

# Vaccines Investor Event

**Part 2**  
**Leading with innovation**

December 1<sup>st</sup>, 2021



# Vaccines Investor Event | Agenda

Introduction		<b>Paul Hudson</b>	Chief Executive Officer
We Play to Win		<b>Thomas Triomphe</b>	Head of Vaccines GBU
Growing current business	Winning in Influenza	<b>Bill Averbeck</b>	Head of Influenza Franchise
	All infant protection against RSV	<b>Kimberly Tutwiler</b>	Head of RSV Franchise
Q&A session			
Building an innovative & diversified pipeline		<b>Jean-François Toussaint</b>	Head of Vaccines R&D
Leading with innovation	Unlocking the potential of mRNA	<b>Frank DeRosa</b>	Head of Research for mRNA CoE
	Broadening the pipeline to address unmet needs	<b>Jean-François Toussaint</b> <b>Thomas Grenier</b>	Head of Vaccines R&D Head of Franchises & Product Strategy
Conclusion		<b>Thomas Triomphe</b>	Head of Vaccines GBU
Q&A session			



# Building an innovative & diversified pipeline

Jean-François Toussaint

Head of Vaccines Research  
& Development



# Building an innovative and diversified pipeline to deliver sustainable growth



Opening a new chapter at Sanofi Vaccines, expanding to new disease areas



Leveraging state of the art immunology & antigen design



Selecting the best technology platform for each target

## R&D objectives

Rejuvenated pipeline, with  
**10 new development candidates by 2025**  
(of which 6 mRNAs)

Focused on  
first-in-class / best-in-class

# Broadening our pipeline & opening new areas for growth

## Deepen our leadership in existing franchises

**Influenza**

- Fluzone HD pediatric
- Influenza QIV mRNA ★
- Next-Gen Flu vaccines

**Meningitis**

- MenB ★
- MenPenta ★

**RSV**

- RSV toddler
- RSV older adults & respiratory combo ★

## New Growth Areas

**Pneumo**

- PCV21 ★

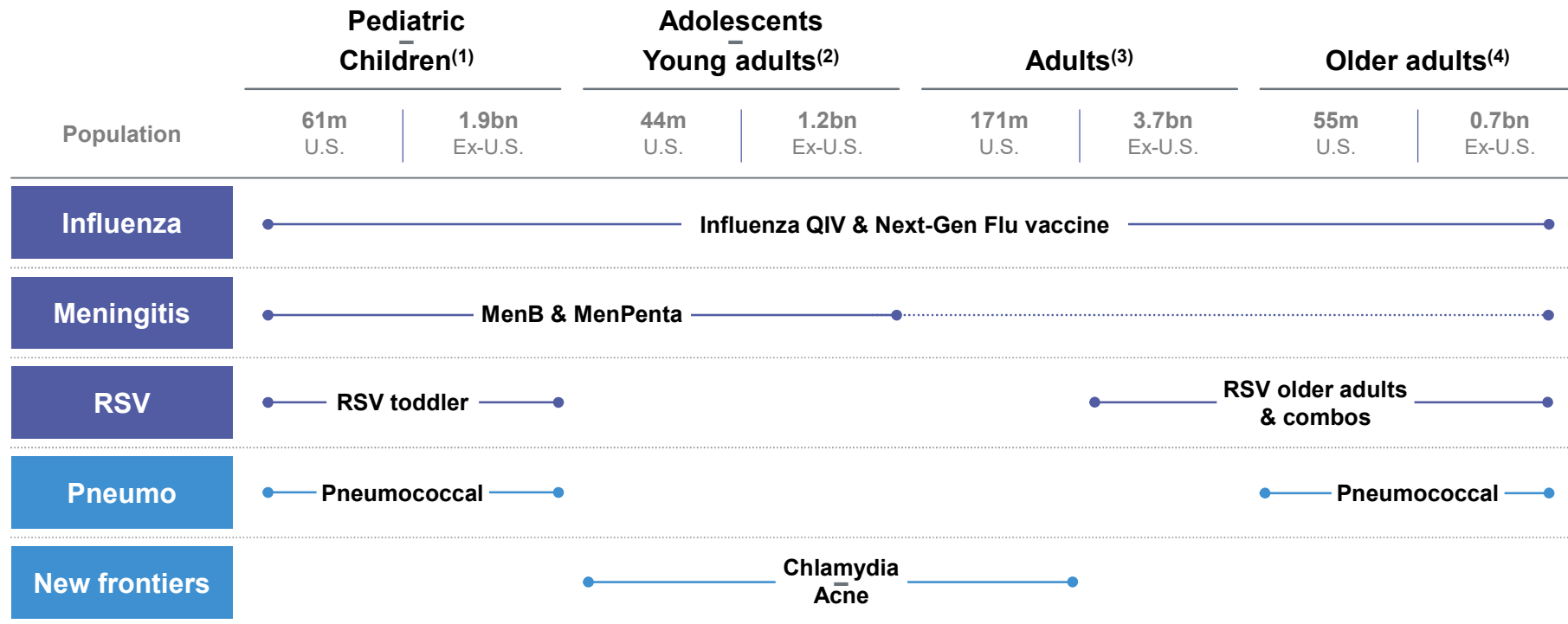
**New frontiers**

- Chlamydia ★
- Acne ★

★ = New

*Expanding research on additional vaccines candidates against chronic diseases*

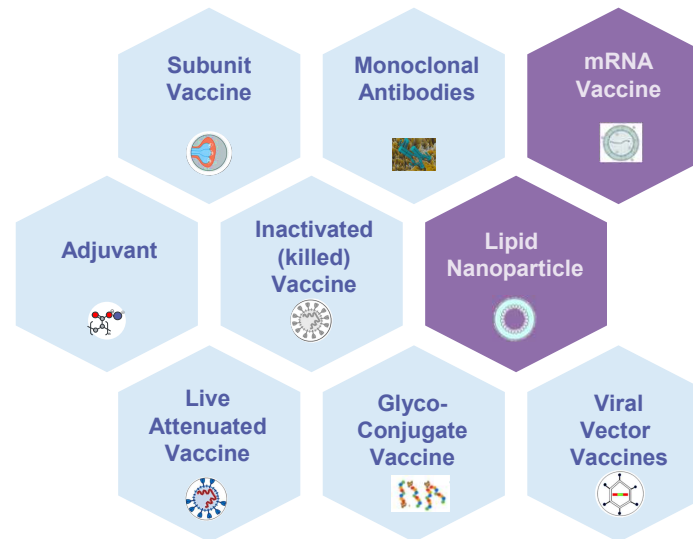
# Innovation addressing a large part of the population



# We added mRNA to our state of the art toolbox

## Established platforms

- **Broad range of antigen targets**
  - Viral & bacterial
  - Protein & polysaccharide
- **Proven efficacy** across multiple diseases & populations
- **Proven tolerability** from babies to older adults



## mRNA & LNP platforms

- Restricted to **protein-based antigens**
- Particularly well suited for (respiratory) **viral pathogens**
- **Fast to clinic** & low CMC costs
- Potential to facilitate **multi-component vaccines**

---

*We select the best platform for each target*

---



# Unlocking the potential of mRNA

Frank DeRosa

Head of Research mRNA CoE



CoE: Center of Excellence



# Sanofi mRNA Center of Excellence

## A biotech environment with Sanofi's powerhouse



- Deep vaccine & antigen design expertise
- Well-established development platforms
- Expertise in running clinical trials
- Global manufacturing scale



- Strong mRNA & LNP know-how
- Proprietary algorithms & large LNP database
- Large scale material production capabilities

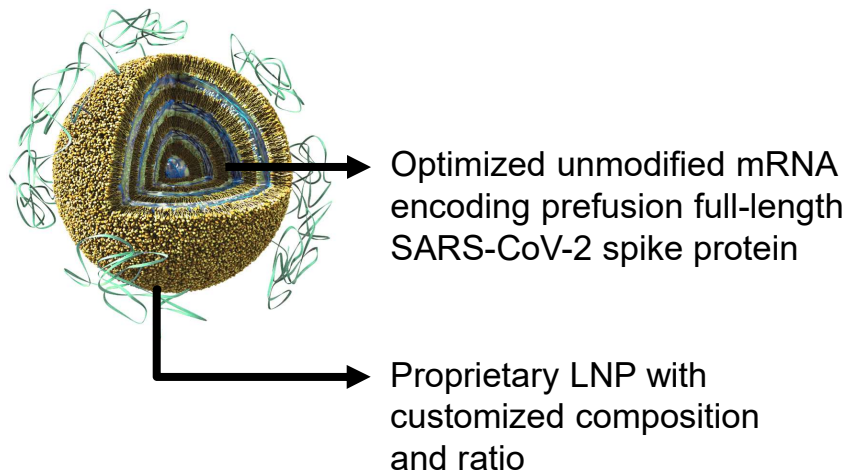
### mRNA Center of Excellence

*Moving fast beyond 1<sup>st</sup> generation mRNA*

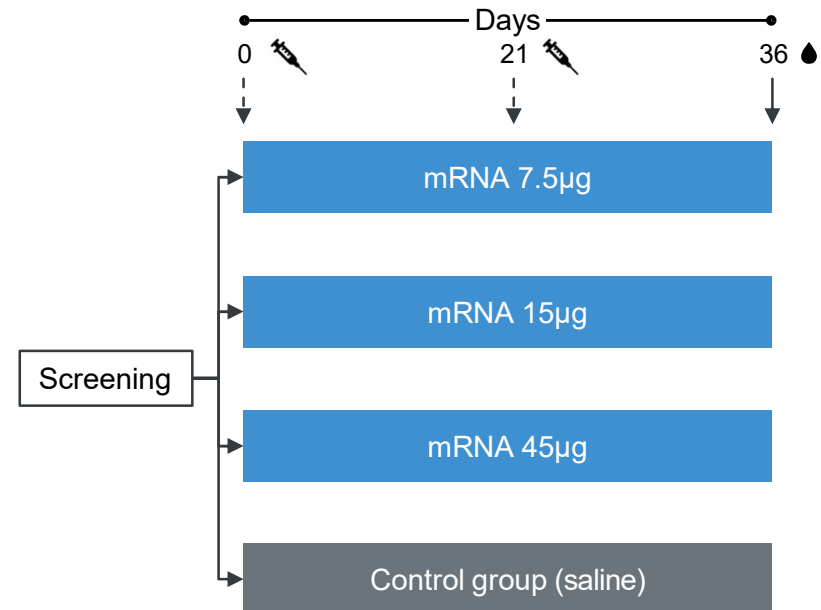
- **400 dedicated employees** in the U.S. (Cambridge) and France (Lyon)
- **Positive clinical results** from COVID-19 and influenza monovalent mRNA candidates
- **Pivot to modified mRNA achieved**; clinical trials planned to start in 2022
- **Expansion of proprietary database** ongoing internally & with partnerships

