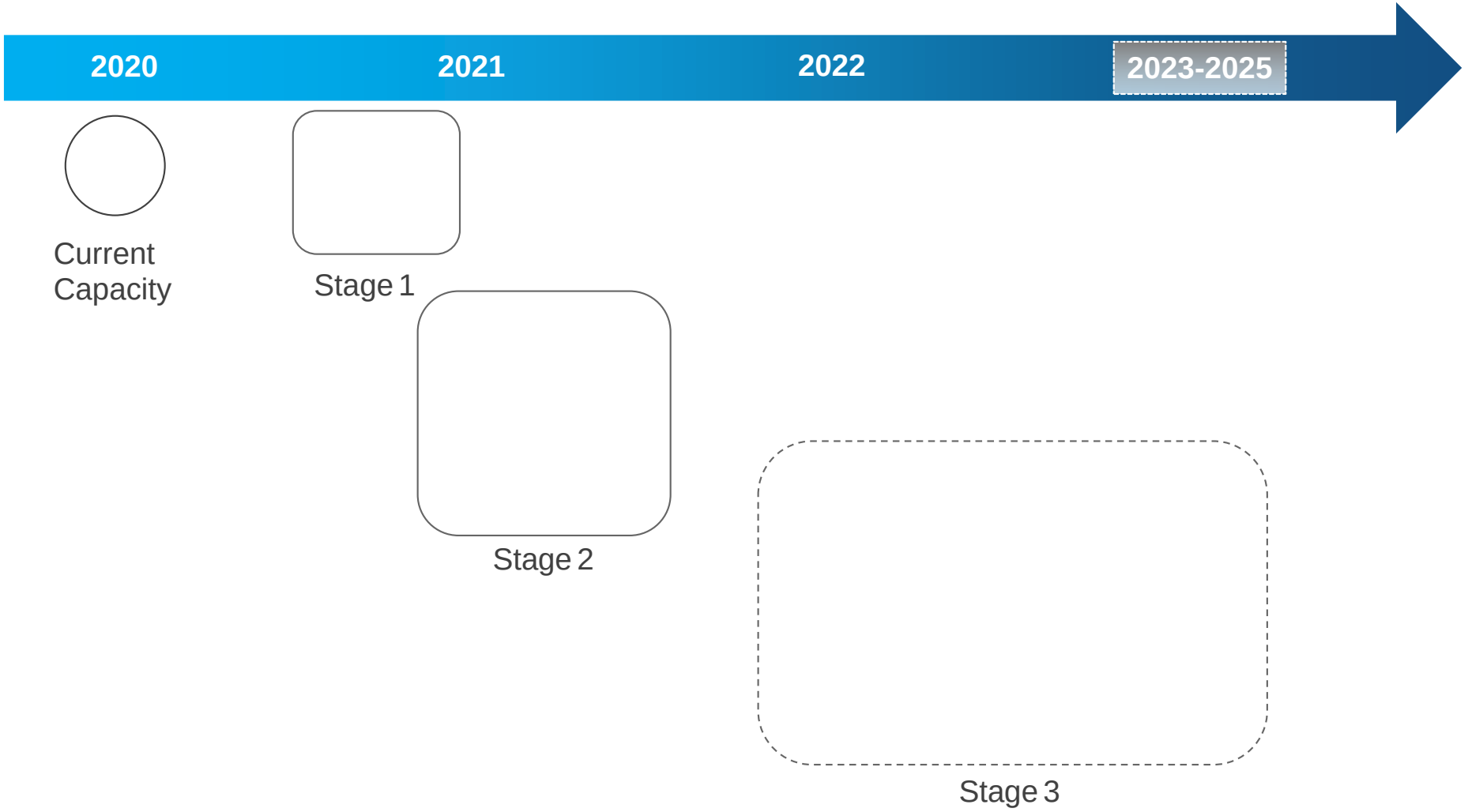
We plan to scale capacity in three different stages



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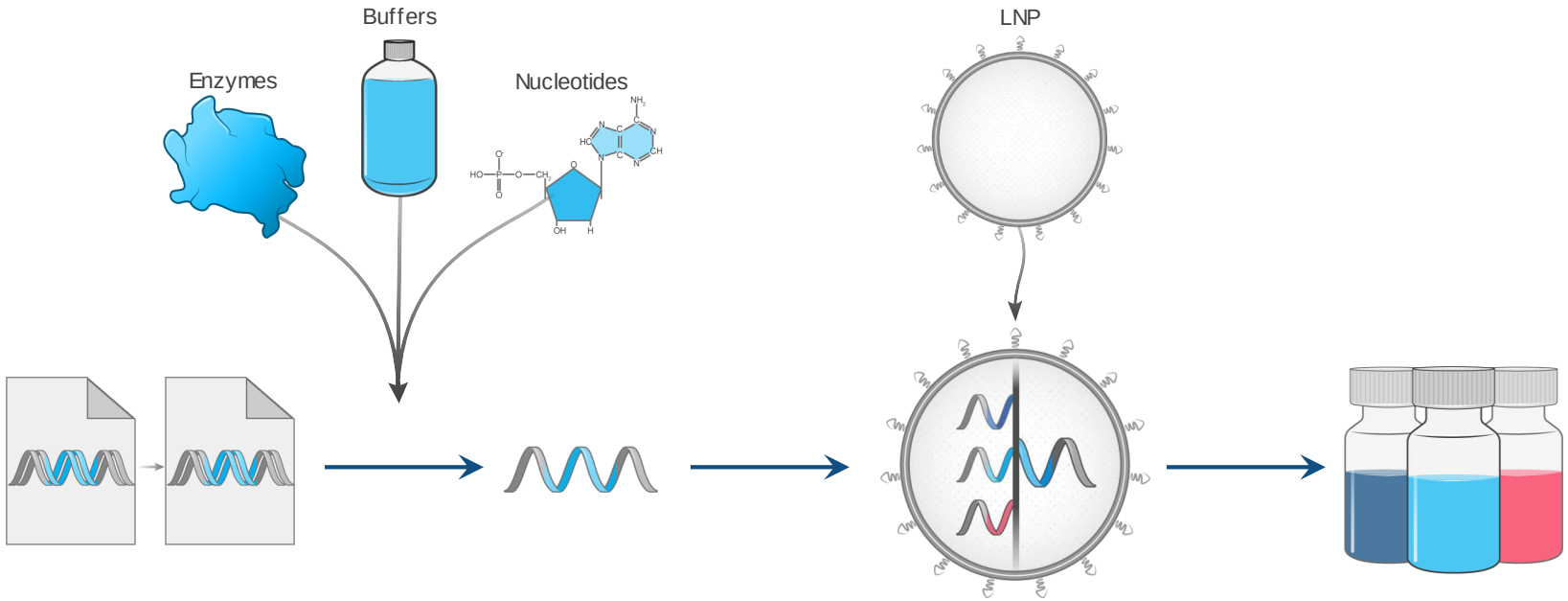
Working on all parts of supply chain

Scale

Quality

Speed



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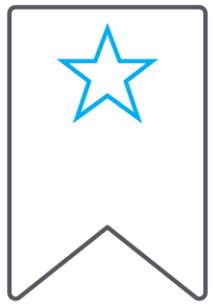
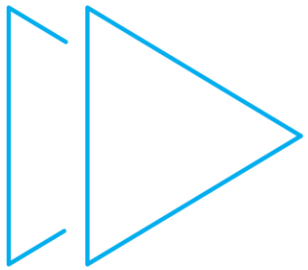
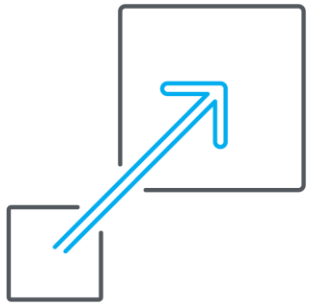
Paving the future…



Quality



Speed



Scale

Cost

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Kathryn M. Edwards, M.D.

