First Vaccines Day
April 14, 2020

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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.

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<table>
<thead>
<tr>
<th>Time</th>
<th>Session Description</th>
<th>Speaker(s)</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00-8:20 AM</td>
<td>Introduction of mRNA Vaccine Platform</td>
<td>Stéphane Bancel, CEO</td>
<td>20 min</td>
</tr>
<tr>
<td>8:20-8:40 AM</td>
<td>Clinical Trial POS</td>
<td>Andrew W. Lo, MIT Sloan School of Management</td>
<td>20 min</td>
</tr>
<tr>
<td>8:40-9:20 AM</td>
<td>Traditional Vaccines Overview</td>
<td>Paul T. Heath, Vaccine Institute, St George’s, University of London</td>
<td>40 min</td>
</tr>
<tr>
<td>9:20-9:50 AM</td>
<td>mRNA Vaccines Differentiation</td>
<td>Stephen Hoge, M.D., President</td>
<td>30 min</td>
</tr>
<tr>
<td>9:50-10:00 AM</td>
<td>Coffee Break</td>
<td></td>
<td>10 min</td>
</tr>
<tr>
<td>10:00-10:30 AM</td>
<td>Vaccines Against Infections From Mother to Baby</td>
<td>Tal Zaks, M.D., Ph.D., Chief Medical Officer</td>
<td>30 min</td>
</tr>
<tr>
<td>10:30-12:10 PM</td>
<td>Vaccines Against Respiratory Diseases</td>
<td>Tal Zaks, M.D., Ph.D., Chief Medical Officer&lt;br&gt; Flor Munoz-Rivas, M.D., Baylor College of Medicine&lt;br&gt; Mark R. Denison, MD, Vanderbilt University Medical Center&lt;br&gt; Tal Zaks, M.D., Ph.D., Chief Medical Officer&lt;br&gt; Juan Andres, Chief Technical Operations and Quality Officer</td>
<td>100 min</td>
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<tr>
<td>12:10-12:40 PM</td>
<td>ACIP Overview/Framework</td>
<td>Kathryn M. Edwards, M.D., Sarah H. Sell and Cornelius Vanderbilt Professor of Pediatrics</td>
<td>30 min</td>
</tr>
<tr>
<td>12:40-12:50 PM</td>
<td>Conclusion</td>
<td>Stéphane Bancel, CEO</td>
<td>10 min</td>
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<tr>
<td>12:50-1:15 PM</td>
<td>Q&amp;A</td>
<td></td>
<td>25 min</td>
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</table>
Central dogma of molecular biology

**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
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
We have focused on managing risk since inception

*With a focus on...*

1. Technology risk
2. Biology risk
3. Execution risk
4. Financing risk
Risk management is essential to building a new class of medicines

Risk management is essential to building a new class of medicines.
2019 was an inflection year in Moderna’s history

Our modality strategy

- **CMV vaccine**
- **Zika vaccine**
- **H10/H7 influenza vaccine**
- **Personalized cancer vaccine**
- **KRAS cancer vaccine**
- **OX40L**
- **OX40L/IL-23/IL-36 (triplet)**
- **VEGF-A (no LNP)**
- **Fabry**
- **Chikungunya antibody**
- **MMA**
- **PA**

**Modality**
- **Prophylactic vaccines**
- **Cancer vaccines**
- **Intratumoral immuno-oncology**
- **Localized regenerative therapeutics**
- **Systemic secreted & cell surface therapeutics**
- **Systemic intracellular therapeutics**

**Biology risk**
- **CMV vaccine**
- **Zika vaccine**
- **H10/H7 influenza vaccine**
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**Technology risk**
- **CMV vaccine**
- **Zika vaccine**
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- **PA**
2019 was an inflection year in Moderna’s history

Our modality strategy

Core

- CMV vaccine
- Zika vaccine
- H10/H7 influenza vaccine
- Chikungunya antibody

Prophylactic vaccines
Systemic secreted & cell surface therapeutics

Exploratory

- Personalized cancer vaccine
- OX40L: IL-23:IL-36y (triplet)
- VEGF-A (no LNP)
- KRAS cancer vaccine
- OX40L

Technology risk

- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic intracellular therapeutics

Biology risk

MMA
PA

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Expanding core modalities with additional development candidates

Core

- CMV vaccine
- Chikungunya antibody

Systemic secreted & cell surface therapeutics
Prophylactic vaccines

Exploratory

- Personalized cancer vaccine
- OX40L/IL-23/IL-36γ (triplet)
- OX40L
- VEGF-A (no LNP)

Technology risk

- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic intracellular therapeutics

MMA
PA
Vaccines Day

Deep dive into opportunities ahead

**Core**
- CMV vaccine
- Chikungunya antibody
- Prophylactic vaccines
- Systemic secreted & cell surface therapeutics

**Exploratory**
- Personalized cancer vaccine
- KRAS cancer vaccine
- OX40L
- VEGF-A (no LNP)
- OX40L/IL-23/IL-36 (inplot)

**Technology risk**
- Cancer vaccines
- Intratumoral immuno-oncology
- Localized regenerative therapeutics
- Systemic intracellular therapeutics

**Biology risk**
- MMA
- PA

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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
Evidence that the platform is delivering in vaccines

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<thead>
<tr>
<th>Large product opportunity</th>
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<th>Greater capital efficiency over time (vs. recombinant)</th>
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<tbody>
<tr>
<td>Market opportunity</td>
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**Evidence that the platform is delivering in vaccines**

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<tr>
<td>Worldwide vaccine market was $35 billion, growing 9% a year¹</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- $1.3 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

Key players in the global vaccine market

WW Vaccines Sales for Key Players¹
(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 year²

1. GSK Annual Report; Merck 4Q19 Financial Disclosures; Pfizer annual report; Sanofi 20-F
Innovative vaccines are a great opportunity

- Vaccines blockbusters by 2024 sales (examples)
  - #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%)
More than 80 new viruses discovered since 1980

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

Year of First Report of Human Infection

# Viruses Discovered per Year

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More than 80 new viruses discovered since 1980

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

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- **Higher probability of technical success**
  - **Probability of success**
    - Vaccines have highest overall POS to approval
    - 42% from Phase 2 start to approval\(^2\)

- **Accelerated research and development timelines**

- **Lower capex and COGS** (de-risking capex)

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- **Accelerated research and development timelines**
  - Time requirements
    - SARS-CoV-2 vaccine (mRNA-1273)
    - Sequence to Phase 1 clinical trial in 63 days

- **Greater capital efficiency over time (vs. recombinant)**
  - Power of the platform

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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

IN 63 DAYS

2 DAYS
42 DAYS
21 DAYS
Evidence that the platform is delivering in vaccines

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Not a traditional biotech

Cell free manufacturing
No dedicated plant to one product
Lower capex requirements
## Evidence that the platform is delivering in vaccines

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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

Information in following slides are from a third-party source. While we believe such information is reliable, we have not independently verified any third-party information, and make no guarantee, express or implied, as to the accuracy and completeness of it.
Biomedicine Is At An Inflection Point

The “omics” Revolution:
- Genomics
- Epigenomics
- Transcriptomics
- Proteomics
- Metabolomics
- Microbiomics

What About Economics??
\[ E[\text{NPV}] = PV[\text{Revenues}] \times \text{PoS} - \text{Costs} \]
Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs

JA DiMasi1, L. Fehma2, A Seckler1 and A Wilson1

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 (1990–2004) through June 2006. The clinical approval success rate in the United States was 10% for self-originated drugs (originating from the pharmaceutical company itself), during both the 1990–1998 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 15%. 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 near the entire study period was 15% for large molecules and 11% for small molecules. The estimated transition rate was highest for small molecules, followed by large molecules.

INTRODUCTION

Numerous studies have found that the drug development process is highly expensive and that these costs have trended upward over the past few decades. 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 1980s through the 1990s, but overall remained relatively stable during the 2000s. 

Thus, development times did not directly contribute to the rapid increase in pharmaceutical R&D costs during the past two decades. However, if clinical trials become larger and more complex, and if 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. The situation is similar for drug development risks. The likelihood of development of a drug will be tempered by efficacy, safety, and 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 the regulatory authorities is an indicator of the effectiveness of drug development across the entire industry. The predictability of outcomes for new compounds can, therefore, significantly increase the probability of drug innovation.

The historical literature focusing specifically on the specification of drug development risks is fairly robust. The aforementioned results on drug development costs include estimates of drug development risks. Early work on development risk suggested that clinical approval rates for self-originated drugs in the 1980s were in the neighborhood of one in eight. Subsequent studies indicated that development risks fell in the 1990s, with approval rates averaging approximately one in five. The risk levels pertaining to the 1970s remained fairly stable in the 1980s.