# First clinical trial with our proprietary mRNA & LNP platform

Unmodified mRNA & proprietary LNP,  
using COVID-19 as a reference antigen



## Phase I design

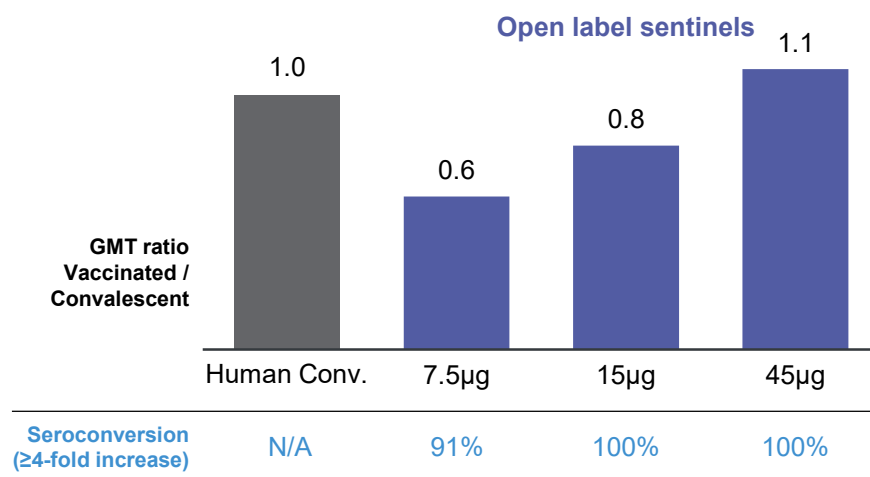


# Platform potential confirmed by positive interim results

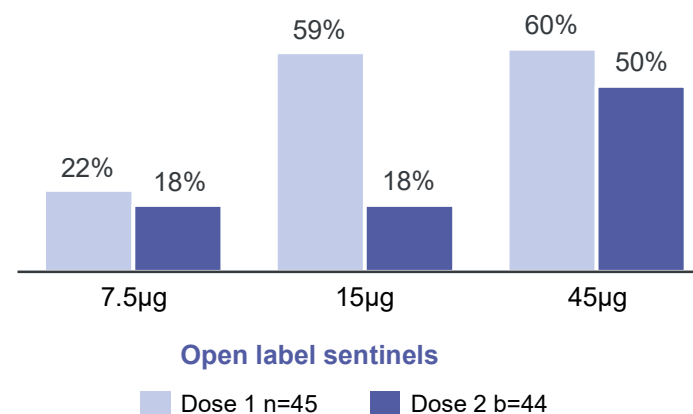
100% seroconversion for all doses  $\geq 15\mu\text{g}$

Tolerability profile in line with other unmodified mRNA COVID-19 vaccines

Pseudovirus nAb to D614G 14 days post-dose 2  
(SARS-CoV-2 seronegative participants, n=41)

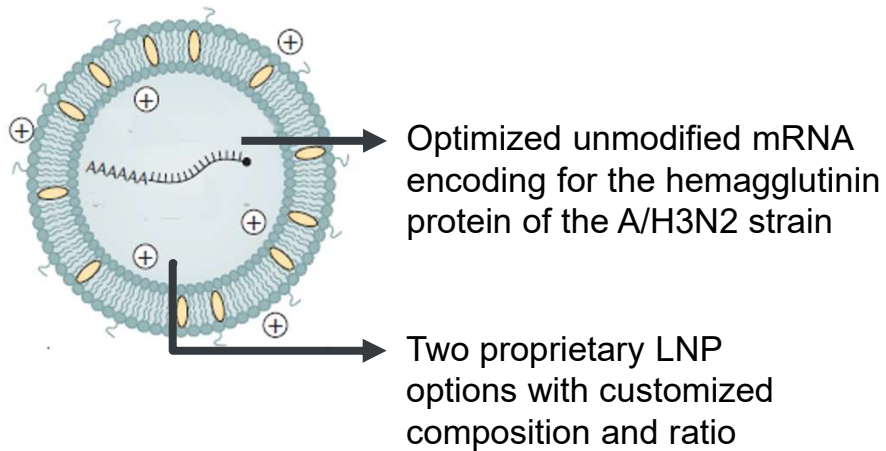


Grade 3 adverse events

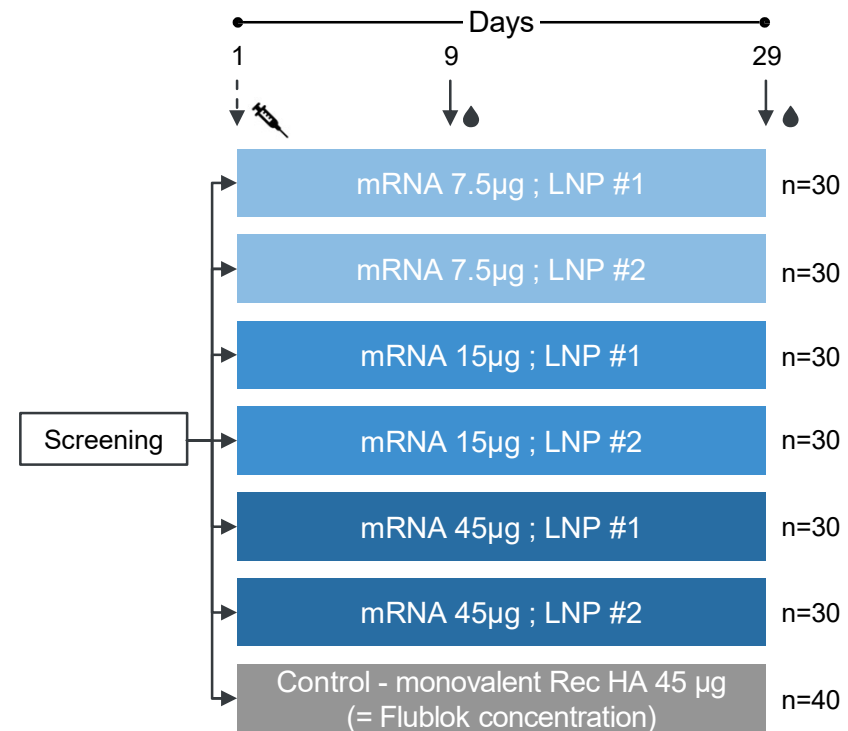


# Progressing to clinic with influenza

Unmodified mRNA & proprietary LNPs,  
for monovalent influenza vaccine



## Phase I design

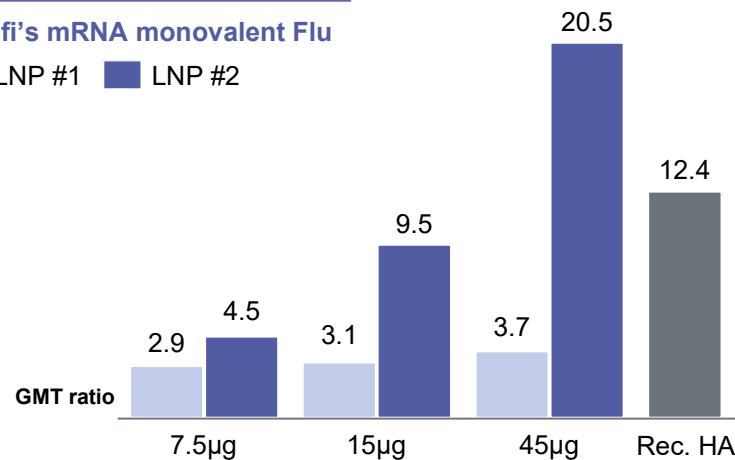


# First evidence that mRNA could work for influenza, pending improved reactogenicity

## Immunogenicity

### Sanofi's mRNA monovalent Flu

■ LNP #1 ■ LNP #2

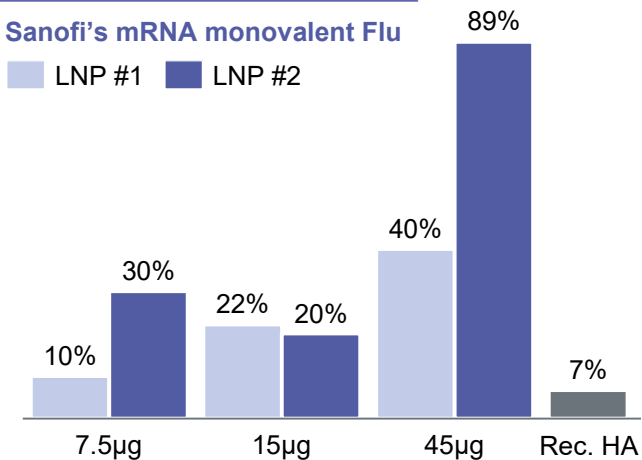


Seroconversion<sup>(1)</sup> 30% 70% 44% 90% 40% 100% 73%

## Reactogenicity<sup>(2)</sup>

### Sanofi's mRNA monovalent Flu

■ LNP #1 ■ LNP #2



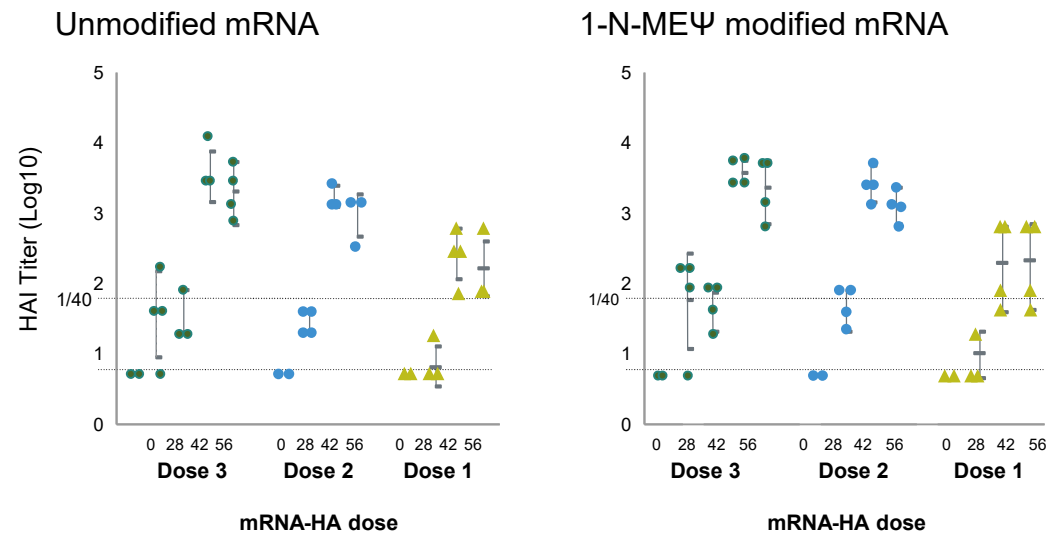
***LNP # 2 identified as a promising candidate for influenza vaccine***

