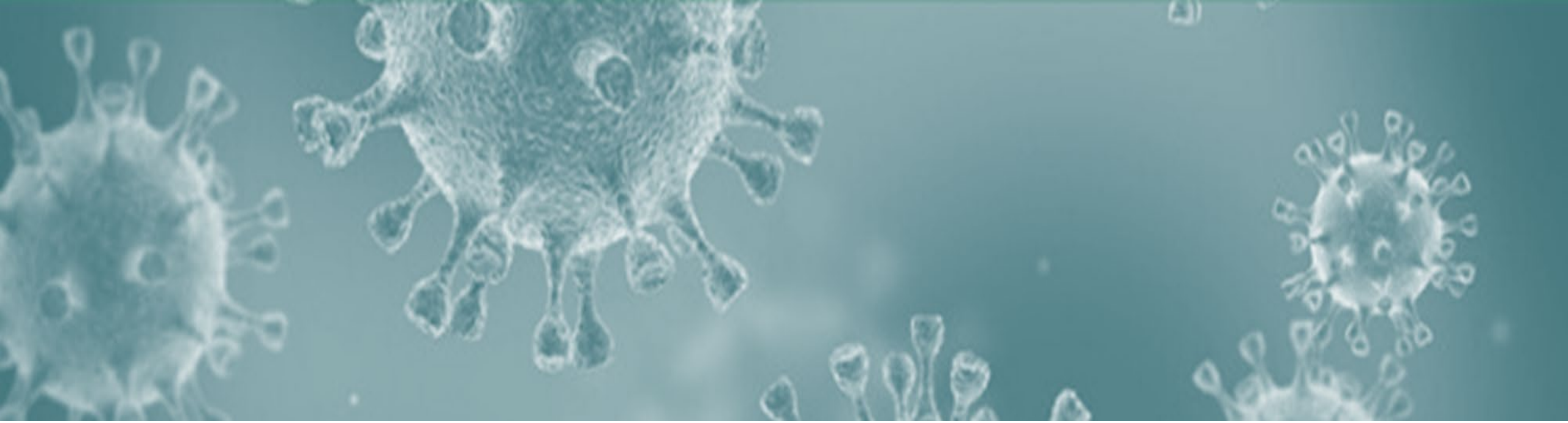

Accelerated Development: How COVID-19 Vaccines are Being Developed Safely in Record Time

Pieter Neels, MD

Independent Regulatory Expert

Ex- CHMP member for Belgium

Ex- Vice-chair VWP (EMA)

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Disclaimer

- Although I have been a member of the CHMP, my presentation might not be the view of the CHMP, the European Medicines Agency (EMA), the Belgian Medicines Commission, neither of the Vaccine Working Party

- My presentation is a personal viewpoint and binds in no way the organizations mentioned before

Declaration of interest

- I have signed consultancy contracts with more than 70 organizations and companies under which
  - WHO
  - B&MGF
  - Universities of Antwerp, Ghent, Leuven, Namur, Brussels, Paris, Lausanne, Köln, …
  - Big pharma
  - Medium pharma
  - Small pharma

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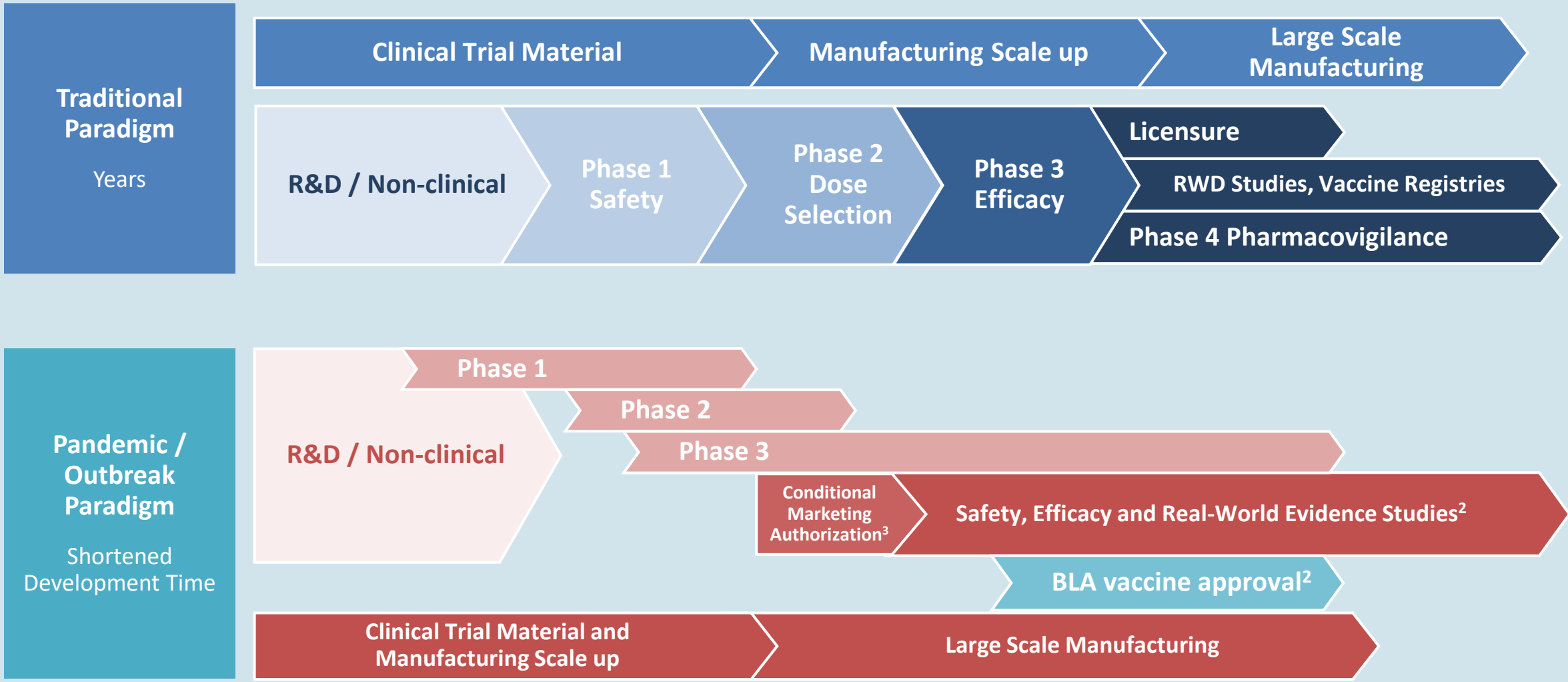
Vaccine Development[1,2]