This study provides updated clinical approval success rates and clinical phase transition analysis 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 rates 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).
With Big Data, We Can Do Better

- Informa data

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<tbody>
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<td>Number of Drugs</td>
<td>15,102</td>
<td>?</td>
<td>5,820</td>
<td>1,316</td>
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<td>Years of source data (time-span)</td>
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<td>2006-2015 (9 years)</td>
<td>2003-2011 (9 years)</td>
<td>1993-2009 (17 years)</td>
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<td>Number of Companies</td>
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<td>9,985</td>
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## Top 30 Drugs by World-Wide Sales

### 2000

<table>
<thead>
<tr>
<th>Rank</th>
<th>Marketer</th>
<th>Drug</th>
<th>Worldwide Sales ($M)</th>
<th>University/Hospital</th>
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<tbody>
<tr>
<td>1</td>
<td>AstraZeneca</td>
<td>Prilosec</td>
<td>6,260</td>
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<tr>
<td>2</td>
<td>Merck</td>
<td>Zocor</td>
<td>5,280</td>
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<tr>
<td>3</td>
<td>Pfizer</td>
<td>Lipitor</td>
<td>5,030</td>
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<tr>
<td>4</td>
<td>Pfizer</td>
<td>Norvasc</td>
<td>3,361</td>
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<tr>
<td>5</td>
<td>TAP Pharmaceuticals</td>
<td>Prevacid</td>
<td>2,740</td>
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<tr>
<td>6</td>
<td>Johnson &amp; Johnson</td>
<td>Procrit</td>
<td>2,709</td>
<td>University of Chicago</td>
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<tr>
<td>7</td>
<td>Pfizer; Pharmacia</td>
<td>Celebrex</td>
<td>2,614</td>
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<td>Glucophage</td>
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<td>Merck</td>
<td>Cozaar</td>
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<tr>
<td>21</td>
<td>Johnson &amp; Johnson</td>
<td>Tylenol</td>
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<td>22</td>
<td>Novo Nordisk</td>
<td>Novolin</td>
<td>1,671</td>
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</tr>
<tr>
<td>23</td>
<td>Bayer</td>
<td>Cipra; Ciprobay</td>
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</tr>
<tr>
<td>24</td>
<td>Johnson &amp; Johnson</td>
<td>Risperdal</td>
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<tr>
<td>25</td>
<td>Bristol-Myers Squibb</td>
<td>Taxol</td>
<td>1,561</td>
<td>Florida State University</td>
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<tr>
<td>26</td>
<td>Pfizer</td>
<td>Zithromax</td>
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<tr>
<td>27</td>
<td>Schering Plough</td>
<td>Intron A</td>
<td>1,360</td>
<td>University of Zurich</td>
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<td>Viagra</td>
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<td>29</td>
<td>Pfizer</td>
<td>Neurontin</td>
<td>1,334</td>
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<tr>
<td>30</td>
<td>GlaxoSmithKline</td>
<td>Filgotide; Flovent</td>
<td>1,334</td>
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### 2015

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

*Blue-shading indicates university/hospital origins.*

- **Total ($M)**: 69,374 (2000) vs. 169,914 (2015)
- **Percent of Total**: 15% (2000) vs. 52% (2015)
Estimating Clinical Trials Success Rates

14 Apr 2020

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Slide 37


Estimating 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

MIT Computer Science and Artificial Intelligence Laboratory & Department of Electrical Engineering and Computer Science, Cambridge, MA 02139, USA, MIT Sloan School of Management and Laboratory for Financial Engineering, Cambridge, MA 02142, USA, and AlphaSimplex Group, LLC, Cambridge, MA 02142, USA
alo-admin@mit.edu

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 466,038 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>
<thead>
<tr>
<th>Therapeutic group</th>
<th>Phase 1 to Phase 2</th>
<th>Phase 2 to Phase 3</th>
<th>Phase 3 to Approval</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total paths</td>
<td>POS(3,1, %) (SE, %)</td>
<td>Total paths</td>
<td>POS(3,1, %) (SE, %)</td>
</tr>
<tr>
<td>Oncology</td>
<td>17368</td>
<td>57.6 (0.4)</td>
<td>6533</td>
<td>32.7 (0.6)</td>
</tr>
<tr>
<td>Metabolic/Endocrine</td>
<td>3589</td>
<td>76.2 (0.7)</td>
<td>2557</td>
<td>59.7 (1.0)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2810</td>
<td>73.3 (0.8)</td>
<td>1858</td>
<td>65.7 (0.9)</td>
</tr>
<tr>
<td>CNS</td>
<td>4924</td>
<td>73.2 (0.6)</td>
<td>3037</td>
<td>51.9 (0.9)</td>
</tr>
<tr>
<td>Autoimmune/Inflammation</td>
<td>5086</td>
<td>69.8 (0.6)</td>
<td>2910</td>
<td>45.7 (0.9)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>757</td>
<td>68.7 (0.6)</td>
<td>475</td>
<td>57.1 (0.9)</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>3963</td>
<td>70.1 (0.7)</td>
<td>2314</td>
<td>58.3 (1.0)</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>674</td>
<td>87.1 (1.3)</td>
<td>461</td>
<td>60.7 (2.0)</td>
</tr>
<tr>
<td>Vaccines</td>
<td>1869</td>
<td>76.8 (1.0)</td>
<td>1235</td>
<td>58.2 (1.4)</td>
</tr>
<tr>
<td>(Infectious)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>41104</td>
<td>66.4 (0.2)</td>
<td>21180</td>
<td>58.3 (0.2)</td>
</tr>
<tr>
<td>All without oncology</td>
<td>23172</td>
<td>73.0 (0.2)</td>
<td>14467</td>
<td>27.3 (0.4)</td>
</tr>
</tbody>
</table>

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.
Estimating 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

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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 21,413 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>
<thead>
<tr>
<th>Therapeutic group</th>
<th>Phase 1 to Phase 2</th>
<th>Phase 2 to Phase 3</th>
<th>Phase 3 to Approval</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total paths</td>
<td>POS_{1,2} % (SE, %)</td>
<td>Total paths</td>
<td>POS_{2,3} % (SE, %)</td>
</tr>
<tr>
<td>Oncology</td>
<td>17,368</td>
<td>57.6 (0.4)</td>
<td>6,533</td>
<td>32.7 (0.3)</td>
</tr>
<tr>
<td>Metabolic/</td>
<td>3,589</td>
<td>76.2 (0.7)</td>
<td>2,257</td>
<td>59.7 (1.0)</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>(0.7)</td>
<td></td>
<td>(1.0)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2,810</td>
<td>73.3 (0.8)</td>
<td>1,858</td>
<td>65.7 (1.1)</td>
</tr>
<tr>
<td>(0.8)</td>
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</tr>
<tr>
<td>CNS</td>
<td>4,924</td>
<td>73.2 (0.6)</td>
<td>3,037</td>
<td>51.9 (0.7)</td>
</tr>
<tr>
<td>Autoimmune/</td>
<td>5,086</td>
<td>69.8 (0.9)</td>
<td>2,910</td>
<td>45.7 (0.9)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>(0.6)</td>
<td></td>
<td>(0.9)</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>757</td>
<td>67.8 (1.7)</td>
<td>475</td>
<td>57.1 (2.3)</td>
</tr>
<tr>
<td>(1.7)</td>
<td></td>
<td></td>
<td>(2.3)</td>
<td></td>
</tr>
<tr>
<td>Infectious disease</td>
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<td>70.1 (1.3)</td>
<td>2,314</td>
<td>58.3 (2.3)</td>
</tr>
<tr>
<td>(0.7)</td>
<td></td>
<td></td>
<td>(1.0)</td>
<td></td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>674</td>
<td>87.1 (1.3)</td>
<td>461</td>
<td>60.7 (2.3)</td>
</tr>
<tr>
<td>(1.3)</td>
<td></td>
<td></td>
<td>(2.3)</td>
<td></td>
</tr>
<tr>
<td>Vaccines</td>
<td>1,869</td>
<td>76.8 (1.0)</td>
<td>1,235</td>
<td>58.2 (1.4)</td>
</tr>
<tr>
<td>(1.0)</td>
<td></td>
<td></td>
<td>(1.4)</td>
<td></td>
</tr>
<tr>
<td>Infectious Disease</td>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All without</td>
<td>41,040</td>
<td>66.4 (0.2)</td>
<td>21,180</td>
<td>58.3 (2.2)</td>
</tr>
<tr>
<td>oncology</td>
<td>(0.2)</td>
<td></td>
<td>(2.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23,672</td>
<td>73.0 (0.4)</td>
<td>14,647</td>
<td>27.3 (0.4)</td>
</tr>
</tbody>
</table>

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.
Project ALPHA

Analytics for Life Sciences Professionals and Healthcare Advocates

https://projectalpha.mit.edu/
Project ALPHA

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

https://projectalpha.mit.edu/
Estimating Probabilities of Success of Clinical Trials for Vaccines and Other Anti-Infective Therapeutics

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

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 monkepox (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 PoS: 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 underserved by private-sector engagement and in need of public-sector support.
More Ambitious Goal
With Machine Learning, We Can Do Better

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.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Group</th>
<th>Type</th>
<th>ML Prediction</th>
<th>Route</th>
<th>Origin</th>
<th>Medium</th>
<th>Target Family</th>
<th>Parent Pharm</th>
</tr>
</thead>
<tbody>
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<td>seasonal influenza nanoparticle vaccine</td>
<td>infection, influenza virus prophylaxis</td>
<td>respiratory infections</td>
<td>vaccine</td>
<td>0.99</td>
<td>oral</td>
<td>injectable</td>
<td>0</td>
<td>1</td>
<td>0</td>
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<tr>
<td>omadacycline</td>
<td>infection, urinary tract, uncomplicated</td>
<td>urinary tract infections</td>
<td>treatment</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>rsv vaccine</td>
<td>infection, respiratory syncytial virus</td>
<td>respiratory infections</td>
<td>vaccine</td>
<td>0.71</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>pneumococcal conjugate vaccine</td>
<td>infection, pneumococcal prophylaxis</td>
<td>respiratory infections</td>
<td>vaccine</td>
<td>0.69</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>hiv mabs</td>
<td>infection, hepatitis-b virus</td>
<td>HBV</td>
<td>treatment</td>
<td>0.68</td>
<td>0</td>
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<td>0</td>
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<td>1</td>
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<tr>
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<td>respiratory infections</td>
<td>treatment</td>
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<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>infection, hiv/aids</td>
<td>HIV</td>
<td>treatment</td>
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<td>0</td>
<td>0</td>
<td>1</td>
</tr>
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<td>cabotegravir</td>
<td>infection, hiv/aids</td>
<td>HIV</td>
<td>treatment</td>
<td>0.59</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>infection, respiratory syncytial virus</td>
<td>respiratory infections</td>
<td>vaccine</td>
<td>0.56</td>
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</tbody>
</table>
Next Steps

