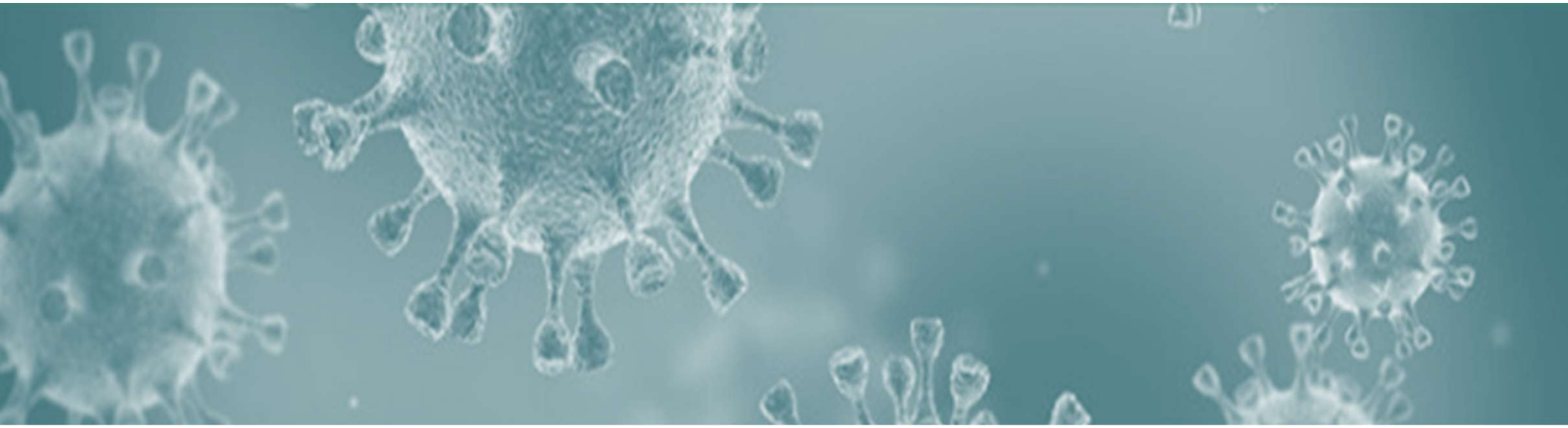

Accelerated Development: How COVID-19 Vaccines are Being Developed Safely in Record Time

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Disclaimer

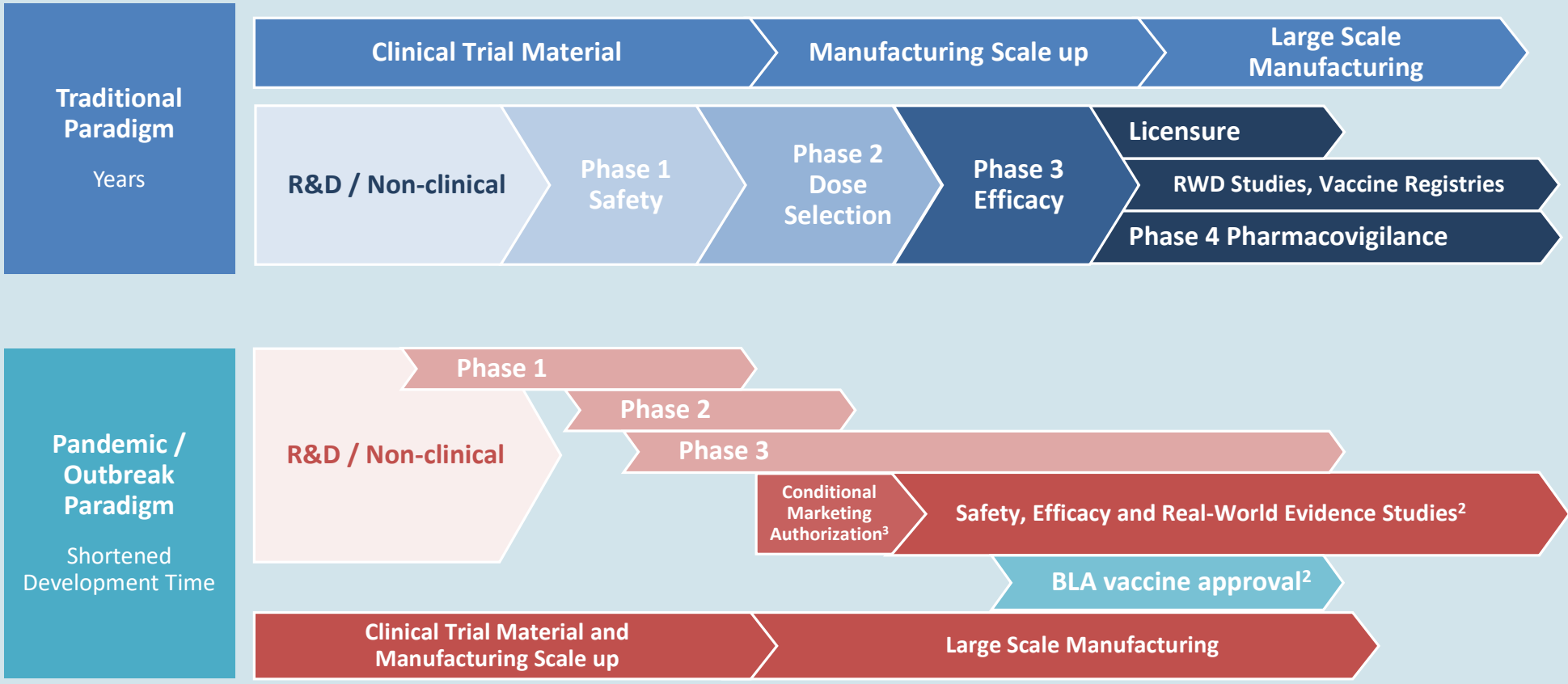
- Although I have been a member of the CHMP, my presentation might not be the view of the CHMP, the European Medicines Agency (EMA), the Belgian Medicines Commission, neither of the Vaccine Working Party

