Development of mRNA-based medicines

Afrigen Colloquium

November 27, 2023
Cape Town, South Africa

BIONTECH

Disclosure and disclaimer

- I am an employee of BioNTech and I own shares of the company
- I was a previous employee of GSK and I own shares of the company
- I have no other disclosures

Safety information

COMIRNATY® ▼(the Pfizer-BioNTech COVID-19 vaccine) has been granted conditional marketing authorization (CMA) by the European Commission to prevent coronavirus disease 2019 (COVID-19) in people from 5 years of age. The vaccine is administered as a 2-dose series, 3 weeks apart. In addition, the CMA has been expanded to include a booster dose (third dose) at least 6 months after the second dose in individuals 18 years of age and older. For immunocompromised individuals, the third dose may be given at least 28 days after the second dose. The European Medicines Agency's (EMA's) human medicines committee (CHMP) has completed its rigorous evaluation of COMIRNATY®, concluding by consensus that sufficiently robust data on the quality, safety and efficacy of the vaccine are now available.

IMPORTANT SAFETY INFORMATION:

- Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine.
- Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.
- Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, tingling sensations and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.
- The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY® may be lower in immunosuppressed individuals.
- As with any vaccine, vaccination with COMIRNATY® may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.
- In clinical studies, adverse reactions in participants 16 years of age and older were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia and chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.
- The overall safety profile of COMIRNATY® in participants 5 to 15 years of age was similar to that seen in participants 16 years of age and older.
- The most frequent adverse reactions in children 5 to 11 years of age were injection site pain (>80%), fatigue (>50%), headache (>30%), injection site redness and swelling (>20%), myalgia and chills (>10%).
- The most frequent adverse reactions in clinical trial participants 12 to 15 years of age were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).
- There is limited experience with use of COMIRNATY® in pregnant women. Administration of COMIRNATY® in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and fetus.
- It is unknown whether COMIRNATY® is excreted in human milk.
- Interactions with other medicinal products or concomitant administration of COMIRNATY® with other vaccines has not been studied.
- For complete information on the safety of COMIRNATY® always make reference to the approved Summary of Product Characteristics and Package Leaflet available in all the languages of the European Union on the EMA website.

The black equilateral triangle ▼ denotes that additional monitoring is required to capture any adverse reactions. This will allow quick identification of new safety information. Individuals can help by reporting any side effects they may get. Side effects can be reported to EudraVigilance or directly to BioNTech using email medinfo@biontech.de, telephone +49 6131 9084 0, or via the website www.biontech.de

Safety information

AUTHORIZED USE IN THE U.S.

- COMIRNATY® (COVID-19 Vaccine, mRNA) is an FDA-approved COVID-19 vaccine for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older. It is also authorized under EUA to provide a 3-dose primary series to individuals 6 months through 4 years of age, 2-dose primary series to individuals 5 years of age and older, a third primary series dose to individuals 5 years of age and older who have been determined to have certain kinds of immunocompromise, a single booster dose to individuals 12 years of age and older who have completed a primary series with Pfizer-BioNTech COVID-19 Vaccine or COMIRNATY®, a single booster dose to individuals 18 years of age and older who have completed primary vaccination with a different authorized COVID-19 vaccine, a second booster dose to individuals 50 years of age and older who have received a first booster dose of any authorized COVID-19 vaccine; and a second booster dose to individuals 12 years of age and older who have been determined to have certain kinds of immunocompromise and who have received a first booster dose of any authorized COVID-19 vaccine.

The booster schedule is based on the labeling information of the vaccine used for the primary series.

IMPORTANT SAFETY INFORMATION

Individuals should not get the vaccine if they:

- had a severe allergic reaction after a previous dose of this vaccine
- had a severe allergic reaction to any ingredient of this vaccine

Individuals should tell the vaccination provider about all of their medical conditions, including if they:

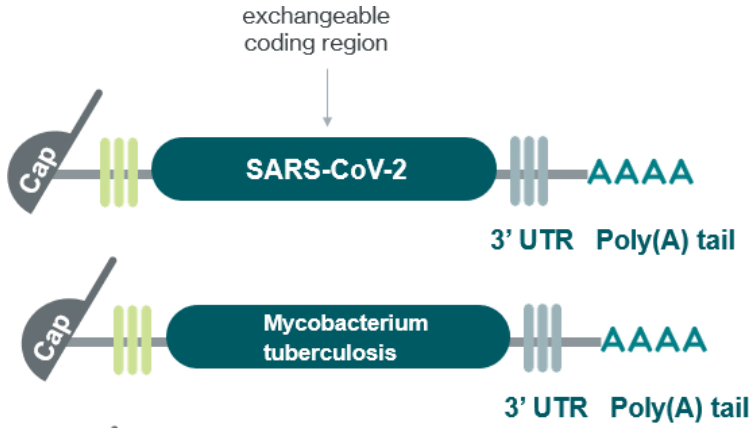
- have any allergies
- have had myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the lining outside the heart)
- have a fever
- have a bleeding disorder or are on a blood thinner
- are immunocompromised or are on a medicine that affects the immune system
- are pregnant, plan to become pregnant, or are breastfeeding
- have received another COVID-19 vaccine
- have ever fainted in association with an injection

The vaccine may not protect everyone. Side effects reported with the vaccine include:

- There is a remote chance that the vaccine could cause a severe allergic reaction
  - A severe allergic reaction would usually occur within a few minutes to 1 hour after getting a dose of the vaccine. For this reason, vaccination providers may ask individuals to stay at the place where they received the vaccine for monitoring after vaccination
  - Signs of a severe allergic reaction can include difficulty breathing, swelling of the face and throat, a fast heartbeat, a bad rash all over the body, dizziness, and weakness
  - If an individual experiences a severe allergic reaction, they should call 9-1-1 or go to the nearest hospital
- Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received the vaccine, more commonly in males under 40 years of age than among females and older males. In most of these people, symptoms began within a few days following receipt of the second dose of the vaccine. The chance of having this occur is very low. Individuals should seek medical attention right away if they have any of the following symptoms after receiving the vaccine:
  - chest pain
  - shortness of breath
  - feelings of having a fast-beating, fluttering, or pounding heart
- Additional side effects that have been reported with the vaccine include:
  - severe allergic reactions; non-severe allergic reactions such as injection site pain; tiredness; headache; muscle pain; chills; joint pain; fever; injection site swelling; injection site redness; nausea; feeling unwell; swollen lymph nodes (lymphadenopathy); decreased appetite; diarrhea; vomiting; arm pain; and fainting in association with injection of the vaccine
- These may not be all the possible side effects of the vaccine. Serious and unexpected side effects may occur. The possible side effects of the vaccine are still being studied in clinical trials. Call the vaccination provider or healthcare provider about bothersome side effects or side effects that do not go away