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...
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!
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.
Immunisation: an overview

Paul T. Heath
Professor of Paediatric Infectious Diseases
Vaccine Institute,
St George’s, University of London

Information in the following slides are from a third-party source. While we believe such information is reliable, we have not independently verified any third-party information, and make no guarantee, express or implied, as to the accuracy and completeness of it.
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
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
<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live attenuated vaccine</td>
<td>Oral polio vaccine (OPV), Measles, mumps and rubella (MMR) vaccine, Rotavirus vaccine, TB (BCG) vaccine</td>
</tr>
<tr>
<td>Inactivated (killed) vaccine</td>
<td>Inactivated polio vaccine (IPV), Whole cell pertussis vaccine (wP)</td>
</tr>
<tr>
<td>Subunit vaccine (purified antigen)</td>
<td>Acellular pertussis vaccine (aP), <em>Haemophilus influenzae</em> b vaccine (Hib), Pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>Toxoid (inactivated toxin) vaccines</td>
<td>Tetanus toxoid vaccine, Diphtheria toxoid vaccine</td>
</tr>
<tr>
<td>Nucleic acid vaccines</td>
<td>DNA, mRNA</td>
</tr>
<tr>
<td>Recombinant vector vaccines</td>
<td>carry extra genes in order to produce specific proteins</td>
</tr>
</tbody>
</table>
- 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
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
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.
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
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

<table>
<thead>
<tr>
<th>Traditional Vaccines (subunit/inactivated)</th>
<th>Nucleic Acid Vaccines (DNA/RNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slower (10-15 years)</td>
<td>Development</td>
</tr>
<tr>
<td>Customized for each vaccine</td>
<td>Process Development</td>
</tr>
<tr>
<td>Bespoke for each vaccine</td>
<td>Facility Scalability</td>
</tr>
<tr>
<td>$200mm-1bn</td>
<td>$$$ Costs</td>
</tr>
<tr>
<td>High volume of finished product requiring replenishment</td>
<td>Stockpiling</td>
</tr>
<tr>
<td>Humoral response May require adjuvant</td>
<td>Potency</td>
</tr>
</tbody>
</table>
Routes of administration vary to maximize effectiveness of vaccine
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
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
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**

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.
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*
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...
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...”
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
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
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
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.
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)
mRNA vaccines

Unique platform mechanism of action (MOA)
mRNA vaccines

Unique platform mechanism of action (MOA)
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+ IFNγ+ and CD4+ TNFα+ cells)

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

**mRNA vaccines**

*T cell responses*

- 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

---

**Neutralizing antibody**
(Fibroblast GMT, Day 84)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean SFC / 10⁶ PBMC</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>50</td>
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<tr>
<td>30µg mRNA-1647</td>
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<tr>
<td>90µg mRNA-1647</td>
<td>405</td>
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<tr>
<td>180µg mRNA-1647</td>
<td>542</td>
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</table>

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.
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
Accelerated research and development

**SARS-CoV-2 vaccine (mRNA-1273)**

Chinese authorities shared the genetic sequence of the novel coronavirus.

- **January 11, 2020**: Sequence for mRNA-1273 against the novel coronavirus finalized.

The first clinical batch, including fill and finishing of vials, was completed.

- **February 7, 2020**: Batch proceeded to analytical testing for release.

- **February 24, 2020**: Clinical batch was shipped to the NIH for use in their Phase 1 clinical study.

- **March 4, 2020**: Investigational New Drug (IND) application filed by the NIH for mRNA-1273 review completed; allowed to proceed to begin clinical trials.

- **March 16, 2020**: First participant in its Phase 1 study for mRNA-1273 was dosed, a total of 63 days from sequence selection to first human dosing.

**CEPI**

Manufacture of this batch was funded by the Coalition for Epidemic Preparedness Innovations (CEPI).
Uniform process allows for fast scale-up

High degree of flexibility

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

CMV
hMPV/PIV3
EBV
COVID-19
### 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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<table>
<thead>
<tr>
<th>Agenda Item</th>
<th>Speaker and Title</th>
<th>Time</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Introduction of mRNA Vaccine Platform</td>
<td>Stéphane Bancel, CEO</td>
<td>8:00-8:20 AM</td>
<td>20 min</td>
</tr>
<tr>
<td>Clinical Trial POS</td>
<td>Andrew W. Lo, MIT Sloan School of Management</td>
<td>8:20-8:40 AM</td>
<td>20 min</td>
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<tr>
<td>Traditional Vaccines Overview</td>
<td>Paul T. Heath, Vaccine Institute, St George’s, University of London</td>
<td>8:40-9:20 AM</td>
<td>40 min</td>
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<tr>
<td>mRNA Vaccines Differentiation</td>
<td>Stephen Hoge, M.D., President</td>
<td>9:20-9:50 AM</td>
<td>30 min</td>
</tr>
<tr>
<td>Coffee Break</td>
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<td>9:50-10:00 AM</td>
<td>10 min</td>
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<tr>
<td>Vaccines Against Infections From Mother to Baby</td>
<td>Tal Zaks, M.D., Ph.D., Chief Medical Officer</td>
<td>10:00-10:30 AM</td>
<td>30 min</td>
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<tr>
<td>Vaccines Against Respiratory Diseases</td>
<td>Tal Zaks, M.D., Ph.D., Chief Medical Officer</td>
<td>10:30-12:10 PM</td>
<td>100 min</td>
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<td>ACIP Overview/Framework</td>
<td>Kathryn M. Edwards, M.D., Sarah H. Sell and Cornelius Vanderbilt Professor of Pediatrics</td>
<td>12:10-12:40 PM</td>
<td>30 min</td>
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<tr>
<td>Conclusion</td>
<td>Stéphane Bancel, CEO</td>
<td>12:40-12:50 PM</td>
<td>10 min</td>
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<tr>
<td>Q&amp;A</td>
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<td>12:50-1:15 PM</td>
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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)

<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
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<td>m RNA-1647</td>
<td></td>
<td>Cytomegalovirus (CMV) vaccine</td>
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<td>Worldwide</td>
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<td>m RNA-1893</td>
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<td>Zika vaccine</td>
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<td>Worldwide BARDA funded</td>
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<td>m RNA-1172/Merck V172</td>
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<td>Respiratory syncytial virus (RSV) vaccine</td>
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<td>Merck to pay milestones and royalties</td>
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<tr>
<td>m RNA-1177</td>
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<td>Respiratory syncytial virus (RSV) vaccine</td>
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<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td>m RNA-1653</td>
<td></td>
<td>hMPV/PIV3 vaccine</td>
<td></td>
<td>Phase 1 (healthy volunteers)</td>
<td>Phase 1b (Age de-escalation) Seropositives</td>
<td></td>
<td>Worldwide</td>
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<tr>
<td>m RNA-1345</td>
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<td>Pediatric respiratory syncytial virus (RSV) vaccine</td>
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<td></td>
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<td>Worldwide</td>
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<tr>
<td>m RNA-1189</td>
<td></td>
<td>Epstein-Barr virus (EBV) vaccine</td>
<td></td>
<td></td>
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<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td>m RNA-1851</td>
<td></td>
<td>Influenza H7N9 vaccine</td>
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<td>Worldwide Advancing subject to funding</td>
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<tr>
<td>m RNA-1273</td>
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<td>Novel coronavirus (SARS-CoV-2) vaccine</td>
<td></td>
<td></td>
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<td>Worldwide CEPI funded</td>
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</tbody>
</table>
Responsiveness of the vaccines platform

Zika virus development history

$125 million BARDA contract awarded for the development of a Zika mRNA vaccine

First generation Zika vaccine (using legacy LNP) Phase 1 results

mRNA-1893 Second generation Zika vaccine (using proprietary LNP) entered the clinic

Positive Phase 1 interim results

Sequence to first in human in 12 months

September 2016

October 2017

mRNA-1325 did not show sufficient immunogenicity at doses up to 100 µg; safe and well tolerable

July 2019

Today

April 14, 2020

Simultaneously working on an improved mRNA sequence. mRNA sequence for mRNA-1893 produces equivalent immunogenicity and better protection compared to the sequence used in mRNA-1325 at 1/20 of the dose in NHPs

Cell

Vaccine Mediated Protection Against Zika Virus-Induced Congenital Disease

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.