Vaccine Advice

1. Lurie N, et al. N Engl J Med. 2020;382:1969–73. 2. US Department of Defense. Coronavirus: Operation Warp Speed. https://media.defense.gov/2020/Nov/05/2002529886/-1/-1/1/OPERATION-WARP-SPEED-VACCINE-DELIVERY-MILESTONES.PDF. Accessed November 2020; 3. European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorization. Accessed December 2020.

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Vaccine Development: Benefit/Risk evaluation

Post-Authorization Effectiveness and Safety studies (PAES/PASS)

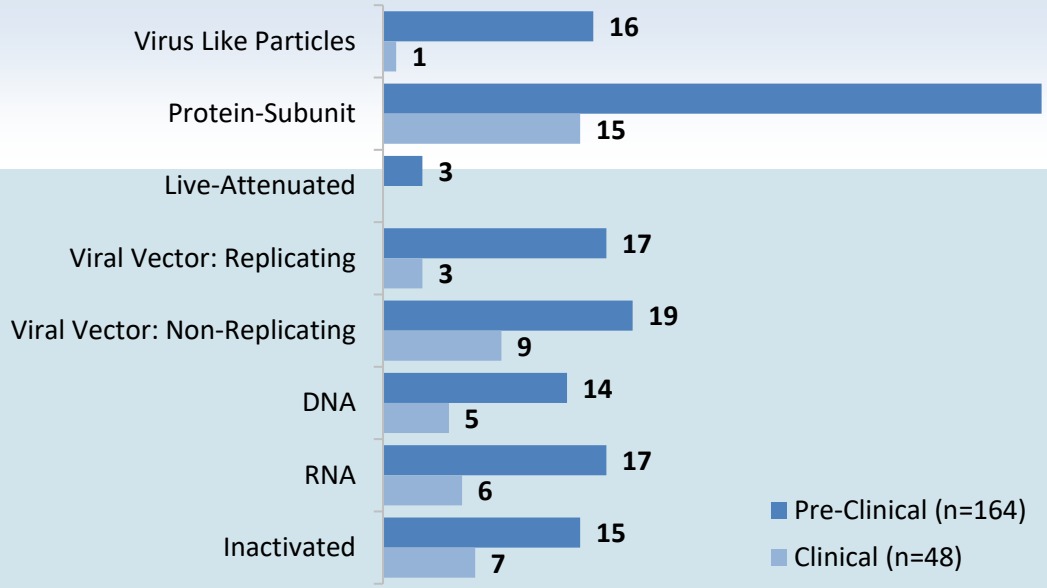
- Are part of the Risk Management Plan and are mandatory in EU[1]
- Need to be reported in PSUR (Periodic Safety Update Report, an obligation for industry to submit every 6 months, containing all known data on safety and efficacy)[1,2]
- Well-known examples:
  - PAES: in the EU effectiveness studies requirement for seasonal influenza vaccines[3]
    - The need to monitor the clinical effectiveness of every year's influenza vaccine: brand specific[3]
  - PASS: after licensing rotavirus vaccines very large safety studies were performed, to identify the real risk of intussusception with these vaccines[4]
    - Regulators wanted reassurance of the positive safety outcome of initial analysis of the submission data (> 70.000) and large safety studies were executed:
      - For Rotarix over 500.000[4]
      - For RotaTeq over 1,2 million[4]
- Real-world evidence to assess safety[5]
- Longer-term follow up for safety from Phase 3 studies[5]

1. European Medicines Agency. Risk Management Plans. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-format-risk-management-plan-european-union-integrated-format-rev-1_en.pdf. Accessed November 2020. 2. European Medicines Agency. Periodic safety update reports (PSURs). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf. Accessed November 2020. 3. European Medicines Agency. Influenza vaccines - non-clinical and clinical module. https://www.ema.europa.eu/en/documents/scientific-guideline/influenza-vaccines-non-clinical-clinical-module_en.pdf. Accessed November 2020. 4. Cohet C, et al. Vaccine. 2017;35:3041-9. 5. U.S. Food & Drug Administration. Real-World Evidence. https://www.fda.gov/media/120060/download. Accessed November 2020.

