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Canada

# COVID-19 Vaccine Candidates in Development, special focus on mRNA and viral vector platforms

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PROTECTING AND EMPOWERING CANADIANS
TO IMPROVE THEIR HEALTH

# Disclosures

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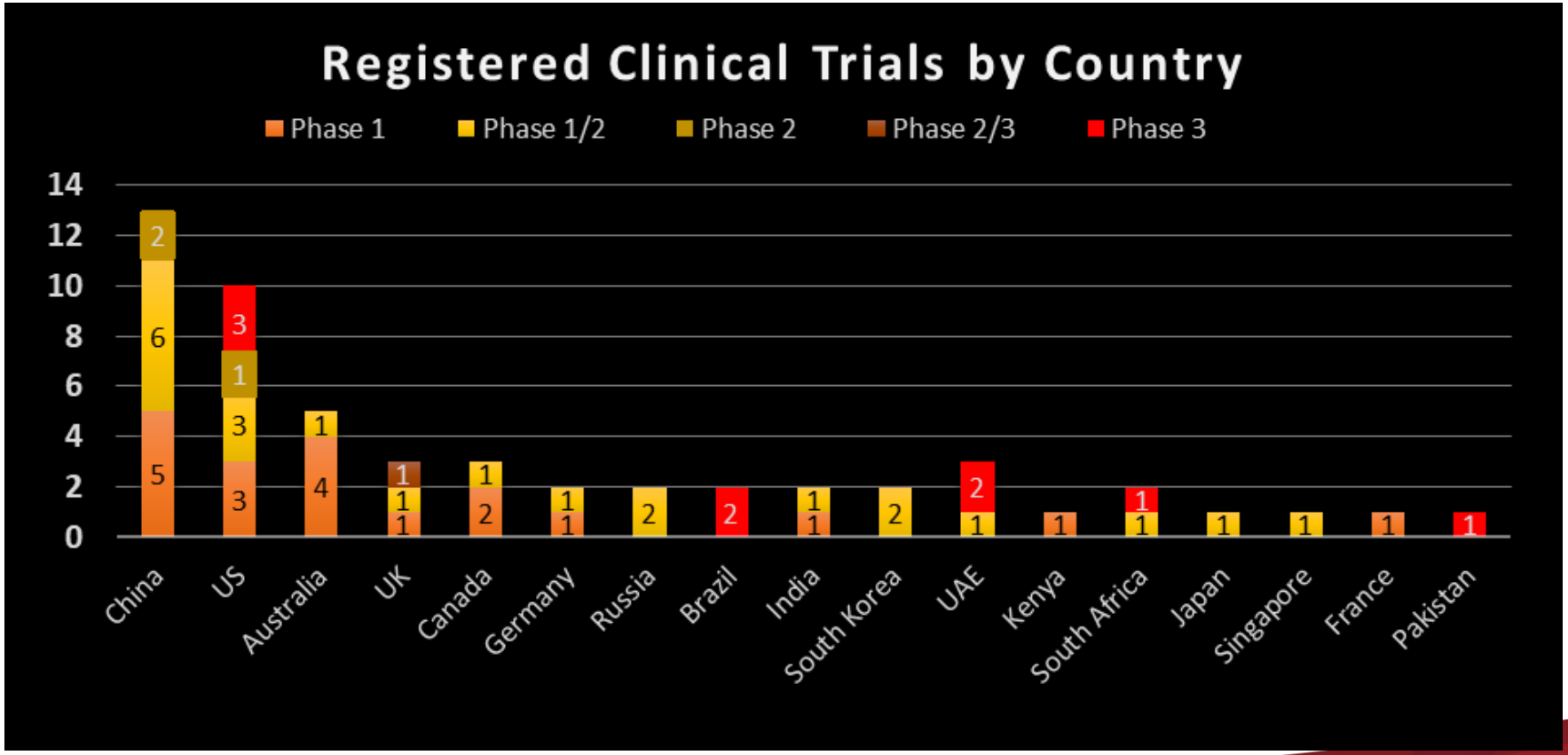
- None of the presenters have potential conflicts of interest to declare.