Sarah H. Sell and Cornelius Vanderbilt Professor of Pediatrics

Dr. Edwards joined the Vanderbilt Vaccine Program in 1980 and has conducted many pivotal vaccine studies since that time. She has had an extensive experience in leading NIH-funded multicenter initiatives; in designing, conducting, and analyzing pivotal Phase I, II, and III clinical studies on vaccines and therapeutics; in facilitating networking with basic and clinical investigators with a wide range of interests and expertise; and in mentoring many of the young investigators who currently work within her research unit.

Dr. Edwards has served on several CDC, NIH, WHO, and IDSA committees. In 2006, she received the IDSA Mentor Award for her exceptional mentoring and in 2014 received the Maureen Andrews Mentoring Award from the Society for Pediatric Research. In 2008 she was elected to the National Academy of Medicine of the National Academy of Sciences. In 2016 she was awarded the Charles Mérieux Vaccinology Award from the National Foundation for Infectious Diseases. In 2018 she was awarded the Maxwell Finland award for Scientific Accomplishments by the National Foundation for Infectious Diseases, and in 2019 she received the Frank Morriss Leadership Award in Pediatrics.

What is the role of the Advisory Committee on Immunization Practices (ACIP) in formulating vaccine recommendations?

Kathryn M. Edwards MD

Sarah H. Sell and Cornelius Vanderbilt Professor

Division of Infectious Diseases

Department of Pediatrics

Vanderbilt University Medical Center

Objectives of Presentation

What is the ACIP and how does it work?

What role does ACIP play in formulating vaccine recommendations?

What criteria are used to formulate vaccine recommendations? Are pharmacoeconomic data considered?

How might CMV vaccines be reviewed by the ACIP?

Is there an equivalent of ACIP outside the US?

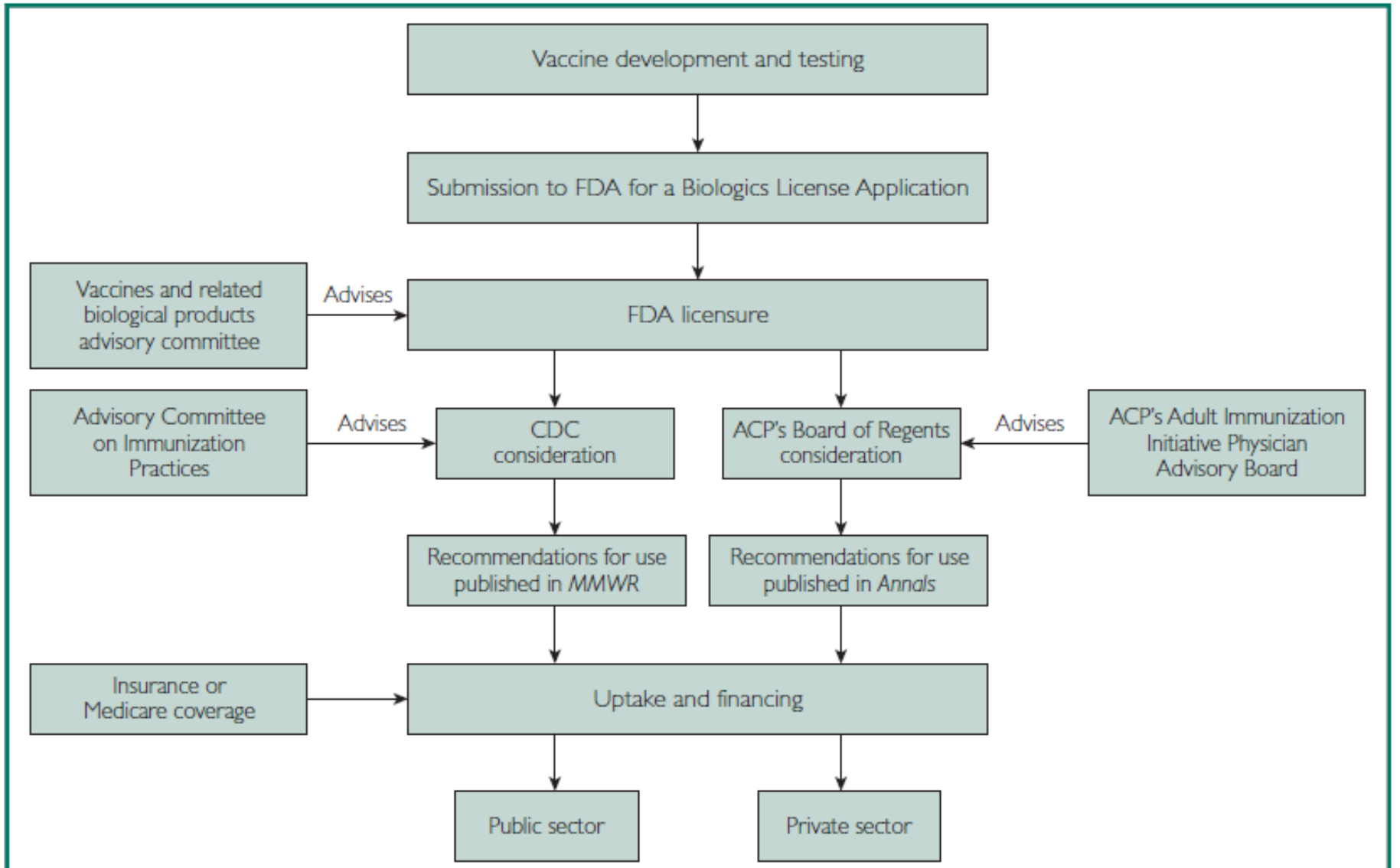


FIGURE 1. Development and dissemination of vaccine recommendations and policies. ACP = American College of Physicians; *Annals* = *Annals of Internal Medicine*; CDC = Centers for Disease Control and Prevention; FDA = Food and Drug Administration; *MMWR* = *Morbidity and Mortality Weekly Report*. From *Ann Intern Med*.[7] Copyright © 2019 American College of Physicians. Used with permission.

Mayo Clin Proc. ■ March 2020;95(3):600-608

TABLE 1. FDA Approval and ACIP Recommendation for Vaccines

Organization	Pathways for approval or recommendation	Description
FDA	Traditional approval	Must show safety in the indicated population
		Pivotal trials report prevention of clinical disease (effectiveness) or achievement of protective level (immunogenicity) of an accepted correlate of protection
		Usual pathway for new vaccines, but may not be feasible for all vaccines
	Accelerated approval	Must show safety in the indicated population
		Targeted disease is considered serious or life-threatening
		Pivotal trials use a surrogate marker (immune response) reasonably likely to predict clinical benefit as an end point
		Adequate and well-controlled postmarketing trial is required to verify the clinical benefit
	Animal Rule	Must show safety in the indicated population
		Targeted condition is considered serious or life-threatening
		Use only if Traditional or Accelerated pathways are not feasible and ethical
		Pivotal studies in relevant animal models to provide substantial evidence of effectiveness in humans
		Postmarketing human study is required to verify the clinical benefit when the study becomes feasible, as during an urgent need
ACIP	Recommendation	Vaccine is recommended for all people in an age- or risk-based group without contraindications
		Recommendations made for selected subpopulations and is based on individual clinical decision making

ACIP = Advisory Committee on Immunization Practices; FDA = Food and Drug Administration.