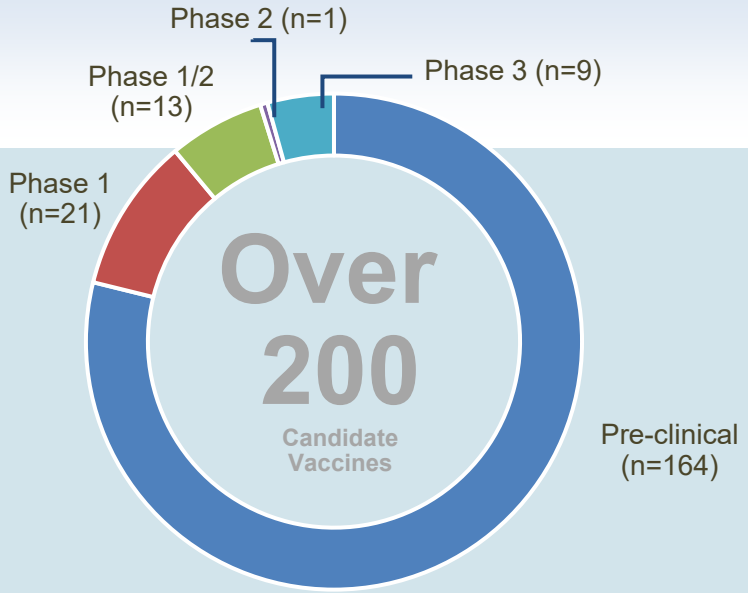
Timelines

- **Dec 31, 2019** — SARS-CoV-2 outbreak first reported in Wuhan[1]
- **Jan 11, 2020** — The genetic sequence of SARS-CoV-2 shared[1]
- **Mar 11, 2020** — WHO declared COVID-19 pandemic[1]
- **Mar 16, 2020** — First COVID-19 vaccine candidate in human testing[2]
- **Late July, 2020** — COVID-19 Phase 3 trials initiated for several candidates[4,5]
- **Oct / Nov 2020** — EMA starts rolling review of several COVID-19 vaccines[6]

Candidate Vaccines in Development[3]



Development Phase[3]



Vaccine Advice

1. World Health Organization. COVID-19 Timeline. Available at: https://www.who.int/news/item/29-06-2020-covidtimeline. Accessed November 2020;
2. Le TT, et al. Nature Reviews Drug Discovery. 2020;19:305-306; 3. World Health Organization. Draft landscape of COVID-19 candidate vaccines. Nov 12, 2020. Available at: https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed November 2020; 4. Pfizer. Pfizer and BioNTech Announce Vaccine Candidate against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against. Accessed November 2020; 5. U.S. National Library of Medicine. Clinical Trial of Efficacy and Safety of Sinovac's Adsorbed COVID-19 (Inactivated) Vaccine in Healthcare Professionals (PROFISCOV). https://clinicaltrials.gov/ct2/show/NCT04456595. Accessed November 2020.
6. European Medicines Agency. Available at: https://www.ema.europa.eu/en/news/ema-starts-first-rolling-review-covid-19-vaccine-eu. Accessed November 2020.

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COVID-19 Vaccination: Authorities and Funding Collaboration

- Department of Health and Human Services (HHS)
- Department of Defense (DOD)
- National Academies of Sciences, Engineering and Medicine
- State and local public health officials
- Industry Partners and Clinical Research Organizations (CROs)
- National Institutes of Health (NIH)
- Biomedical Advanced Research Development Authority (BARDA)
- Operation Warp Speed
- Centers for Disease Prevention and Control (CDC)
- European Centre for Disease Prevention and Control (ECDC)
- Food and Drug Administration (FDA)
- European Medicines Agency (EMA)
- Medicines and Healthcare products Regulatory Agency (MRHA, UK)
- Paul-Ehrlich-Institut (PEI, Germany)
- Federal Agency for Medicines and Health Products (FAMHP, Belgium)
- World Health Organization (WHO)
- Coalition for Epidemic Preparedness Innovations (CEPI)
- Vaccines and Related Biological Products Advisory Committee (VRBPAC)
- …

Vaccine Advice

U.S. Department of Health & Human Services. Fact Sheet: Explaining Operation Warp Speed. https://www.hhs.gov/coronavirus/explaining-operation-warp-speed/index.html. Accessed November 2020.