Data on administration of this vaccine at the same time as other vaccines have not yet been submitted to FDA. Individuals considering receiving this vaccine with other vaccines should discuss their options with their healthcare provider. Patients should always ask their healthcare providers for medical advice about adverse events. Individuals are encouraged to report negative side effects of vaccines to the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). Visit https://www.vaers.hhs.gov or call 1-800- 822-7967. In addition, side effects can be reported to Pfizer Inc. at www.pfizersafetyreporting.com or by calling 1-800-438-1985.

Building on the Pfizer-BioNTech COVID-19 vaccine as a platform for future mRNA vaccines



- Flexibility of mRNA means it can be directed to a different pathogen by exchanging only the part of mRNA coding for the protein
- Extensive clinical and real-world safety data from the Pfizer-BioNTech COVID-19 vaccine can support development of other vaccines using the same platform

3.4 billion

doses administered
as of April 2022

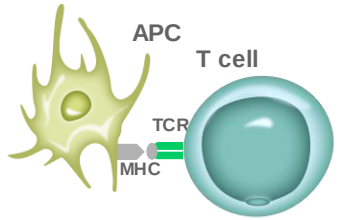
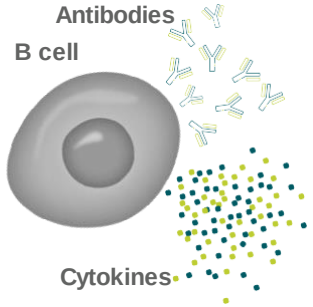
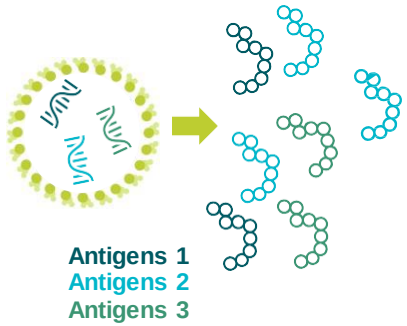
SAFETY

1+ billion

vaccinated persons
safety database

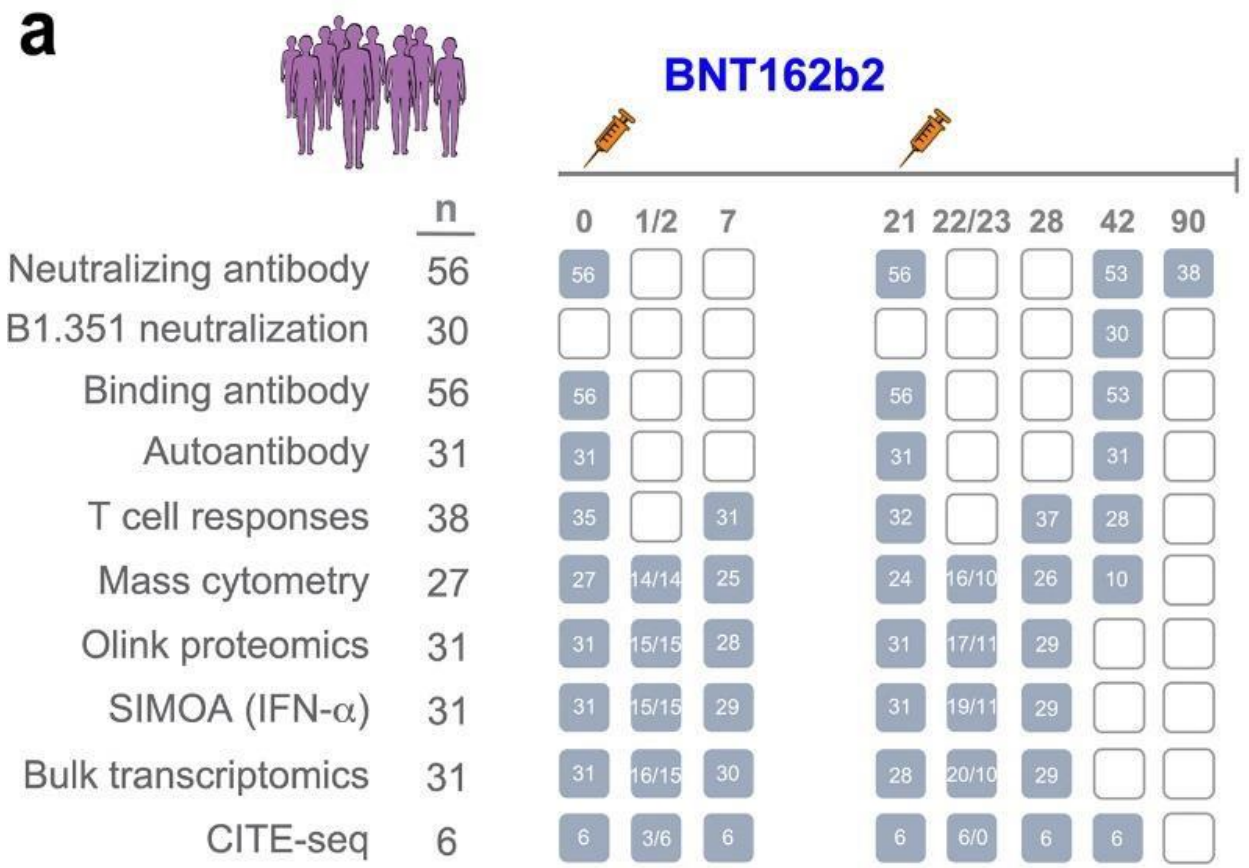
https://investors.biontech.de/static-files/edee73bd-1620-4f51-a419-7ce7782ffa0f

mRNA-based vaccines for infectious diseases: each mRNA format is optimized for specific application