# OBJECTIVE

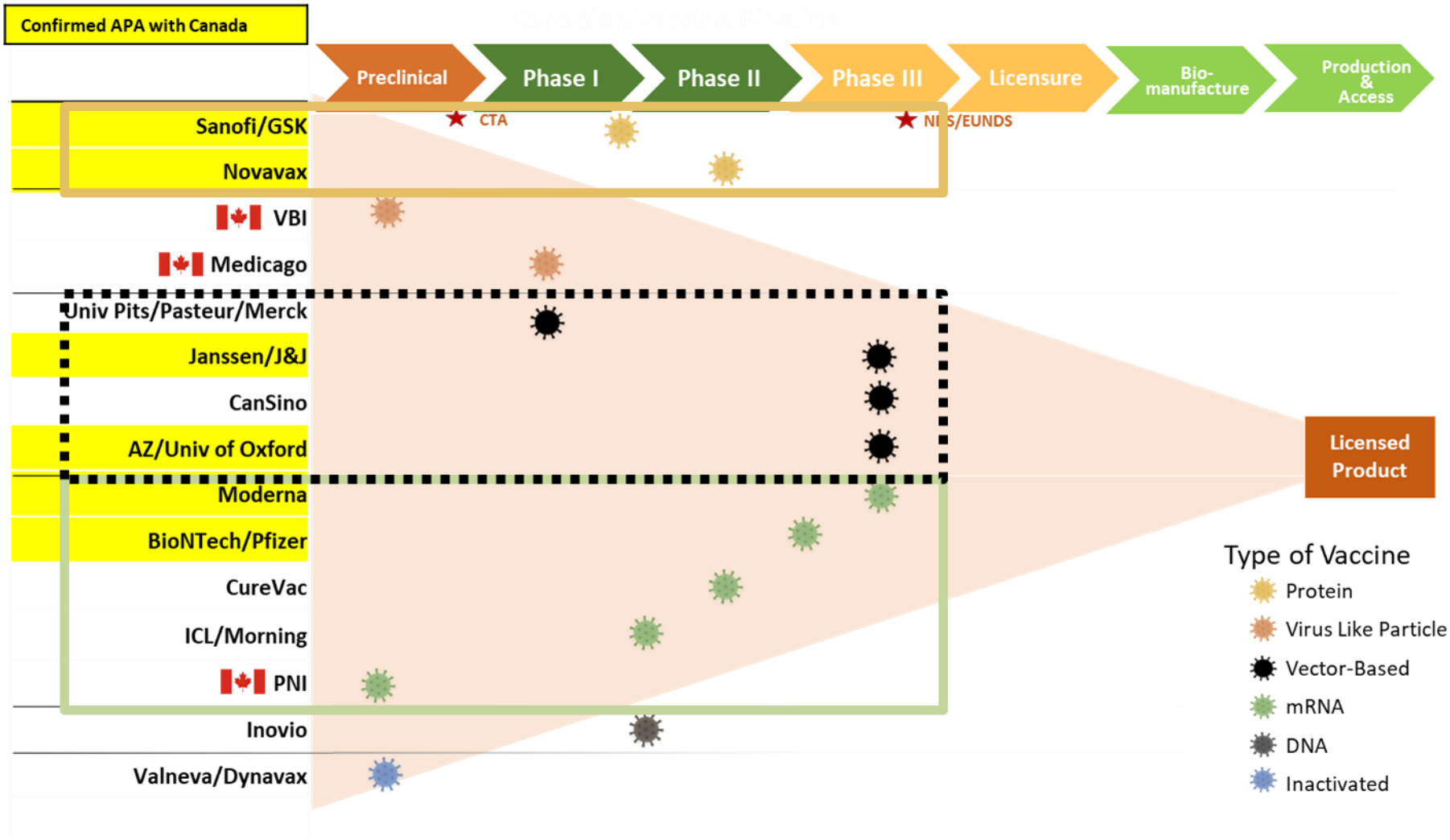
- Describe the mechanism of action of mRNA, viral vector and protein-based vaccines
- Discuss the evidence available for vaccines in development that may be available in Canada if proved safe and effective

# Global COVID-19 Vaccine Development Landscape:

- As of September 24, 2020, **63** clinical trials have been registered for developmental vaccine candidates against COVID-19.
- Two anti-SARS-COV-2 vaccine candidates have obtained regulatory authorization to initiate clinical trials in Canada and one vaccine candidate has begun clinical testing in Canada (**Medicago**).