# Successfully pivoted to modified mRNA

## Switch to modified mRNA achieved

- Pre-clinical data generated in multiple animal models
- GMP material produced
- On track to start clinical trials in influenza
  - H1 2022 for monovalent
  - H2 2022 for quadrivalent

## Similar immunogenicity with modified mRNA in NHP

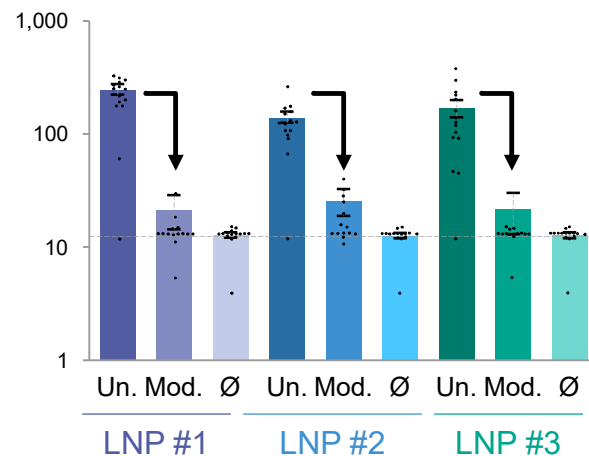


*First clinical data with modified mRNA expected in 2022*

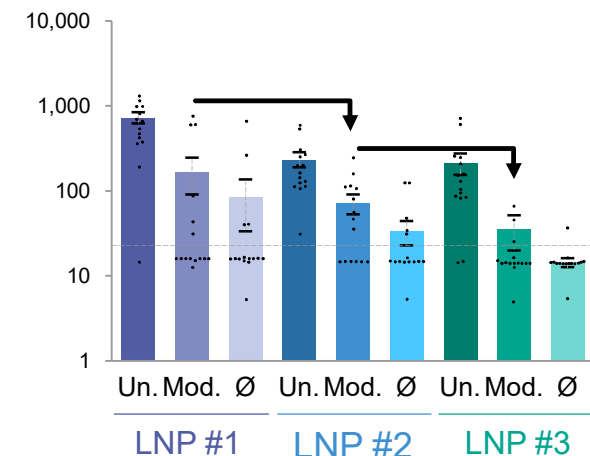
# Biomarkers show clear path to reduce reactogenicity with modified mRNA and optimized LNPs

Proprietary ex-vivo MIMIC System<sup>®</sup> assay enabling evaluation of immune responses

IFN $\alpha$ 2



MCP-3

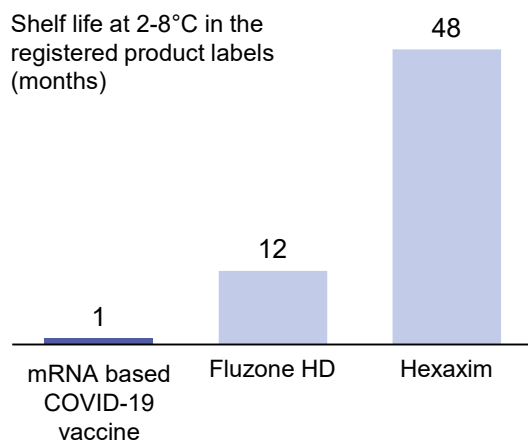


***Modified mRNA & LNP optimization expected to reduce reactogenicity in the clinic***

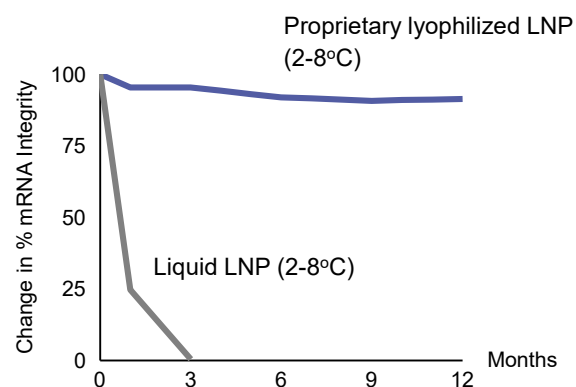
# Overcoming mRNA thermostability challenges

Storage at 4°C is needed for vaccines outside pandemic

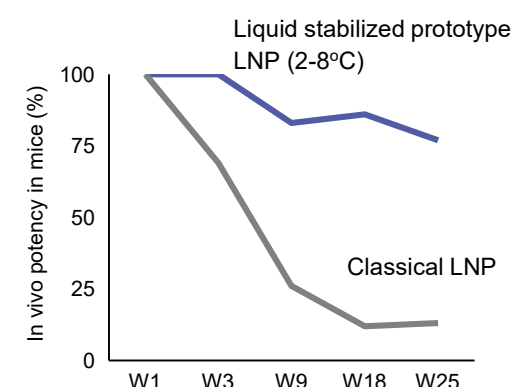
Shelf life at 2-8°C in the registered product labels (months)



Stability of lyophilized mRNA drug product achieved






Development of fully liquid formulation underway



*Ready to go with lyophilized*



# Breaking barriers to unlock mRNA potential

	1 <sup>st</sup> gen mRNA	2 <sup>nd</sup> gen mRNA	3 <sup>rd</sup> gen mRNA
<b>Immunogenicity</b>	✓ High	✓ High	✓ High
<b>Reactogenicity</b>	— Moderate to high	✓ Tolerability profile in line with established vaccines	✓ Tolerability profile in line with established vaccines
<b>Thermostability</b>	— ~1 month shelf life (2-8°C)	✓ Lyophilized or 9 – 12 months fully liquid	✓ Lyophilized or 9 – 12 months fully liquid
<b>Duration of expression</b>	— 1 – 3 days	— 1 – 3 days	✓ Extended half-life
<b>Targeting</b>	— -	— -	✓ Efficient cell & organ specificity
	 <b>Applicable to pandemic market</b>	 <b>Required profile for general vaccine markets</b>	 <b>Optimal profile for therapeutics</b>



Jean-François  
Toussaint

**Head of Vaccines  
Research  
& Development**



Thomas Grenier

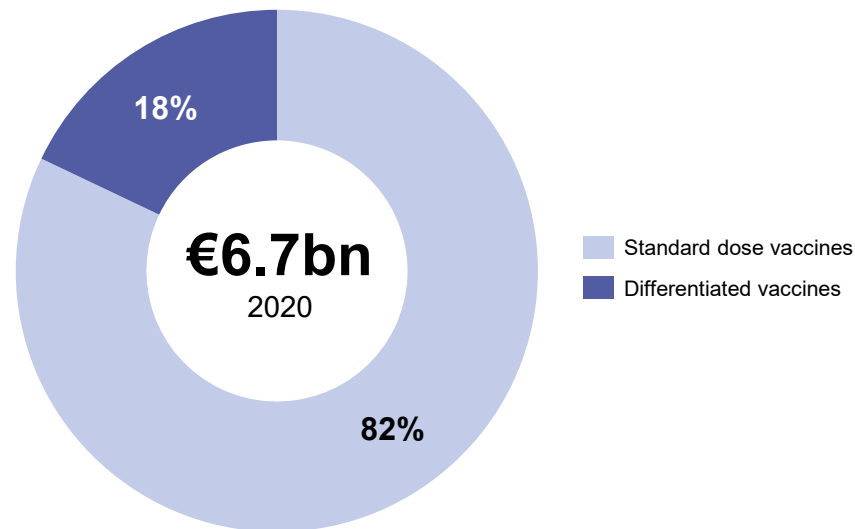
**Head of Franchises &  
Product Strategy**

**Broadening the pipeline  
to address unmet needs**



# Influenza: further raising the bar

## Market overview

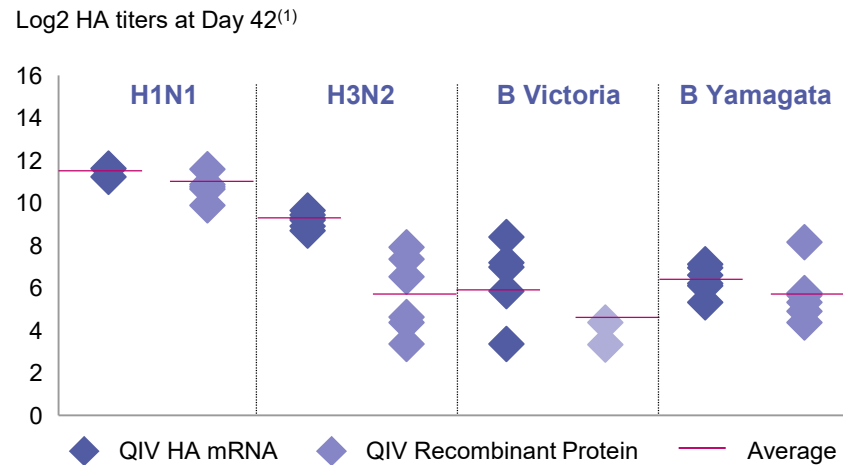


## Sanofi strategy to keep winning in flu

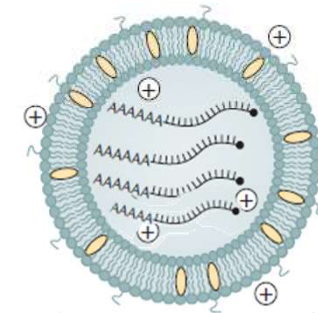
- Accelerated mRNA QIV Influenza development
- Raising the bar further with Next-Gen Flu
  - Machine Learning for better strain selection
  - Expanding on neuraminidase to induce greater protection

# First milestone achieved for Sanofi mRNA QIV

## Pre-clinical data generated with unmodified mRNA



## Pivoted to modified for final candidate



- Optimized modified mRNA sequence
- Encoding for 4 HA proteins
- Optimized LNP to reduce reactogenicity

# Influenza mRNA QIV development with objective to demonstrate Protection Beyond Flu

## Phase I/II – Targeted initiation in 2022

- Two age cohorts (18-64yo & 65yo+)
- Dose-selection trial
- Comparison against standard of care

---

**Selection of final composition  
for each population**

## Phase III – Targeted Initiation in 2023

- Quadrivalent vaccine based on WHO selected strains
- Comparison to standard of care