Mayo Clin Proc. ■ March 2020;95(3):600-608

ACIP Functions

- Advise the Director of the CDC regarding use of vaccines for effective control of vaccine-preventable diseases in the civilian population of the United States.
- Provide advice regarding the use of a new vaccine when it is licensed in the U.S. by the FDA.
- Establish and periodically review the list of vaccines for administration to children and adolescents eligible to receive vaccines through the Vaccines for Children Program, along with schedules regarding the appropriate dose and dosing interval, and contraindications to administration of the pediatric vaccines.

Group	n	Description of members
Voting members	14	Subject matter experts in vaccinology, immunology, pediatrics, internal medicine, nursing, family medicine, virology, public health, infectious diseases, and/or preventive medicine
	1	Consumer representative who provides perspectives on the social and community aspects of vaccination.
Ex officio members (non-voting)	8	Individuals in the roles listed below or their designees. • Director, Division of Vaccine Injury Compensation, Bureau of Health Professions, Health Resources and Services Administration • Deputy Director for Scientific Activities, Office of the Assistant Secretary of Defense for Health Affairs, Department of Defense • Under Secretary for Health, Department of Veterans Affairs • Director, Center for Biologics Evaluation and Research, Food and Drug Administration • Director, Center for Medicaid and State Operations, Centers for Medicare and Medicaid Services • Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health • Director, Indian Health Service • Director, National Vaccine Program Office, HHS

ACIP Members

Liaison representatives from professional organizations (non-voting)	31	Participating organizations: • American Academy of Family Physicians • American Academy of Pediatrics • American Academy of Physician Assistants • American College Health Association • American College of Nurse Midwives • American College of Obstetricians and Gynecologists • American College of Physicians • American Geriatrics Society; • America's Health Insurance Plans • American Medical Association • American Nurses Association • American Osteopathic Association • American Pharmacists Association • Association of Immunization Managers • Association for Prevention Teaching and Research • Association of State and Territorial Health Officials • Biotechnology Industry Organization • Council of State and Territorial Epidemiologists • Canadian National Advisory Committee on Immunization • Infectious Diseases Society of America • National Association of County and City Health Official • National Association for Pediatric Nurse Practitioners • National Foundation for Infectious Diseases • National Immunization Council and Child Health Program, Mexico
		• National Medical Association • National Vaccine Advisory Committee • Pediatric Infectious Diseases Society • Pharmaceutical Research Manufacturers of America • Society for Adolescent Health and Medicine • Society for Healthcare Epidemiology of America

ACIP Members

Work Groups

- ACIP uses subgroups of the Committee, known as Work Groups, to review relevant published and unpublished data and develop recommendations for presentation to the ACIP.
- Work Groups are responsible for collection, analysis, and preparation of information for presentation, discussion, deliberation, and vote by the ACIP in an open public forum.
- Work Groups review specific topics in detail and clarify issues in a way that helps ACIP voting members make informed and efficient decisions, with the best and most current information available.
- Four Permanent Work Groups—the Adult Immunization Schedule, Child/Adolescent Immunization Schedule, General Best Practices, and Influenza Vaccines Work Groups
- The remaining Work Groups are task oriented. **These task-oriented Work Groups are developed in response to specific needs** and are disbanded when the task at hand has been completed.

Members of the Work Groups

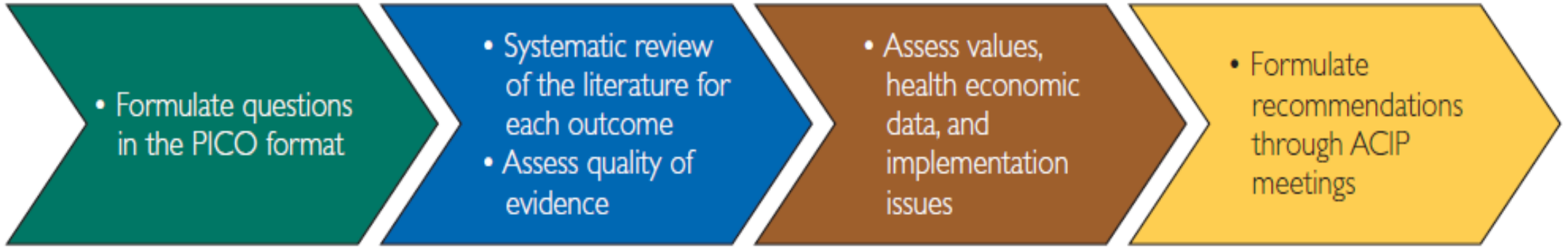
- ACIP Work Groups 1) must include two or more ACIP voting members, one of whom serves as Chair; 2) must include CDC staff members; 3) should include an FDA staff member, if appropriate; and 4) may include *ex officio* members and liaison representatives.
- Only appointed ACIP voting members may chair a Work Group. On occasion, disease/vaccine experts may be asked to serve as consultants to a Work Group.
- Members with a potential financial conflict of interest cannot serve on a Work Group. If the individual has unique expertise to the Work Group, that person may serve as a scientific consultant but should not participate in policy deliberations.
- Conflict of interest declarations are signed by Work Group members annually and changes will be announced during Work Group teleconferences.

Function of the Work Groups

- Work Groups are formed to extensively review relevant published and unpublished data and develop recommendation options for presentation to the ACIP during its public meetings.
- Work Groups are formed when updates to existing recommendations are anticipated based on new data or the **when the licensure of a new vaccine** or new indications for existing vaccines are anticipated.
- In general, Work Groups begin reviewing data 12-18 months prior to a potential decision on licensure; the length of time required for the Work Group to review data in anticipation of vaccine licensure will depend upon the complexity of the topic and the amount of available data existing.

Dissemination of ACIP Findings

- The ACIP develops recommendations on how to use vaccines to control disease in the United States.
- The Committee's recommendations are forwarded to CDC's Director for approval. Once the ACIP recommendations have been reviewed and approved by the CDC Director and the U.S. Department of Health and Human Services, they are published in CDC's Morbidity and Mortality Weekly Report (MMWR). The MMWR publication represents the final and official CDC recommendations for immunization of the U.S. population.
- Professional organizations that work with the ACIP to develop the annual childhood and adult schedules include the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Physicians (ACP).



PICO definition: **P**atient, **P**opulation, or **P**roblem; **I**ntervention, Prognostic Factor, or Exposure; **C**omparison or Intervention (if appropriate); **O**utcome you would like to measure or achieve

FIGURE 2. Steps for the development of recommendations by the Advisory Committee on Immunization Practices (ACIP) using the Grading of Recommendations, Assessment, Development and Evaluation system. Reprinted from *MMWR Morb Mortal Wkly Rep.*[18] Used with permission of *AAP News*, October 2019.

ACIP Evidence to Recommendations Framework

Question: Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework. The question should be very precise and identify the specific intervention, comparison, and outcome, as well as the target population and the setting (specific subpopulations) in PICO format.
Population: Target population for vaccine (e.g., age range, sex, immune status, pregnancy)
Intervention: Vaccination (if applicable, dosage and schedule)
Comparison(s): No Vaccination/Placebo/Control/Standard care/An existing vaccine/Other prevention options
Outcome: Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)

Background: The addressed PICO question should be described in detail, and important background information for understanding the question and why a recommendation or decision is needed should be briefly provided. If a recommendation is preferential or represents off-label use, this should be indicated.
Include sample language: Additional background information supporting the ACIP recommendations on the use of xxx vaccine can be found in the relevant publication of the recommendation referenced on the ACIP website.

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐	Provide available scientific evidence on burden of disease, preferably within the target population for the recommendation. If no published evidence is available, provide expert judgment on the public health priority considerations.	Identify any additional public health priority considerations, including consideration of disparities.
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	*Minimal* ☐ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies*	Describe the magnitude of the beneficial effects of vaccination on individual (vaccine effectiveness, duration of protection) and population (herd immunity) levels.	Take into consideration: Is the baseline benefit similar across subgroups (by age, gender, pregnancy or lactation status, occupation [i.e., healthcare workers], immune status, race, SES, and other groups)? Are there indirect effects that should be considered (e.g., herd immunity)?

