Viral Vaccine Makeup and Development Issues

(Why it Typically Takes 15 Years to Develop a Vaccine)

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Vaccines, from concept to implementation

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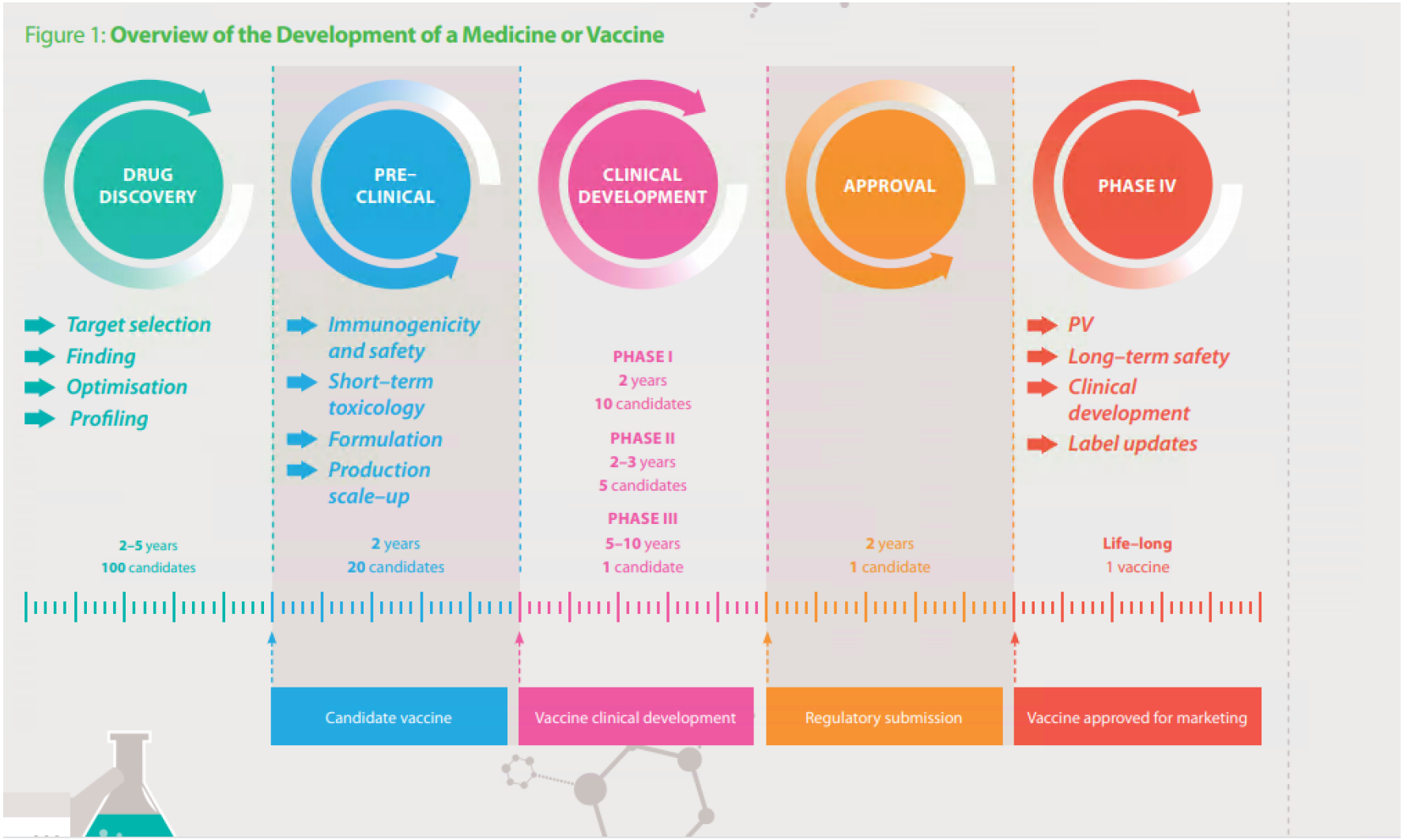
IRVING MEDICAL CENTER

I am a paid member of the Pfizer COVID-19 vaccine Data Monitoring Committee

Vaccine Development Timeline



https://www.ifpma.org/wp-content/uploads/2019/07/IFPMA-ComplexJourney-2019_FINAL.pdf

1. Market Need

- Epidemiology
- Target population
- Disease Burden
- Health economics

Image source: https://www.tenego.com/making-your-vision-meet-the-market-need

2. Technical Feasibility

- Does prior infection afford durable protection against reinfection?
- Protection mechanism known?
- Target antigen(s) identified?
- Appropriate vaccine platform available?
- Do you have the intellectual property required to create the vaccine?

3. Concept Development

- Antigen(s) identified
- Vaccine platform selected
- Adjuvant (if needed) selected
- Route of administration selected

3a. Viral Vaccine Platforms

- Live attenuated
- Killed/inactivated
- Viral vectored
  - Replication competent
  - Replication incompetent
- Nucleic acid (plasmid)
  - DNA or RNA
- Protein and subunit

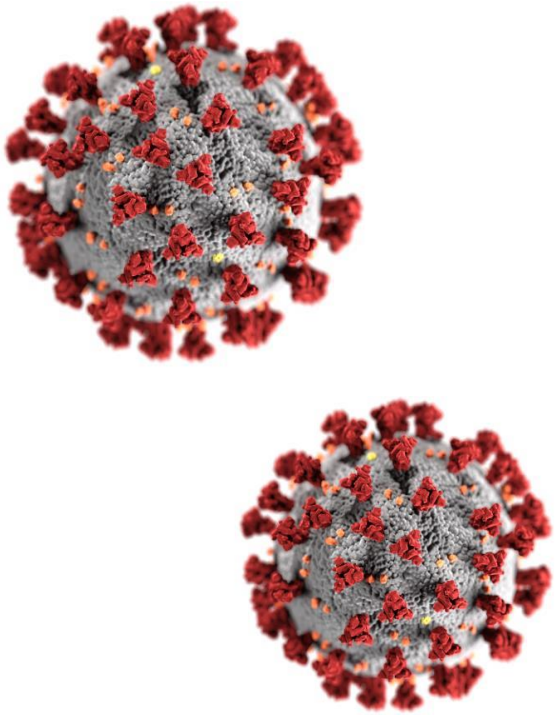


Image source: https://phil.cdc.gov/Details.aspx?pid=23312

3b. Adjuvants

- Enhances and directs immune responses
- Dose-sparing strategy
- Approved adjuvant examples
  - Aluminum salts (Alum) – Hepatitis B vaccine
  - Monophosphoryl lipid A (MPL) – HPV vaccine
  - MF59 – Influenza vaccine
  - MPL + Saponin QS-21 – Zoster vaccine
  - CpG-oligodeoxynucleotide – Hepatitis B vaccine

3c. Route of administration

- Intramuscular
- Oral
- Intranasal spray
- Dermal electroporation
- Subcutaneous injection
- Intradermal

Image source: https://pixnio.com/science/medical-science/administering-the-h1n1-live-attenuated-intranasal-vaccine-laiv-to-a-female-recipient
Image source: https://ichef.bbci.co.uk/news/624/cpsprodpb/11A61/production/_100398227_gettyimages-697573320.jpg

SARS CoV-2 Vaccines in Development

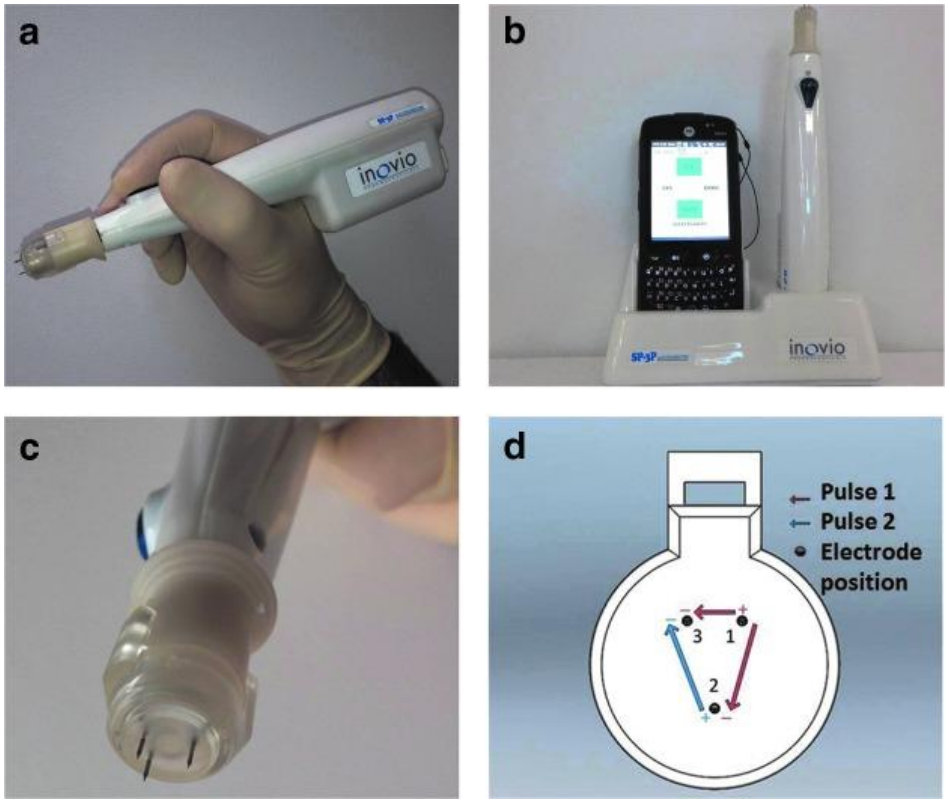
- 59 vaccines are currently being tested in humans
- 16 have reached the final phase 3 stage of testing
- BioNtech/ Pfizer: RNA vaccine - Intramuscular
- Moderna/NIH: RNA vaccine - Intramuscular
- Oxford vaccine: Chimp adenovirus vector - Intramuscular
- Sinopharm BBIBP-CorV: Inactivated whole virion + alum