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Role of National Authorities in Vaccine Approval

Medicine developers who wish to conduct clinical trials in the EU need to submit applications to the **national competent authorities (NCA's)** of the countries where they want to conduct the trials,[1] for example, the **Paul-Ehrlich-Institut (PEI)** for Germany[2], **FAMPH** for Belgium and **MHRA** for UK, …)

These agencies have h

The

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- Au
- Processing
- Pharmacovigilance, resea

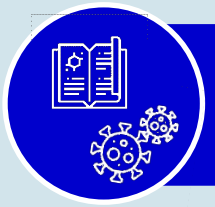
Once the vaccine has been approved: every produced batch (= ± 100.000 samples) needs a control by the authorities![4]
Only one EU authority lab for the EU: OMCL = Official Medicines Control Laboratory. OMCL is a network, that will perform the control, and is led by EDQM: European Directorate on Quality of Medicines[5]

1. European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring. Accessed November 2020 2. Paul-Ehrlich-Institut. Official duties. https://www.pei.de/EN/institute/official-duties/duties-node.html. Accessed November 2020. 3. Paul-Ehrlich-Institut. Advice. https://www.pei.de/EN/regulation/advice/advice-node.html. Accessed November 2020. 4. Professor Neels, personal opinion. 5. European Directorate on Quality of Medicines. Available at: https://www.edqm.eu/en/batch-release-human-biologicals-vaccines-blood-and-plasma-derivatives#Legal%20framework. Accessed December 2020.

Vaccine Advice

COVID-19 Vaccine development

Main factors that led to a shortening of timelines



1 **Knowledge of the virus**

- Work on vaccines against SARS & MERS[1]
- Fast recognition of some scientists SARS-CoV-2 ≠ H1N1 influenza virus[1,2]
- International collaboration: data have been exchanged[2]

Vaccine Advice

1. Lurie N, et al. N Engl J Med. 2020;382:1969–73. 2. Professor Neels, personal opinion.

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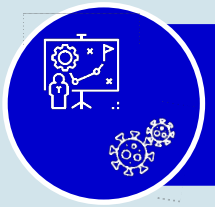
COVID-19 Vaccine development

Main factors that led to a shortening of timelines



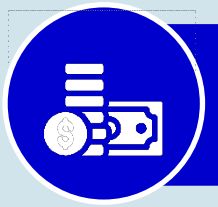
2 **Pandemic preparedness**

- **Joint FDA/EMA (VWP) working group on pandemic preparedness started in 2003[1,2]**
- **For EMA the major strategies:**
  - **Mock-up influenza vaccines = license of a potential pandemic vaccine for which the strain is not recognised as pandemic (e.g. H5N1 – H7N9), showing the company's ability to produce a safe and efficacious pandemic vaccine[3]**
  - **In case of a pandemic: a rolling review procedure to win time for a positive opinion…[4]**
  - **Intensive collaboration with the other leading agencies, WHO, FDA, Health Canada, PMDA (Japan), TGA (Au)…[5]**

1. European Medicines Agency. Vaccines Working Party. https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/vaccines-working-party. Accessed December 2020. 2. U.S. Food & Drug Administration. Partnering with the European Union and Global Regulators on COVID-19. https://www.fda.gov/news-events/fda-voices/partnering-european-union-and-global-regulators-covid-19. 3. European Medicines Agency. Vaccines for pandemic influenza. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/pandemic-influenza/vaccines-pandemic-influenza. 4. European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring. Accessed November 2020. 5. European Medicines Agency. COVID-19: latest updates. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/covid-19-latest-updates. Accessed December 2020.

COVID-19 Vaccine development

Main factors that led to a shortening of timelines



3

Money: many good teams had interesting pandemic vaccines in development, but no budget to start…[1]

- A large number of sponso
  - Operation Warp
  - B&MGF
  - CEPI
  - BARDA (U
  - IMI (EU)
  - Horizon 2020 (
  - Carlos Slim (Mex)
  - Soros (US) and many others
- Millions of €/$ have been made available for many different projects[2]

This in sharp contrast to previous pandemics:

- **H1N1, SARS, MERS,…**

The funding for this pandemic is unprecedented![1,3]

Vaccine Advice

1. Professor Neels, personal opinion; 2. New York Times. Pfizer Gets $1.95 Billion to Produce Coronavirus Vaccine by Year's End. https://www.nytimes.com/2020/07/22/us/politics/pfizer-coronavirus-vaccine.html. Accessed December 2020. 3. International Monetary Fund. An ounce of prevention. https://www.imf.org/external/pubs/ft/fandd/2020/09/vaccine-finance-epidemics-and-prevention-bloom.htm. Accessed December 2020.

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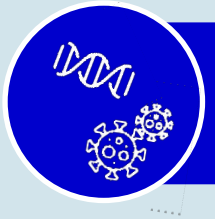
COVID-19 Vaccine development

Main factors that led to a shortening of timelines



4 **Acceptance of "Platform technology"**

- **IABS & CEPI promote Platform Master File (PfMF)[1]:**
  - **Description of a Technique based on development of a vaccine[2]**
- **European Commission has accepted PfMF for veterinarian vaccines[3]:**
  - **Page 89. Annex II - CVMP scientific recommendations (europa.eu)**