ACIP Evidence to Recommendations Framework

	CRITERIA	JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	How substantial are the undesirable anticipated effects?	☐ Minimal ☐ Small ☐ Moderate ☐ Large ☐ Don't know ☐ Varies	Are there undesirable effects of the vaccine, either on the individual (e.g., adverse events following immunization) or population (e.g., age-shift of disease, serotype replacement) levels?	Take into consideration: Is the baseline risk for harm similar across subgroups (see above)? Should there be separate recommendations for subgroups based on harms?
	Do the desirable effects outweigh the undesirable effects?	☐ Favors intervention ☐ Favors comparison ☐ Favors both ☐ Favors neither ☐ Unclear	Describe the balance of benefits of the vaccine with possible harms (individual and population level).	
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention ☐ No included studies ☐ 4 Very low ☐ 3 Low ☐ 2 Moderate ☐ 1 High Safety of the intervention ☐ No included studies ☐ 4 Very low ☐ 3 Low ☐ 2 Moderate ☐ 1 High	Please refer to GRADE (safety and effectiveness) tables for detailed assessment of the certainty of the evidence. For more information, please see the ACIP Handbook for Developing Evidence-Based Recommendations.	If GRADE was not used to evaluate the evidence, please provide justification and the method and outcome of any other tools used to evaluate the body of evidence relevant to the critical outcomes.
VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies	Provide any available evidence on target population values & preferences related to vaccination and comparative health benefits and risks. Describe the source of these estimates.**	Are values and preferences for relevant outcomes measured? Are the benefits, harms and costs of vaccination valued differently by different subgroups? If the target group doesn't value the intervention, or attributes little value to the harms and benefits, consider whether potential education measures are needed.

ACIP Evidence to Recommendations Framework

	CRITERIA	JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes	Please provide available data used to determine the relative importance that the target population attributes to the desirable and the undesirable outcomes related to the intervention as well as the comparison.**	Describe the source of variability, if any. Are there methods for determining values satisfactory for this recommendation? If not, systematic assessment of values and preferences of target group may be considered.
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies	Provide assessment of whether intervention would be acceptable to stakeholders (ethically, programmatically, financially, etc.)	
RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes	Provide summary of findings of cost-effectiveness analyses (CEAs) of the vaccine in the target population. Include base case results and a sensitivity range. Include any other notable findings, for example, specific policy-relevant scenarios.	Overall findings: Summarize the findings from available CEAs, including major differences in baseline assumptions. Uncertainty: Does the analysis capture the full range of uncertainty? For example, are the findings from the uncertainty of evidence analysis, identified earlier in this document (the EtR Framework), appropriately represented in the methods of the CEAs? Multiple assessments: Are there multiple CEAs? If so, what are the major differences in methods and results?
FEASIBILITY	Is the intervention feasible to implement?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies	Are there any barriers to implementation?	Please refer to the Implementation Considerations checklist.

ACIP Evidence to Recommendations Framework

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐	There is insufficient evidence to determine the balance of consequences ☐
Is there sufficient information to move forward with a recommendation? Yes ☐ No ☐						
Type of recommendation	We do not recommend the intervention ☐	We recommend the intervention for individuals based on clinical decision-making ☐	We recommend the intervention ☐			
Recommendation (text)	Please provide the draft recommendations proposed to ACIP.					
Additional considerations (optional)	Please outline any significant additional considerations (e.g., aspects related to implementation, monitoring and evaluation, research priorities, etc.).					

i This Evidence to Recommendation table is based on the GRADE Evidence to Decision framework developed through the *DECIDE* project. Furthe

ACIP Evidence to Recommendations Framework

Question: Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework. The question should be very precise and identify the specific intervention, comparison, and outcome, as well as the target population and the setting (specific subpopulations) in PICO format.
Population: Target population for vaccine (e.g., age range, sex, immune status, pregnancy)
Intervention: Vaccination (if applicable, dosage and schedule)
Comparison(s): No Vaccination/Placebo/Control/Standard care/An existing vaccine/Other prevention options
Outcome: Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐	Provide available scientific evidence on burden of disease, preferably within the target population for the recommendation. If no published evidence is available, provide expert judgment on the public health priority considerations.	Identify any additional public health priority considerations, including consideration of disparities.

Congenital CMV: Disease Burden

- Each year in the US, 1 in 200 infants (20,000) are born with congenital CMV infection.
- Most infants (80%) with congenital CMV infections are asymptomatic and will not have long-term health problems.
- Each year, about 4,000 (20%) infected infants will have long-term health problems.

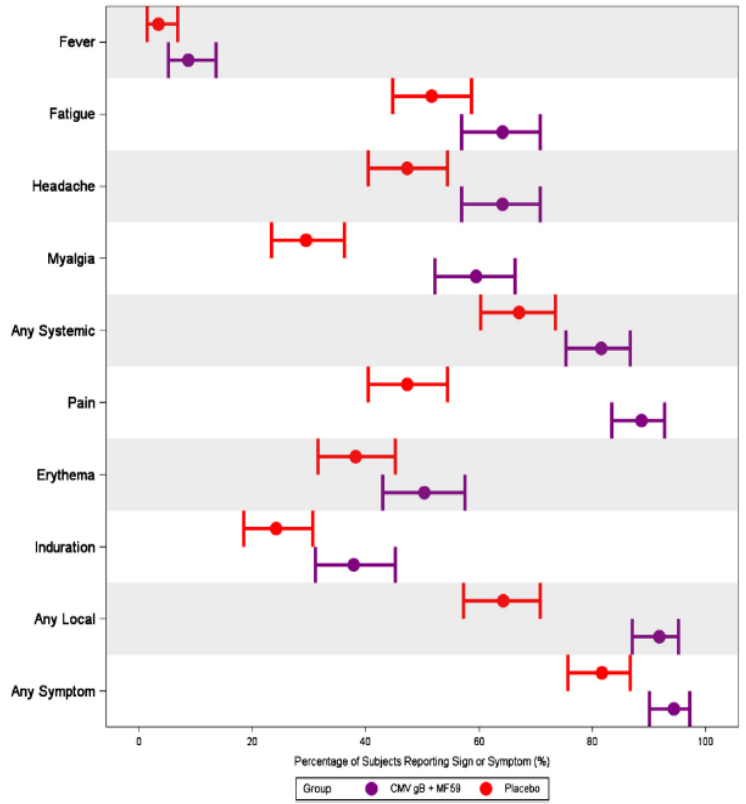
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	*Minimal* ☐	*Small* ☐	*Moderate* ☐	*Large* ☐	*Don't know* ☐	*Varies*	Describe the magnitude of the beneficial effects of vaccination on individual (vaccine effectiveness, duration of protection) and population (herd immunity) levels.	Take into consideration: Is the baseline benefit similar across subgroups (by age, gender, pregnancy or lactation status, occupation [i.e., healthcare workers], immune status, race, SES, and other groups)? Are there indirect effects that should be considered (e.g., herd immunity)?

Table 3
Vaccine efficacy.