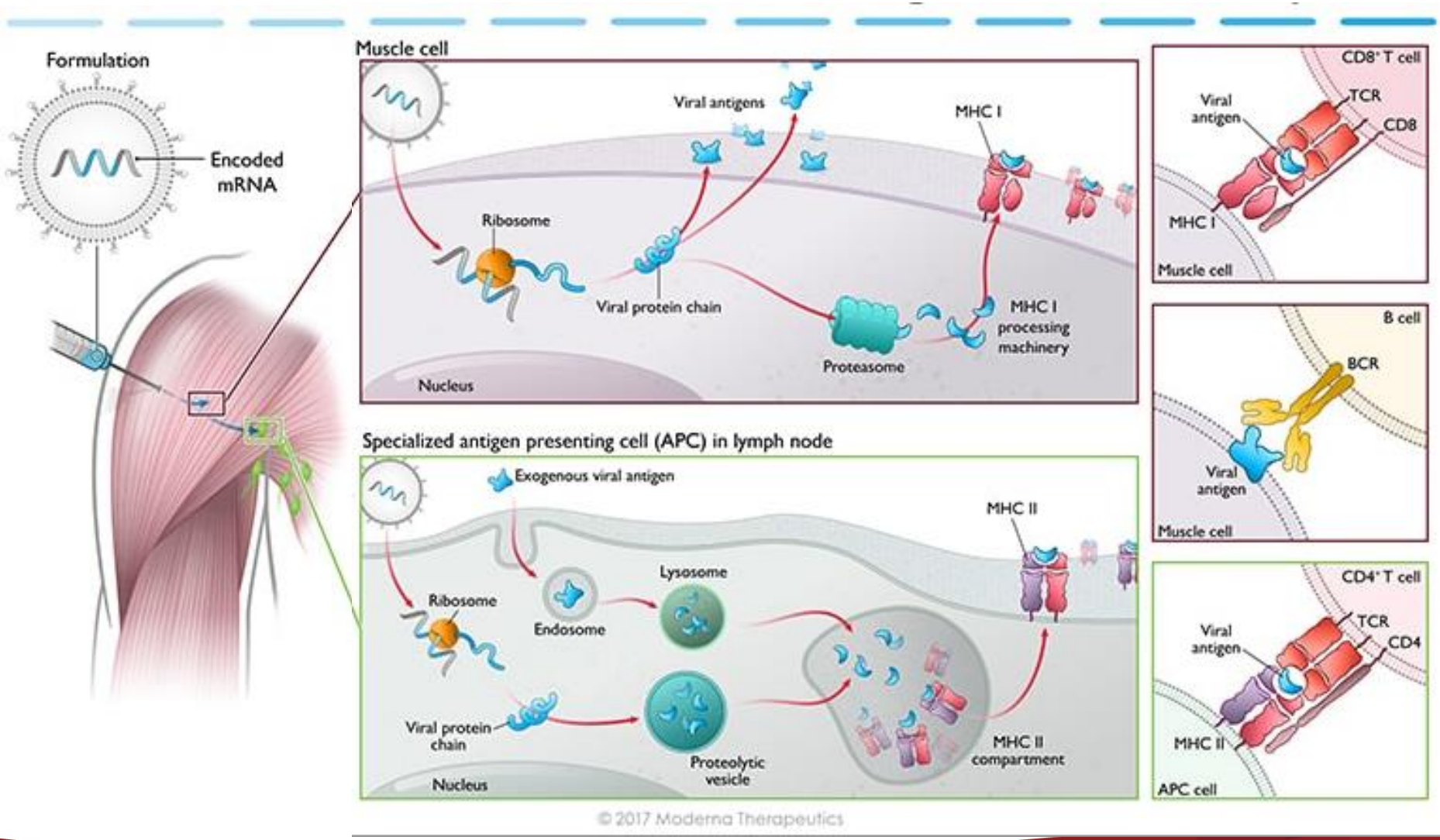
# Lead Candidate COVID-19 Vaccine Development Landscape:




**Protein-based (top box), viral vector based (middle box) and mRNA (bottom box) and technology constitute the majority of the front running COVID-19 vaccine technologies.**

# mRNA

# mRNA Vaccines: Mechanism of Action



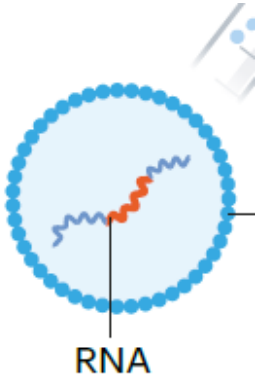
# Two Nucleic Acid-Based Vaccine Platforms: DNA vs mRNA

| | DNA | mRNA |
|---|---|---|
| Stability | DNA is **more stable** than RNA, and remains intact longer inside and outside the cell. | RNA is far **less stable**. Companies use tricks like modified nucleic acids to try to increase stability. |
| Mechanism of Action | DNA needs to get **inside the cell** and then **inside the nucleus**. DNA needs to be first transcribed into mRNA and then translated into protein antigens to elicit cellular and humoral immune responses. DNA needs to cross **two membranes** may require specialized technology to enter the nucleus (ie: electroporation). | RNA skips a step and needs **only to enter into the cell** for translation alone. RNA needs only to cross one membrane therefore RNA can be delivered via a lipid coating which is commonly referred to as a **lipid nanoparticle**. |
| Risk of genomic integration | Some risk | No Risk |