Multiple mRNA formats	Targeted application	Platforms
Backbone-optimized uridine mRNA (uRNA) 	Potent T cell response Repeat administration 	Shared antigen mRNA vaccines Individualized neoantigen mRNA vaccines
Backbone-optimized nucleoside-modified mRNA (modRNA) 	Potent B cell response Non-immunogenic vector 	Infectious disease vaccines mRNA-encoded antibodies mRNA-encoded cytokines
Self-amplifying mRNA (saRNA) 	Sustained expression High potency at low dose 	Potentially used in infectious disease vaccines
Ongoing improvements on mRNA platform		

Understanding the underlying molecular mechanisms

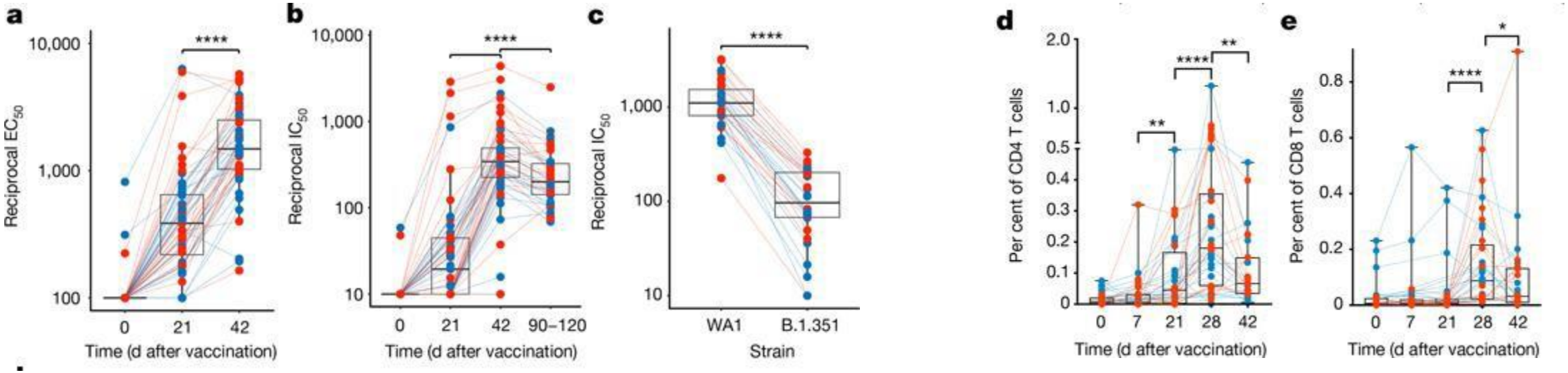
- Clinical research study to study the immune responses induced by Pfizer-BioNTech COVID-19 Vaccine (n = 56)
- Focus on early (innate) responses, as well as antibodies and T cells
- “Systems Vaccinology” study with high-dimensional immunology readouts



Arunachalamet al, Nature 596: 410, 2021 doi 10.1038/s41586-021-03791-x

Antibody and T cell responses in the study

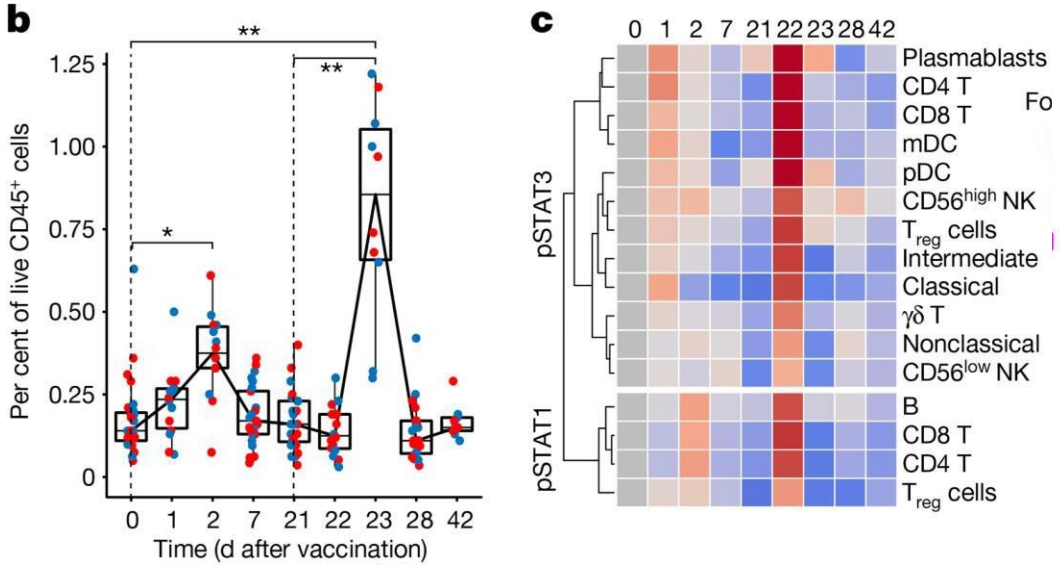
- Binding (a) and neutralizing antibody (b) titers and impact of VoC on neutralizing titers (c)
- CD4 (d) and CD8 (e) T cell kinetics by ICS