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Zika is an arbovirus and member of the Flaviviridae family

Early evidence of Zika circulation

- All types: <1960, 1960s, 1970s, 1980s, 1990s, 2000s, 2010s
- Virologic: Human, Mosquito
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

<table>
<thead>
<tr>
<th>Neonatal period</th>
<th>Microcephaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other severe brain defects</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infancy, childhood, adulthood</th>
<th>Fever</th>
<th>Rash</th>
<th>Headache</th>
<th>Joint pain</th>
<th>Red eyes</th>
<th>Muscle pain</th>
</tr>
</thead>
</table>

Slide 101
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

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
Zika vaccine (mRNA-1893)

Dosing regimen

Zika Phase 1 dosing regimen

Day 1

Day 29

Study has completed dosing

Interim analysis
Day 57
(10 and 30 µg)

April 2020

April 14, 2020

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Zika vaccine (mRNA-1893) Phase 1 interim analysis

Safety profile (10 and 30 µg cohorts)

<table>
<thead>
<tr>
<th></th>
<th>Solicited ARs post-Dose 1 (solicited safety set)</th>
<th>Solicited ARs post-Dose 2 (solicited safety set)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=12 (%)</td>
<td>10µg N=24 (%)</td>
</tr>
<tr>
<td><strong>Local reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1/12 (8.3%)</td>
<td>12/24 (50%)</td>
</tr>
<tr>
<td>Redness</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Swelling</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fever</td>
<td>–</td>
<td>1/24 (4.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>3/12 (25)</td>
<td>7/24 (29.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2/12 (16.7)</td>
<td>8/24 (33.3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1/12 (8.3)</td>
<td>5/24 (20.8)</td>
</tr>
<tr>
<td>Arthalgia</td>
<td>–</td>
<td>2/24 (8.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>–</td>
<td>4/24 (16.7)</td>
</tr>
<tr>
<td>Chills</td>
<td>–</td>
<td>1/24 (4.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>–</td>
<td>1/24 (4.2)</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>10µg</th>
<th>30µg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRNT&lt;sub&gt;50&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.0</td>
<td>9.5</td>
<td>8.0</td>
</tr>
<tr>
<td>GMT post-dose 1</td>
<td>8.0</td>
<td>8.5</td>
<td>14.4*</td>
</tr>
<tr>
<td>GMT post-dose 2</td>
<td>8.0</td>
<td>195.6</td>
<td>303.4</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td>0%; 0%</td>
<td>5%; 94.4%</td>
<td>42.1%*; 100%</td>
</tr>
<tr>
<td>Post-dose 1; Post-dose 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>10µg</th>
<th>30µg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MN</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>14.0</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td>GMT post-dose 1</td>
<td>14.0</td>
<td>58.9</td>
<td>129.7</td>
</tr>
<tr>
<td>GMT post-dose 2</td>
<td>14.0</td>
<td>1,195.3</td>
<td>1,478.0</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td>0%; 0%</td>
<td>75%; 100%</td>
<td>85%; 100%</td>
</tr>
<tr>
<td>Post-dose 1; Post-dose 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reporter Virus Particle neutralization (RVP) data are pending.

Seroconversion is defined as a change in PRNT<sub>50</sub> from below the lower limit of quantification to a PRNT<sub>50</sub> equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing PRNT<sub>50</sub> 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**

<table>
<thead>
<tr>
<th></th>
<th>PRNT&lt;sub&gt;50&lt;/sub&gt;</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>10µg</td>
<td>30µg</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.0</td>
<td>41.5</td>
<td>12.3</td>
</tr>
<tr>
<td>GMT post-dose 1</td>
<td>8.0</td>
<td>147.9</td>
<td>88.1</td>
</tr>
<tr>
<td>GMT post-dose 2</td>
<td>8.0</td>
<td>224.1</td>
<td>150.9</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-dose 1; Post-dose 2</td>
<td>0%; 0%</td>
<td>50%; 50%</td>
<td>75%; 75%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MN</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>10µg</td>
<td>30µg</td>
</tr>
<tr>
<td>Baseline</td>
<td>14.0</td>
<td>54.0</td>
<td>39.4</td>
</tr>
<tr>
<td>GMT post-dose 1</td>
<td>14.0</td>
<td>375.0</td>
<td>226.7</td>
</tr>
<tr>
<td>GMT post-dose 2</td>
<td>14.0</td>
<td>645.9</td>
<td>578.5</td>
</tr>
<tr>
<td>Seroconversion rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-dose 1; Post-dose 2</td>
<td>0%; 0%</td>
<td>100%; 75%</td>
<td>75%; 75%</td>
</tr>
</tbody>
</table>

Seroconversion is defined as a change in PRNT<sub>50</sub> from below the lower limit of quantification to a PRNT<sub>50</sub> equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing PRNT<sub>50</sub> 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)

- MN data are consistent with the PRNT\textsubscript{50} data
- MN titers are higher compared to those reported by PRNT\textsubscript{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

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

## CMV vaccine (mRNA-1647)

<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA-1647</td>
<td>Oytomegalovirus (CMV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>World wide</td>
</tr>
<tr>
<td>mRNA-1893</td>
<td>Zika vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>World wide</td>
</tr>
<tr>
<td>mRNA-1172/ Merck V172</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Merck to pay milestones and royalties</td>
</tr>
<tr>
<td>mRNA-1177</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRNA-1653</td>
<td>hMPV/PV3 vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>World wide</td>
</tr>
<tr>
<td>mRNA-1345</td>
<td>Pediatric respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>World wide</td>
</tr>
<tr>
<td>mRNA-1189</td>
<td>Epstein-Barr virus (EBV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>World wide</td>
</tr>
<tr>
<td>mRNA-1851</td>
<td>Influenza H1N1 vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>World wide</td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>Novel coronavirus (SARS-CoV-2) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>World wide</td>
</tr>
</tbody>
</table>

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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

<table>
<thead>
<tr>
<th>CMV infection sequelae</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal period</strong></td>
<td>Jaundice, Microcephaly</td>
</tr>
<tr>
<td></td>
<td>Hearing loss</td>
</tr>
<tr>
<td></td>
<td>Vision loss</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Low birth weight</td>
</tr>
<tr>
<td><strong>Infancy, childhood, adulthood</strong></td>
<td>Deafness/Hearing loss</td>
</tr>
<tr>
<td></td>
<td>Neurodevelopmental delay</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
</tbody>
</table>

mRNA vaccine, IM-administered, designed to make gB and Pentamer antigens in their natural conformations to prevent or control CMV infection
Congenital CMV vaccine includes 6 mRNAs
5 encode the Pentamer, 6th encodes gB antigen
CMV data generation to date

CMV Phase 1 dosing regimen

- Month 0 (day 1)
- Month 2
- Month 6

- 3-month interim analysis
- 7-month interim analysis

- September 2019 R&D Day
- January 10, 2020
Neutralizing antibody titers

Participants

Neutralizing antibody titers

Serial dilutions of serum added to wells containing fibroblasts or epithelial cells, then challenged with CMV infection

Neutralizing antibody titer = serum dilution at which 50% of the cells are uninfected after CMV challenge

Blood draw (1 month, 3 month and 7 month)

CMV
Immunogenicity in CMV-seronegative participants, per-protocol set

- 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.

### Neutralizing Antibodies Against Epithelial Cell Infection

| Subject at each timepoint, epithelial cell and fibroblast infection |
|---|---|---|---|---|---|

<table>
<thead>
<tr>
<th></th>
<th>30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
<th>300 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMT baseline</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>GMT post 1st vaccination (month 1)</td>
<td>8</td>
<td>37</td>
<td>708</td>
<td>1,387</td>
</tr>
<tr>
<td>GMT post 2nd vaccination (month 3)</td>
<td>12</td>
<td>3,263</td>
<td>15,305</td>
<td>30,743</td>
</tr>
<tr>
<td>GMT post 3rd vaccination (month 7)</td>
<td>18</td>
<td>16,587</td>
<td>63,929</td>
<td>62,118</td>
</tr>
<tr>
<td>GMT/benchmark post 2nd vaccination</td>
<td>---</td>
<td>0.6</td>
<td>2.6</td>
<td>5.2</td>
</tr>
<tr>
<td>GMT/benchmark post 3rd vaccination</td>
<td>---</td>
<td><strong>2.8</strong></td>
<td><strong>10.8</strong></td>
<td><strong>10.5</strong></td>
</tr>
</tbody>
</table>

### Neutralizing Antibodies Against Fibroblast Infection

| Subject at each timepoint, epithelial cell and fibroblast infection |
|---|---|---|---|---|---|

<table>
<thead>
<tr>
<th></th>
<th>30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
<th>300 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMT baseline</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>GMT post 1st vaccination (month 1)</td>
<td>8</td>
<td>8</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>GMT post 2nd vaccination (month 3)</td>
<td>10</td>
<td>305</td>
<td>1,141</td>
<td>1,264</td>
</tr>
<tr>
<td>GMT post 3rd vaccination (month 7)</td>
<td>17</td>
<td>1,131</td>
<td>1,890</td>
<td>2,029</td>
</tr>
<tr>
<td>GMT/benchmark post 2nd vaccination</td>
<td>---</td>
<td>0.2</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>GMT/benchmark post 3rd vaccination</td>
<td>---</td>
<td>0.8</td>
<td>1.3</td>
<td>1.4</td>
</tr>
</tbody>
</table>

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

The seropositive benchmark at the 3-month interim analysis as disclosed in September was 5,917 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 cell and fibroblast respectively, with an n=68.
**Immunogenicity in CMV-seropositive participants, per-protocol set**

### Neutralizing Antibodies Against Epithelial Cell Infection

**CMV-seropositive GMT benchmark = 5,917**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Placebo</th>
<th>30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
<th>Placebo</th>
<th>300 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMT baseline</td>
<td>8,189</td>
<td>3,614</td>
<td>5,634</td>
<td>5,700</td>
<td>6,900</td>
<td>7,179</td>
</tr>
<tr>
<td>GMT post 1st vaccination (month 1)</td>
<td>7,891</td>
<td>24,752</td>
<td>39,020</td>
<td>52,775</td>
<td>6,673</td>
<td>84,628</td>
</tr>
<tr>
<td>GMT post 2nd vaccination (month 3)</td>
<td>7,490</td>
<td>49,390</td>
<td>62,400</td>
<td>119,829</td>
<td>5,974</td>
<td>156,583</td>
</tr>
<tr>
<td>GMT post 3rd vaccination (month 7)</td>
<td>7,647</td>
<td>76,914</td>
<td>141,020</td>
<td>211,503</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

- In seropositive subjects, the third vaccination boosted neutralizing antibody titers by 22-fold and 40-fold over baseline levels.