Note: Lipid nanoparticle technology was developed in/around UBC and Vancouver is currently a hub for RNA vaccines

# mRNA-based Vaccine Platform:

| | |
|---|---|
| Advantages: | • Fast manufacturing and interchangeable antigen<br>• Anticipated activation of cellular and humoral immune responses |
| Disadvantages: | • No RNA vaccine is authorized, unknown stability, durability and safety<br>• Supply chains of materials may be unstable |




| Organizations | Platform | Stage of Development |
|---|---|---|
| Moderna (US) | Non-replicating mRNA lipid nanoparticle | Phase 3 clinical trials in the US. |
| BioNTech SE/Pfizer (Germany/USA) | Non-replicating, modified mRNA lipid nanoparticle | Phase 2/3 clinical trials in the US and Germany. |
| CureVac (Germany) | RNA lipid nanoparticle | Phase 1 clinical trials in Belgium and Germany. |
| Imperial College London (UK) | Self amplifying RNA lipid nanoparticle | Phase 1 clinical trials in the UK. |
| Precision Nanosystems (British Columbia) | RNA lipid nanoparticle | Preclinical. |

Moderna and BioNTech/Pfizer are the first to have signed Advanced Purchase Agreements (APAs) with the Canadian government.

# Pfizer/BioNTech Vaccine Candidate:

**Walsh et al preprint data for Phase 1 NCT04368728:**

Vaccine: Two doses IM of BNT162b2 (Non-replicating RNA expressing SARS-COV-2 spike glycoprotein formulated as a lipid nanoparticle) 21 days apart compared to BNT162b1 (RBD antigen) and placebo controls. Four dose levels were investigated for each candidate vaccine.

Population: Two Cohorts 18-55 (n=15) and 65-85 (n=15) non-pregnant adults with no-comorbid conditions.

Safety: **Dose and Age Dependant**

- Solicited adverse events were dose-dependant and more were reported in the younger vs the older cohorts.
- BNT162b2 elicited fewer SAEs than BNT162b1.
- Severe systemic events (fatigue, headache, chills, muscle pain, and joint pain) were reported in small numbers of younger BNT162b2 recipients, but no severe systemic events were reported by older BNT162b2 recipients.

Immunogenicity:

- Antigen-binding and neutralizing antibodies were dose-dependant, consistent across age groups and within the range of convalescent sera.

# Moderna Vaccine Candidate:

**Jackson et al NEJM for Phase 1 NCT04283461**

Vaccine: Two doses IM of mRNA-1273 (Non-replicating RNA expressing pre-fusion SARS-COV-2 spike glycoprotein formulated as a lipid nanoparticle) 29 days apart compared to placebo. Five dose levels were investigated for each candidate vaccine.

Population: Non-pregnant adults with no-comorbid conditions. One age cohort in the publication 18-55 (n=45), two additional age cohorts in the trial 56-70 and 71+.