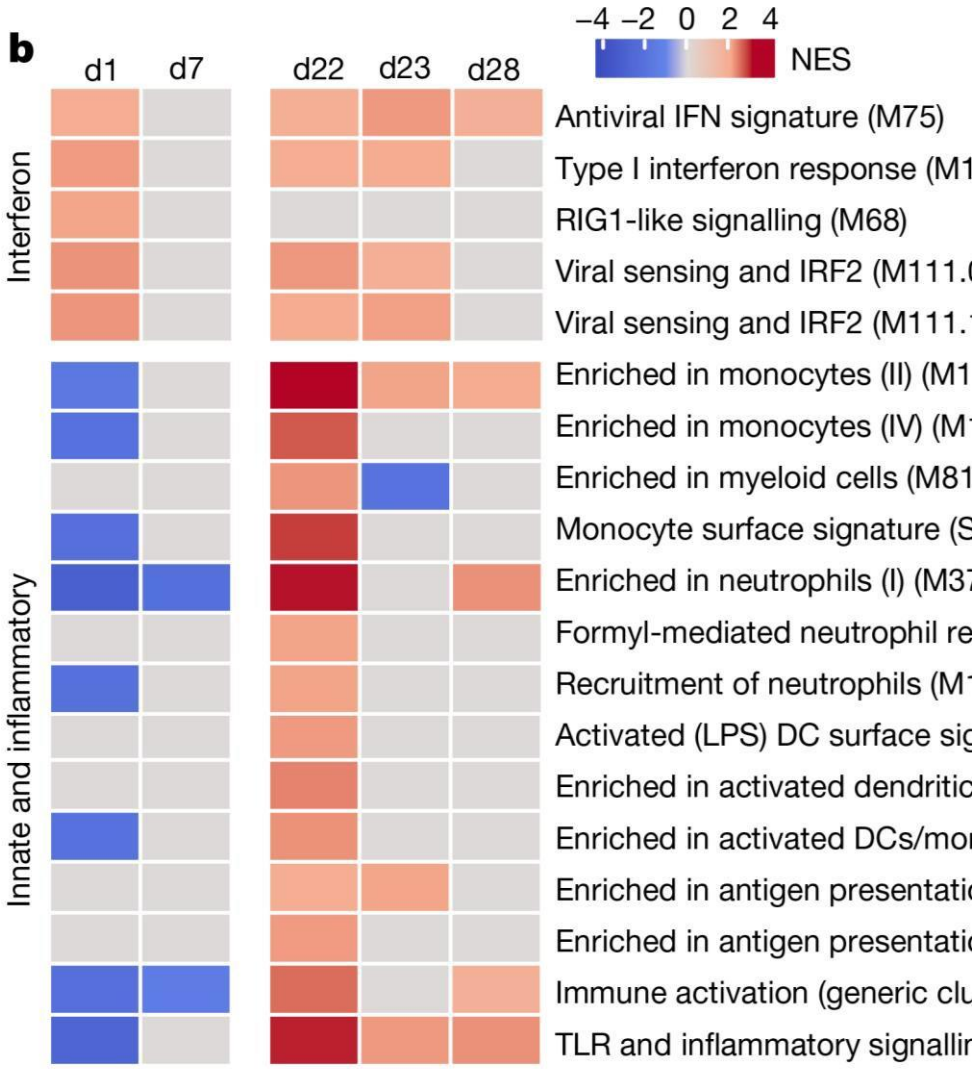


Arunachalamet al, Nature 596: 410, 2021 doi 10.1038/s41586-021-03791-x

Describing the very early immune responses

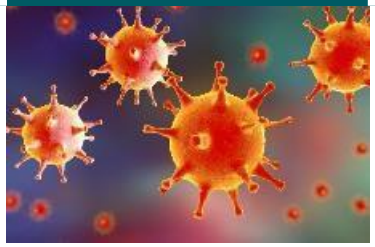
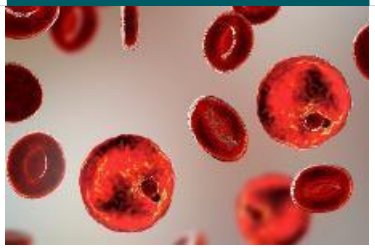
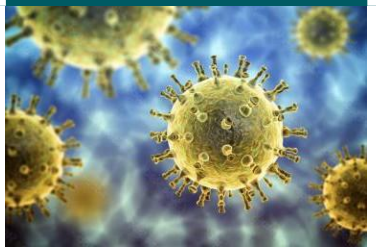
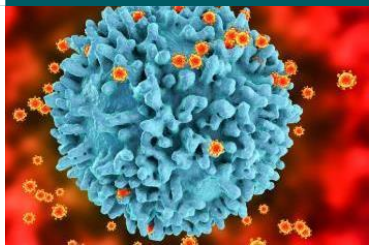
- Immune cells can be detected in blood at 1 day after vaccination
- These are mostly monocytes
- Monocytes can detect the ‘danger signals’ and activate T and B cells
- The cytokine IFN-ψis detected in serum post dose 2 (f)
- Day 1 post dose 2 transcriptomics response => => =>





Arunachalamet al, Nature 596: 410, 2021 doi 10.1038/s41586-021-03791-x

BioNTech is using its platform to tackle the high burden infectious diseases

Mpox in clinical trial	**HSV** in clinical trial	**Malaria** in clinical trial	**Tuberculosis** in clinical trial	**Shingles** in clinical trial	**HIV** clinical trial planned
					
~90 thousand cases and 157 deaths from Jan 2022-Sept 2023	**~491 million people** aged 15 – 49 infected worldwide Once infected, **HSV stays in the body for life** with recurring symptomatic outbreaks	**~247 million cases** in 2021 across the WHO Africa Region **691,000 deaths** in 2021 in the WHO African Region (80% in children <5 years)	**10,6 million cases** globally in 2021 **1.6 million deaths** globally in 2021	**~95%** of the population >50 years is at risk of developing shingles	**38,7 million cases** **1,4 million new** infections globally in 2021

Other ongoing clinical programs:

COVID-19 + Influenza

COVID-19 + RSV

Other planned clinical trials:

BNT331: Gardn. vaginalis

WHO, World Health Organization.

World Health Organization fact sheets. https://www.who.int/news-room/fact-sheets (accessed April 14, 2023).