https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html

SARS CoV-2 Vaccines in Development

- NOVIO: DNA vaccine – Dermal electroporation

CELLECTRA-3P, Portable Next-Generation Dermal Electroporation Device



Human Gene Therapy Methods, 31 Jul 2015, 26(4):134-146

4. Preclinical Assessment

WHO Technical Report Series, No. 927, 2005

Annex 1

WHO guidelines on nonclinical evaluation of vaccines

This document provides guidance to national regulatory authorities (NRAs) and vaccine manufacturers on the nonclinical evaluation of vaccines by outlining the international regulatory expectations in this area. It should be read in conjunction with the Guidelines on clinical evaluation of vaccines: regulatory expectations (1), in order to complete the understanding of the whole process of vaccine evaluation. Vaccines are a diverse class of biological products and their nonclinical testing programmes will depend on product-specific features and clinical indications. The following text has therefore been written in the form of guidelines rather than recommendations. Guidelines allow greater flexibility than recommendatisons with respect to specific issues related to particular vaccines.

https://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/ANNEX%201Nonclinical.P31-63.pdf?ua=1

4. Preclinical Assessment

- *Antigen definition and purification process*
- Formulation selection
- Assay development and validation
- *Immunology and efficacy in relevant animal models*
- Development of correlates of protective immunity
- Toxicology and QA evaluation
- Production of GMP lots for PI/PII clinical trials

4a. Formulation Selection

- Virus components
- Adjuvant(s)
- Excipients, e.g. cell culture materials, inactivating agents
- Stabilizers
- Antibiotics
- Preservatives

CDC Vaccine Excipient Summary. https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf

4b. Assay Development

- Humoral immune responses to the vaccine.
  - Ligand-binding assay, viral-neutralization assay
- Cellular immune responses to the vaccine.
  - ELISpot, flow cytometry
- Serologic assay to screen trial participants.
- Assay(s) to determine seroconversion to non-vaccine SARS-CoV-2 antigens as a measure of infection.
- Assay to detect acute SARS-CoV-2 infection.

4c. Animal Studies

- Antigen definition and purification process
- Formulation selection
- *Immunology and efficacy in relevant animal models*
  - Dose ranging
  - FDA two animal rule
- Experiments on mechanism of action
- Toxicology evaluation
- Production of GMP lots for PI/PII clinical trials

4d. Toxicology and QA Evaluations

- Must be conducted in a GLP-compliant labs
- Must involve two species and include genotoxic and reproductive toxicology
- Analysis of all the known relevant physical and chemical parameters of the immunogen
- Assessment for adventitious agents
- Assessment for reactogenicity
- Define testing required for lot release

5. Manufacturing Scale Up

- Produced according to good manufacturing practices (GMP).
- Each step of production must be documented and validated.
- Must specify personnel education and training; facility design and maintenance; equipment design, calibration, maintenance, and operation; raw material sources and specifications; aseptic processing; segregation of pre- and post-inactivation steps; safety/purity assessment; potency assessment; analytical laboratory procedures; packaging procedures; and storage and shipping procedures.
- Establish an FDA Master File

5. Manufacturing Scale Up

- Regulatory approval of a vaccine requires demonstration that the vaccine is safe and effective AND that the regulatory agency is satisfied with the manufacturing process and QA procedures.
- *For purposes of your vaccine development you need only explain whether you require a BSL-3 or BSL-4 facility, whether you will produce single dose units or multi-dose vials and how many doses you plan to manufacturer.*

6. Investigational New Drug Application

a. Background and discovery of the vaccine

b. Chemistry, manufacturing, and controls of the vaccine and information on the final product formulation

c. Documentation of controlled and validated assay results supporting the product characterization including safety, consistency, stability, potency, and lot release criteria for the vaccine

6. Investigational New Drug Application

d. Results of the preclinical (animal) toxicology and immunogenicity studies to support safety and animal efficacy data if available

e. Any human experience with either the experimental vaccine or similar products

f. Detailed clinical trial protocols

g. Investigators' brochure

h. Any additional information necessary to facilitate review and evaluation

7. Clinical Trials

- Identify clinical trial sites and investigators
- Obtain IRB approval
- Develop trial monitoring plan
- Establish data and safety monitoring board
- Conduct and analyze phase 1-3 clinical to meet good clinical practice (GCP) standards

7. Clinical Trials

- Phase I – small safety, immunogenicity and dose-ranging studies.
- Phase II – larger safety and immunogenicity (± dose-ranging, ±efficacy) studies; *can involve human challenge studies.*
- Phase III – Large efficacy trials with multiple secondary outcome measures.

Human Challenge Trials in Vaccine Development

Human challenge trials have proven to be useful to explore vaccine targets, identify immune correlates of protection, and evaluate clinical efficacy.

Sheets RL. et al., Human challenge trials in vaccine development, Biologicals, 44, p37-50, 2016

Image source: https://www.knowablemagazine.org/article/health-disease/2019/human-challenge-trials

Human Challenge Trials in Vaccine Development

- **Which pathogen has NOT been used in human challenge vaccine studies?**
  - Vibrio cholera, Shigella, Enteropathic E. coli, Salmonella typhi, Campylobacter jejuni, **Neisseria gonorrhea (1)**, Helicobacter pylori, Streptococcus pneumonia
  - **Influenza (2)**, Respiratory Syncytial Virus, Norovirus, Rhinovirus, Rotavirus, **Dengue (3)**
  - **Malaria (4)**, Giardia, Cryptosporidium

7. Clinical Trials

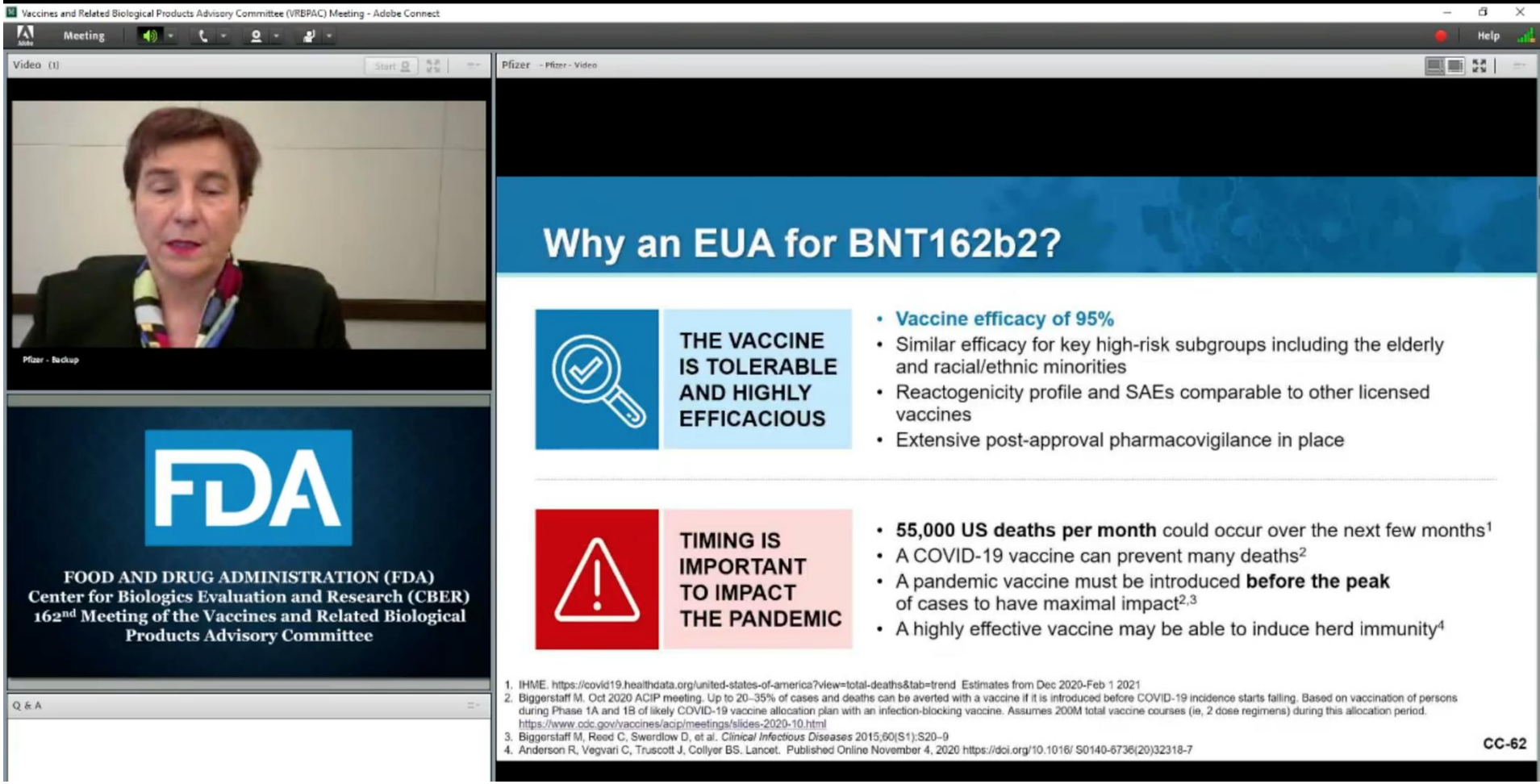
- Lot consistency studies to evaluate vaccine physicochemical and biological quality and effect among different vaccine lots.
- Bridging studies for age groups not included in the phase III trials.
- Phase IV – post-licensure trials assessing safety (very rare adverse events) or new indications.