3. Vaccine platform technology[3]

3.1 Principles

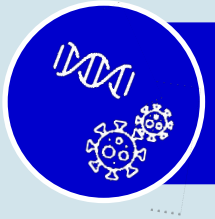
Vaccine platform technology is a collection of technologies that have in common the use of a 'backbone' carrier or vector that is modified with a different antigen ……. protein-based platforms (virus-like particles), DNA vaccine platforms, mRNA-based platforms, replicons (self-replicating RNA) and viral and bacterial vector vaccines. Applications for marketing authorisations of immunological veterinary medicinal products manufactured based on vaccine platform technologies are considered to be eligible for reduced data requirements. A full dossier is required for the first product from a manufacturer based on a particular platform technology for a particular target species. At the time of submission of the first (full) dossier based on the platform technology, the applicant may submit in parallel a 'Platform Technology Master File' comprising all data relative to the platform ……

The nature of the data to be included in the Platform Technology Master File will depend on the type of platform. Once a Platform Technology Master File is certified, the certificate may be used to fulfil the relevant data requirements in subsequent applications for marketing authorisations based on the same platform and intended for the same target species.

1. Professor Neels, personal opinion. 2. Johns Hopkins University. Vaccine Platforms: State of the Field and Looming Challenges. https://www.centerforhealthsecurity.org/our-work/publications/vaccine-platforms-state-of-the-field-and-looming-challenges. Accessed December 2020. 3. European Medicines Agency. Implementation of the new Veterinary Medicines Regulation. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/advice-implementing-measures-under-article-1462-regulation-eu-2019/6-veterinary-medicinal-products-scientific-recommendation-revision-annex-ii-regulation-eu-2019/6-veterinary-medicinal-products_en.pdf. Accessed December 2020.

COVID-19 Vaccine development

Main factors that led to a shortening of timelines



4 Acceptance of “Platform technology”

- ***Vaccine platform technology is a collection of technologies that have in common the use of a ‘backbone’ carrier or vector that is modified with a different antigen or set of antigens for each vaccine derived from the platform. This includes, but may not be limited to, protein-based platforms (virus-like particles), DNA vaccine platforms, mRNA-based platforms, replicons (self-replicating RNA) and viral and bacterial vector vaccines[1].***
  - **Moderna: mRNA (data on cancer immunotherapy)[2,3]**
  - **BioNTech: mRNA (data on cancer immunotherapy)[2,4]**
  - **JNJ: AD26 vector technology: (Ebola vaccines)[2,5]**
  - **AstraZeneca: ChAdOx1 vector: (cancer immunotherapy)[2,6]**
  - **Curevac: mRNA (data on cancer immunotherapy)[2,7]**
  - **…**
- **Most packages contained safety & Proof of Concept data from Phase 1 & 2 studies in humans from other antigens[7]**

1. European Medicines Agency. Implementation of the new Veterinary Medicines Regulation. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/advice-implementing-measures-under-article-1462-regulation-eu-2019/6-veterinary-medicinal-products-scientific-recommendation-revision-annex-ii-regulation-eu-2019/6-veterinary-medicinal-products_en.pdf. Accessed December 2020. 2. Lurie N, et al. N Engl J Med. 2020;382:1969–73. 3. Moderna. Moderna’s pipeline. https://www.modernatx.com/pipeline. Accessed December 2020. 4. BioNTech. Pipeline. https://biontech.de/science/pipeline. Accessed December 2020. 5. Johnson & Johnson. The 5 Stages of COVID-19 Vaccine Development: What You Need to Know About How a Clinical Trial Works. https://www.jnj.com/innovation/the-5-stages-of-covid-19-vaccine-development-what-you-need-to-know-about-how-a-clinical-trial-works. Accessed November 2020; 6. Cappuccini F, et al. Cancer Immunol Immunother. 2016; 65:701–713; 7. CureVac. Pipeline. https://www.curevac.com/en/pipeline/. Accessed December 2020. 8. Johns Hopkins University. Vaccine Platforms: State of the Field and Looming Challenges. https://www.centerforhealthsecurity.org/our-work/publications/vaccine-platforms-state-of-the-field-and-looming-challenges. Accessed December 2020.