The Joint United Nations Programme on HIV/AIDS (**UNAIDS**). https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

Tuberculosis vaccine program

Tuberculosis

10.6 million cases
globally in 2021

1.6 million deaths
globally in 2021

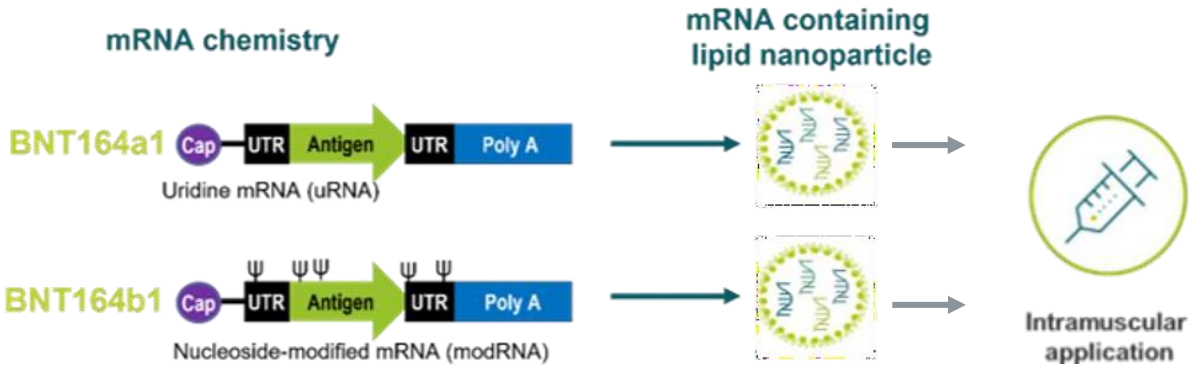
- BioNTech is developing a **multi-antigen** mRNA vaccine candidate to be administered intramuscularly and aimed at eliciting **diverse immune effector functions** for prevention of tuberculosis disease.
- BNT has **2 clinical candidates: BNT164a1 and BNT164b1**
- BNT164 encodes **multiple antigens** to establish protection by:
  - targeting antigens expressed by **Mtb in different environments and stages**
  - eliciting **diverse immune effectors** (i.e. humoral and cellular immune response)
  - Including both CD4+ and CD8+T-cells epitopes that we believe will be presented by a range of polymorphic HLAs to **potentially provide population level coverage**
- **Phase 1 Trials:**
  - Two randomized, placebo-controlled, observer-blind, **dose-finding** evaluation trials (BNT164-01 in Germany; BNT164-02 in Republic of South Africa).
  - **Three dose levels** tested to select a safe and tolerable dose in a **three-dose schedule** (0, 2mo, 6mo)
  - Describe the **safety, reactogenicity, and immunogenicity** of two vaccines against tuberculosis in IGRA-negative, BCG naïve and IGRA-positive, BCG vaccinated healthy subjects.

https://clinicaltrials.gov/ct2/show/NCT05547464

HIV, human immunodeficiency virus; WHO, World Health Organization.
World Health Organization fact sheets. https://www.who.int/news-room/fact-sheets (accessed June 09, 2022).

Rationale of vaccine design

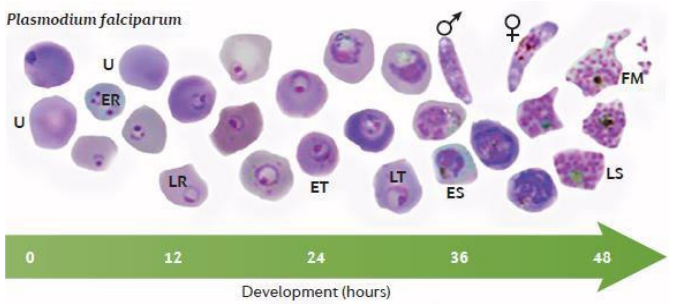
- BNT has **2 clinical candidates: BNT164a1 and BNT164b1**
- **Drug Substance** - BNT164 encodes **multiple antigens** to establish protection by:
  - targeting antigens expressed by **Mtb in different stages of infection**
  - eliciting **diverse immune effectors** (i.e. humoral and cellular immune response)
  - containing **full-length proteins** with both CD4+ and CD8+T-cells epitopes with potential to be presented by a range of polymorphic HLAs to **provide population level coverage**
- **Drug Product** – IM Formulation used in COMIRNATY®



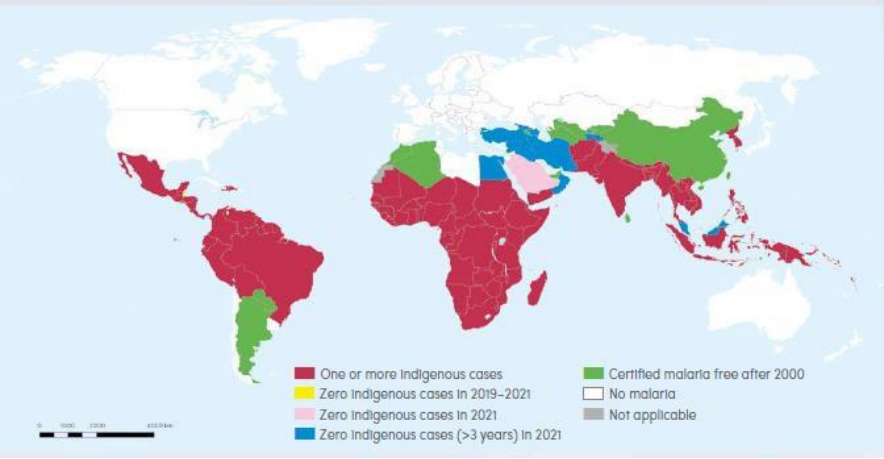
Malaria vaccine program

Malaria

- Caused by the parasite *Plasmodium*
- Transmitted by mosquito bites



Thin blood smear showing blood stage development



Phillips, M, Nat Rev Dis Primers 2017.
WHO World Malaria Report 2022.

- BioNTech is developing the first mRNA-based malaria vaccine candidate aimed at eliciting **diverse immune effector functions** for **prevention of *P falciparum* infection** and to contribute to malaria elimination

- **Phase I Trial**[1]
  - A randomized, placebo-controlled, observer-blind, **dose-escalation** trial
  - Using a staggered dose escalation schema with sentinel participants for Dose 1 in all cohorts, **three dose levels** will be tested to select a safe and tolerable dose in a three-dose schedule
  - Describe the **safety, reactogenicity,** and **immunogenicity** of the **BNT165b1** vaccine in healthy, malaria-naïve adults
  - Five trials sites in the U.S.