---

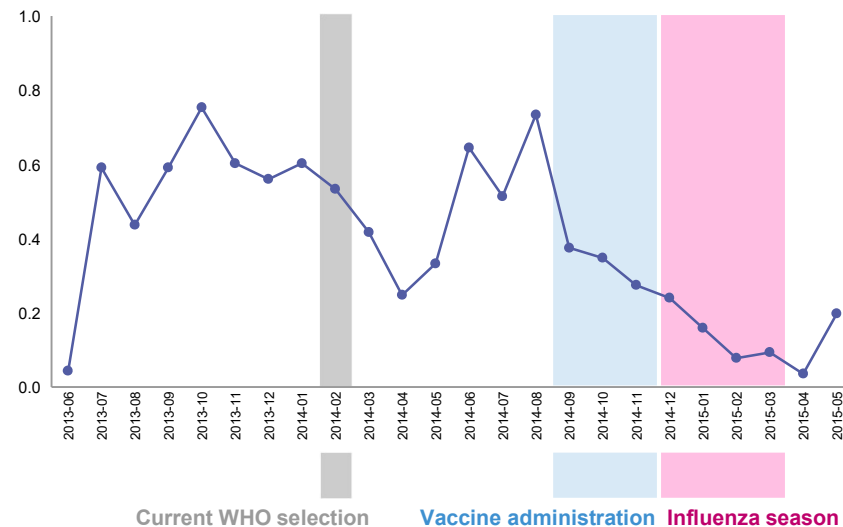
**Registration trial designed to  
demonstrate vaccine efficacy & build  
safety database**

# Later strain selection not the solution for improved efficacy

Only 2 out of past 10 years with strain mismatch      Shift in strain dynamic can occur late in season

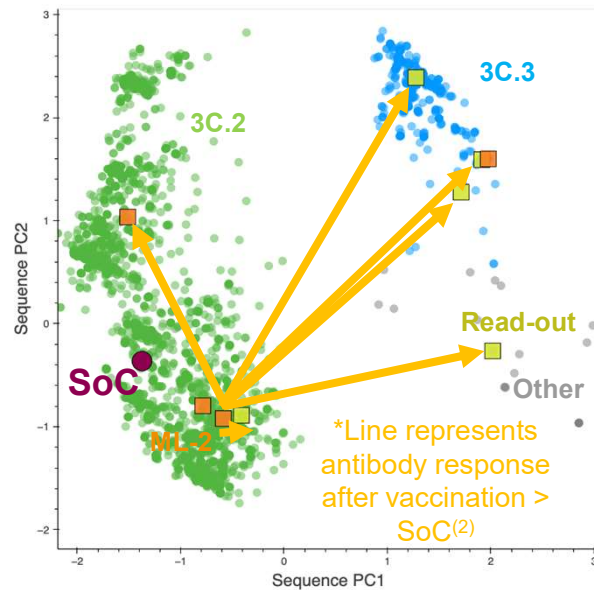
Season	Predominant strain in adults ≥ 65yo <sup>(1)</sup>	Vaccine strain to predominant circulating strain similarity <sup>(1, 2)</sup>
<b>2010-11</b>	A/H3N2 (80.4%)	97%
<b>2011-12</b>	A/H3N2 (87.0%)	82%
<b>2012-13</b>	A/H3N2 (86.4%)	100%
<b>2013-14</b>	A/H1N1 (57.2%)	100%
<b>2014-15</b>	A/H3N2 (90.6%)	19%
<b>2015-16</b>	A/H1N1 (48.4%)	100%
<b>2016-17</b>	A/H3N2 (79.0%)	97%
<b>2017-18</b>	A/H3N2 (69.4%)	93%
<b>2018-19</b>	A/H3N2 (53.3%)	11%
<b>2019-20</b>	A/H1N1 (71.0%)	54%

Example of 2014-2015 season (H3N2 late mismatch)<sup>(3)</sup>

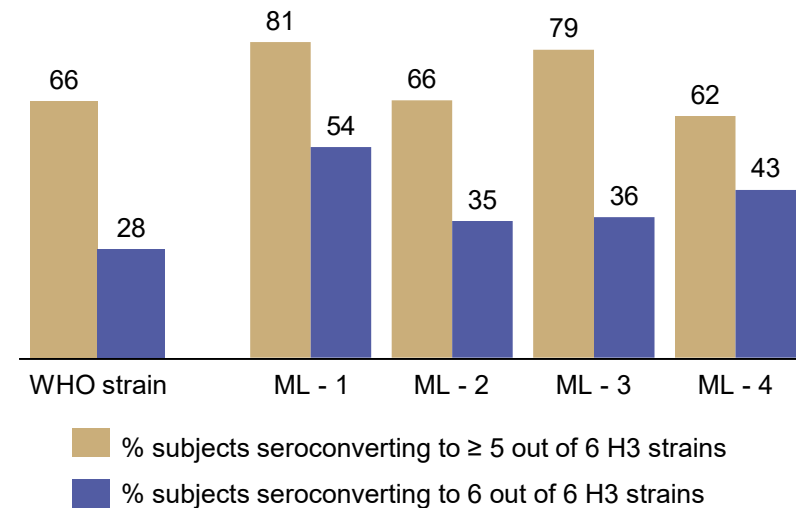


# Striving for better strain selection with Machine Learning

Antigens selected for cross-clade protection



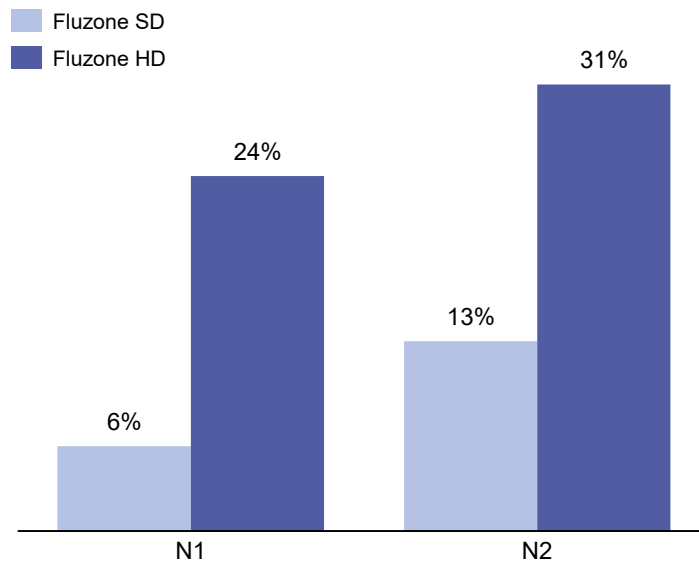
Higher seroconversion for ML-selected antigens<sup>(1)</sup>



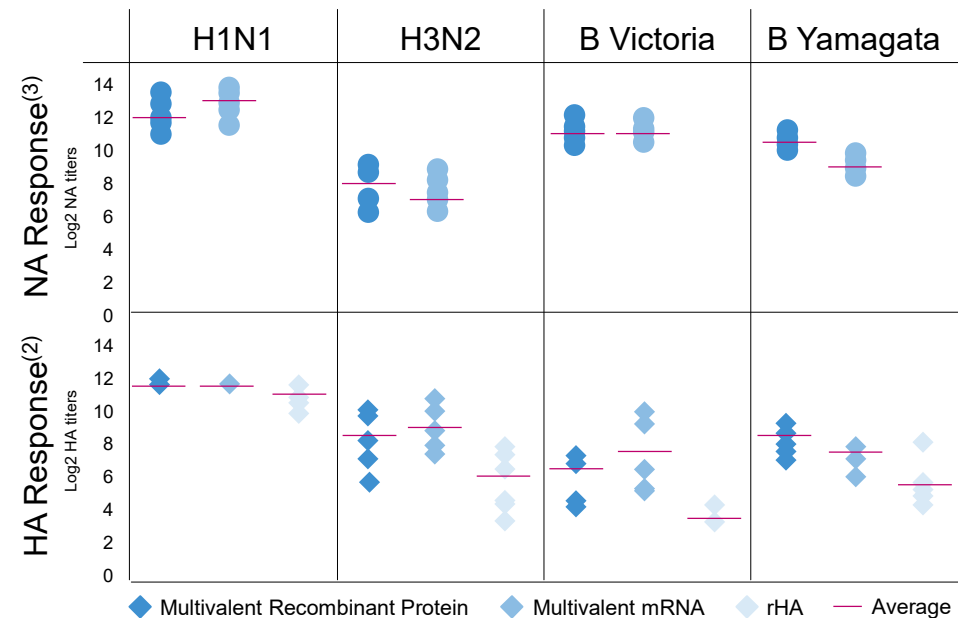
***ML selected antigens showed greater breadth in Phase I translational study***

# Exploring the potential of neuraminidase to further build Protection Beyond Flu

Fluzone SD/Fluzone HD already increase anti-NA titers<sup>(1)</sup>



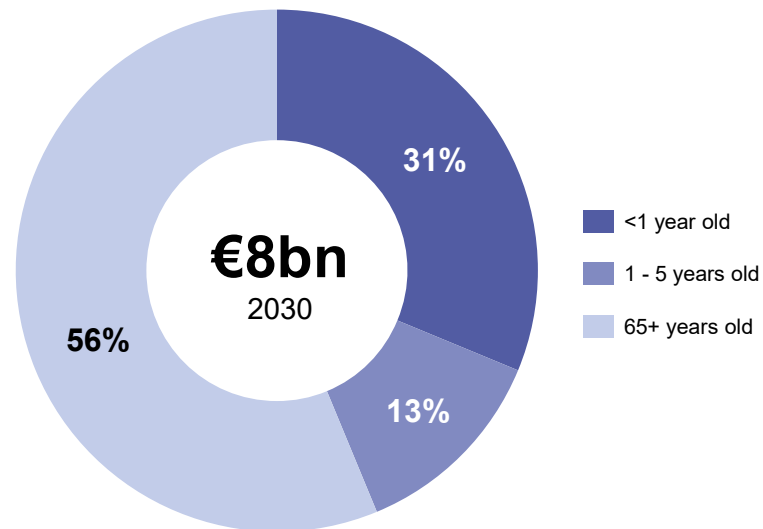
Exploring combined HA + NA multivalent vaccines  
Response in ferrets of multivalent protein and mRNA vaccines