Safety: **Dose Dependant Reactogenicity**

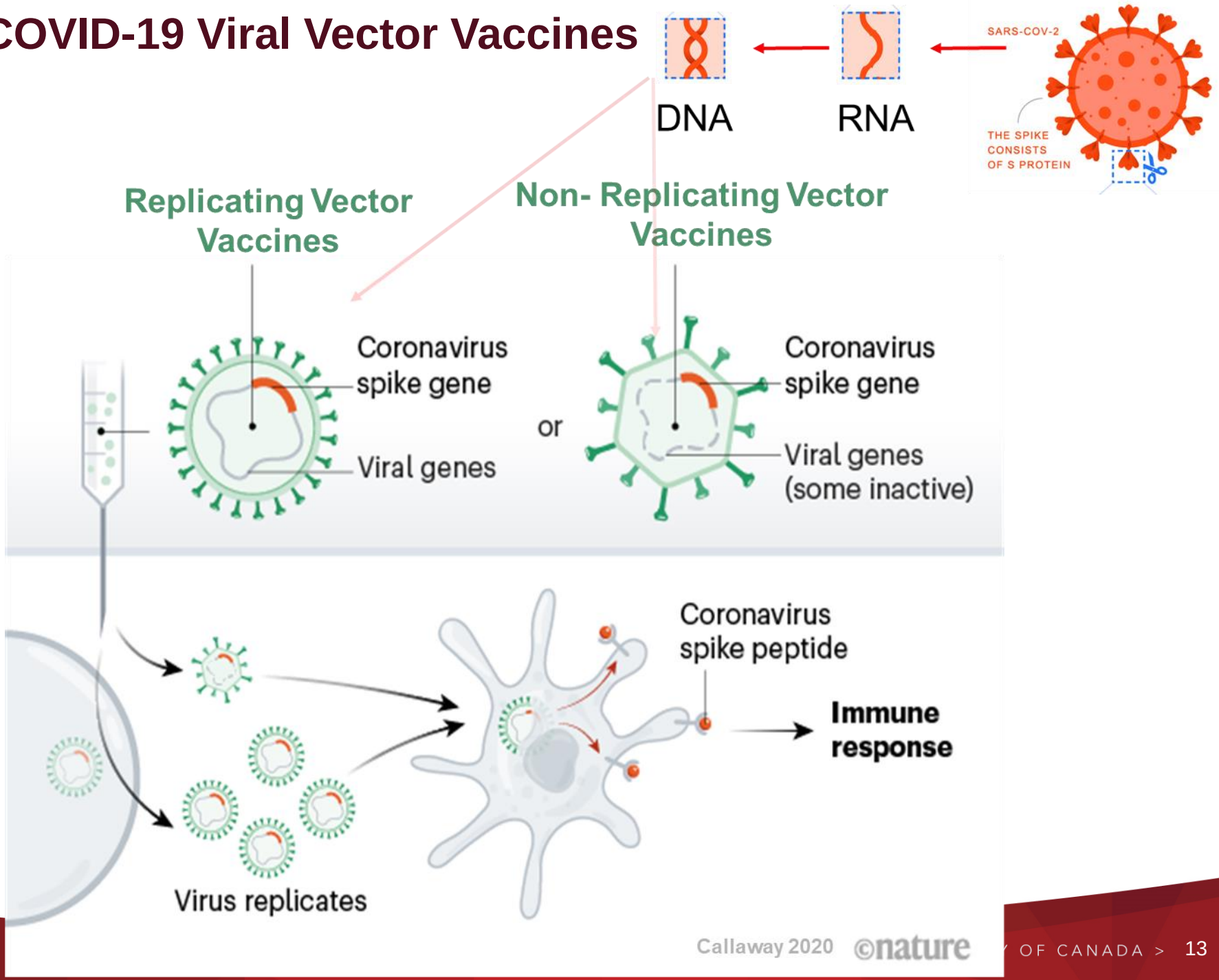
- Solicited adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site.
- Systemic adverse events were **more common after the second vaccination**, particularly with the highest dose, and three participants (21%) in the 250-μg dose group reported one or more severe adverse events.

Immunogenicity:

Antigen-binding and neutralizing antibodies were dose-dependant, consistent across age groups and within the range of convalescent sera

# Viral Vectors

# COVID-19 Viral Vector Vaccines



# Viral Vector Vaccines

**Advantages:**

- Established activation of humoral and cellular responses without adjuvant
- Potential for boosted immunity to vector
- 3 vaccines already approved for human use (*see below*)

**Disadvantages:**

- Potential for dampened immune responses due to vector seropositivity
- Potential blunting of future vaccines using the same platform

| *Vaccine* | *Indication* | *Jurisdiction* | *Viral Vector Platform* |
|---|---|---|---|
| *DengVaxia* | *Dengue, Yellow Fever* | *Over 20 countries including US and Mexico* | *CYD-TDV is a tetravalent, live attenuated, chimeric dengue vaccine in a yellow fever 17D backbone* |
| *Zabdeno / Mvabea* | *Ebola* | *Europe* | *Ebola vaccine consists of 2 components, Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo).* |
| *Ervebo* | *Ebola* | *Europe, US* | *Ebola vaccine based on the VSV vector platform* |