Phase I/IIa[2]

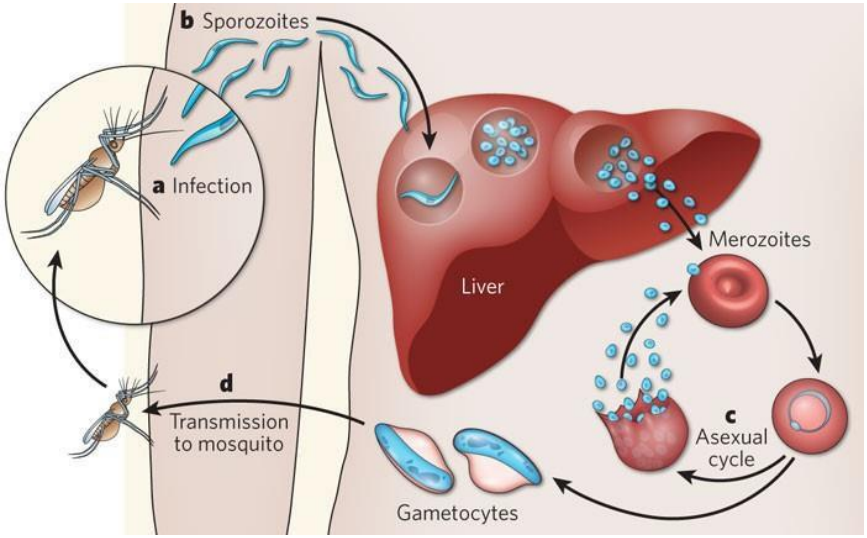
- Intends to evaluate the **safety, tolerability, immunogenicity** and **efficacy** of the **BNT165e** vaccine in healthy malaria-naïve adults
- Five trial sites in the US

1. https://clinicaltrials.gov/ct2/show/record/NCT05581641
2. https://clinicaltrials.gov/study/NCT06069544?cond=malaria%20&intr=RNA%20vaccine&rank=2

Rationale of vaccine design

- BNT has **2 clinical candidates: BNT165b1 and BNT165e**

Circumsporozoite protein (*Pf*CSP) **+/-** **conserved, immunogenic segments of liver stage-expressed proteins**



- **<u>Drug Substance</u>** - BNT165 encodes **multiple antigens** to establish protection by:
  - targeting antigens expressed **in different stages of infection**
  - eliciting **diverse immune effectors** (i.e. humoral and cellular immune response)

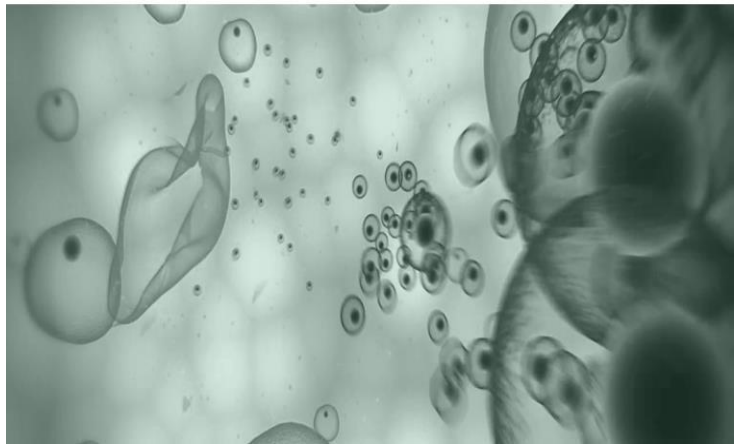
- **<u>Drug Product</u>** – IM Formulation used in Pfizer-BioNTech COVID-19 vaccine

https://www.clinicaltrials.gov/study/NCT05581641
https://www.clinicaltrials.gov/study/NCT06069544

Michalakis and Renaud, Nature, 2009

Herpes Simplex Virus vaccine program

HSV



491.5 million people aged between 15-49 yoa have HSV-2, globally in 2016

Neonatal herpes occurs in 10 out of every 100 000 births globally and can lead to neurologic disability or death

https://www.who.int/news-room/fact-sheets/detail/herpes-simplex-virus
*Latest estimate per WHO Facts Sheet

- BioNTech is developing a **multi-antigen** mRNA prophylactic vaccine candidate to be administered intramuscularly and aimed at eliciting **diverse immune effector functions** for prevention of infection and/or disease caused by Herpes Simplex Virus (HSV)-2 and potentially HSV-1 disease.
- BNT has **1 clinical candidate: BNT163**

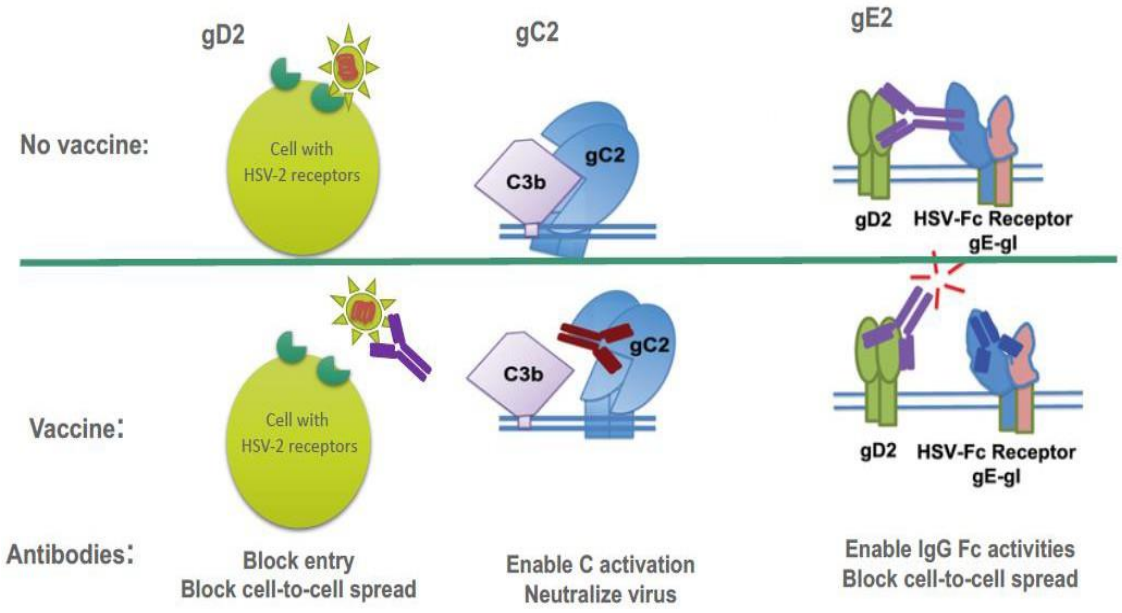
Phase 1 Trial:

- Randomized, observer-blinded, dose-finding and safety expansion trial
- **Multiple doses** will be tested to select a safe and tolerable dose in a three-dose schedule
- Describe the **safety, reactogenicity, and immunogenicity** of one investigational vaccine for the prevention of genital lesions caused by HSV-2 and potentially HSV-1
- Trial being conducted in the U.S.

https://clinicaltrials.gov/ct2/show/NCT05432583

Rationale of vaccine design

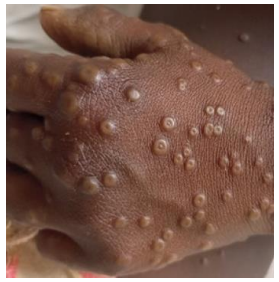
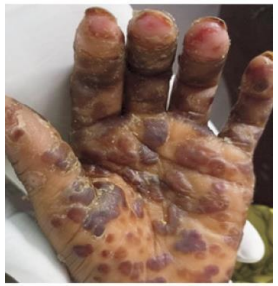
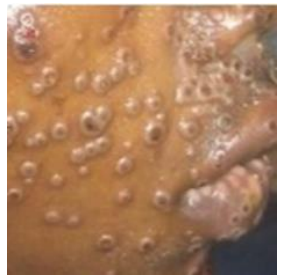
- BNT has **1 clinical candidate: BNT163**
- **Drug Substance** - BNT163 encodes **multiple antigens** to establish protection by:
  - encoding HSV-2 proteins involved in virus invasion, virus spread and immune evasion
  - eliciting diverse immune effectors (i.e. humoral and cellular immune response)
  - eliciting cross-reactive immune effectors to HSV-2 and HSV-1
- **Drug Product** – IM Formulation used in Pfizer-BioNTech COVID-19 vaccine



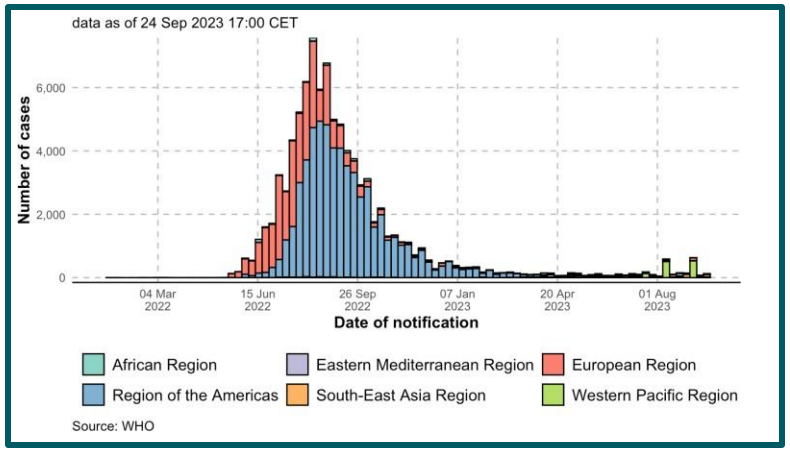
Egan et al. *Transl Res*. 2020;220:138-152

Mpox vaccine program

Mpox

WHO declared mpox a public health emergency of international concern (July 2022 – May 2023)



https://worldhealthorg.shinyapps.io/mpx_global/cdc.gov
Gessain,NEJM, 2022

BioNTech is developing a **multi-antigen mpox vaccine** candidate for active immunization against monkeypox virus and variola virus (causative agent of smallpox).

In the context of an Orthopoxvirus naive world population there is an unmet need for a vaccine that can be rapidly manufactured at scale and adapted in the event of recurrent mpox or related virus outbreaks.

Phase I/II Trial

- A first-in-human, randomized, partially observer-blind, dose-escalation trial
- Evaluating the **safety** and **immunogenicity** of investigational RNA-based mpox vaccine
- Sites in the UK and US

Clinical candidate BNT166a

- MPXV infection produces two distinct infectious forms: enveloped **(EV)** and mature **(MV) virions.** BNT166a is designed to induce immune responses against both forms.
- Targeting broad protection against orthopoxviruses via:

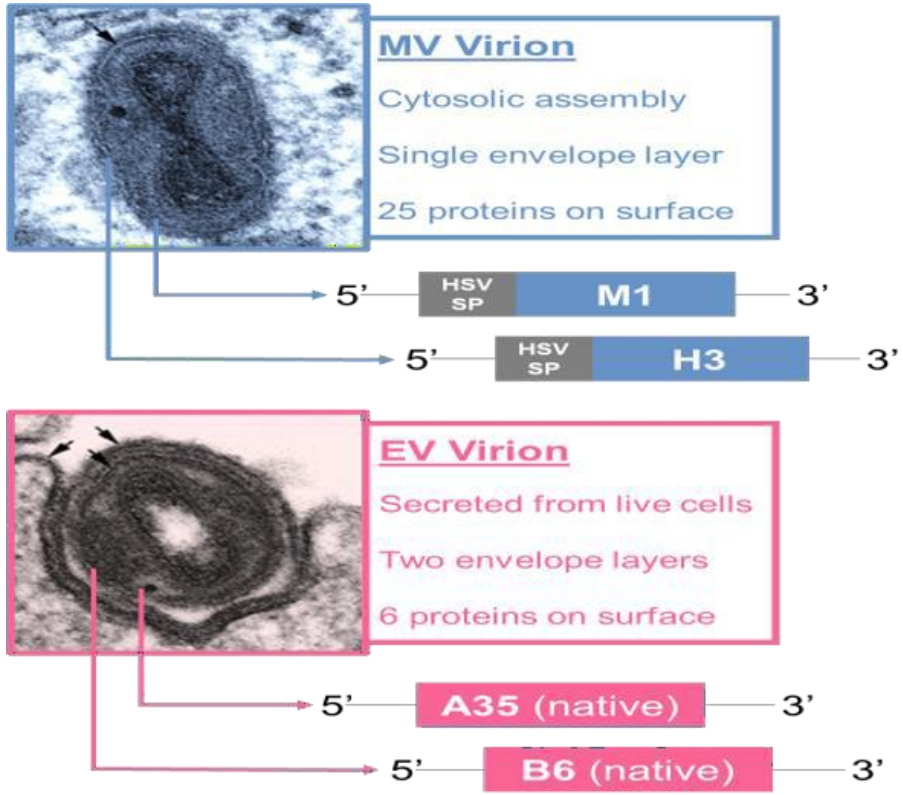
  1) Multi-antigen design

  2) Inclusion of targets in MPXV that are highly conserved with vaccinia virus (VACV) and variola virus VARV