# Respiratory Syncytial Virus: protection across all age groups

## Market overview



## Best-in-class protection for all ages



**Nirsevimab:** best-in-class mAb for *All Infant Protection* in first season

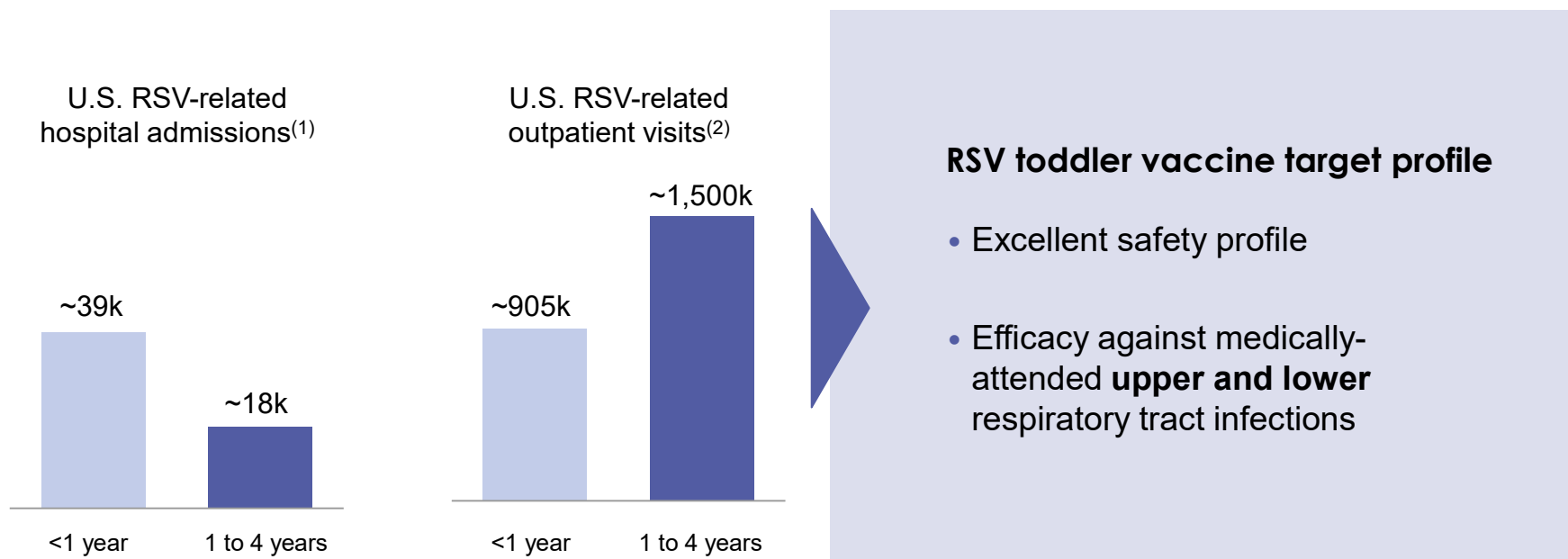


**RSV toddler:** first-in-class Live Attenuated Virus vaccine for second season onwards

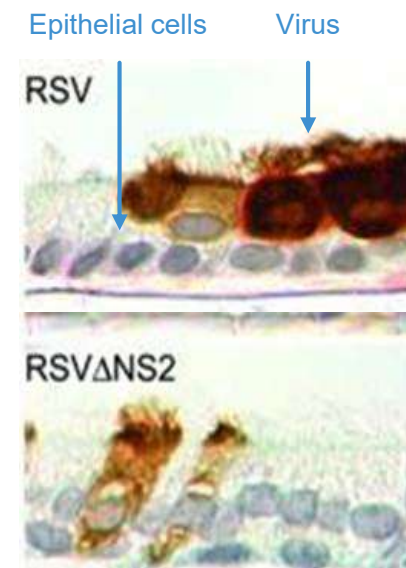
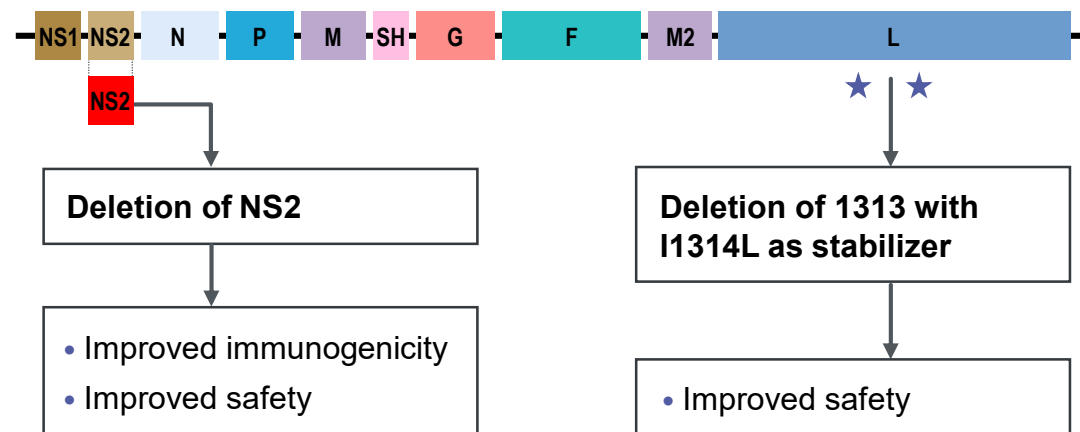


**RSV older adults:** initiating standalone mRNA vaccine, and paving the way for respiratory combos in older adults

# RSV burden does not stop after the first season



# FiC RSV toddler vaccine designed by reverse genetics



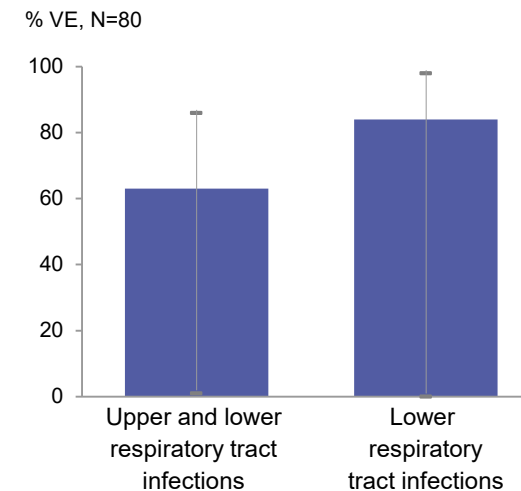
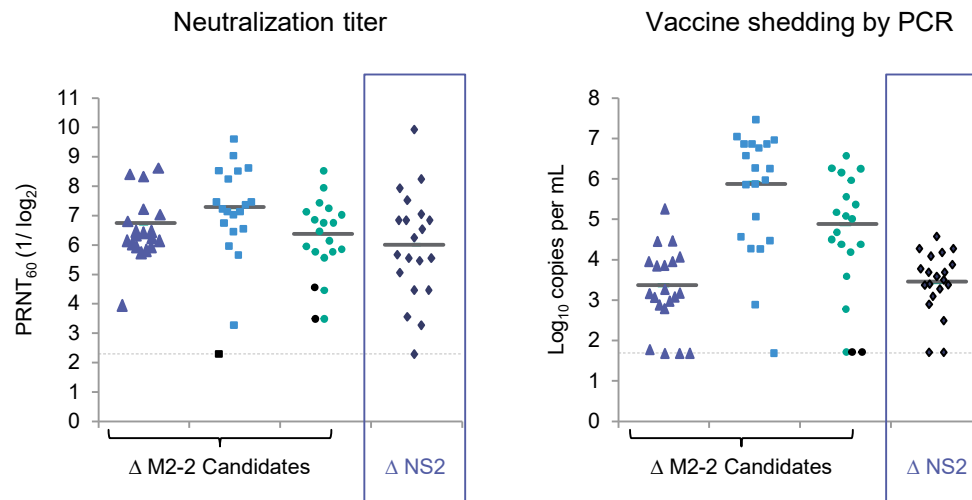
*Ongoing Phase I/II in U.S. and Latin America (n=360 participants) – read-out expected in 2022*

# Clinical data shows evidence of efficacy by reducing medically attended acute respiratory illnesses



**ΔNS2 vaccine candidate selected for further development**

**Evidence of efficacy<sup>(1)</sup> for both upper and lower respiratory tract infections**



# RSV in older adults: addressing a large burden



	Estimated U.S. outpatient acute infection amid 65yo+	Estimated U.S. hospitalizations amid 65yo+	Virus evolution
<b>RSV</b>	1,041k <sup>(1)</sup>	105k <sup>(2)</sup>	Low
<b>HMPV</b>	603k <sup>(1)</sup>	88k <sup>(2)</sup>	Low
<b>PIV</b>	329k <sup>(1)</sup>	82k <sup>(2)</sup>	Low
<b>Influenza</b>	1,808k <sup>(1)</sup>	204k <sup>(3)</sup>	High

- Initiating standalone RSV mRNA vaccine to address high burden of disease in older adults
- Low variability of RSV may allow for multiyear protection

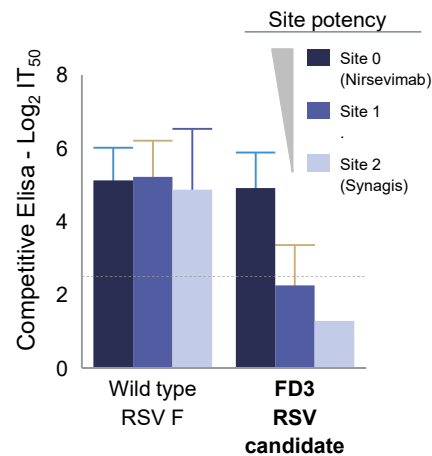
## Opportunity for RSV-based combos

- Cumulated burden of RSV and HMPV comparable to Influenza
- Potential for additional convenience and cost-effectiveness benefits

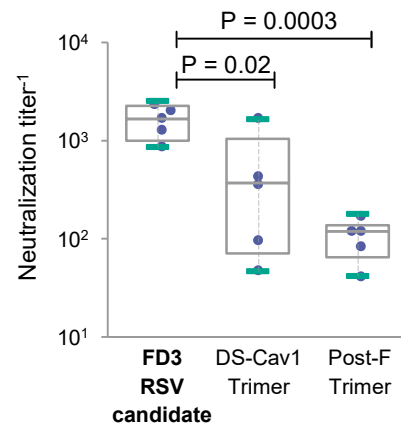
# Best-in-class RSV antigen through innovative design



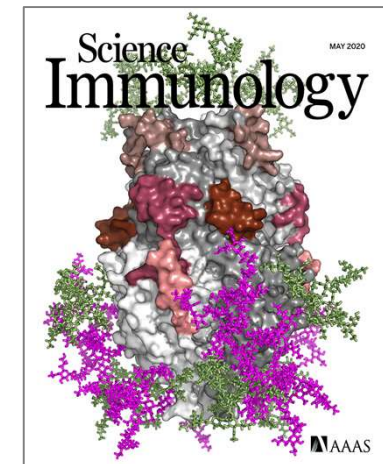
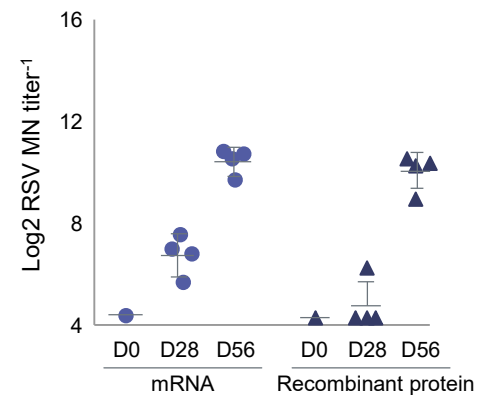
RSV F antigen designed to focus on potent site 0