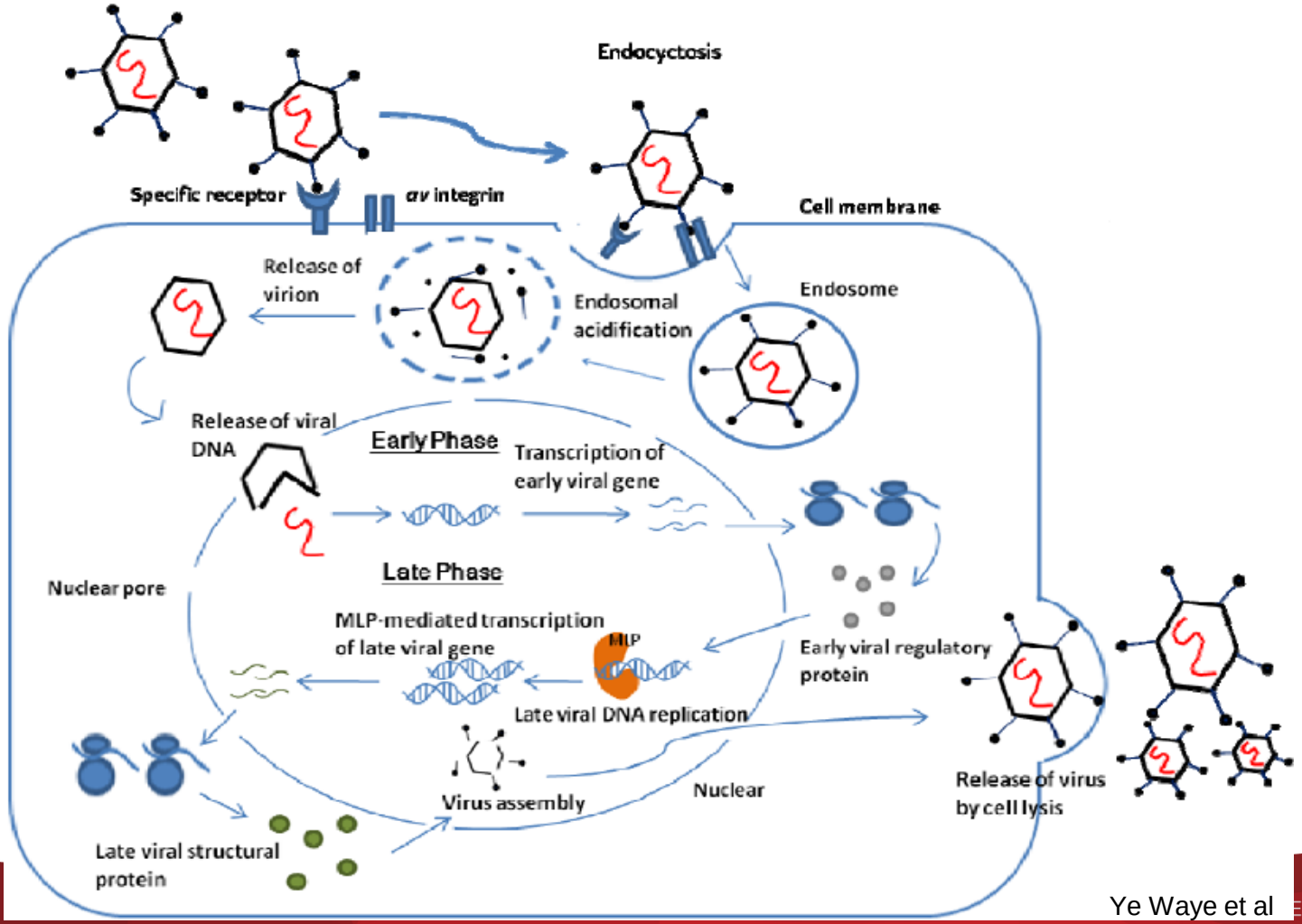
# COVID-19 Antigen Vectors

| | *Non-Replicating* | | | *Replicating* | | |
|---|---|---|---|---|---|---|
| | **AD5** | **AD26** | **NHP-AD** | **VSV** | **Measles** | **Infl A** |
| **Developers** | • Cansino<br>• Gamaleya RI | • **Janssen/J&J**<br>• Beth Israel/J&J<br>• Gamaleya RI | Chimpanzee:<br>• **AstraZeneca**<br><br>Simian:<br>• Reithera | • Meck/IAVI | • Merck/Pasteur | • Univ HK |
| **Human Sero-prevalence** | Region dependant:<br>• Africa 70-80%,<br>• Asia 60%,<br>• **North America 30%** | Region dependant:<br>• Africa and Asia 60%,<br>• **North America 10%** | None | Limited (insect and livestock virus) | Vaccine status dependant | High |
| **Potential for wild-type reversion** | Possible | Possible | Unlikely | Unlikely | Very Unlikely | Unknown |
| **Potential for genomic insertion** | Possible | Possible | Possible | Unlikely | Unlikely | Unlikely |
| **Platform Used in Previously Licenced Vaccines** | No | Yes (Ebola) | No | Yes (Ebola) | Yes | Yes |