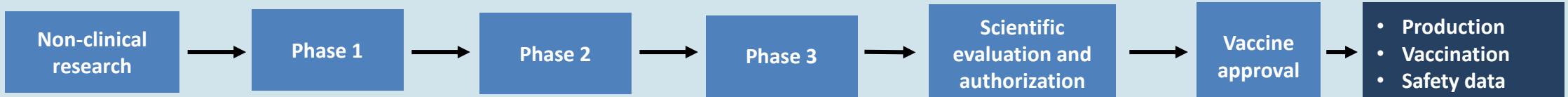
COVID-19 Vaccine development

Main factors that led to a shortening of timelines

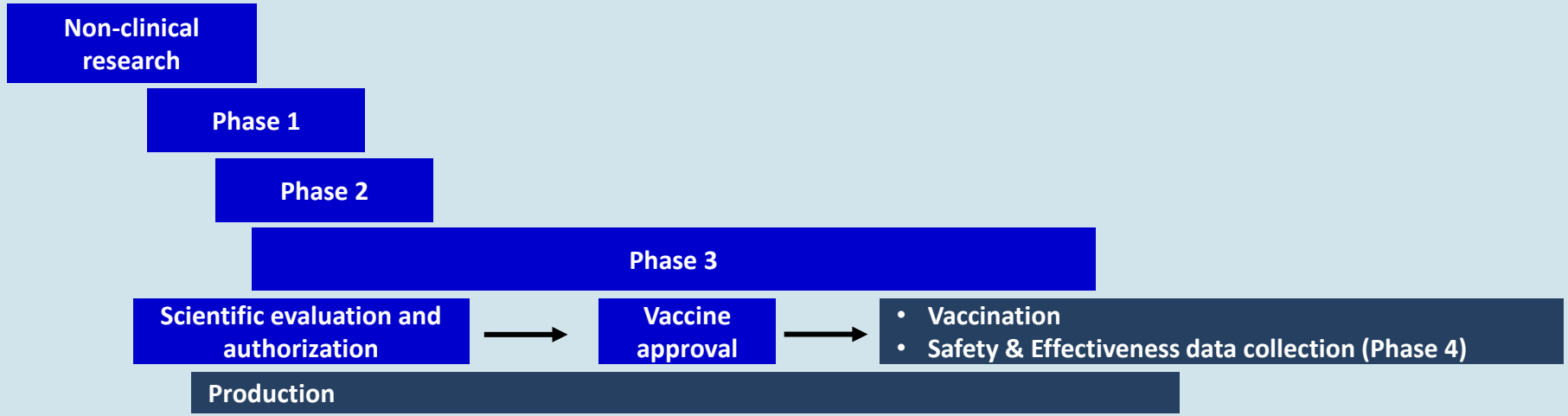
4

Acceptance of "Platform technology"
This is unprecedented:

Standard Vaccine



COVID-19 Vaccine



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European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring. Accessed November 2020.

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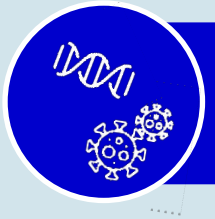
COVID-19 Vaccine development

Main factors that led to a shortening of timelines



4

Acceptance of "Platform technology" This is unprecedented:

- EU NCA's are responsible for the Clinical Trials (CT)[1]
  - This means good evaluation of all parts of the development[1]
  - Phase 3 trials will be huge: all safety requirements are important
  - Safety rules:
    - Installing a DSMB (Data and Safety Monitoring Board): evaluation of adverse events[2]
    - Setting up "stopping rules" for CT's[3]

⇒ No compromise on the "normal" way of working on safety evaluation[1]

- Both JnJ and AZ paused phase 3 study due to one serious adverse event[4,5]

Vaccine Advice

1. European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring. Accessed November 2020. 2. European Medicines Agency. Data Monitoring Committees issues. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-monitoring-committees_en.pdf. Accessed December 2020. 3. European Medicines Agency. Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf. Accessed December 2020. 4. Johnson & Johnson. Johnson & Johnson Prepares to Resume Phase 3 ENSEMBLE Trial of its Janssen COVID-19 Vaccine Candidate in the U.S. https://www.jnj.com/our-company/johnson-johnson-prepares-to-resume-phase-3-ensemble-trial-of-its-janssen-covid-19-vaccine-candidate-in-the-us. Accessed November 2020. 5. AstraZeneca. FDA authorises restart of the COVID-19 AZD1222 vaccine US Phase III trial. https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/fda-authorises-restart-of-the-covid-19-azd1222-vaccine-us-phase-iii-trial.html. Accessed November 2020.

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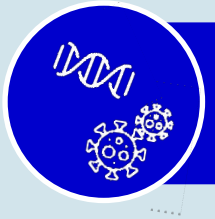
COVID-19 Vaccine development[1]

Main factors that led to a shortening of timelines



4

Acceptance of "Platform technology"
This is unprecedented:

- **Platform technology based has been accepted by FDA & EMA and several national EU authorities like PEI, MHRA, FAMPH, …!**
  (CTA approval is a national responsibility!)
  - **Tox studies could be performed in parallel with FIH studies, based on data from other files**
  - **Phase 2 & 3 studies were started very early after evaluation of the Phase 1 data**
- **A lot of time has been saved by the vaccine developers due to the acceptance of the "Platform Technology"**

Vaccine Advice

1. Professor Neels, personal opinion.

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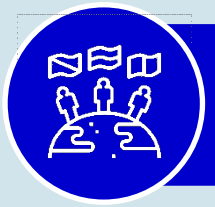
COVID-19 Vaccine development

Main factors that led to a shortening of timelines



5

Role of National Authorities in Vaccine Approval

In the EU, national competent authorities are responsible for the approval of the clinical trial applications[1]

- **They showed great flexibility:**
  - **Reduction of evaluation times (e.g. FAMHP 14 → 4 days for FIH CTA)[2]**
  - **Priority for SA for COVID-19, meetings could be organised in half of the normal time[2]**
  - **Good collaboration for SA in the SN/SA joint project for national advice[2]**
  - **Phase 2 & 3 studies were started very early after evaluation of the Phase 1 data[3]**
- **Many questions could be discussed[4]:**
  - **CMC / tox / clinical**
  - **Shortening of timelines: platform technology**

Vaccine Advice

1. European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring. Accessed November 2020. 2. Federal Agency for Medicine and Health Products. Biological Medicinal Products. https://www.famhp.be/sites/default/files/content/guidance_on_the_management_of_clinical_trials_during_the_covid-19_coronavirus_pandemic.pdf. Accessed December 2020. 3. Professor Neels, personal opinion. 4. Paul-Ehrlich-Institut. Advice. https://www.pei.de/EN/regulation/advice/advice-node.html. Accessed November 2020.