	CMV gB/MF59		Placebo				
	n CMV infection (%)	N	*n* CMV infection (%)	N	Vaccine efficacy (%) [1]	95%CI for vaccine efficacy [2]	*p*-Value [3]
CMV infection after 3 doses							
Per protocol after 3 doses	8 (6.5%)	124	14 (11.2%)	125	42.9	−36.2, 76.0	0.200
Intention to treat after 3 doses	13 (7.7%)	168	18 (9.9%)	181	23.2	−56.7, 62.4	0.466
CMV infection after 2 doses							
Per protocol after 2 doses	13 (7.9%)	164	24 (14.0%)	172	44.5	−8.9, 71.8	0.082
Intention to treat after 2 doses	20 (10.8%)	186	25 (12.6%)	199	15.0	−53.1, 52.8	0.589
CMV infection after 1 dose							
Per protocol after 1 dose	18 (9.5%)	189	26 (13.5%)	192	30.7	−26.4, 62.0	0.229
Intention to treat after 1 dose	21 (10.8%)	195	27 (13.2%)	205	18.5	−44.1, 53.9	0.480

Note: *N* = number of subjects in specific treatment group. *n* = number of subjects with CMV infection. Ref. [1] vaccine efficacy is obtained from Cox regression. Ref. [2] 95% CI = 95% confidence interval obtained from Cox regression. Ref. [3] *p*-value = result of comparison of Kaplan–Meier survival curves between groups by Log-rank test.

CRITERIA	JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
How substantial are the undesirable anticipated effects?	*Minimal* ☐ *Small* ☐ *Moderate* ☐ *Large* ☐ *Don't know* ☐ *Varies*	Are there undesirable effects of the vaccine, either on the individual (e.g., adverse events following immunization) or population (e.g., age-shift of disease, serotype replacement) levels?	Take into consideration: Is the baseline risk for harm similar across subgroups (see above)? Should there be separate recommendations for subgroups based on harms?
Do the desirable effects outweigh the undesirable effects?	*Favors intervention* ☐ *Favors comparison* ☐ *Favors both* ☐ *Favors neither* ☐ *Unclear*	Describe the balance of benefits of the vaccine with possible harms (individual and population level).	



D.I. Bernstein et al. / Vaccine 34 (2016) 313–319

Table 2 Treatment-emergent adverse events

Type of event	All TEAEs		Drug-related TEAEs	
	N (%)	Events	*N* (%)	Events
All TEAEs	9 (100)	272	6 (67)	23
Serious TEAEs	9 (100)	31	0	0
Leading to discontinuation of ASP0113	0	0	0	0
NCI-CTCAE grade v4.03				
3	9 (100)	69	1 (11)	1
4	9 (100)	28	0	0
5	1 (11)	1	0	0
≥3	9 (100)	98	1 (11)	1
Death[a]	1 (11)	1	0	0
Injection site reactogenic event	5 (56)	19	5 (56)	19
Infection other than CMV	8 (89)	25	0	0

TEAE treatment-emergent adverse event, *NCI-CTCAE v4.03* National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

[a] The death was not considered drug related

Int J Hematol (2017) 105:206–212

What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention ☐ No included studies ☐ 4 Very low ☐ 3 Low ☐ 2 Moderate ☐ 1 High Safety of the intervention ☐ No included studies ☐ 4 Very low ☐ 3 Low ☐ 2 Moderate ☐ 1 High	Please refer to GRADE (safety and effectiveness) tables for detailed assessment of the certainty of the evidence. For more information, please see the ACIP Handbook for Developing Evidence-Based Recommendations.	If GRADE was not used to evaluate the evidence, please provide justification and the method and outcome of any other tools used to evaluate the body of evidence relevant to the critical outcomes.
Does the target population feel that the desirable effects are large relative to undesirable effects?	☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies	Provide any available evidence on target population values & preferences related to vaccination and comparative health benefits and risks. Describe the source of these estimates.**	Are values and preferences for relevant outcomes measured? Are the benefits, harms and costs of vaccination valued differently by different subgroups? If the target group doesn't value the intervention, or attributes little value to the harms and benefits, consider whether potential education measures are needed.

Table 2. Issues to Consider: Vaccination of Women of Childbearing Age

Screen for CMV IgG antibodies
Recruit seronegatives in contact with children, contemplating pregnancy, including postpartum
Randomize to receive vaccine or placebo
Primary endpoint for phase 2: seroconversion
If phase 2 results encouraging:
Adaptive design to phase 3
Primary endpoint for phase 3: congenital infection
The trial patient information sheet may empower women to avoid exposures to CMV
Increased sample size needed for phase 2
The effect of vaccination on intrauterine transmission may be more potent than expected
Decreased sample size needed for phase 3
Plan large sample size for phase 2 + 3 and deploy DSMB with clear rules for stopping and switching phases
Recruit the seropositives and randomize them to vaccine/placebo also

Abbreviations: CMV, cytomegalovirus; DSMB, Data Safety Monitoring Board; IgG, immunoglobulin G.

Table 3. Issues to Consider: Vaccination of Toddlers

Vaccine is given to toddler to protect others
Mother
Unborn sibling
There is a precedent for this:
MMR vaccine to prevent congenital rubella
If vaccine reduces CMV viral load it may protect others without preventing infection of toddler
A vaccine that "fails" to protect the toddler may nevertheless be useful clinically
Ensure parent gives consent for vaccine "to reduce the effect CMV may have on my family"

Abbreviations: CMV, cytomegalovirus; MMR, measles, mumps, and rubella.

JID 2020:221 (Suppl 1) • Griffiths and Hughes

RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐	Provide summary of findings of cost-effectiveness analyses (CEAs) of the vaccine in the target population. Include base case results and a sensitivity range. Include any other notable findings, for example, specific policy-relevant scenarios.	Overall findings: Summarize the findings from available CEAs, including major differences in baseline assumptions. Uncertainty: Does the analysis capture the full range of uncertainty? For example, are the findings from the uncertainty of evidence analysis, identified earlier in this document (the EtR Framework), appropriately represented in the methods of the CEAs? Multiple assessments: Are there multiple CEAs? If so, what are the major differences in methods and results?

Table 2
Percentages of selected characteristics among cost-effectiveness models (N = 12) presented at ACIP.

Model characteristics		Percentages of studies
What perspectives were considered?	Societal	100%
	Healthcare	17%
What types of health outcomes were considered?	QALYs	100%
	Cases Averted	33%
	Deaths Averted	8%
	Life Years Saved	17%
	Hospitalizations Averted	8%
	Number Needed to Vaccinate	17%
What kinds of direct costs were included?	General Medical	100%
	Adverse Events	33%
	General Non-Medical	25%
	Caregiver Time	17%
	Patient Time	33%
What kinds of indirect costs were included?	Mortality	33%
	Morbidity	42%
What program costs were included?	Vaccine Materials	100%
	Vaccine Administration	83%
	Other	17%
What discount rate was used?	0.03 (or 3%)	100%
What kind of sensitivity analyses were presented?	Any kind (univariate or multivariate)	100%
	Any univariate	100%
	Effectiveness	75%
	Costs	83%
	Discount Rates	17%
	Any multivariate	83%
	Scenario-based	83%
	Threshold	0%
	Probabilistic	17%

Vaccine 37 (2019) 7–10

ACIP Evidence to Recommendations Framework

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☐	There is insufficient evidence to determine the balance of consequences ☐
Is there sufficient information to move forward with a recommendation? Yes ☐ No ☐						
Type of recommendation	We do not recommend the intervention ☐	We recommend the intervention for individuals based on clinical decision-making ☐	We recommend the intervention ☐			

Examples of FDA Vaccine Approval and ACIP Recommendations

2015	Fluad	Prevention of influenza disease by subtypes A and type B contained in the vaccine in ≥ 65 yo	**Accelerated**	**A**
	Quadrasil	Prevention of diphtheria, tetanus, pertussis and poliomyelitis as 4th or 5th dose of IPV series in 4-6 yo who received 4 doses of Pentacel and/or Daptacel	**Traditional**	**A**
	Bexsero	Prevention of invasive disease caused by *Neisseria meningitidis* serogroup B in 10-25 yo	**Accelerated**	**A** for ≥ 10 yo at high-risk **B** for 16-23 yo of general population
	Biothrax††	Post-exposure prophylaxis following suspected or confirmed exposure to anthrax in 18-65 yo, used in conjunction with antibiotics	**Animal Rule**	**A** **B**