### Neutralizing Antibodies Against Fibroblast Infection

**CMV-seropositive GMT benchmark = 1,449**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Placebo</th>
<th>30 µg</th>
<th>90 µg</th>
<th>180 µg</th>
<th>Placebo</th>
<th>300 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMT baseline</td>
<td>1,298</td>
<td>1,094</td>
<td>1,458</td>
<td>1,371</td>
<td>3,631</td>
<td>1,836</td>
</tr>
<tr>
<td>GMT post 1st vaccination (month 1)</td>
<td>1,278</td>
<td>2,654</td>
<td>3,885</td>
<td>3,879</td>
<td>3,382</td>
<td>5,419</td>
</tr>
<tr>
<td>GMT post 2nd vaccination (month 3)</td>
<td>1,451</td>
<td>2,517</td>
<td>3,891</td>
<td>5,578</td>
<td>2,797</td>
<td>7,788</td>
</tr>
<tr>
<td>GMT post 3rd vaccination (month 7)</td>
<td>2,673</td>
<td>3,412</td>
<td>8,433</td>
<td>6,098</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

- Neutralizing antibody titers against fibroblast infection were boosted 4-fold to 6-fold over baseline levels.

**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.

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

### CMV Serostatus at Baseline

<table>
<thead>
<tr>
<th>CMV-seronegative</th>
<th>CMV-seropositive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase B</strong></td>
<td><strong>Phase C</strong></td>
</tr>
<tr>
<td>Placebo 30 µg</td>
<td>Placebo 300 µg</td>
</tr>
<tr>
<td>11 (73%)</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>11 (79%)</td>
<td>-</td>
</tr>
<tr>
<td>12 (80%)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>2 (14)</td>
<td>-</td>
</tr>
<tr>
<td>Pain</td>
<td>-</td>
</tr>
<tr>
<td>-</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Redness</td>
<td>-</td>
</tr>
<tr>
<td>3 (21)</td>
<td>2 (22)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Swelling</td>
<td>-</td>
</tr>
<tr>
<td>2 (25)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (25)</td>
</tr>
<tr>
<td>-</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (17)</td>
</tr>
<tr>
<td>-</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (8)</td>
</tr>
<tr>
<td>-</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (27)</td>
</tr>
<tr>
<td>-</td>
<td>5 (36)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (8)</td>
</tr>
<tr>
<td>-</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (20)</td>
</tr>
<tr>
<td>-</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

### Local 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)

### Most common systemic ARs

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

- **CMV Serostatus at Baseline**
  - CMV-seronegative: Placebo 30 µg, 11 (73%); Placebo 300 µg, 10 (91%)
  - CMV-seropositive: Placebo 30 µg, 9 (75%); Placebo 300 µg, 9 (100%)

- **Local ARs**
  - Pain: Placebo 30 µg, 2 (14); Placebo 300 µg, 2 (18)
  - Redness: Placebo 30 µg, 3 (21); Placebo 300 µg, 2 (22)
  - Swelling: Placebo 30 µg, 2 (25); Placebo 300 µg, 1 (13)

- **Most common systemic ARs**
  - Headache: Placebo 30 µg, 3 (25); Placebo 300 µg, 2 (14)
  - Fatigue: Placebo 30 µg, 2 (17); Placebo 300 µg, 1 (7)
  - Myalgia: Placebo 30 µg, 1 (8); Placebo 300 µg, 1 (7)
  - Arthralgia: Placebo 30 µg, 4 (27); Placebo 300 µg, 3 (25)
  - Nausea: Placebo 30 µg, 1 (8); Placebo 300 µg, 1 (7)
  - Chills: Placebo 30 µg, 3 (20); Placebo 300 µg, 3 (23)
  - Fever: Placebo 30 µg, 3 (20); Placebo 300 µg, 3 (23)

**Slide 121**
Solicited adverse reactions (AR) post 3rd vaccination, solicited safety set

<table>
<thead>
<tr>
<th>CMV Serostatus at Baseline</th>
<th>Placebo</th>
<th>30 μg</th>
<th>90 μg</th>
<th>180 μg</th>
<th>Placebo</th>
<th>30 μg</th>
<th>90 μg</th>
<th>180 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV-seronegative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>1 (9%)</td>
<td>8 (73%)</td>
<td>7 (54%)</td>
<td>9 (75%)</td>
<td>-</td>
<td>8 (73%)</td>
<td>6 (60%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>Redness</td>
<td>-</td>
<td>-</td>
<td>2 (15)</td>
<td>1 (8)</td>
<td>-</td>
<td>-</td>
<td>2 (20)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Swelling</td>
<td>-</td>
<td>-</td>
<td>1 (8)</td>
<td>1 (8)</td>
<td>-</td>
<td>-</td>
<td>1 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (9)</td>
<td>4 (36)</td>
<td>4 (31)</td>
<td>6 (50)</td>
<td>3 (23)</td>
<td>5 (46)</td>
<td>6 (60)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (9)</td>
<td>4 (36)</td>
<td>5 (39)</td>
<td>7 (58)</td>
<td>1 (8)</td>
<td>5 (46)</td>
<td>7 (70)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>-</td>
<td>3 (27)</td>
<td>6 (46)</td>
<td>6 (50)</td>
<td>-</td>
<td>5 (46)</td>
<td>6 (60)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>-</td>
<td>3 (27)</td>
<td>5 (39)</td>
<td>6 (50)</td>
<td>-</td>
<td>4 (36)</td>
<td>4 (40)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>2 (18)</td>
<td>3 (23)</td>
<td>4 (33)</td>
<td>1 (8)</td>
<td>4 (36)</td>
<td>5 (50)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Chills</td>
<td>-</td>
<td>2 (18)</td>
<td>5 (39)</td>
<td>4 (33)</td>
<td>-</td>
<td>3 (27)</td>
<td>6 (60)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Fever</td>
<td>-</td>
<td>1 (9)</td>
<td>1 (8)</td>
<td>3 (25)</td>
<td>-</td>
<td>1 (9)</td>
<td>4 (40)</td>
<td>3 (50)</td>
</tr>
</tbody>
</table>

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
Additional boosting demonstrated in seropositive cohort

Neutralizing antibodies against epithelial cell infection
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**
### Late stage development for CMV vaccine (mRNA-1647)

<table>
<thead>
<tr>
<th>Phase 2 dose confirmation study</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 3 dose levels; randomized, observer-blind, placebo-controlled, multicenter</td>
</tr>
<tr>
<td>- 252 seronegative &amp; seropositive adults</td>
</tr>
<tr>
<td>- Utilizes intended Phase 3 formulation; same lipid nanoparticle (LNP) used in Phase 1</td>
</tr>
<tr>
<td>- Phase 2 study fully enrolled; Closely monitoring trial given COVID-19 impact</td>
</tr>
<tr>
<td>- 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</td>
</tr>
<tr>
<td>- Evaluating the impact on the integrity of the trial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Planned pivotal Phase 3 trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>Primary endpoint</strong>: prevention of primary CMV infection in a population that includes women of childbearing age (WOCBA)</td>
</tr>
<tr>
<td>- Intended to begin in 2021 in USA and Europe; RFP sent to CROs</td>
</tr>
<tr>
<td>- Expect <strong>&lt;8,000 participants</strong></td>
</tr>
<tr>
<td>- Preparation and product manufacturing underway</td>
</tr>
<tr>
<td>- Phase 3 trial in WOCBA: costs currently estimated at $200-250 million(^1)</td>
</tr>
</tbody>
</table>

1. Current estimates based on benchmarks; final trial design and costs remain to be determined
Determining prevention of infection in baseline seronegative vaccinated participants

Cytomegalovirus (CMV)

CMV surface antigens

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

- gB
- gM
- gN
- gO
- PC

Antigens included in mRNA-1647

Blood draw

Antibodies against other CMV antigens not included in vaccine indicates infection

Vaccinated participant (baseline seronegative)
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\(^\circledast\) is a registered trademark of Merck & Co., Inc
3. Gross margin at scale in the U.S.
CMV vaccine (mRNA-1647) conclusion

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

Tal Zaks, M.D., Ph.D., Chief Medical Officer
April 14, 2020
<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mRNA-1647</td>
<td>Cytomegalovirus (CMV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1653</td>
<td>hMPV/PIV3 vaccine</td>
<td></td>
<td></td>
<td>Phase 1 (healthy volunteers)</td>
<td>Phase 1b (Age de-escalation) Seropositives</td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1893</td>
<td>Zika vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1172/ Merck V172</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Merck to pay milestones and royalties</td>
</tr>
<tr>
<td></td>
<td>mRNA-1177</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1345</td>
<td>Pediatric respiratory syncytial virus (RSV) vaccine</td>
<td>Future respiratory combo</td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1189</td>
<td>Epstein-Barr virus (EBV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1851</td>
<td>Influenza H1N1 vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1273</td>
<td>Novel coronavirus (SARS-CoV-2) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1851</td>
<td>Influenza H1N1 vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

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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/PIV3 vaccine (mRNA-1653)

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

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.
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 tested: mRNA-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**