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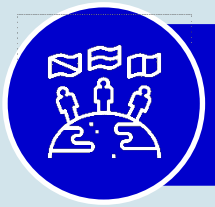
COVID-19 Vaccine development

Main factors that led to a shortening of timelines



5

Role of National Authorities in Vaccine Approval (continued)

- On initiative of the EC: national suspension of GMO legislation
  - GMO legislation is an agricultural legislation (corn, potatoes, tomatoes,…) applied on vaccines!
  - For most GMO's, need for a "deliberate release" procedure, addition of 3 to 7 months before approval is possible
  - Phase 1 data

Vaccine Advice

Regulatory Affairs Professional Society. European Commission proposes relaxing GMO regs for COVID-19 vaccines. https://www.raps.org/news-and-articles/news-articles/2020/6/european-commission-proposes-relaxing-gmo-regs-for. Accessed December 2020.

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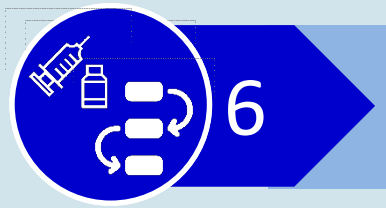
COVID-19 Vaccine development

Main factors that led to a shortening of timelines



EMA's rolling review

- "Normal" review takes 210 days, prolonged with 90 to 180 days to respond to questions, and can only take place when the full file has been submitted[1]
- EMA's "fast track" initiatives:
  - Constant communication[2]
  - Submission of relevant parts of the dossier[2]
  - Continuous evaluation of incoming data until all data are submitted and evaluated to come to a Benefit / Risk balance + or -[1]

Vaccine Advice

1. European Medicines Agency. Treatments and vaccines for COVID-19. https://www.ema.europa.eu/en/documents/leaflet/infographic-fast-track-procedures-treatments-vaccines-covid-19_en.pdf. Accessed November 2020. 2. European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring. Accessed November 2020.

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COVID-19 Vaccine development

Main factors that led to a shortening of timelines

6

EMA's rolling review (continued)

- **"All administrative rules can be fulfilled"[1]:**
  - **Submission and evaluation of Risk Management Plan inclusive:**
  - **Post-authorization safety studies**
  - **Post-authorization effectiveness studies**
- **Extremely important is the discussion on how both safety and effectiveness will be measured post authorization via Phase 4 studies; due to the rolling review these discussion have started, and risk management plans were submitted as part of the submission process[2]**

Vaccine Advice

1. European Medicines Agency. Pharmacovigilance: Overview. https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf. Accessed December 2020. 2. Professor Neels, personal opinion.

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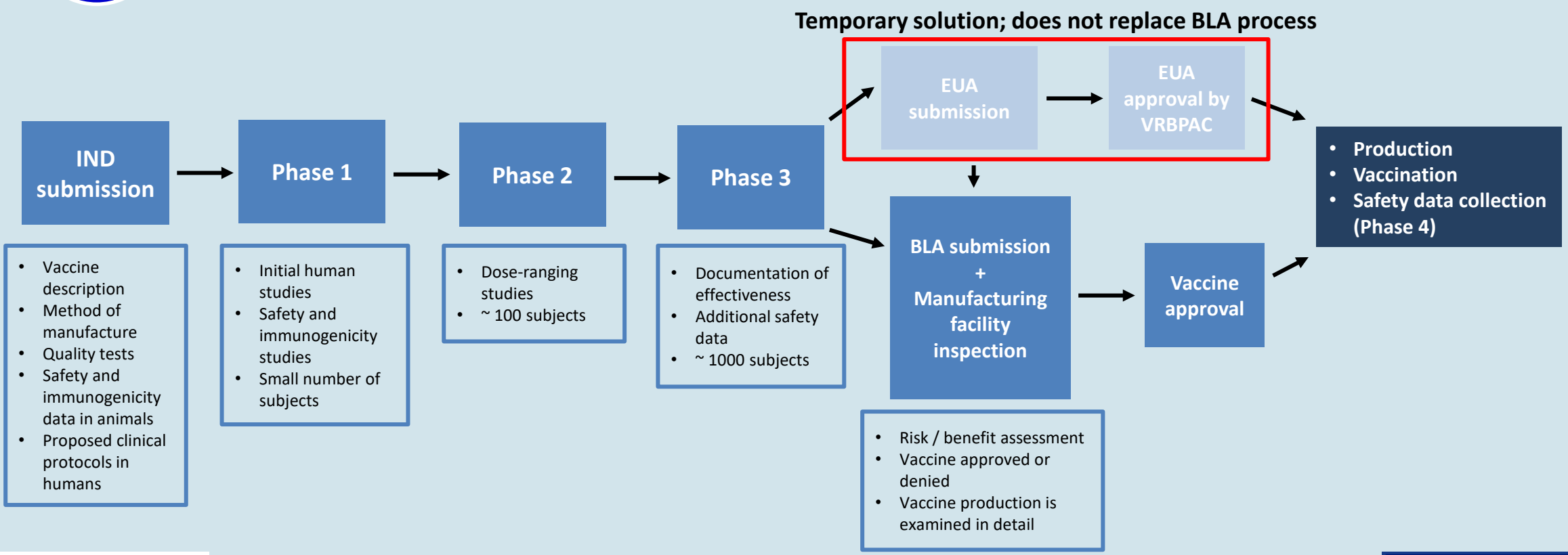
COVID-19 Vaccine development