FDA Approval and ACIP Recommendations 2106

Vaxchora	Prevention of disease caused by *Vibrio cholerae* serogroup O1 in 18-64 yo travelers to cholera-affected areas	**Traditional**	**A** Travelers
Flucelvax	Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 4- <18 yo	**Accelerated**	**A**
Flucelvax Quadrivalent	Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 4- <18 yo	**Accelerated**	**A**
Trumemba	Addition of 2-dose regimen for prevention of invasive disease caused by *Neisseria meningitidis* serogroup B in 10-25 yo	**Accelerated**	**A** for ≥ 10 yo at high-risk **B** for 16-23 yo of general population
Gardasil 9	Addition of 2-dose regimen for Prevention of cervical CA, genital warts and pre-cancerous lesions in 9-26 yo females	**Traditional**	**A**
	Addition of 2-dose regimen for Prevention of anal CA, genital warts and pre-cancerous lesions in 9-15 yo males		**A**
QPAN-H5N1	Prevention of disease caused by the influenza A virus H5N1 subtype in 6 mo - 17 yo at increased risk of exposure	**Traditional**	**No recommendation** (stockpile)
FluBlok Quadrivalent	Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in ≥ 18 yo	**Traditional**	**A**
Afluria Quadrivalent	Prevention of disease caused by influenza virus subtypes A and type B in the vaccine ≥ 18 yo	**Traditional**	**A**
FluLaval	Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 6-35 mo	**Traditional**	**A**
FluLaval Quadrivalent	Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 6-35 mo	**Traditional**	**A**

Global Vaccine Advisory Groups

Strategic Advisory Group of Experts (SAGE)
Terms of reference

Functions

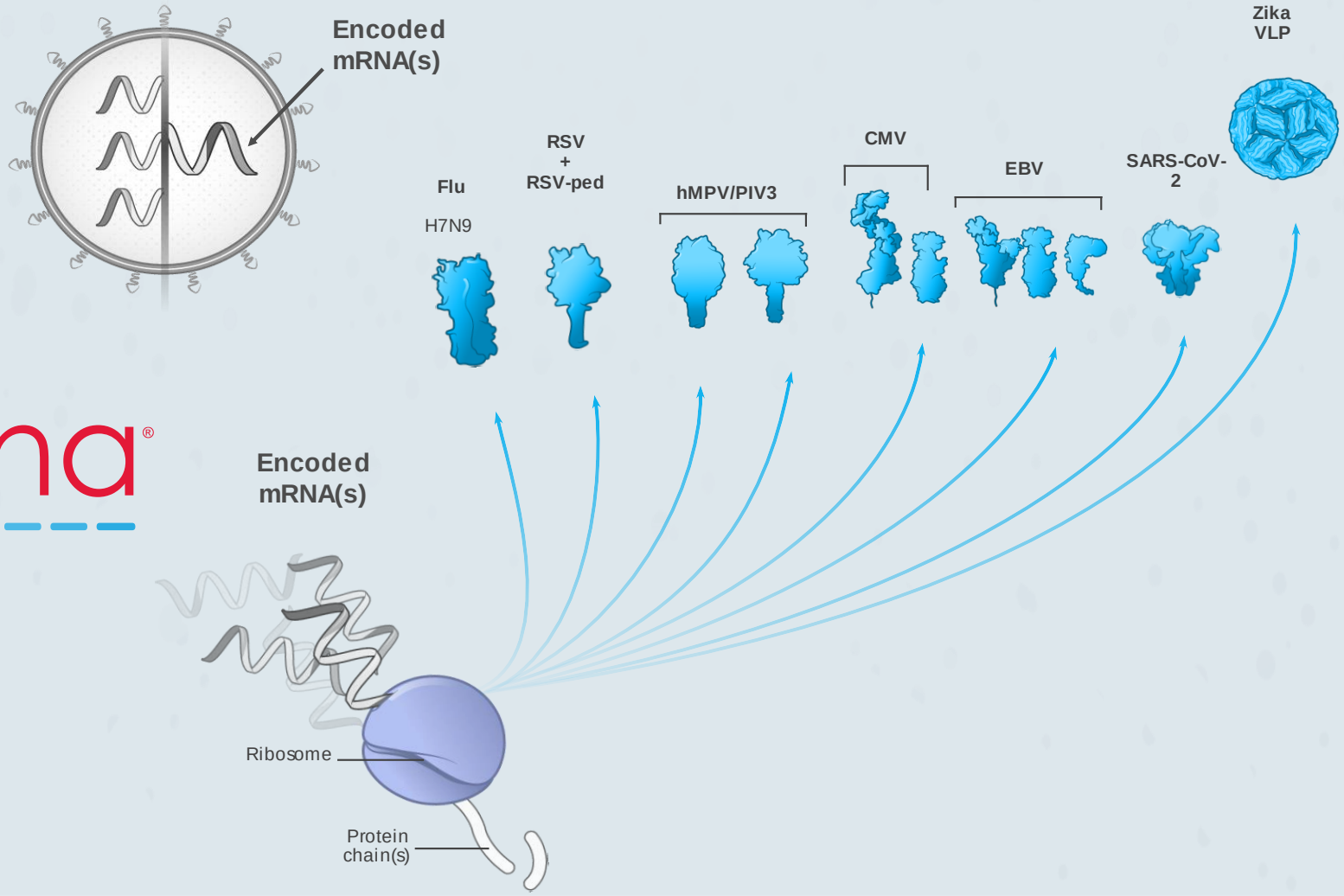
SAGE is the principal advisory group to WHO for vaccines and immunization. It is charged with advising WHO on overall global vaccination policies and strategies, ranging from vaccines and technology, research and development, to delivery of vaccination and its linkages with other health interventions. SAGE's remit extends to the control of all vaccine-preventable diseases as part of an integrated, people centred platform of disease prevention that spans the human life-course and in the context of health systems strengthening.

SAGE advises the WHO Director-General specifically on the:

1. adequacy of progress towards the achievement of the goals of control of vaccine-preventable diseases worldwide such as those laid out in the Decade of Vaccines Global Vaccine Action Plan 2011-2020.
2. major issues and challenges to be addressed with respect to achieving the disease control goals, including issues and challenges to achieving and sustaining high and equitable vaccination coverage;
3. immunization programme response to current public health priorities;
4. major general policies, goals and targets including those related to vaccine research and development;
5. adequacy of WHO's strategic plan and priority activities consistent with its mandate and considering the comparative advantages and the respective roles of partner organizations;
6. engagement of WHO in partnerships that will enhance achievement of global immunization goals.

Conclusions

- The ACIP recommends how licensed vaccines are to be used.
- The ACIP considers **disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, the quality of evidence reviewed, economic analyses, and implementation issues** in making their recommendations.
- Recommendations for the use of CMV and HMPV/PIV vaccines when they are licensed will be guided by all these factors.
- The global vaccine advisory group at the WHO is SAGE.