8. Emergency Use Authorization (EUA)

- With a declared emergency, FDA can judge that it's worth releasing a new vaccine even without all the evidence that would fully establish its effectiveness and safety. If evidence strongly suggests that patients have benefited from a vaccine, FDA can issue an EUA to make it available.
- The FDA will issue guidance as to what is expected for EUA.
- FDA and the Vaccines and Related Biological Products Advisory Committee will review safety, efficacy and manufacturing data in order to determine if EUA should be issued.

https://www.fda.gov/advisory-committees/blood-vaccines-and-other-biologics/vaccines-and-related-biological-products-advisory-committee

8. Emergency Use Authorization (EUA)



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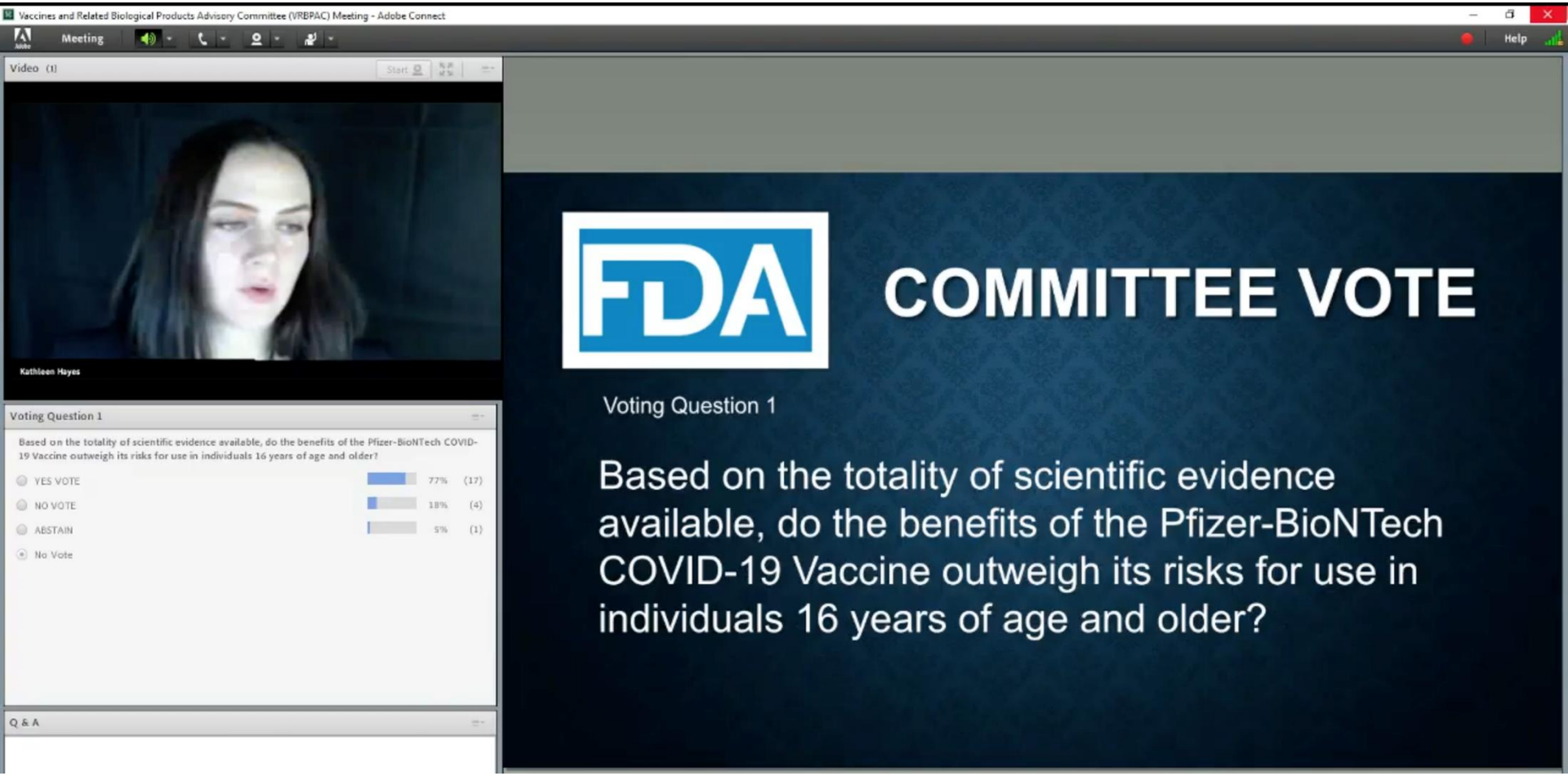


9. Biologics License Application (BLA)

- BLA contains information needed for the FDA's multidisciplinary review team to evaluate the product safety and efficacy and risks and benefits.
- During the BLA review process, the FDA conducts a pre-approval inspection of the planned manufacturing facility with detailed examination of the manufacturing processes and GLP compliance.
- FDA may also conduct audits of the IND clinical studies, including site visits, to evaluate the conduct of studies and to ensure satisfactory record keeping.

9. Biologics License Application (BLA)

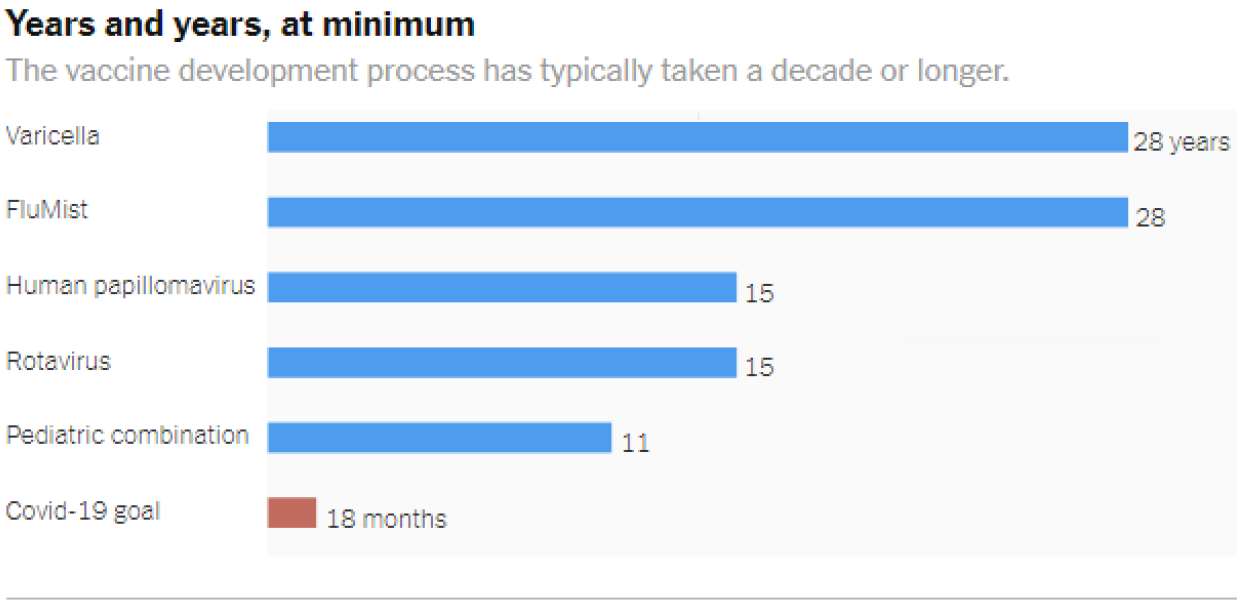
- Advice regarding the vaccine's safety and efficacy may be sought from the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC), an independent panel of 12 experts.
- Adequate product labeling is a requirement for vaccine licensure.
- FDA approval of the new product may be contingent upon the conduct of phase 4 studies, also referred to as post-marketing studies.