<table>
<thead>
<tr>
<th></th>
<th>RSV: Respiratory syncytial virus</th>
<th>hMPV: Human metapneumovirus</th>
<th>PIV3: Parainfluenza virus type 3</th>
</tr>
</thead>
</table>
| **Epidemiology** | • Hospitalization rate in children < 5 years old in the U.S.: ~3:1000<sup>1</sup>  
• Associated with estimated 2 million medically attended infections | • Hospitalization rate in children < 5 years old in the U.S.: ~1.2:1000<sup>1</sup>  
• Associated with estimated 1 million outpatient clinic visits and > 250k ED visits annually among U.S. children < 5 years old<sup>2</sup> | • Hospitalization rate in children < 5 years old in the U.S.: ~0.5:1000<sup>1</sup> |
| **Clinical disease** | Upper and lower respiratory tract infection | mRNA-1345 (RSV) | mRNA-1653 (hMPV+PIV3) |

# Pediatric respiratory diseases

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

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>RSV Respiratory syncytial virus</th>
<th>hMPV Human metapneumovirus</th>
<th>PIV3 Parainfluenza virus type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization rate in children &lt; 5 years old in the U.S.: ~3:1000&lt;br&gt;Associated with estimated 2 million medically attended infections</td>
<td>Hospitalization rate in children &lt; 5 years old in the U.S.: ~1.2:1000&lt;br&gt;Associated with estimated 1 million outpatient clinic visits and &gt; 250k ED visits annually among U.S. children &lt; 5 years old</td>
<td>Hospitalization rate in children &lt; 5 years old in the U.S.: ~0.5:1000</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical disease**<br>Upper and lower respiratory tract infection

---

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

Flor M. Munoz, M.D.
Associate Professor
Pediatrics and Molecular Virology and Microbiology
Baylor College of Medicine
Texas Children’s Hospital
Houston, Texas

Information in the following slides are from a third-party source. While we believe such information is reliable, we have not independently verified any third-party information, and make no guarantee, express or implied, as to the accuracy and completeness of it.
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)
Pneumoviruses and Paramyxoviruses
Enveloped, Single Stranded RNA

RSV

HMPV

PIV

https://oncohemakey.com/
Ruckwardt T.J. 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
RSV is the most important cause of infant bronchiolitis
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
RSV Hospitalization – New Vaccine Surveillance Network* (NVSN) Data

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

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
Parainfluenza Viruses

Cases of Croup

Parainfluenza Virus Type 1 Isolates

Parainfluenza Virus Type 2 Isolates

Parainfluenza Virus Type 3 Isolates

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
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

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>RSV Protein</th>
<th>hMPV Protein</th>
<th>PIV Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>Fusion</td>
<td>F</td>
<td>Fusion</td>
</tr>
<tr>
<td>G</td>
<td>Attachment</td>
<td>G</td>
<td>HN</td>
</tr>
<tr>
<td>M</td>
<td>Matrix</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>N</td>
<td>Nucleoprotein</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>P</td>
<td>Phosphoprotein</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>L</td>
<td>Large polymerase complex</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>SH</td>
<td>Short hydrophobic</td>
<td>SH</td>
<td>Short hydrophobic</td>
</tr>
<tr>
<td>M2-1</td>
<td>Nonstructural</td>
<td>M2-1</td>
<td>Nonstructural</td>
</tr>
<tr>
<td>M2-2</td>
<td>Nonstructural</td>
<td>M2-2</td>
<td>Nonstructural</td>
</tr>
<tr>
<td>NS1</td>
<td>Nonstructural</td>
<td>NS1</td>
<td>Nonstructural</td>
</tr>
<tr>
<td>NS2</td>
<td>Nonstructural</td>
<td>NS2</td>
<td>Nonstructural</td>
</tr>
</tbody>
</table>

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

Vaccines VS mAbs
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

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

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

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.

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
RSV Vaccines in Development

### Historical

<table>
<thead>
<tr>
<th>Vaccine Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant or chimeric viruses</td>
</tr>
<tr>
<td>WT or attenuated virus</td>
</tr>
<tr>
<td>Whole-inactivated virus</td>
</tr>
<tr>
<td>Postfusion F or G subunit</td>
</tr>
<tr>
<td>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; &gt;10-20 fold rise in ELISA titers)</td>
</tr>
</tbody>
</table>

### New

<table>
<thead>
<tr>
<th>Vaccine Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefusion F subunit or SH pentamer</td>
</tr>
<tr>
<td>Vectors</td>
</tr>
<tr>
<td>Naked DNA or mRNA</td>
</tr>
<tr>
<td>VLPs or virosomes</td>
</tr>
<tr>
<td>Genetically modified and recombinant chimeric viruses</td>
</tr>
</tbody>
</table>

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

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

Source: B. Graham lecture ADVAC
Ruckwardt TJ. Immunity Review. 2019
# RSV Vaccines in Development

<table>
<thead>
<tr>
<th>Vaccine Type/Manufacturers</th>
<th>Viral Target</th>
<th>Target Population</th>
<th>Administration route</th>
<th>Clinical Development</th>
<th>Advantages</th>
<th>Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Particle based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV F nanoparticle; (Novavax)</td>
<td>Prefusogenic</td>
<td>Maternal*** Elderly* Pediatric*</td>
<td>Systemic</td>
<td>Phase-3*** Phase-2** Phase-1*</td>
<td>Safe, Immunogenic</td>
<td>Post-F based? Risk of ERD Ab durability</td>
</tr>
<tr>
<td><strong>Subunit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US-Cav1, (NIAID)</td>
<td>Pre-F</td>
<td>Maternal &amp; Elderly</td>
<td>Systemic</td>
<td>Phase-1</td>
<td></td>
<td>Factors affecting transplacental transfer Instability of pre-F Ab durability No protection for premature infants</td>
</tr>
<tr>
<td>GSK RSV F; (GlucoSmithXline)</td>
<td>sPre-F</td>
<td>Maternal &amp; Elderly</td>
<td>Systemic</td>
<td>Phase-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPX-RSV;</td>
<td>SHe</td>
<td>Elderly</td>
<td>Systemic</td>
<td>Phase-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV-F; (Janssen)</td>
<td>Pre-F</td>
<td>Elderly</td>
<td>Systemic</td>
<td>Phase-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV-F; (Pfizer)</td>
<td>Pre-F</td>
<td>Maternal &amp; Elderly</td>
<td>Systemic</td>
<td>Phase-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV-G (BioNtech)</td>
<td>G</td>
<td>Pediatrics &amp; Elderly</td>
<td>Systemic</td>
<td>Phase-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vector-based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AdV26 RSV;</td>
<td>Pre-F</td>
<td>Pediatric &amp; Elderly</td>
<td>Systemic</td>
<td>Phase-2</td>
<td></td>
<td>Not attenuated Low risk of ERD No interference with maternal Abs</td>
</tr>
<tr>
<td>(Janssen)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ChAdV155S-RSV; (GlucoSmithXline)</td>
<td>Pre-F, N, MZ-1</td>
<td>Pediatrics</td>
<td>Systemic</td>
<td>Phase-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VXA-RSV (AdV5); (Vaxart)</td>
<td>Post-F</td>
<td>Elderly</td>
<td>Mucosal &amp; Systemic</td>
<td>Phase-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVA-BN RSV;</td>
<td>Post-F, GA/GB, Elderly</td>
<td>Systemic</td>
<td>Phase-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Bavarian Nordic)</td>
<td>N, M2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Live attenuated/chimeric</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nMVA/N-RSV; (Universidad de Chile)</td>
<td>N</td>
<td>Newborn</td>
<td>Systemic</td>
<td>Phase-1</td>
<td>Predominant Th1 immune responses</td>
<td></td>
</tr>
<tr>
<td>RSV/JAG</td>
<td>Lacks G</td>
<td>Pediatric</td>
<td>Mucosal</td>
<td>Phase-1</td>
<td></td>
<td>Low risk of ERD Intranasal delivery Replication in presence of maternal Ab Abnormal stimulation of immune response</td>
</tr>
<tr>
<td>RSV ANS2 A1313/1314</td>
<td>Pre-F/Post-F</td>
<td>Pediatric</td>
<td>Mucosal &amp; Systemic</td>
<td>Phase-1</td>
<td></td>
<td>Balance of attenuation/ immunogenicity Reverse to wild type Stability for mass production</td>
</tr>
<tr>
<td>RSV 276</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV G120/ANS2/1030, (BeneFit Pasteur &amp; NIAID)</td>
<td>Pre-F</td>
<td>Pediatric</td>
<td>Mucosal &amp; Systemic</td>
<td>Phase-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SeV/RSV;</td>
<td>F</td>
<td>Pediatric</td>
<td>Mucosal &amp; Systemic</td>
<td>Phase-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(St Jude Hospital)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Information in the following slides are from a third-party source. While we believe such information is reliable, we have not independently verified any third-party information, and make no guarantee, express or implied, as to the accuracy and completeness of it.
Collaborators

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**Gilead Sciences**
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Thomas Cihlar

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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
**COVID-19 Response and countermeasures**

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

*Monoclonal Antibodies*
- Prevent / treat infection
- Temporary immunity
- Interrupt transmission
- Prophylax populations

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

*Public Health Response*
- Limit transmission
- Limit genetic variation
- Assess mechanisms of transmission
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

- HCoV-NL63 (~1200-1500)
- HCoV-OC43 (~1890)
- HCoV-229E (~1700-1800)
- HCoV-HKU1 (~1950s)
- SARS-CoV (2002-2004)
- MERS-CoV (2012-2020)
- SARS-CoV-2 (2019)
Models for CoV Zoonoses

Host Range
Mutations

Specialist

- Host-range mutation
- Random
- Rare

a
- Secondary host (reservoir)
- Adaptation
- Human infection
- Adaptation

b
- Direct human infection
- Adaptation
- Secondary host (reservoir)

Epidemic strain

Models for CoV Zoonoses

Host Range Mutations

Specialist

Opportunity

Generalist

“Ready-Made Pre-Pandemic

Hurdles to Virus Movement and Adaptation

Adapted from M. Vignuzzi
Murine Hepatitis Virus (MHV)

MERS-CoV

SARS-CoV

HCoV-HKU1

HCoV-OC43

HCoV-229E

HCoV-NL63

“SARS-like”
Bt-SHC014
Bt-WIV1

19-nCoV

Ready-made pre-pandemic

Menachery et al (Alphacoronaviruses)
Phylogeny of SARS-like betacoronaviruses including novel coronavirus SARS-CoV-2


Showing 45 of 45 genomes.