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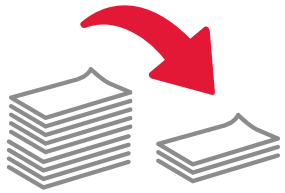
Conclusion

Stéphane Bancel

April 14, 2020

mRNA vaccines are a disruptive technology

As transformational as live-attenuated and recombinant vaccines were…

Large product opportunity	Higher probability of technical success	Accelerated research and development timelines	Greater capital efficiency over time (vs. recombinant)
			
Market opportunity	**Probability of success**	**Time requirements**	**Power of the platform**
Worldwide vaccine market was $35 billion in 2019, growing 9% a year[1] Total addressable market for Moderna's vaccine platform potentially much larger	Vaccines have highest overall POS to approval 42% from Phase 2 start to approval[2]	SARS-CoV-2 vaccine (mRNA-1273) Sequence to Phase 1 clinical trial in 63 days	Cell free drives lower capex (vs. recombinant proteins) Capex leverage across the value chain Ability to maximize sales at launch (flexible manufacturing to handle uncertainty in launch forecast)

1. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020)
2. Chi Heem Wong, Kien Wei Siah, Andrew W Lo, Estimation of clinical trial success rates and related parameters, *Biostatistics*, Volume 20, Issue 2, April 2019, Pages 273–286

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We believe our vaccines have a large peak sales potential

Wholly-owned vaccines

hMPV/PIV3 + RSV
hMPV/PIV3 (mRNA-1653)
Pediatric RSV (mRNA-1345)
CMV (mRNA-1647)
EBV (mRNA-1189)
Zika (mRNA-1893)
SARS-CoV-2 (mRNA-1273)

$6.5-$12 billion
peak sales potential with current portfolio of vaccine candidates[1,2]

1. All figures are estimates and subject to change
2. Does not include potential royalty revenue from mRNA-1172/mRNA-1777 targeting RSV

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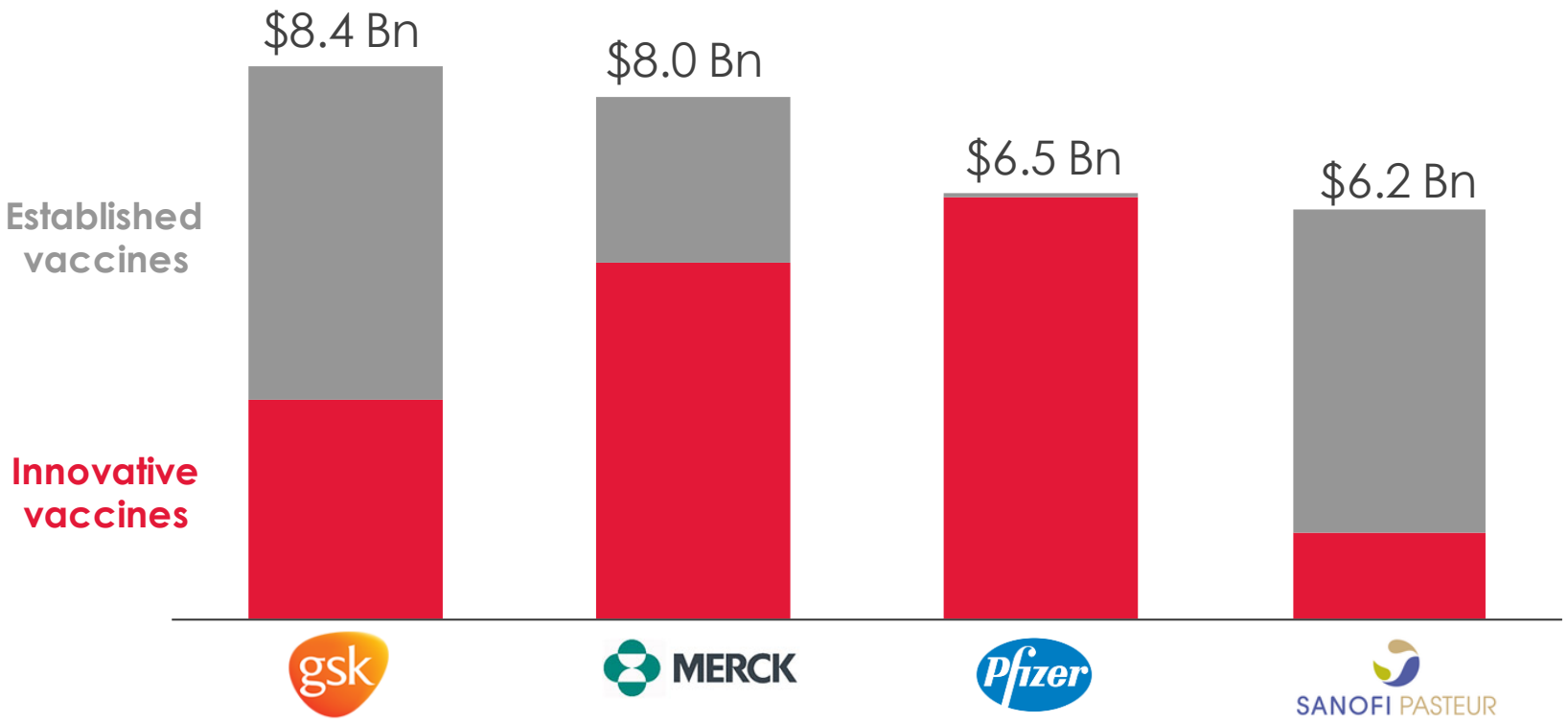
Key players in the global vaccine market

WW Vaccines Sales for Key Players[1]
(2019)



Assumes an exchange rate of 1 Pound Sterling : 1.18 USD, and 1 Euro : 1.09 USD

Accounts for **$29 billion of a $35 billion** vaccine market (>80% of WW vaccine sales)

Growing **9%** a year[2]

1. GSK Annual Report; Merck 4Q19 Financial Disclosures; Pfizer annual report; Sanofi 20-F
2. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020).

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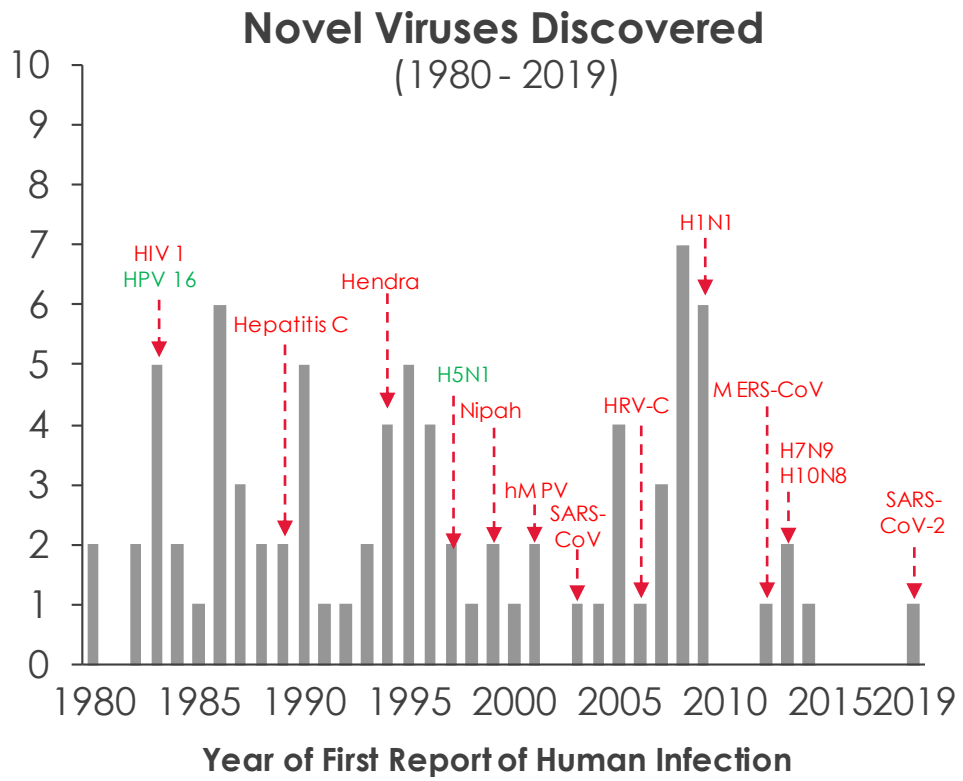
Plus more innovative vaccines to come…



Discovered before 1980

Select viruses:

- Yellow fever (1901)
- Rubella (1941)
- Dengue (1943)
- PIV3 (1950s)
- Chikungunya (1952)
- Zika (1952)
- VZV (1954)
- RSV (1956)
- CMV (1956-1957)
- EBV (1964)
- Hepatitis B (1965)
- Marburg (1967)
- Lassa (1969)
- Ebola (1976)

Large unmet medical need

Only **4%** have a vaccine commercially available in the US

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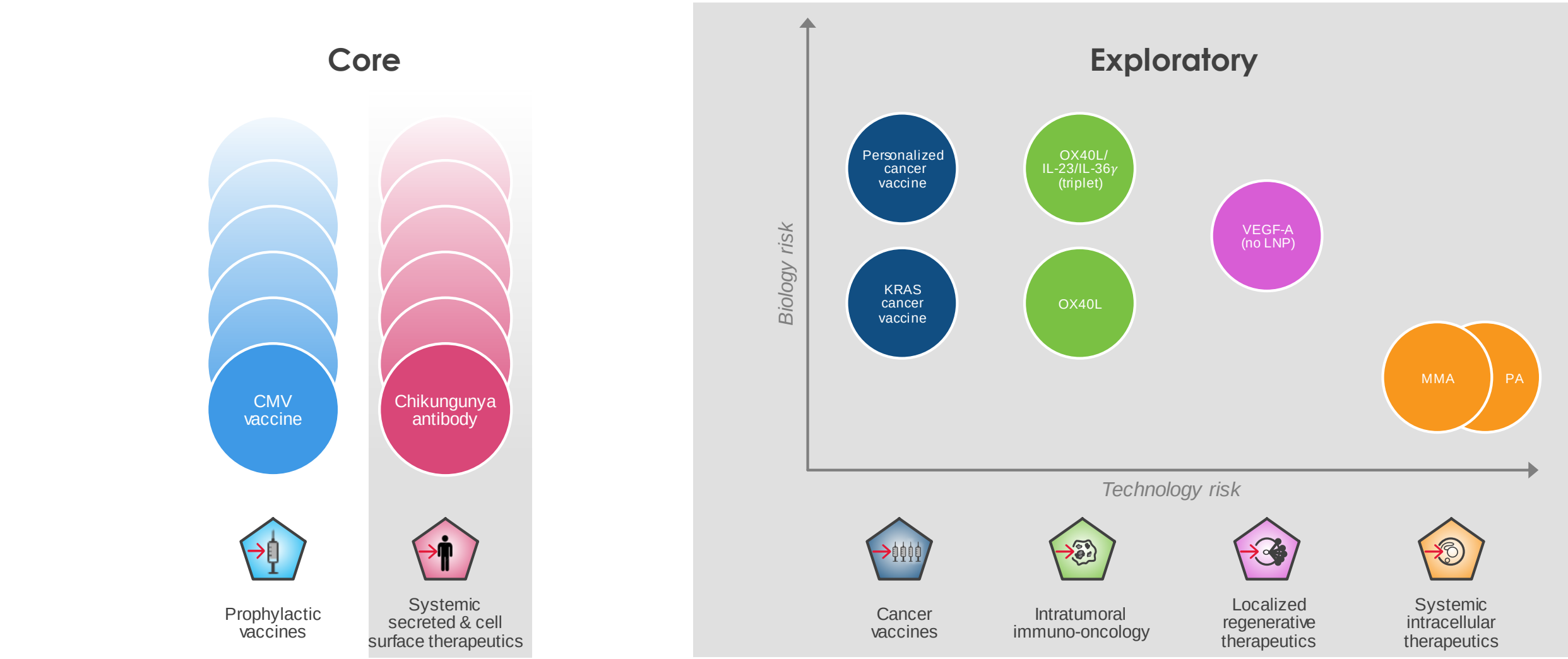
And today was just infectious disease vaccines…



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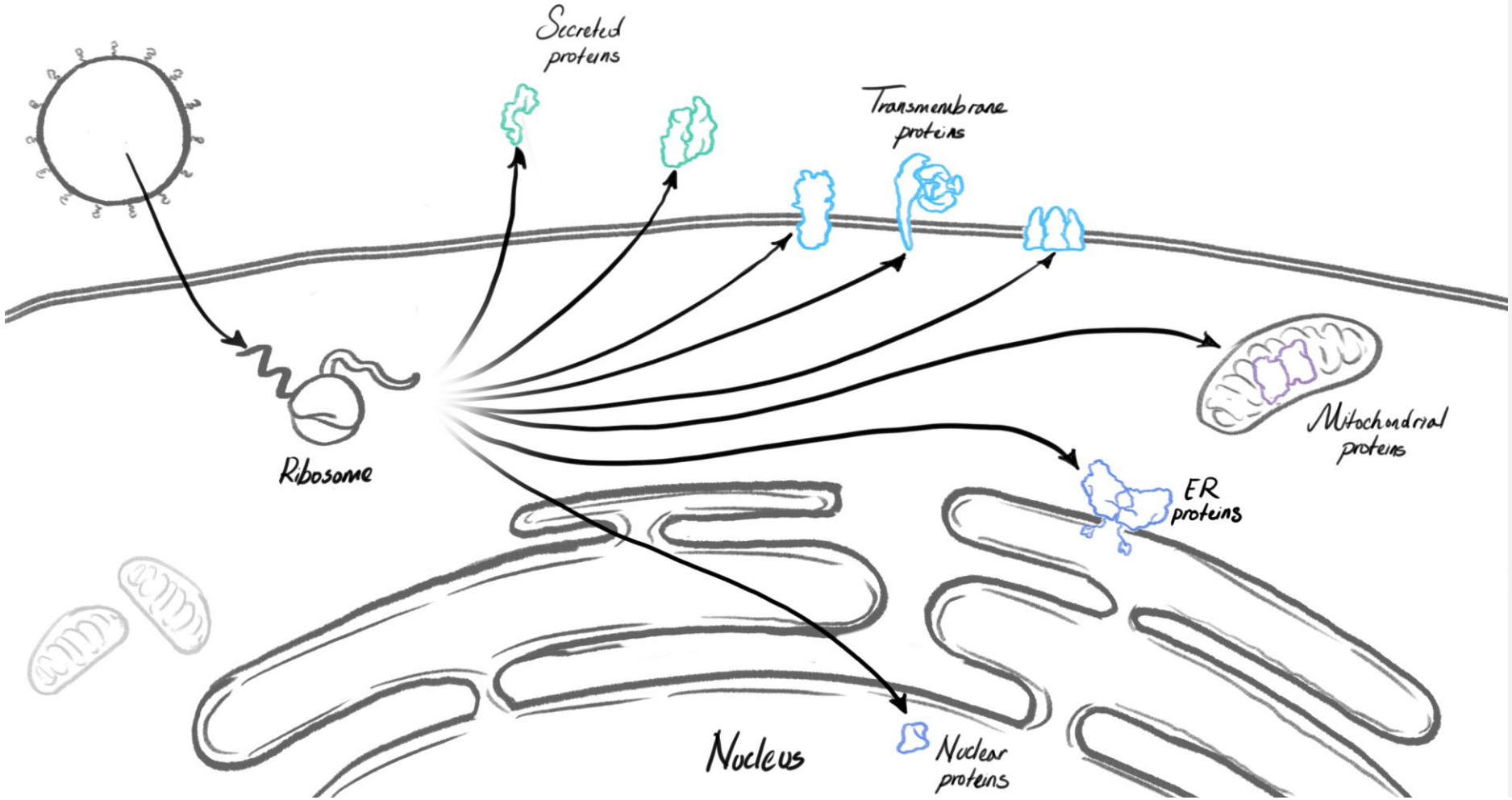
mRNA as a potential new class of medicines



1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology

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Q&A