9. Immunization Recommendations/ Implementation

- In the U.S. following licensure, several committees of experts make recommendations for use of the vaccine.
- CDC's Advisory Committee on Immunization Practices
- AAP's Committee on Infectious Diseases.
- AAFP's Commission on Clinical Policies and Research.
- These committees independently assess the evidence to recommend what populations should receive the vaccine, at what ages, the number of doses and dosing interval, and precautions and contraindications.

10. Post-marketing Surveillance

- During vaccine development rare or uncommon adverse events may be unrecognized.
- Surveillance programs are intended to identify problems that may develop following licensure and marketing.
- In the U.S., the vaccine adverse event reporting system (VAERS) and the vaccine safety datalink are used to identify problems.



https://www.nytimes.com/interactive/2020/04/30/opinion/coronavirus-covid-vaccine.html?searchResultPosition=2

How Long Will a Vaccine Really Take?

By Stuart A. Thompson

New York Times April 30, 2020

https://www.nytimes.com/interactive/2020/04/30/opinion/coronavirus-covid-vaccine.html?searchResultPosition=2

COVID-19 Vaccine Timeline

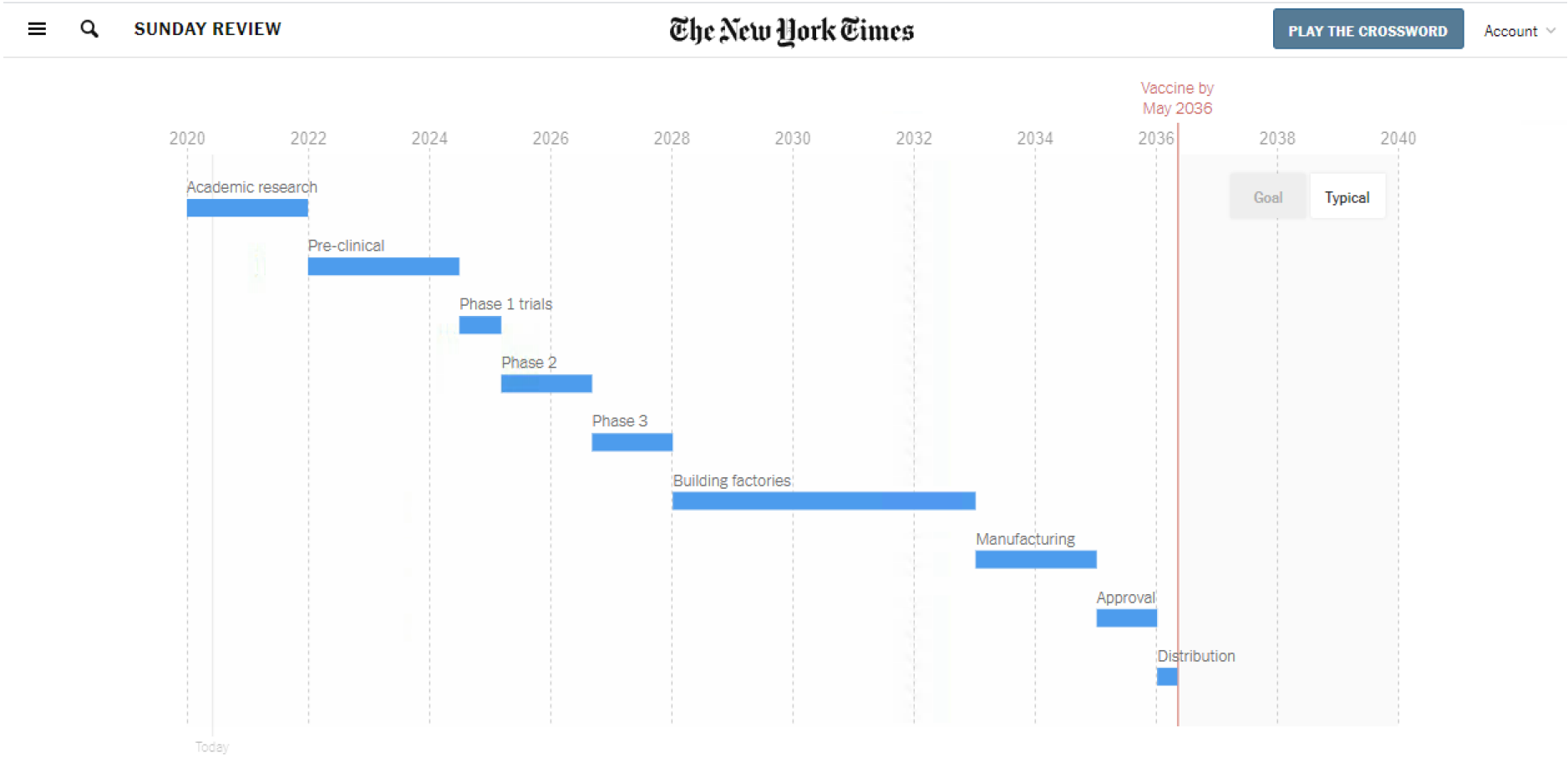
- December - First cases of COVID-19 in Wuhan China
- Dec 24 – Novel coronavirus isolated
- Jan 3 – China officially informs WHO of outbreak
- Jan 10 – First genetic sequence reported
- Jan 30 – WHO declares public health emergency of international concern
- Nov 9 – Pfizer reports interim analysis – efficacy >90%
- Dec 11 – FDA issues EUA for Pfizer/BioNTech vaccine

Thanks – Questions?

References

1. Stanberry LR, Barrett ABT. Vaccine Development Pathway, in Barrett ADT and Stanberry LR (eds): Vaccines for Biodefense and Emerging and Neglected Diseases, London, Elsevier, 2009, pp. 45-54.
2. 2018 NIAID Strategic Plan for Research on Vaccine Adjuvants. https://www.niaid.nih.gov/sites/default/files/NIAIDStrategicPlanVaccineAdjuvants2018.pdf, accessed May 17, 2020.
3. CDC Vaccine Excipient Summary. https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf, accessed May 18, 2020
4. Metz B, et al. Quality control issues and approaches in vaccine development, Expert Rev Vaccines 8-pp 227-38, 2009.

Classical Timeline ~ 16 Years



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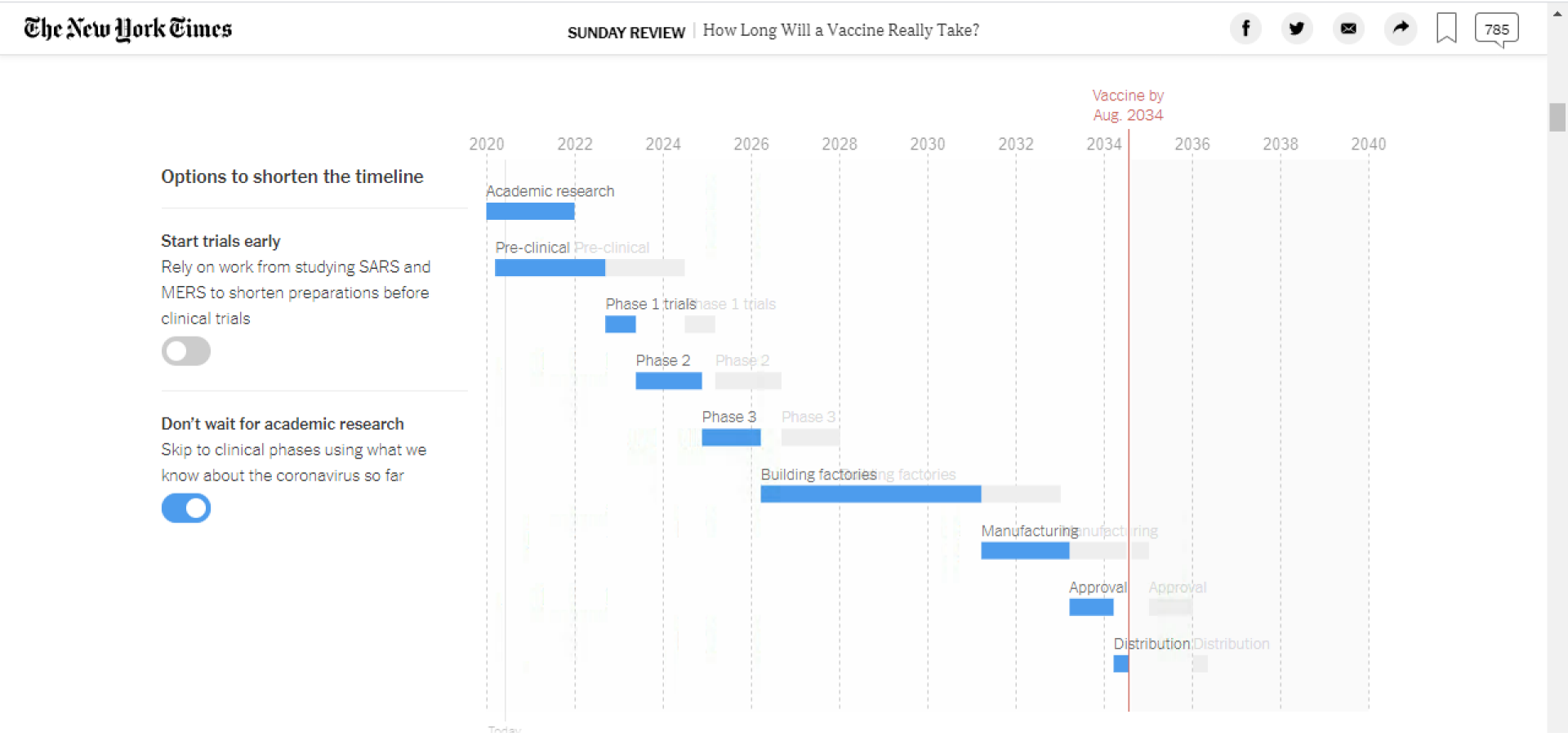
Start w/o Academic Research ~ 14 Years