Improved immunogenicity over competing antigens



Proven potency in mRNA format

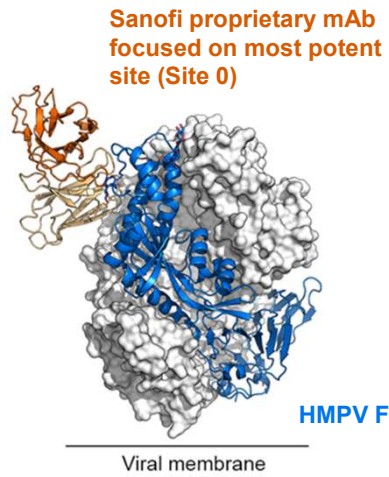


*Initiating Phase I with modified mRNA in 2022*

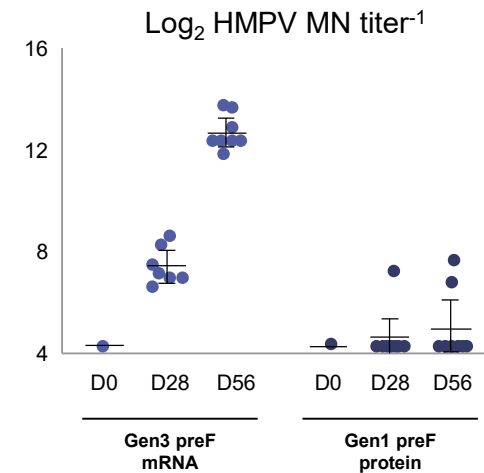
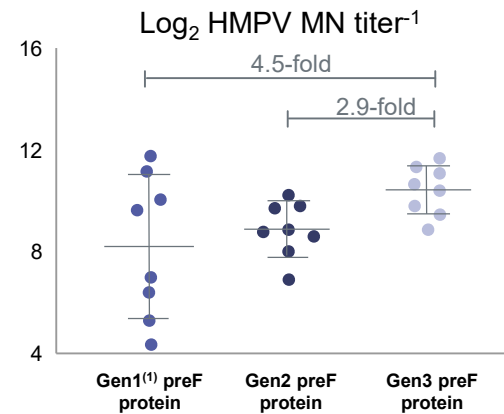
# State of the art HMPV antigen candidate identified



## Cutting edge antigen design



## Proven potency in mRNA format



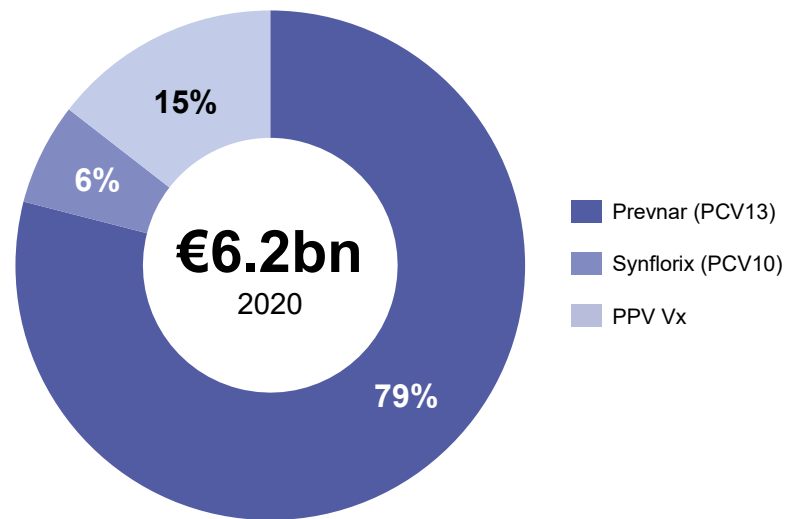
*Initiation of Phase I with RSV older adults combo planned for 2023*



mAb: monoclonal antibody HMPV: Human metapneumovirus  
Note: Figure is from manuscript in preparation through SP/UT collaboration. SP innovation  
(1) Gen1 was unstable, necessitating next generation designs Source: Data on file

# Pneumococcal: more serotypes for better protection

## Large established market



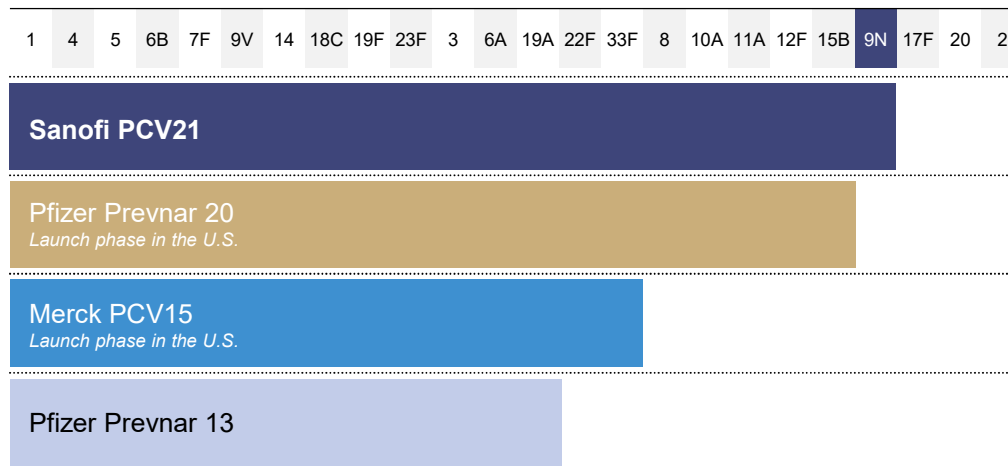
## Strong fit with existing franchises

- **Synergy** with pediatric and older adult portfolio
- **State of the art formulation expertise** with multi-valent vaccines
- **Partnership with SK Bioscience**
  - Complementary capabilities
  - Investment and risk sharing

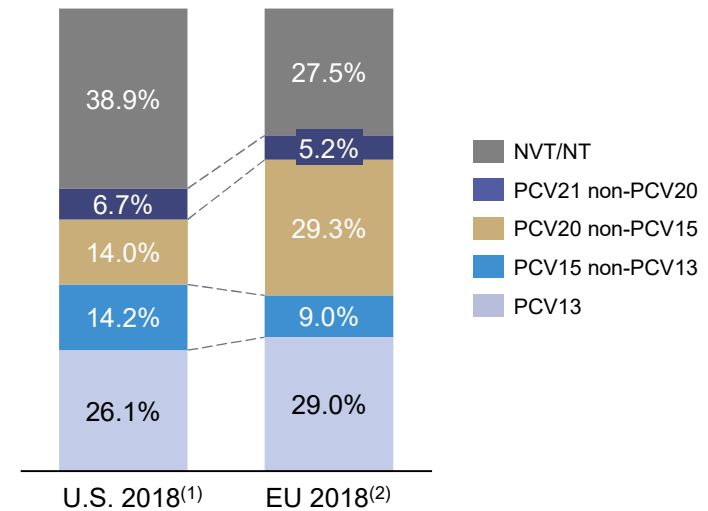


# Raising the bar with PCV21 candidate

## Serotype composition per vaccine



## IPD coverage in all ages by serotype (%)



**Addition of 9N serotype allowing for ~5-7% pts gain in IPD coverage**

# Extensive Phase II program across all age groups



## Infant Primary

n=700

- 2-4-6 months primary series & booster dose
- 3 PCV21 formulations vs. PCV13



## Toddler

n=140

- Booster dose for toddlers having received 3 doses of PCV13
- 3 PCV21 formulations vs. PCV13



## Adult $\geq 50$ years old

n=750

- Subjects naïve to prior PCV vaccination
- 3 PCV21 formulations vs. PCV13 & Pneumovax23

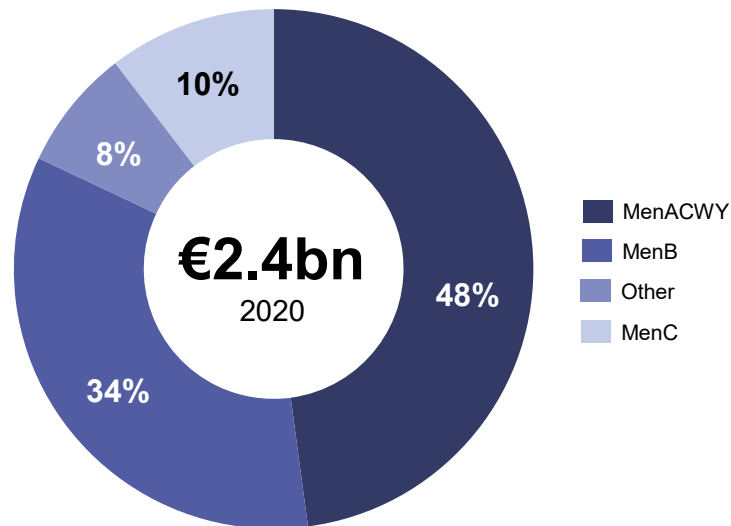
---

***Read-out in all 3 populations expected end of 2022; Phase III initiation planned in 2023***

---




# Meningitis: Strengthening our leadership

## Market overview



- **Established leader** with Menactra in the U.S.
- **MenQuadfi as a new standard in MenACWY**, with superior serotype C response to ease market conversion to quadrivalent
- **Aiming for competitive MenB** with broader strain coverage & longer duration of protection
- **Paving the way for best-in-class MenPenta** in fully liquid format

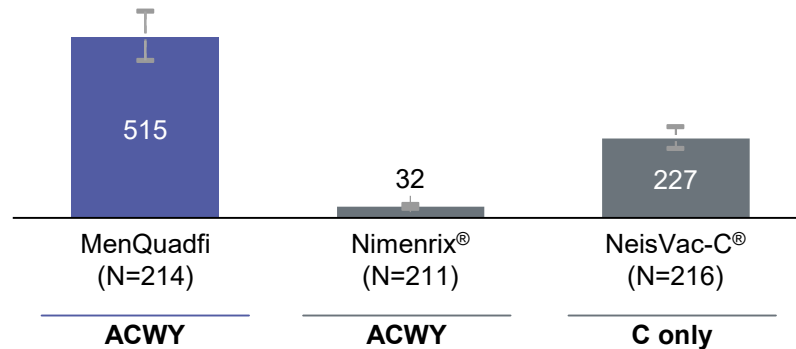
# MenQuadfi as a new standard in MenACWY