NHP- Non Human Primate VSV- Vesicular stomatitis virus

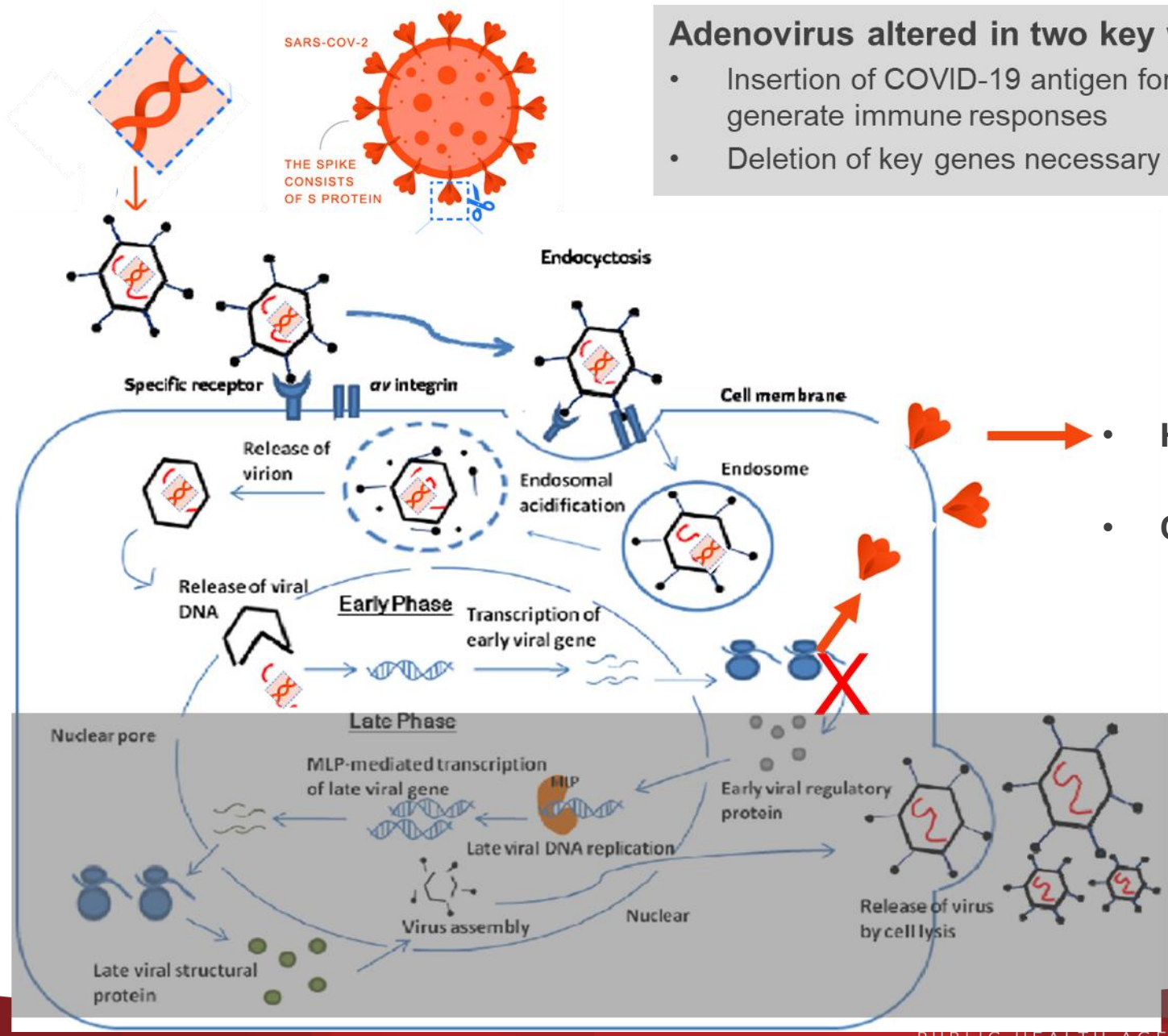
# Adenovirus Infection

- Most common serotypes in clinical samples [Respiratory infections: 1, 2, 3, **5**, 7] and [Gastroenteritis infections: 40, 41]
- Age dependant seroprevalence: [First year of life: 1, 2, **5**, 6] [School-age: 3, 7] and [Adulthood: 4, 8, 19]
- Ad26 infection: mild rhinitis and conjunctivitis