Feb 24, 2020

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

New Clade of SARS-like Viruses
5000 nt difference

SARS-CoV

SARS-Like-CoV

Wuhan SARS-CoV-2

BAT RaTG13 from Cave Bat in Yunnan Province
96% nt identity (1200 nt)
COVID-19 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%) compared to those with no comorbidities (0.9%)
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

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

Coronavirus Replication

- 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

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

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
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-N⁴-Hydroxycytidine (EIDD-1931/2801, NHC) inhibit CoV replication

EC₅₀ = 0.03 μM

EC₅₀ = 0.17 μM

Agostini et al mBio 2017

Agostini et al J Virol 2019
Remdesivir - IV

- 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

EIDD-2801-NHC
oral

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

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

Monoclonal Antibodies
• Prevent / treat infection
• Temporary immunity
• Interrupt transmission
• Prophylax populations

COVID-19 Response and countermeasures
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?
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

Representative preclinical information regarding a related coronavirus, MERS

We observed an induction of neutralizing antibodies which were sufficient to affect a \(\sim 3\)-log reduction in viral titers in the nose, and \(\sim 4\)-log reduction in viral titers detected from BAL. Viral titers in the throat were reduced to the lower limit of detection.
SARS-CoV-2 vaccine (mRNA-1273)

Encodes for the full spike S protein
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 250µg Cohort initiated week of April 8
All regulatory paths require a positive benefit/risk assessment

<table>
<thead>
<tr>
<th>Phase</th>
<th>Size</th>
<th>Endpoint</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>10s</td>
<td>Safety and tolerability, Immunogenicity</td>
<td>Tolerability (predicted local and systemic vaccine adverse events)</td>
</tr>
<tr>
<td>Phase 2</td>
<td>100s</td>
<td>Dose confirmation (Immunogenicity), Safety and tolerability</td>
<td>Safety (unpredicted)</td>
</tr>
<tr>
<td>Phase 3</td>
<td>1,000s</td>
<td>Less disease, Less infection, Safety and tolerability</td>
<td>Enhanced disease</td>
</tr>
</tbody>
</table>

Regular Approval
- Clinical efficacy demonstrated

Accelerated Approval
- A surrogate “reasonably likely” to predict benefit

Emergency Use Authorization
- “May have benefit”
Manufacturing introduction
Juan Andres, Chief Technical and Quality Officer
April 14, 2020
We are a platform...
We have solved many questions

- mRNA structure
- mRNA + Lipid encapsulation

How to measure?

- Purity
- Stability
- Size of LNP
- LNP Stability
Platform research + technical development = “create”
Before having our own manufacturing site
Plasmid >> mRNA >> LNP >> Fill/Finish >> QC
Our manufacturing site is scalable
3 Engines

PRECLINICAL

PERSONALIZED VACCINE UNIT

CLINICAL
PRECLINICAL

Batches

23,500

Scale

10mg

PERSONALIZED VACCINE UNIT

1 batch/1 patient; 90 to date

>100mg

CLINICAL

1 batch/many patients

5g-75g+
What we know now.... Platform technology

- Similar processes
- Fast process improvements
- Cell-free
- Less capital investment

- Quality
- Speed
- Scale
- Cost
## Prophylactic vaccines modality

### SARS-CoV-2 vaccine (mRNA-1273)

<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic vaccines</td>
<td>mRNA-1647</td>
<td>Cytomegalovirus (CMV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1893</td>
<td>Zika vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1172/ Merck V172</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Merck to pay milestones and royalties</td>
</tr>
<tr>
<td></td>
<td>mRNA-1177</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1653</td>
<td>hMPV/PV3 vaccine</td>
<td>Phase 1 (healthy volunteers)</td>
<td>Phase 1b (Age de-escalation) Seropositives</td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1345</td>
<td>Pediatric respiratory syncytial virus (RSV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1189</td>
<td>Epstein-Barr virus (EBV) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1851</td>
<td>Influenza H7N9 vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td>mRNA-1273</td>
<td>Novel coronavirus (SARS-CoV-2) vaccine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

© 2020 Moderna Therapeutics
Firing up on all engines…

**PRECLINICAL**

- Batches: 23,500

**PERSONALIZED VACCINE UNIT**

- Scale: 1 batch/1 patient; 90 to date

**CLINICAL**

- Scale: 1 batch/many patients
  - 5g-75g+
Concept to Phase 1 in 42 days

- Jan 13
- Feb 7
- Feb 23

Day 1: Selecting amino acid sequence

Day 2-4: Digital sequence engineering and DNA design

Day 5-17: Manufacture plasmid, mRNA, LNP

Day 17-25: Technical development and documentation preparation

Day 41-42: 1st Shipment to the clinic

Day 63: First participant dosed

Day 66: Initiated Phase 2 Manufacturing

Day 75: Started scale up activities
We plan to scale capacity in three different stages

- **Current Capacity**
- **Stage 1**
- **Stage 2**
- **Stage 3** (2023-2025)

Scale
Working on all parts of supply chain

- **Scale**
- **Quality**
- **Speed**

Plasmid → mRNA → mRNA + LNP → Drug product

Fill Finish

Distribution

---

© 2020 Moderna Therapeutics
Paving the future...

Quality
Speed
Scale
Cost
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
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?
<table>
<thead>
<tr>
<th>Organization</th>
<th>Pathways for approval</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA</strong></td>
<td>Traditional approval</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Accelerated approval</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Animal Rule</strong></td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td><strong>ACIP</strong></td>
<td>Recommendation</td>
<td>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.</td>
</tr>
</tbody>
</table>

*ACIP = Advisory Committee on Immunization Practices; FDA = Food and Drug Administration.*
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.
<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Description of members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voting members</td>
<td>14</td>
<td>Subject matter experts in vaccinology, immunology, pediatrics, internal medicine, nursing, family medicine, virology, public health, infectious diseases, and/or preventive medicine</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Consumer representative who provides perspectives on the social and community aspects of vaccination.</td>
</tr>
<tr>
<td>Ex officio members (non-voting)</td>
<td>8</td>
<td>Individuals in the roles listed below or their designees.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Director, Division of Vaccine Injury Compensation, Bureau of Health Professions, Health Resources and Services Administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Deputy Director for Scientific Activities, Office of the Assistant Secretary of Defense for Health Affairs, Department of Defense</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Under Secretary for Health, Department of Veterans Affairs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Director, Center for Biologics Evaluation and Research, Food and Drug Administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Director, Center for Medicaid and State Operations, Centers for Medicare and Medicaid Services</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Director, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Director, Indian Health Service</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Director, National Vaccine Program Office, HHS</td>
</tr>
<tr>
<td>Liaison representatives from professional organizations (non-voting)</td>
<td>Participating organizations:</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>
| 31 | • 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 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.
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).
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.*

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGMENTS</th>
<th>EVIDENCE</th>
<th>ADDITIONAL INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the problem of public health importance?</td>
<td>No □ Probably no □ Uncertain □ Probably yes □ Yes □</td>
<td>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.</td>
<td>Identify any additional public health priority considerations, including consideration of disparities.</td>
</tr>
<tr>
<td>Benefits &amp; Harms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How substantial are the desirable anticipated effects?</td>
<td>Minimal □ Small □ Moderate □ Large □ Don't know □</td>
<td>Describe the magnitude of the beneficial effects of vaccination on individual (vaccine effectiveness, duration of protection) and population (herd immunity) levels.</td>
<td>Take into consideration: Is the baseline benefit similar across subgroups (by age, gender, pregnancy or lactation status, occupation [e.g., healthcare workers], immune status, race, SES, and other groups)? Are there indirect effects that should be considered (e.g., herd immunity)?</td>
</tr>
</tbody>
</table>
## ACIP Evidence to Recommendations Framework