		MenQuadfi Sanofi (ACWY)	Menveo GSK (ACWY)	Nimenrix Pfizer (ACWY)
	<b>Enhanced immunogenicity,</b> with superiority against MenC in toddlers	✓	✗	✗
	<b>Fully liquid quadrivalent</b>	✓	✗ <sup>(1)</sup>	✗
	<b>Broadest age indication</b>	<div>U.S. ≥2 yo</div> <div>EU ≥12 months old</div> <div>Int'l ≥12 months old</div>	<div>≥6 weeks as of 2025</div> <div>2 months to 55 yo</div> <div>≥2 yo<sup>(2)</sup></div> <div>≥2 yo</div>	<div>Not registered</div> <div>≥6 weeks</div> <div>≥6 weeks</div>

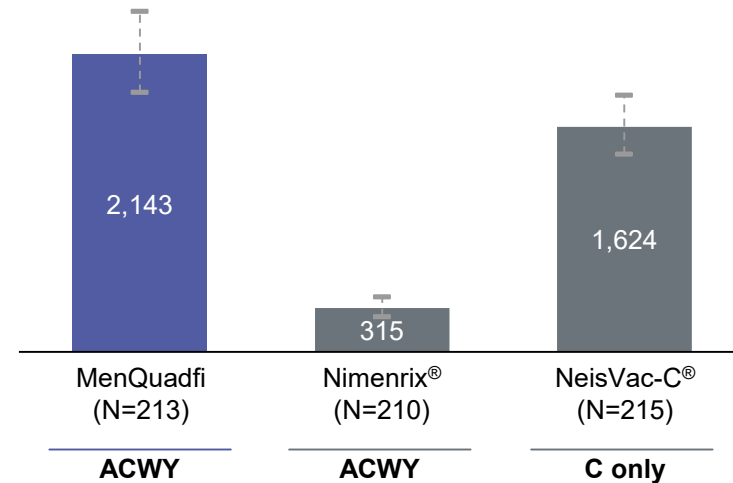
# MenQuadfi is the first & only ACWY vaccine to demonstrate superior immune response against serogroup C

Enabling switch from MenC to MenACWY without compromising on serotype C

Human complement SBA GMTs at D30  
(hSBA GMTs)



Rabbit complement SBA GMTs at D30  
(rSBA GMTs)



*Paving the way for MenPenta*

# Novel MenB vaccine aiming for increased protection

## MenB antigen formulation



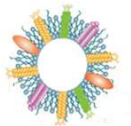
### Non-Lipidated fHBP A+B

- Two fHBP covering all MenB strains
- Non-lipidated formulation allowing for better safety



### NadA

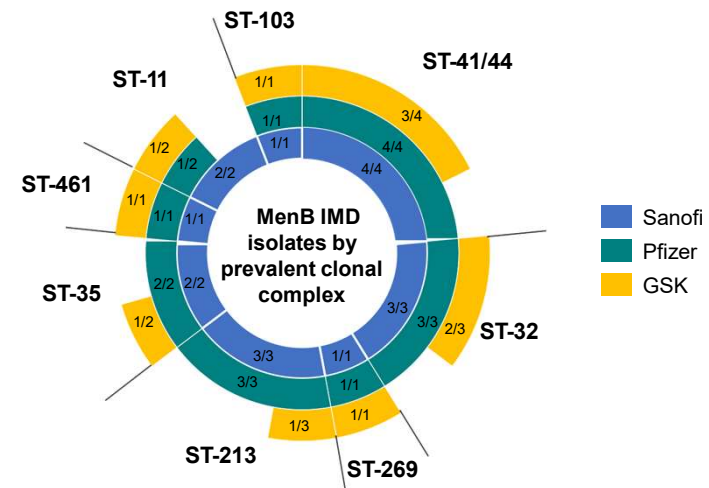
- Increasing strain coverage



### Outer Membrane Vesicle

- Increasing strain coverage
- Potential adjuvant effect

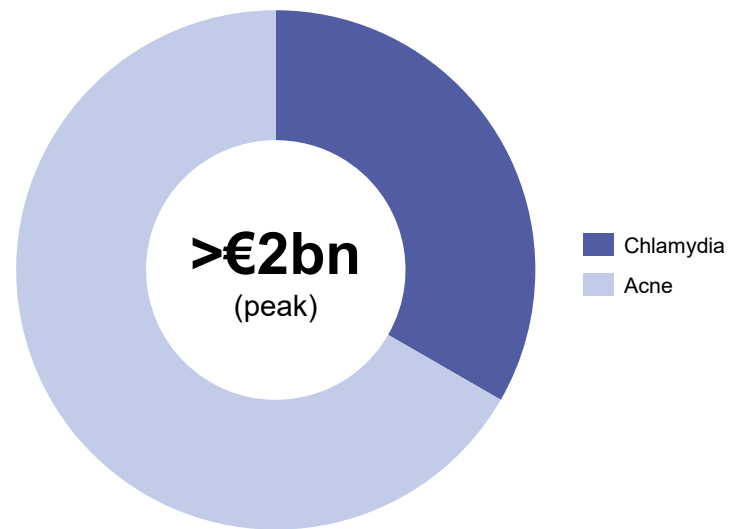
## Broader coverage of MenB strains<sup>(1)</sup>



**MenB Phase II read-out expected in 2022 – MenPenta Phase I initiation in 2023**

# Pioneering science to open new growth areas

## Market overview (estimate)

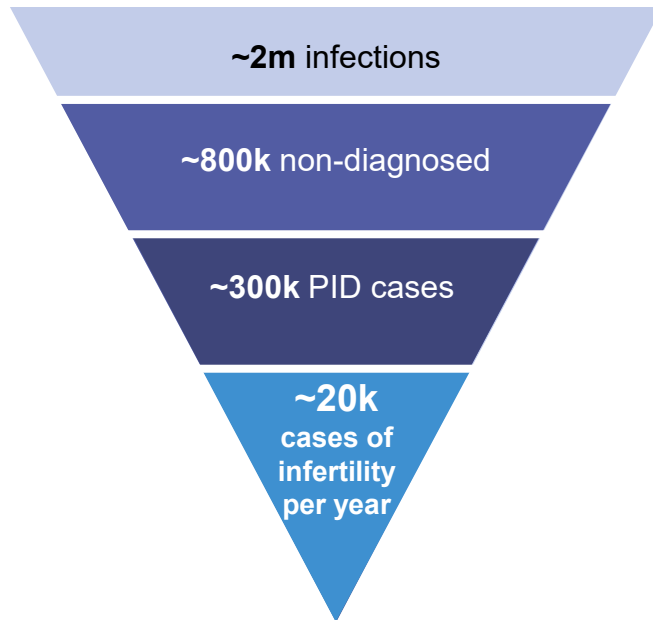


## Delivering first-in-class vaccines

- **Chlamydia:** tackling the most common infectious cause of female infertility
- **Acne:** first immunotherapy to treat acne

# Chlamydia: a silent cause of infertility in women

## Annual U.S. incidence in women



## Overwhelming burden in young women

- **69% of estimated annual cases amid young women aged 24 years old or less**
- **Undiagnosed cases can lead to severe complications, particularly in women**
  - Pelvic Inflammatory Cases
  - Tubal infertility
  - Ectopic pregnancy
  - Chronic pelvic pain

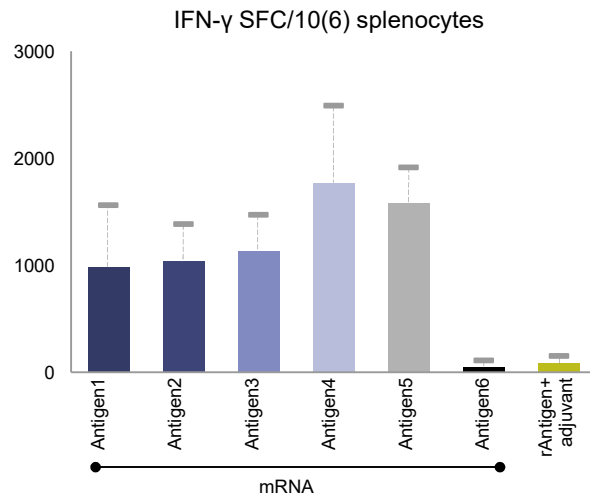
PID: Pelvic inflammatory disease

Source: Multiple sources for estimate reconstitution: CDC - Sexually Transmitted Disease Surveillance, 2019 & Chlamydia Fact Sheet, 2018; Land JA, Van Bergen JE, Morré SA, Postma MJ, Hum Reprod. Update, 2010; Price MJ, Ades AE, De Angelis D, et al. Am J Epidemiol., 2013 ; Heisterberg L. Obstet Gynecol., 1993; Ades AE, Price MJ, Kounali D, et al. Am J Epidemiol., 2017; World Bank demographic data 2020