- 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

Vaccine Development[1,2]



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Vaccine Development: Benefit/Risk evaluation

Today's regulatory science in the decision process of granting a marketing authorisation, decisions are based on Benefit – Risk evaluation

- **The Benefit defined as prevention or treatment of disease**
- **The Risk, defined as possible causal related Serious Adverse Events (SAE)**
  - **Serious is Death, hospitalisation, disabling**

- **In a pandemic with a Case Fatality Rate (CFR) of 1% (probably much higher in a vulnerable population)**
  - ❑ **Assuming that in a unvaccinated population of 1million people, 50% get the disease, 5000 people will die.**
  - ❑ **The current vaccines prevent almost 100% against mortality and ICU admission**

⇒ **How much SAE causally related, can we have before the B/R equation becomes negative?**

Vaccine Development: Benefit/Risk evaluation

Pharmacovigilance is difficult

- Pharmacovigilance (PV or PhV), also known as drug safety, is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products.[1]
- Is based on spontaneous reporting or active research via studies
  - Spontaneous reporting, not easy, cultural driven (e.g. homo sapiens belgisciensis ≠ a registration type)
  - Active research = Post-authorization studies

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

- Are part of the Risk Management Plan and are mandatory in EU[2]
- 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)[,2,3]

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1. Wikipedia 2. 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. 3. 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.

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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.

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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.

Vaccine Advice

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.

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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

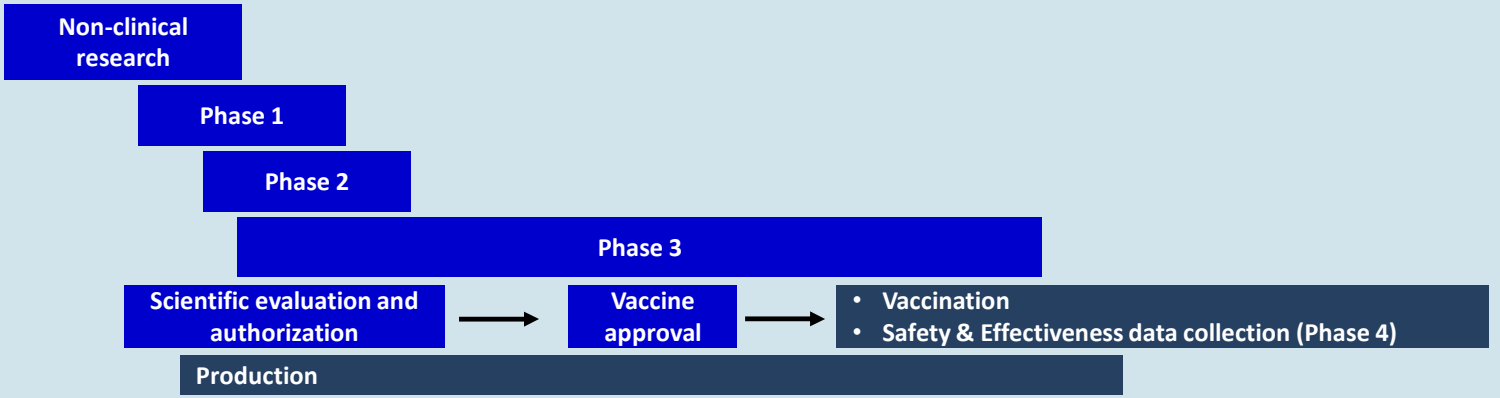
Main factors that led to a shortening of timelines

4 Acceptance of "Platform technology" This is unprecedented:

Standard Vaccine

Non-clinical research → Phase 1 → Phase 2 → Phase 3 → Scientific evaluation and authorization → Vaccine approval → • Production • Vaccination • Safety & effectiveness data collection (Phase 4)

COVID-19 Vaccine



Vaccine Advice

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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Thank you for your attention