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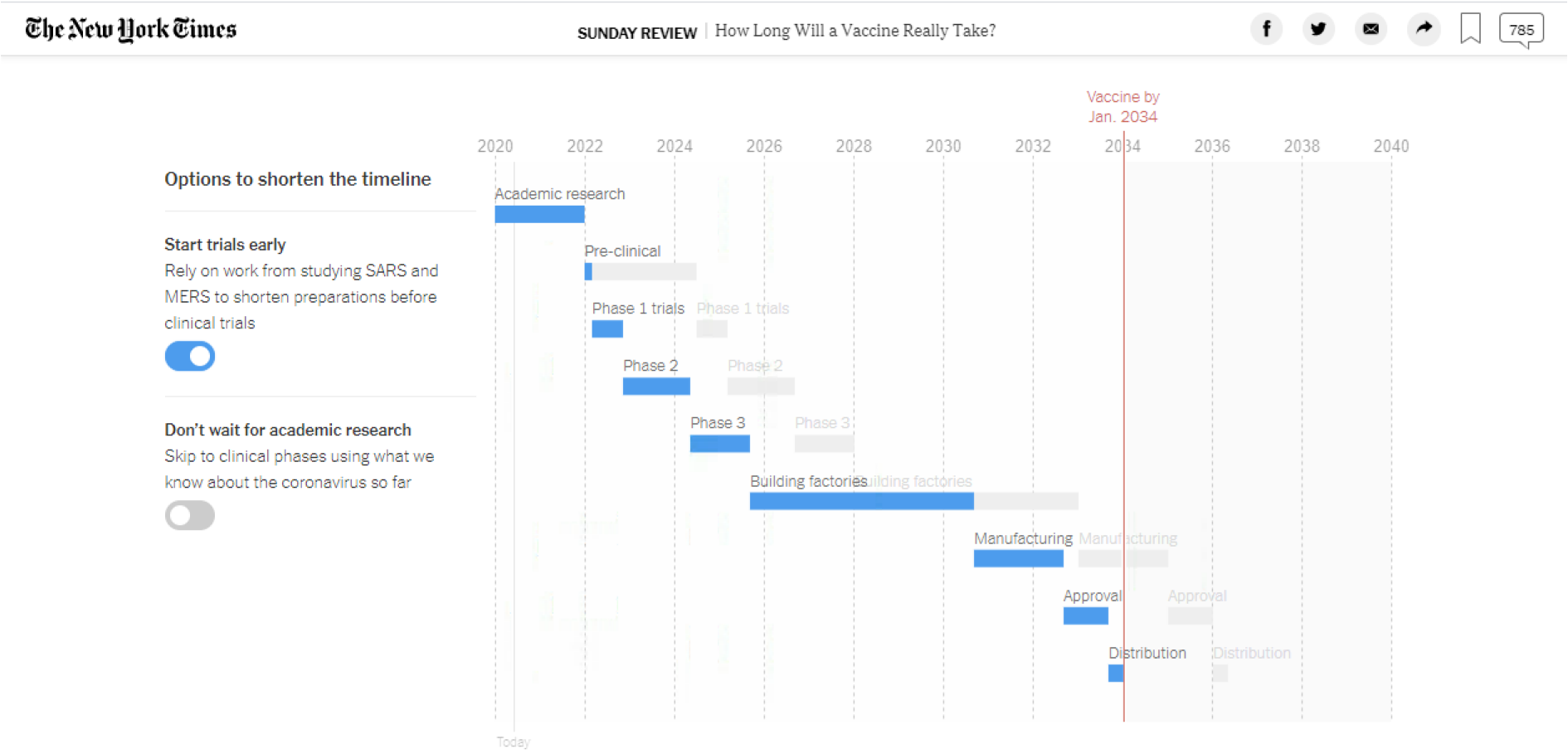
Start Trials Early ~ 13.5 years



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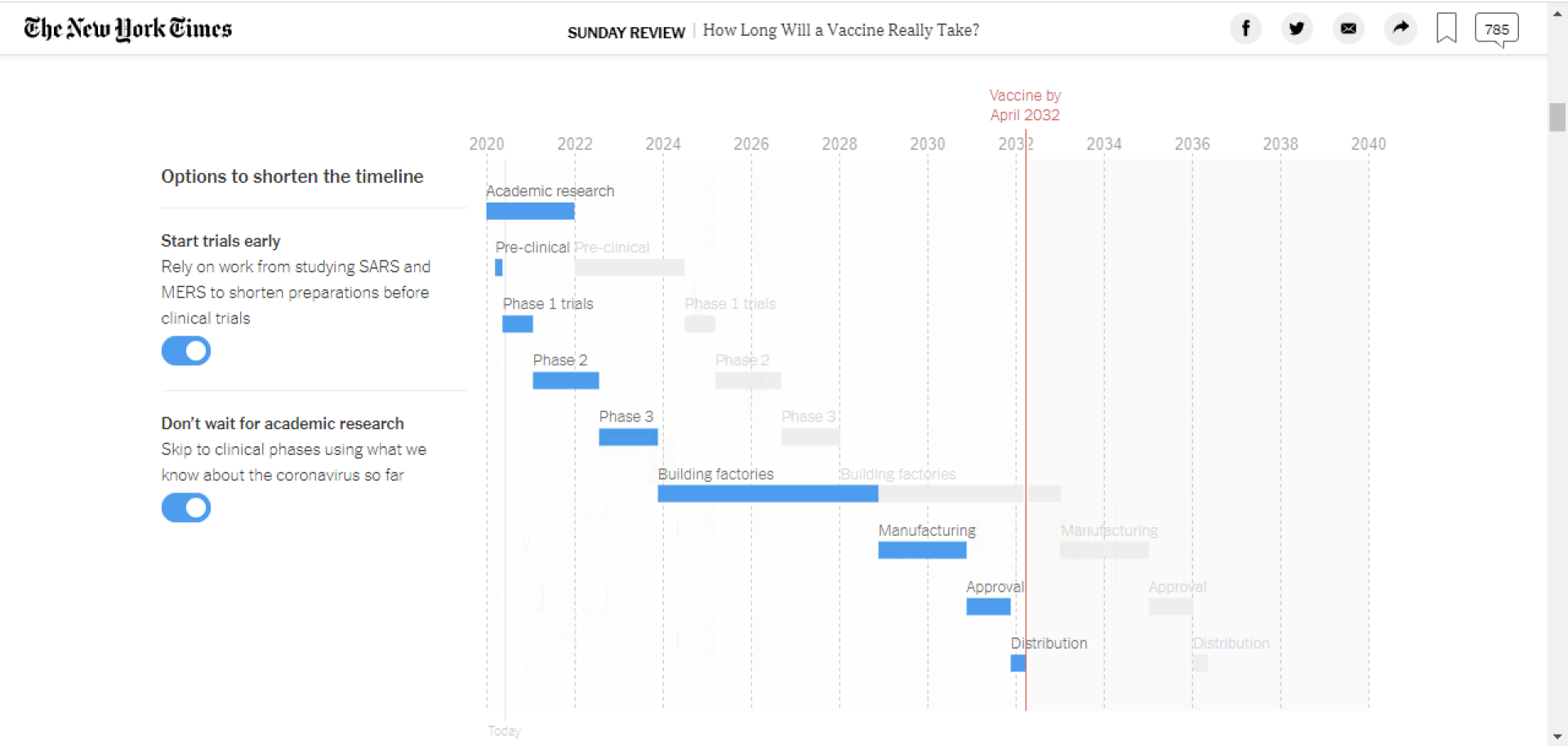
Early Trials & No Academic Research ~ 12 Years