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGMENTS</th>
<th>RESEARCH EVIDENCE</th>
<th>ADDITIONAL INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>How substantial are the undesirable anticipated effects?</td>
<td>□ Minimal □ Small □ Moderate □ Large □ Don’t know □ Varies</td>
<td>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?</td>
<td>Take into consideration: Is the baseline risk for harm similar across subgroups (see above)? Should there be separate recommendations for subgroups based on harms?</td>
</tr>
<tr>
<td>Do the desirable effects outweigh the undesirable effects?</td>
<td>□ Favors intervention □ Favors comparison □ Favors both □ Favors neither □ Unclear</td>
<td>Describe the balance of benefits of the vaccine with possible harms (individual and population level).</td>
<td></td>
</tr>
<tr>
<td>What is the overall certainty of this evidence for the critical outcomes?</td>
<td>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</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Values</td>
<td>No □ Probably □ Uncertain □ Probably Yes □ Varies</td>
<td>Provide any available evidence on target population values &amp; preferences related to vaccination and comparative health benefits and risks. Describe the source of these estimates.**</td>
<td>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.</td>
</tr>
<tr>
<td>CRITERIA</td>
<td>JUDGMENTS</td>
<td>RESEARCH EVIDENCE</td>
<td>ADDITIONAL INFORMATION</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?</td>
<td>No</td>
<td>Possibly no</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Is the intervention acceptable to key stakeholders?</td>
<td>No</td>
<td>Possibly no</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Is the intervention a reasonable and efficient allocation of resources?</td>
<td>No</td>
<td>Possibly no</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Is the intervention feasible to implement?</td>
<td>No</td>
<td>Possibly no</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>
### ACIP Evidence to Recommendations Framework

<table>
<thead>
<tr>
<th>Balance of consequences</th>
<th>Undesirable consequences clearly outweigh desirable consequences in most settings</th>
<th>Undesirable consequences probably outweigh desirable consequences in most settings</th>
<th>The balance between desirable and undesirable consequences is closely balanced or uncertain</th>
<th>Desirable consequences probably outweigh undesirable consequences in most settings</th>
<th>Desirable consequences clearly outweigh undesirable consequences in most settings</th>
<th>There is insufficient evidence to determine the balance of consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Is there sufficient information to move forward with a recommendation?

Yes □

No □

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We do not recommend the intervention</th>
<th>We recommend the intervention for individuals based on clinical decision-making</th>
<th>We recommend the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

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.).

---

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

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGMENTS</th>
<th>EVIDENCE</th>
<th>ADDITIONAL INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the problem of public health importance?</td>
<td>No</td>
<td>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.</td>
<td>Identify any additional public health priority considerations, including consideration of disparities.</td>
</tr>
</tbody>
</table>
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.
How substantial are the desirable anticipated effects?

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 [e.g., 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.

<table>
<thead>
<tr>
<th>CMV gB/MF59</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine efficacy (%)</td>
</tr>
<tr>
<td>CMV infection after 3 doses</td>
<td></td>
</tr>
<tr>
<td>Per protocol after 3 doses</td>
<td>42.9</td>
</tr>
<tr>
<td>Intention to treat after 3 doses</td>
<td>23.2</td>
</tr>
<tr>
<td>CMV infection after 2 doses</td>
<td></td>
</tr>
<tr>
<td>Per protocol after 2 doses</td>
<td>44.5</td>
</tr>
<tr>
<td>Intention to treat after 2 doses</td>
<td>15.0</td>
</tr>
<tr>
<td>CMV infection after 1 dose</td>
<td></td>
</tr>
<tr>
<td>Per protocol after 1 dose</td>
<td>30.7</td>
</tr>
<tr>
<td>Intention to treat after 1 dose</td>
<td>18.5</td>
</tr>
</tbody>
</table>

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.
Table 2: Treatment-emergent adverse events (based on harms) for subgroups by treatment group

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>M+ Events</th>
<th>M- Events</th>
<th>N+ Events</th>
<th>N- Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL-1</td>
<td>9 (109)</td>
<td>9 (109)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Type of event</td>
<td>All-1</td>
<td>All-1</td>
<td>All-1</td>
<td>All-1</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CNV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

The death was not considered drug related.
What is the overall certainty of this evidence for the critical outcomes?

<table>
<thead>
<tr>
<th>Effectiveness of the intervention</th>
<th>Safety of the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>No included studies</td>
<td>4</td>
</tr>
<tr>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>No</th>
<th>Probably no</th>
<th>Uncertain</th>
<th>Probably yes</th>
<th>Yes</th>
<th>Varies</th>
</tr>
</thead>
<tbody>
<tr>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

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

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

Abbreviations: CMV, cytomegalovirus; DSMB, Data Safety Monitoring Board; IgG, immunoglobulin G.
Table 3. Issues to Consider: Vaccination of Toddlers

<table>
<thead>
<tr>
<th>Vaccine is given to toddler to protect others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Unborn sibling</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Is the intervention a reasonable and efficient allocation of resources?</th>
<th>No</th>
<th>Probably no</th>
<th>Uncertain</th>
<th>Probably yes</th>
<th>Yes</th>
</tr>
</thead>
</table>

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.

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

Is there sufficient information to move forward with a recommendation?

Yes ☐

No ☐

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We do not recommend the intervention</th>
<th>We recommend the intervention for individuals based on clinical decision-making</th>
<th>We recommend the intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
## Examples of FDA Vaccine Approval and ACIP Recommendations

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine</th>
<th>Description</th>
<th>Approval Type</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Fluad</td>
<td>Prevention of influenza disease by subtypes A and type B contained in the vaccine in ≥ 65 yo</td>
<td>Accelerated</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Quadrasil</td>
<td>Prevention of diphtheria, tetanus, pertussis and poliomyelitis as 4&lt;sup&gt;th&lt;/sup&gt; or 5&lt;sup&gt;th&lt;/sup&gt; dose of IPV series in 4-6 yo who received 4 doses of Pentacel and/or Daptacel</td>
<td>Traditional</td>
<td>A</td>
</tr>
</tbody>
</table>
|      | 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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Description</th>
<th>Administration</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flucelvax</td>
<td>Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 4-18 yo</td>
<td>Accelerated</td>
<td>A</td>
</tr>
<tr>
<td>Flucelvax Quadrivalent</td>
<td>Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 4-18 yo</td>
<td>Accelerated</td>
<td>A</td>
</tr>
<tr>
<td>Trumeba</td>
<td>Addition of 2-dose regimen for prevention of invasive disease caused by <em>Neisseria meningitidis</em> serogroup B in 10-25 yo</td>
<td>Accelerated</td>
<td>for ≥10 yo at high-risk</td>
</tr>
<tr>
<td>Gardasil 9</td>
<td>Addition of 2-dose regimen for Prevention of cervical CA, genital warts and precancerous lesions in 9-26 yo females</td>
<td>Traditional</td>
<td>A</td>
</tr>
<tr>
<td>QPAN-H5N1</td>
<td>Prevention of disease caused by the influenza A virus H5N1 subtype in 6 mo - 17 yo at increased risk of exposure</td>
<td>Traditional</td>
<td>No recommendation [stockpile]</td>
</tr>
</tbody>
</table>

### Additional Information

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Description</th>
<th>Administration</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FluBlok</td>
<td>Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in ≥18 yo</td>
<td>Traditional</td>
<td>A</td>
</tr>
<tr>
<td>Afluria Quadrivalent</td>
<td>Prevention of disease caused by influenza virus subtypes A and type B in the vaccine ≥18 yo</td>
<td>Traditional</td>
<td>A</td>
</tr>
<tr>
<td>FluLaval</td>
<td>Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 6-35 mo</td>
<td>Traditional</td>
<td>A</td>
</tr>
<tr>
<td>FluLaval Quadrivalent</td>
<td>Prevention of disease caused by influenza virus subtypes A and type B in the vaccine in 6-35 mo</td>
<td>Traditional</td>
<td>A</td>
</tr>
</tbody>
</table>
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.
Conclusion
Stéphane Bancel
April 14, 2020

© 2020 Moderna Therapeutics
mRNA vaccines are a disruptive technology
As transformational as live-attenuated and recombinant vaccines were...

<table>
<thead>
<tr>
<th>Large product opportunity</th>
<th>Higher probability of technical success</th>
<th>Accelerated research and development timelines</th>
<th>Greater capital efficiency over time (vs. recombinant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market opportunity</td>
<td>Probability of success</td>
<td>Time requirements</td>
<td>Power of the platform</td>
</tr>
<tr>
<td>Worldwide vaccine market was $35 billion in 2019, growing 9% a year(^1)</td>
<td>Vaccines have highest overall POS to approval 42% from Phase 2 start to approval(^2)</td>
<td>SARS-CoV-2 vaccine (mRNA-1273) Sequence to Phase 1 clinical trial in 63 days</td>
<td>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)</td>
</tr>
</tbody>
</table>

1. Alliance Bernstein research report: Vaccines: The Robin Hood of Therapeutics – THE PRIMER on the oldest biotech drugs in the world (Feb 2020)
We believe our vaccines have a large peak sales potential

<table>
<thead>
<tr>
<th>Wholly-owned vaccines</th>
<th>$6.5-$12 billion peak sales potential with current portfolio of vaccine candidates¹,²</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMPV/PIV3 + RSV</td>
<td></td>
</tr>
<tr>
<td>hMPV/PIV3 (mRNA-1653)</td>
<td></td>
</tr>
<tr>
<td>Pediatric RSV (mRNA-1345)</td>
<td></td>
</tr>
<tr>
<td>CMV (mRNA-1647)</td>
<td></td>
</tr>
<tr>
<td>EBV (mRNA-1189)</td>
<td></td>
</tr>
<tr>
<td>Zika (mRNA-1893)</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 (mRNA-1273)</td>
<td></td>
</tr>
</tbody>
</table>

¹. All figures are estimates and subject to change
². Does not include potential royalty revenue from mRNA-1172/mRNA-1777 targeting RSV
Key players in the global vaccine market

WW Vaccines Sales for Key Players¹
(2019)

- GSK: $8.4 Bn
- Merck: $8.0 Bn
- Pfizer: $6.5 Bn
- Sanofi Pasteur: $6.2 Bn

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

Growing 9% a year²

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

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).
Plus more innovative vaccines to come...

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
And today was just infectious disease vaccines...
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