Main factors that led to a shortening of timelines

7 FDA's Emergency Use evaluation[1,2]



1. U.S. Food & Drug Administration. Emergency Use Authorization for Vaccines to Prevent COVID-19. https://www.fda.gov/media/142749/download. Accessed November 2020. 2. U.S. Food & Drug Administration. Vaccine Development – 101. https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/vaccine-product-approval-process. Accessed November 2020.

COVID-19 Vaccine development

Benefit Risk Evaluation elements

- **EMA's rolling review will not be executed on a lower level: the normal evaluation standards will be used for CMC/Tox/Phase 1, 2, 3, but many things will be done in parallel[1,2]**
- **Quality of clinical trials will be high[2]:**
- **E.g., numbers of healthy volunteers:**
  - **Normal new vaccines 3.000 to 10.000, sometimes more[1]**
  - **Now the Phase 3 trials are all large e.g.:**
    - **Pfizer / BioNTech: Over 43.000[3]**
    - **Moderna: Over 30.000[4]**
    - **AstraZeneca: Over 40.000[5]**
- **Very important to show efficacy and safety[1]**
- **Age groups are well represented[3,4,5,6]**
- **Possibility to define correlation of protection if all companies work together[2]**

1. European Medicines Agency. COVID-19 vaccines: development, evaluation, approval and monitoring. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines-development-evaluation-approval-monitoring. Accessed November 2020. 2. Professor Neels, personal opinion. 3. Pfizer. Pfizer and BioNTech Announce Vaccine Candidate against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against. Accessed November 2020. 4. U.S. National Library of Medicine. A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19 https://clinicaltrials.gov/ct2/show/NCT04470427?term=NCT04470427. Accessed November 2020. 5. U.S. National Library of Medicine. Phase III Double-blind, Placebo-controlled Study of AZD1222 for the Prevention of COVID-19 in Adults. https://clinicaltrials.gov/ct2/show/NCT04516746?term=azd1222&draw=2&rank=1. Accessed November 2020; 6. Professor Neels, personal opinion.

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COVID-19 Vaccine development

Benefit Risk Evaluation elements

- How to avoid the safety issues from the past:
  - E.g., 1976 Swine flu US[1]; narcolepsy 2009[2]
- Prelicensure: magnitude of the Phase 3 trials[3]: √
- Post licensure[3]:
  - Good collaboration worldwide: FDA/WHO/EMA/NRA's, etc:√
  - Large post-authorization safety programs √
  - Large post-authorization effectiveness studies√
- A lot of work to be done: social media[3]
  - Social media are mostly not scientific
  - Are used to share misconceptions / false information
  - Are very powerful tools in the hands of the anti-vaxxers

Vaccine Advice

1. Sencer DJ, et al. Emerg Infect Dis. 2006;12:29-33. 2. Centers for Disease Control and Prevention. Narcolepsy Following 2009 Pandemrix Influenza Vaccination in Europe. https://www.cdc.gov/vaccinesafety/concerns/history/narcolepsy-flu.html. Accessed December 2020. 3. Professor Neels, personal opinion.

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Conclusions for a controlled human infection model (CHIM) for COVID-19[1]

- **Given:**
  - **The worldwide very high CFR in the elderly population[2]**
  - **The social and economic burden of lockdowns[2]**
  - **The extreme overloading of the healthcare system[2]**
    - **The system does not have enough capacity**
    - **Workload turning into burn-out**
    - **Non-urgent medical acts are postponed, resulting in more severity and disease complications, leading to more deaths**
  - **The willingness of people (18–30) to be part of CHIM[1]**
  - **The extreme low risk for this group to attend such CHIM[1]**
  - **The actual knowledge of the disease and the standard of treatment[1]**
- **I conclude that a CHIM trial should be performed to add more knowledge for the disease and vaccine pipeline[1,3,4]**

Vaccine Advice

1.Seán O'Neill McPartlin, Covid-19 vaccines: Should we allow human challenge studies to infect healthy volunteers with SARS-CoV-2? BMJ. 2020;371:m4258. DOI: http://dx.doi.org/10.1136/bmj.m4258; 2. Kirby T. Lancet Respir Med. 2020. DOI: https://doi.org/10.1016/S2213-2600(20)30518-X; 3. Baay M, Neels P. Biologicals. 2020;67:69–74; 4. Professor Neels, personal opinion.

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Thank you for your attention