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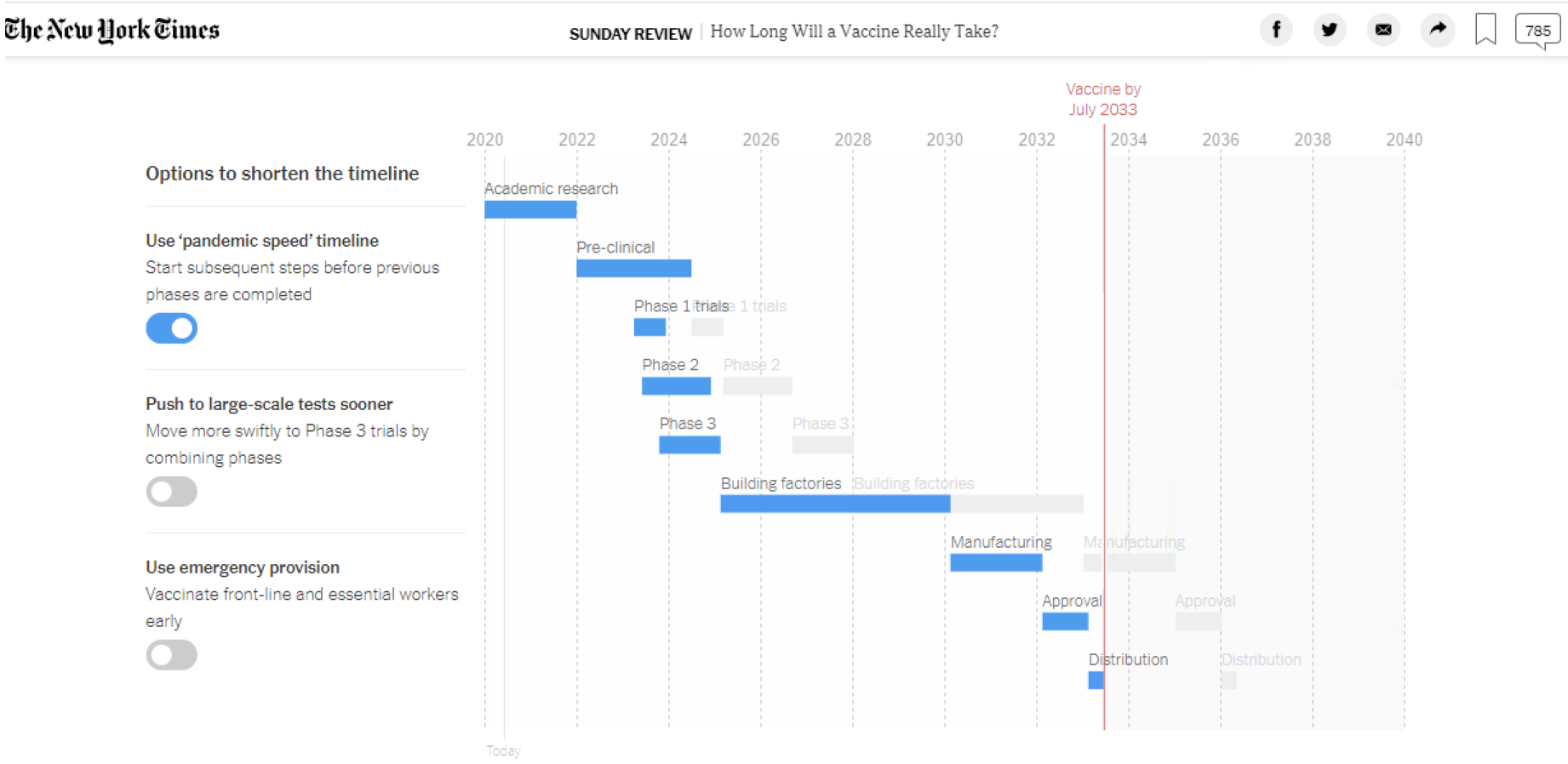
Start Phase II & III Earlier ~ 13 Years



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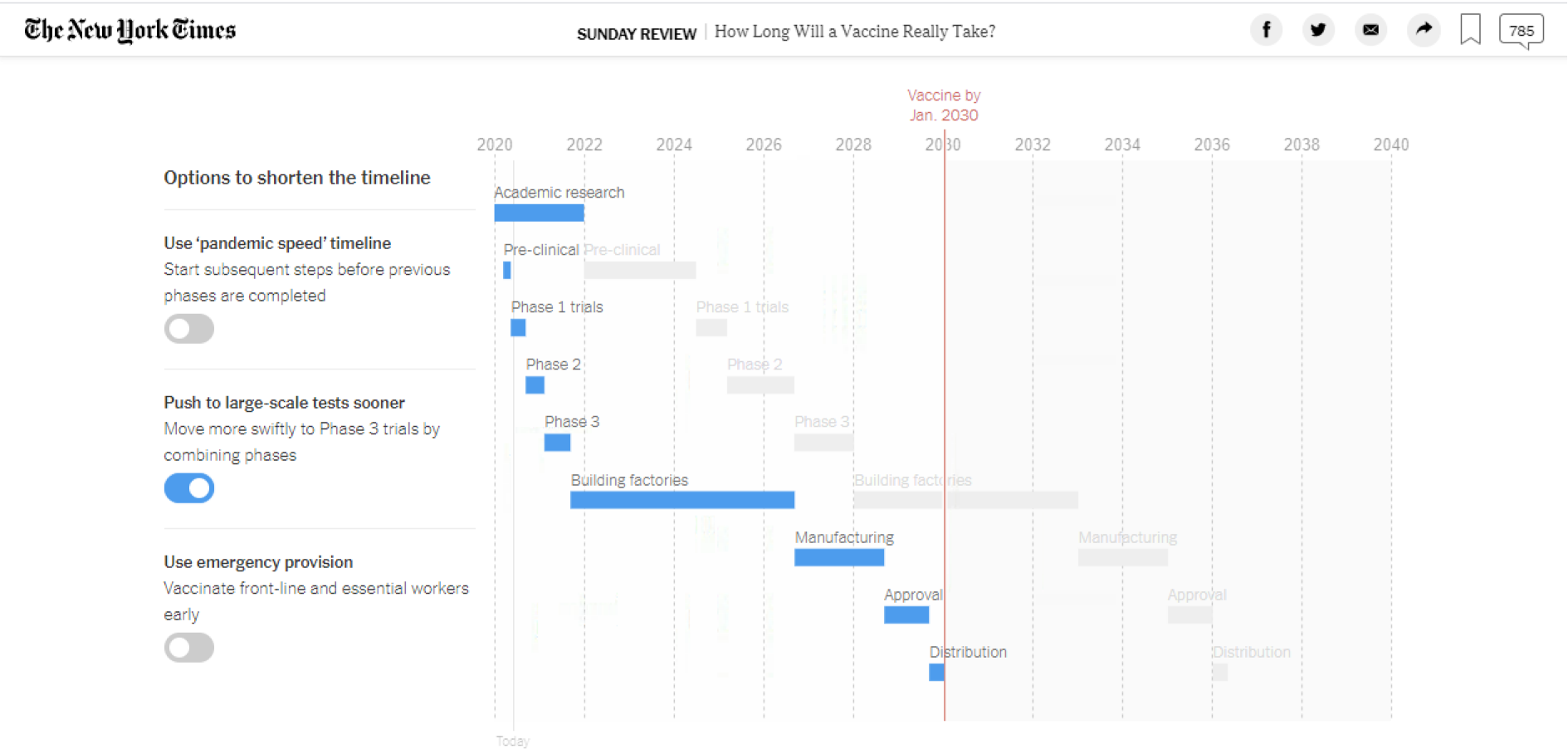
Overlap Clinical Trial Phases ~ 9.5 Years