Rationale of vaccine design

- **Drug Substance** - BNT166a encodes **four antigens** targeting both infectious forms of MPXV: **MV virions** and **EV virions**
  - Chosen antigens have high sequence similarity to variola virus (VARV) and vaccina virus (VACV)

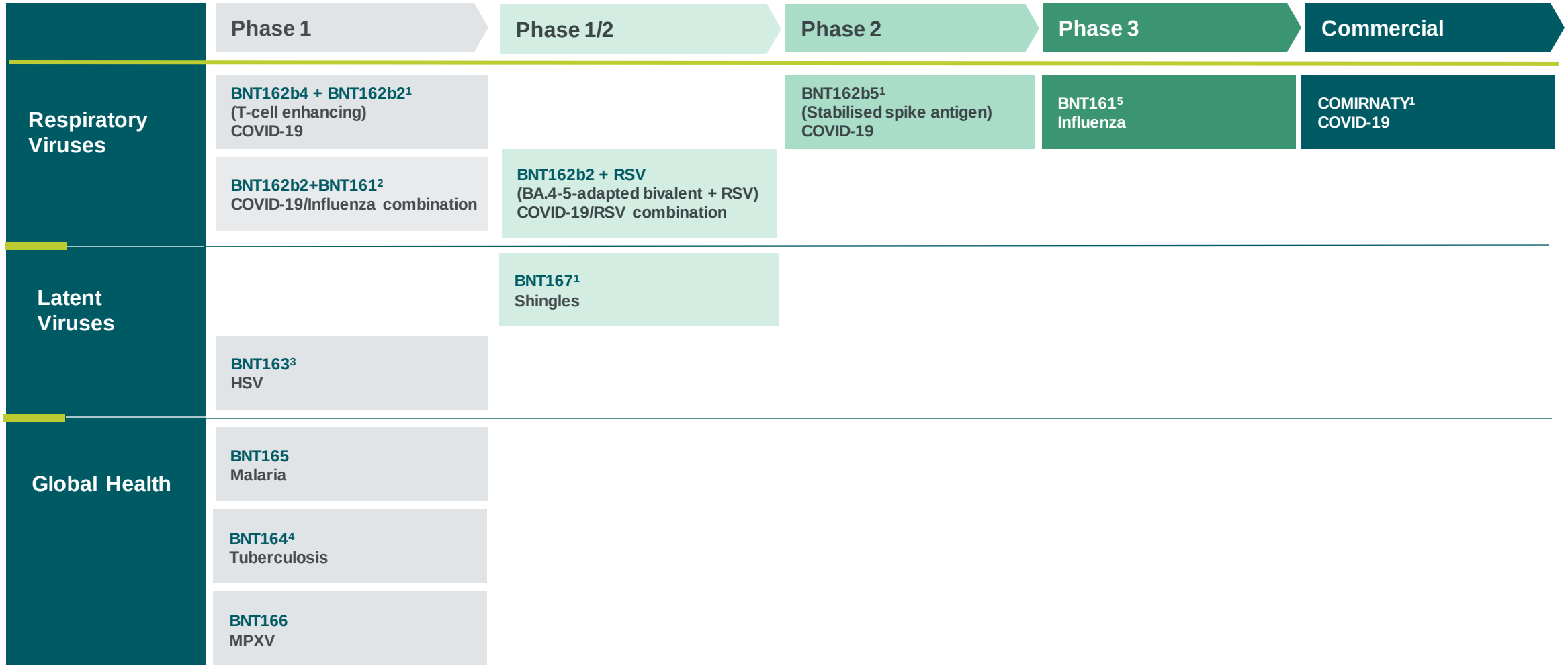
- **Drug Product** – IM Formulation used in Pfizer-BioNTech COVID-19 vaccine



	MPXV protein	VACV protein	Identity	VARV protein	Identity
EV	A35	A33	96%	A36	92%
EV	B6	B5	97%	B7	93%
MV	M1	L1	98%	M1	99%
MV	H3	H3	94%	I3	94%

Data on file, submitted for publication, Cell, Oct 2023

Broad Infectious Disease Pipeline Built on Versatile mRNA Technology



1. Partnered with Pfizer; 2. Collaboration with Pfizer and subject to reaching agreement with our partners; 3. Collaboration with University of Pennsylvania; 4. In collaboration with Bill & Melinda Gates Foundation; 5. Exclusive license to Pfizer.
HSV = Herpes simplex virus.

Please find current product information for Comirnaty at https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf and https://www.fda.gov/media/151707/download.

Summary

- mRNA technology enabled the rapid development of highly protective vaccines during a pandemic
- Pre-clinical and emerging clinical data show that mRNA technology can also be applied to development of vaccines against other pathogens, including non-viral pathogens
- BioNTech is currently evaluating multiple vaccine candidates for various infectious diseases with high unmet medical need
- Systems vaccinology and ‘precision immunology’ approaches can provide key data on vaccine mode of action
- Effort to build local partnerships for biomarker analyses and immunology (NCT05547464)

Access: BioNTainer - a platform for localized and sustainable mRNA production

The challenge

Establishing GMP production of mRNA is complex and requires overcoming challenges at many levels

A solution

Turnkey package that includes modular production units, GMP-compliant setup and personnel training

Thank you

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