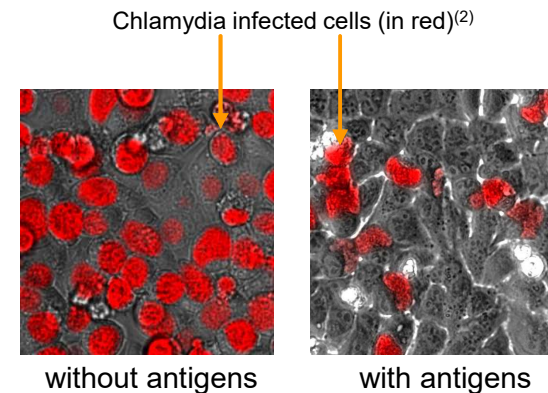


# Chlamydia: mRNA best-suited platform to deliver desired immune response

Optimized antigen for strong CD4 T-cells response<sup>(1)</sup>

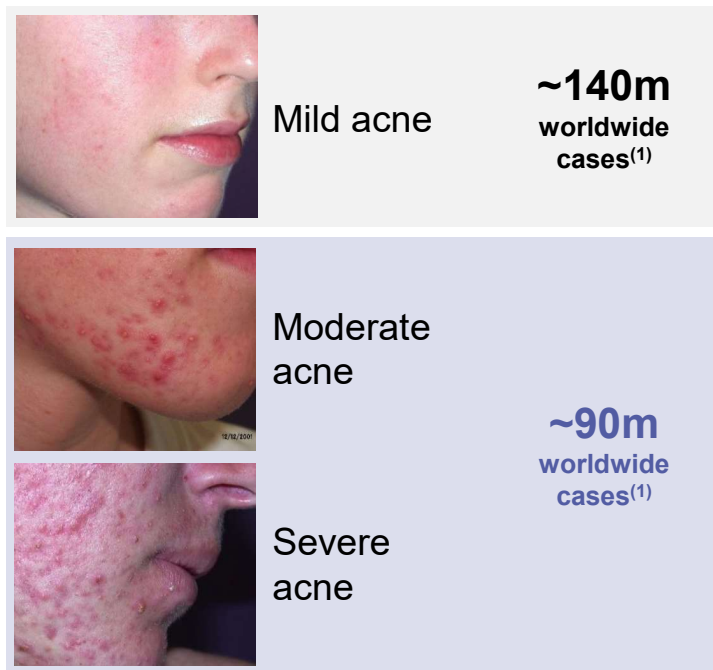


Selecting additional antigens to prevent Chlamydia entry in endocervical cells



*mRNA-based multi-component vaccine Phase I launch expected in 2023*

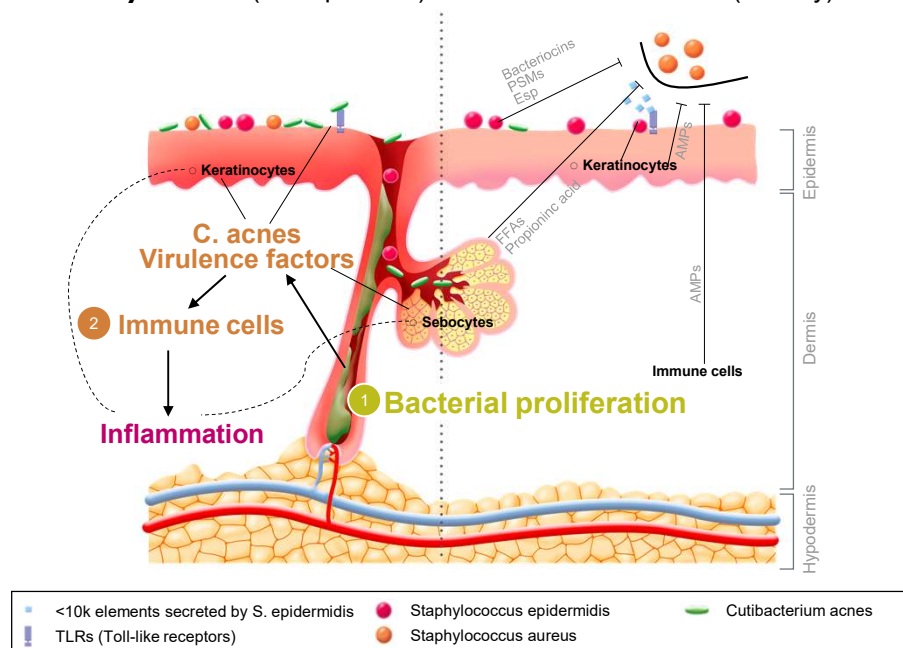
# Acne: a stigmatizing condition



- Significant **psychological** impact
- **Current SoC** (oral isotretinoin) with **severe side effects**
- **Significant out-of-pocket expenses** (\$360-\$720<sup>(2)</sup> / year in the U.S.)
- *P. acnes* bacterium also associated with **several conditions beyond acne**:
  - Other dermatological conditions<sup>(3)</sup>
  - Medical device-related infections<sup>(4)</sup>
  - Prostatic inflammation thought to contribute to prostate cancer<sup>(5)</sup>

# Immune system plays a significant role in moderate-to-severe acne

**Skin dysbiosis (acne patients)**    **Skin homeostasis (healthy)**



**Origimm's antigen induce a functional immune response against *C. acnes* virulent strains**

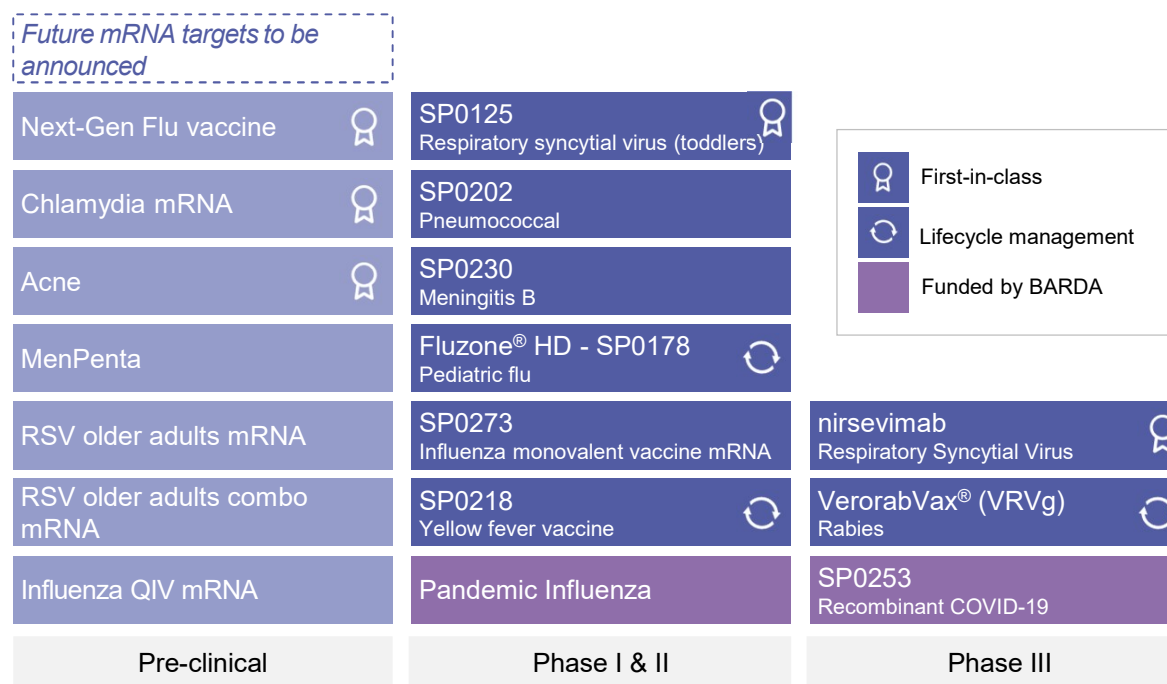
<i>C. acnes</i> phylotype	Origimm's antigens
IA1	+++
IA2	+++
IB	++
IC	+++
II	++
III	(+)

Opsonophagocytic killing by antigen specific mouse sera

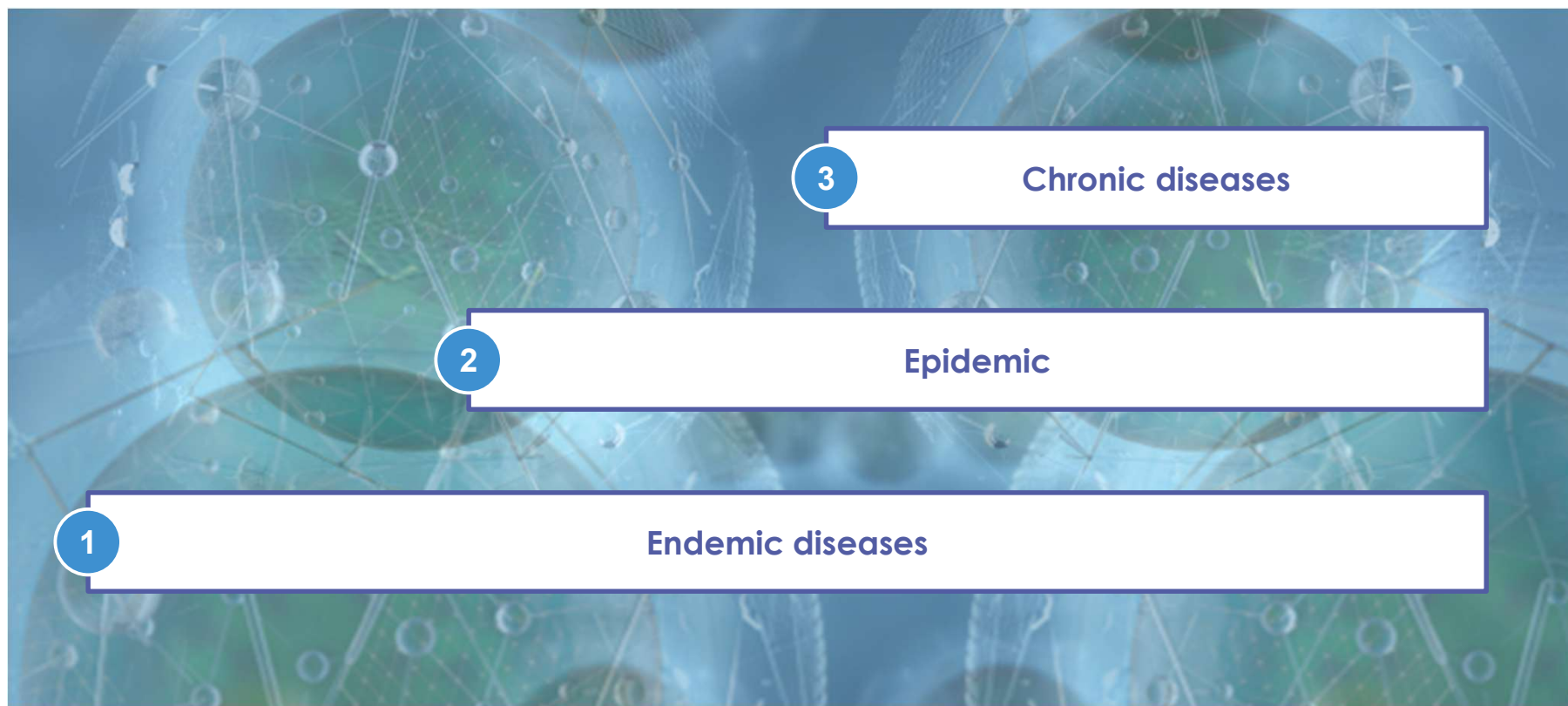
***Vaccine solution as a first immunotherapy to safely treat moderate-to-severe acne***

# Building an industry leading pipeline in Vaccines

- Target to advance **10 clinical candidates by 2025**, incl. 6 mRNA vaccines
- Opportunity to be **first-in-class** and lead in several new therapeutic fields
- Right mix between **LCM**, **proven targets** and **breakthrough vaccines**



# Opening a new chapter for Sanofi Vaccines R&D





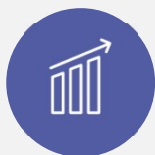
## Conclusion

Thomas Triomphe

Head of Vaccines GBU



# Our ambition in Vaccines



**Continued strong growth  
driven by four core franchises:  
Influenza, Meningitis, PPH &  
Boosters, RSV**



**Unlocking the potential of  
mRNA in Vaccines with  
Next-Generation platform**



**Building an industry  
leading pipeline to  
address unmet needs**

---

***More than doubling Vaccine sales by 2030<sup>(1)</sup>***

---

## Q&A session | Leading with innovation



**Thomas Triomphe**  
Head of Vaccines GBU



**Jean-François  
Toussaint**  
Head of Vaccines R&D



**Frank DeRosa**  
Head of Research for  
mRNA CoE



**Thomas Grenier**  
Head of Franchises &  
Product Strategy



**Jon Heinrichs**  
Head of R&D RSV  
Franchise