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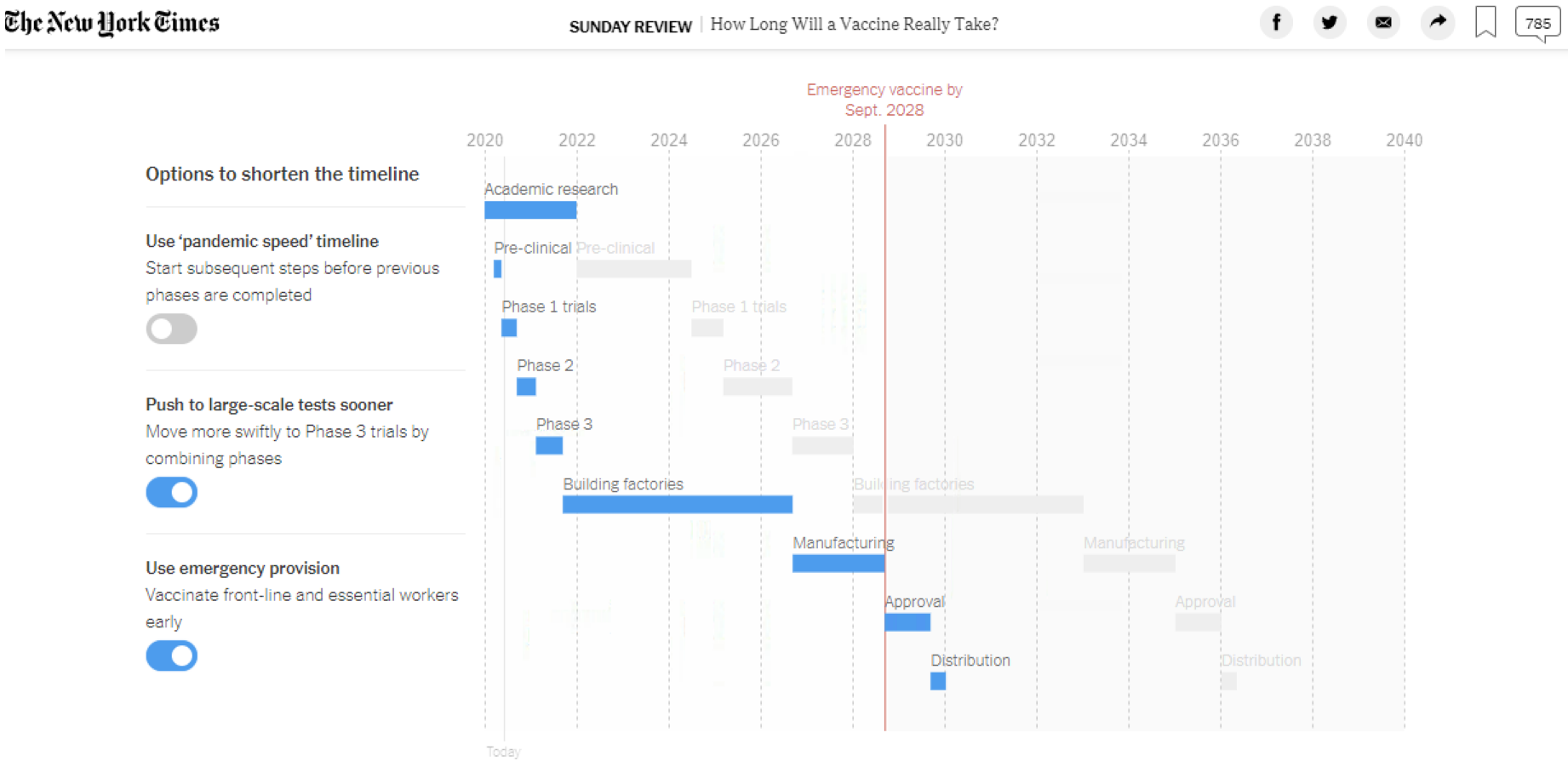
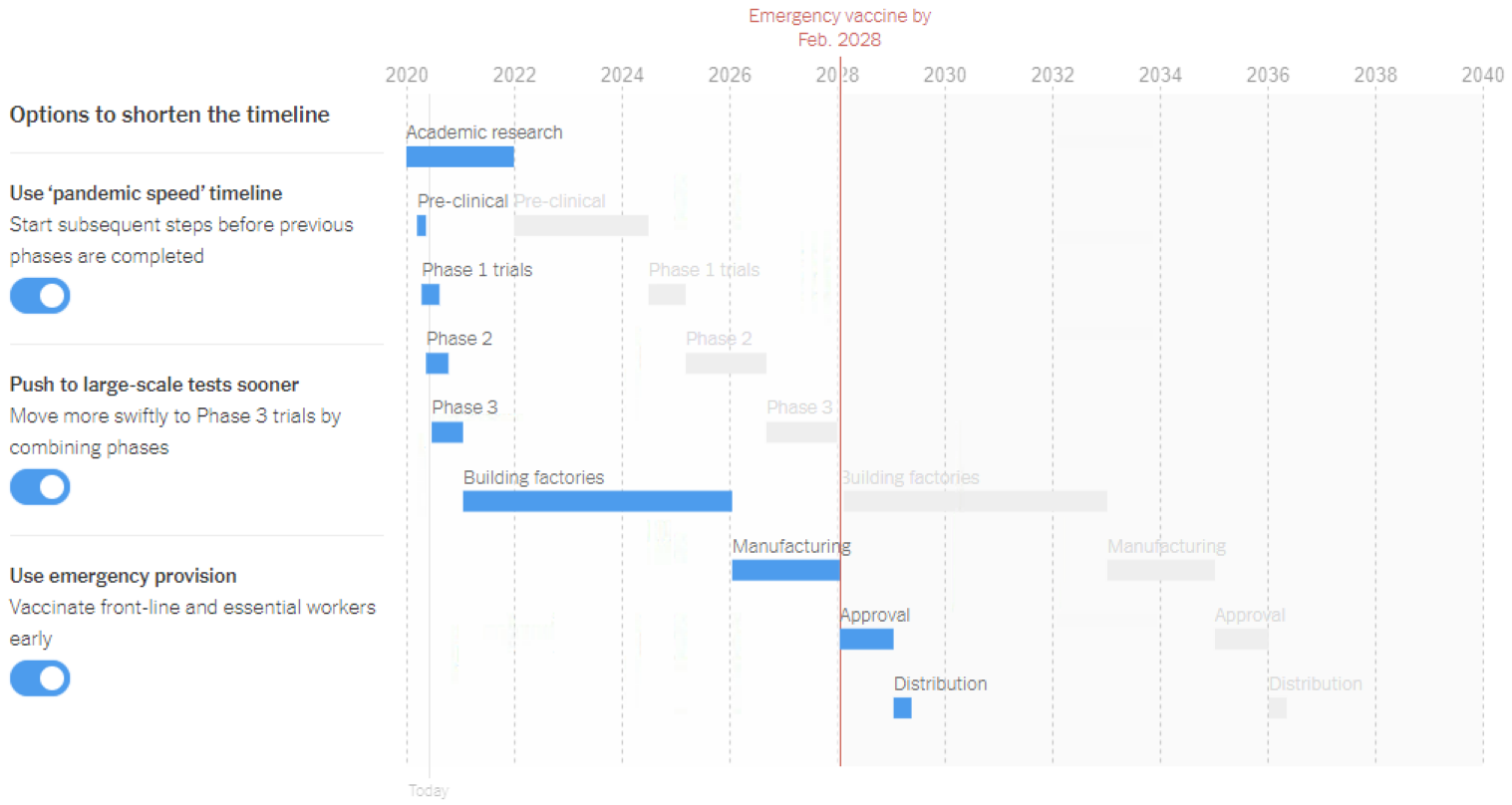
Push Trials/Emergency Provision ~8 Years



https://www.nytimes.com/interactive/2020/04/30/opinion/coronavirus-covid-vaccine.html?searchResultPosition=2

Earlier Start/Push Trials/Emergency Provision ~7.7 Years

The New York Times | SUNDAY REVIEW | How Long Will a Vaccine Really Take?



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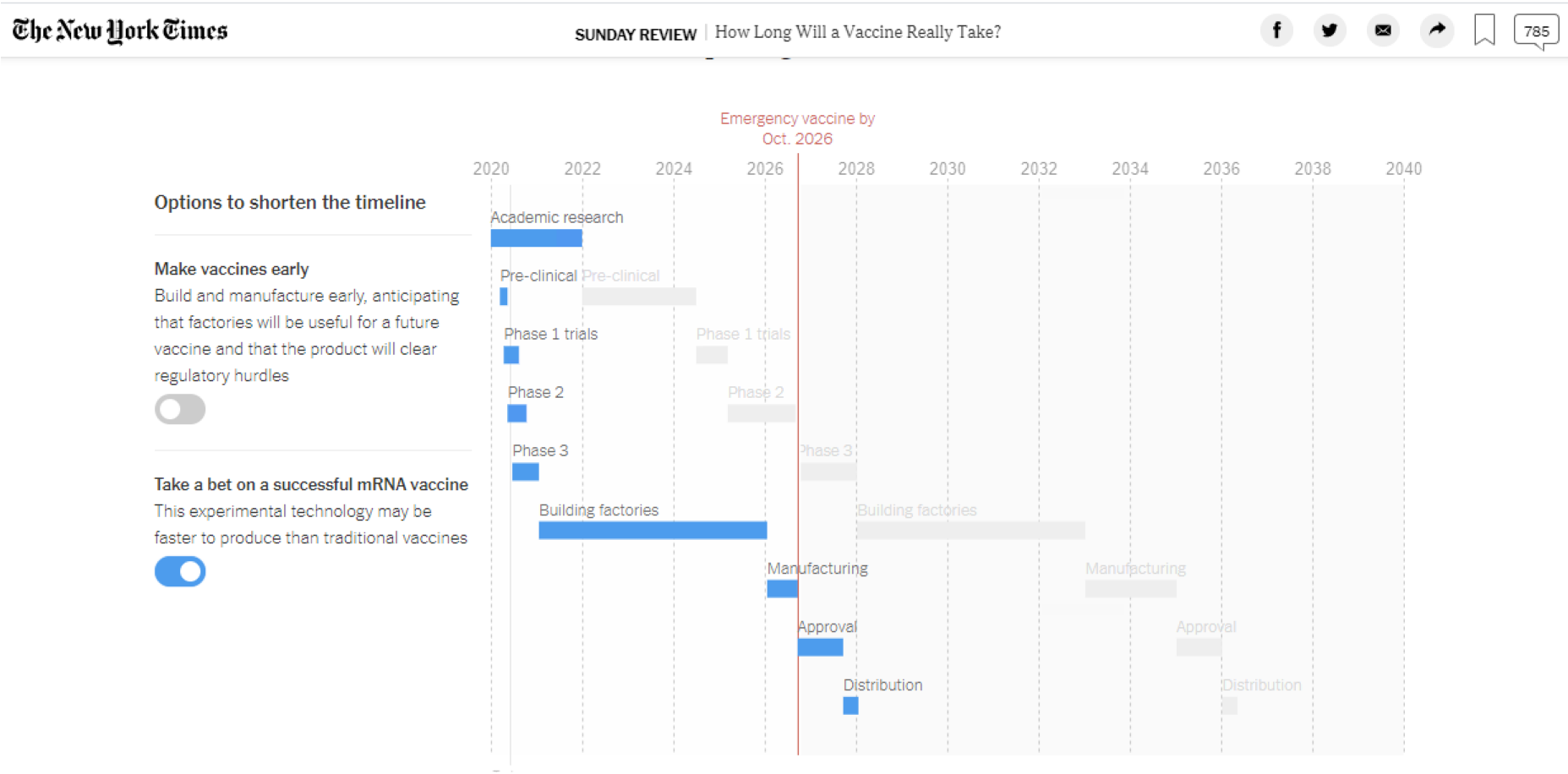
Bet on a Successful RNA Vaccine ~ 6.5 Years



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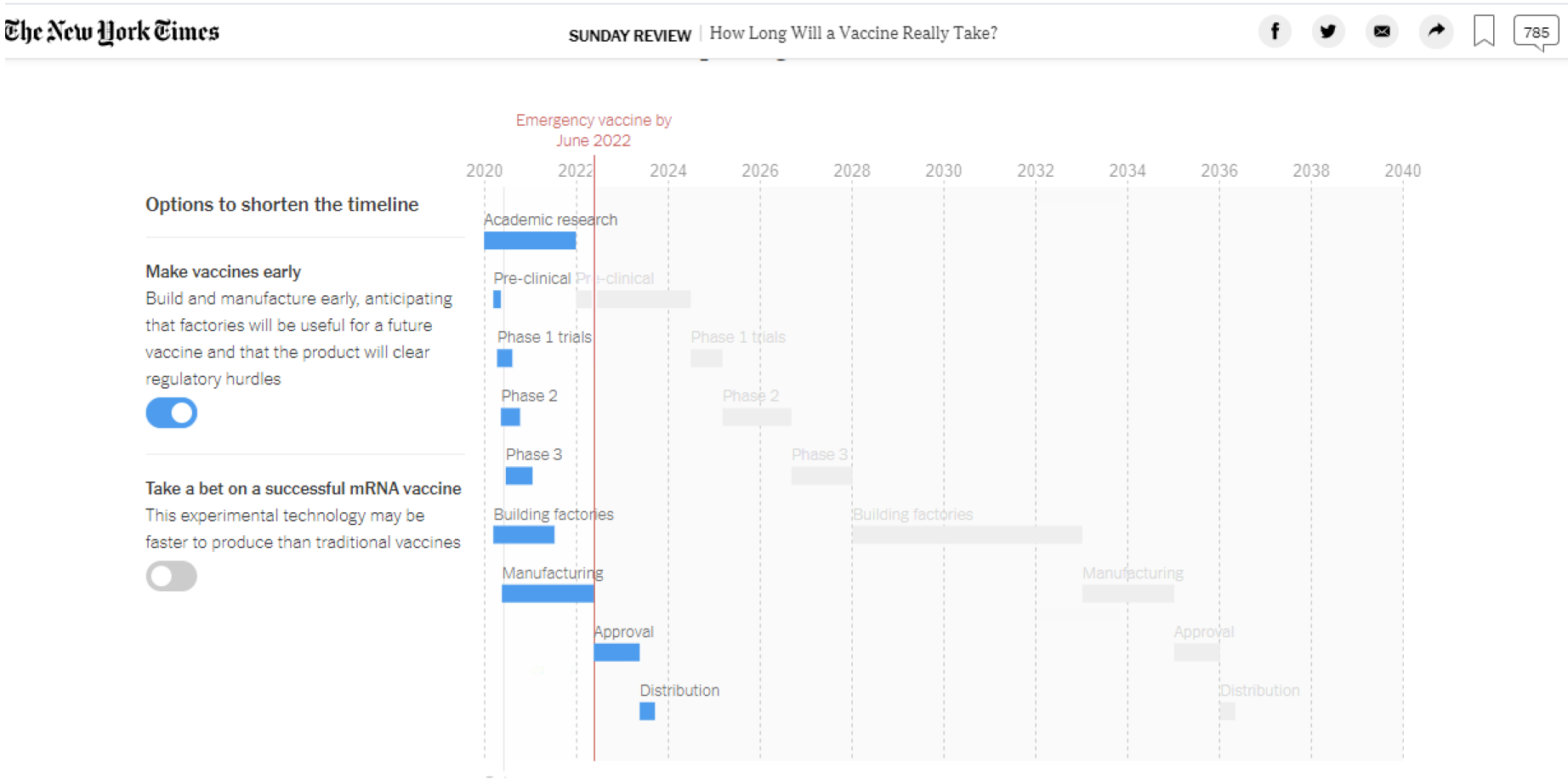
Manufacture Vaccines Early ~ 14 Months

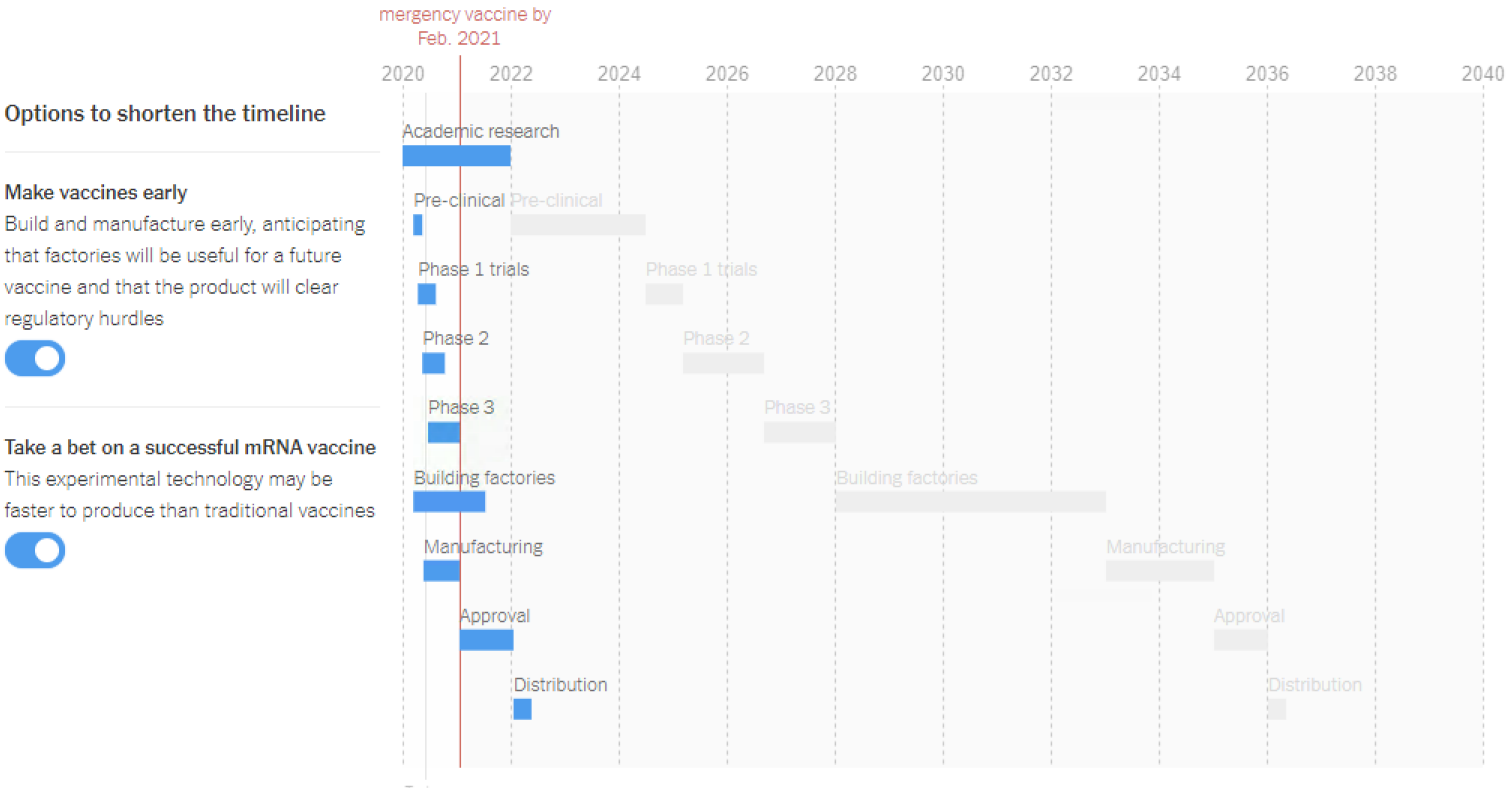


https://www.nytimes.com/interactive/2020/04/30/opinion/coronavirus-covid-vaccine.html?searchResultPosition=2

Early Production of a successful RNA Vaccine ~ 10 Months

The New York Times

SUNDAY REVIEW | How Long Will a Vaccine Really Take?



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