Ye Waye et al

# Non-Replicating Adenovirus Vaccine Vectors




**Adenovirus altered in two key ways:**

- Insertion of COVID-19 antigen for transit into host cells to generate immune responses
- Deletion of key genes necessary for viral replication

- **Humoral Immunity** (antibodies)
- **Cellular Immunity** (CD8 and CD4 T Cells)

# COVID-19 Viral Vector-Based Vaccines:

| Organizations | Platform | Stage of Development |
|---|---|---|
| Janssen/Johnson&Johnson | Non-replicating Adenovirus 26 viral vector | Phase 3 in US |
| AstraZeneca / University of Oxford (UK) | Non-replicating Chimpanzee adenovirus viral vector | Phase 3 clinical trials in UK, South Africa, Brazil, US and Russia |
| CanSino Biological Inc. (China) | Non-replicating Adenovirus 5 viral vector | Phase 3 in Pakistan and Russia |
| Gamaleya Research Institute (Russia) | Combination of Non-replicating Ad5 and Ad26 platforms | Phase 3 in Russia* |
| Johnson&Johnson/Beth Israel (US) | Non-replicating adenovirus 26 viral vector | Phase 1/2 in US |
| Reithera (Italy) | Non-replicating simian adenovirus vector | Phase 1 in Italy |
| Merck/Themis/Institut Pasteur (US/Aus/France) | Replicating measles virus vaccine platform | Phase 1 in France |
| University of Hong Kong/Xiamen University (China) | Replicating flu virus vaccine platform | Phase 1 in China |

Janssen/Johnson&Johnson and AstraZeneca/University of Oxford have made a commitment in principle to supply vaccines to the Canadian government.

*Approved by Russian Government

# Ad26 Immunogenicity and Safety Data: Janssen/Johnson&Johnson

**Sadoff et al Preprint NCT04436276**

***Interim Analysis at day 29 after one dose***

Population: 18-55 years old (n=402), 65+ (n=394, n=15 in interim analysis) in the US and Belgium evaluating two dose levels and for either one or two doses (8 weeks apart).

Safety: ***(blinded) Age and dose dependant Reactogenicity***

- Solicited local adverse events were observed in 58% (younger) and 27% (older) of cohorts. More reactogencitiy observed in higher dose groups.
- The most frequent local adverse event (AE) was injection site pain and the most frequent solicited AEs were fatigue, headache and myalgia.
- No grade 4 AEs, solicited or unsolicited, were reported in any cohort

Immunogenicity: ***(unblinded)***

- *Humoral Responses*: >90% of the younger cohort seroconverted via measures of binding and neutralizing antibodies by day 29. Responses within range of convalescent plasma. Data was incomplete for the older cohort
- *Cellular Responses*: By day 14, subset of younger and older cohort members showed no evidence of Th-2 biased CD4 responses.

Effect of Vector Immunity: ***Unknown***

- No evaluation in this interim analysis

# Ad5 Immunogenicity and Safety Data: CanSino

**Zhu et al Lancet Phase 2 NCT04341389.**

Population**:** Phase 2 trial of 508 healthy adults 18+ with no history of COVID and HIV negative in Wuhan, China.

Safety: ***Highly Reactogenic Vaccine***

Solicited adverse reactions were reported by ~70% both the low and high dose groups. Severe adverse reactions were reported by 9% participants in the high dose group and 1% participant in the low dose group. No serious adverse reactions were documented.

Immunogenicity ***Time and Age-dependant responses***

- All participants seroconverted by day 14 as measured by binding and neutralizing antibodies.
- Immune responses were time dependant (higher at day 28 vs day 14)
- Older participants had lower binding and neutralizing antibody responses.

Effect of Vector Immunity: ***Ad pre-immunity may limit neutralizing antibodies***

- Among the 508 participants, 266 (52%) had high pre-existing immunity and 242 (48%) had low pre-existing immunity to the Ad5 vector.
- Participants with **high pre-existing anti-Ad5 immunity** had binding and neutralizing antibody levels that were approximately **two-times lower** than the participants with low pre-existing anti-Ad5 immunity.
- High pre-existing Ad5 immunity correlated with age.

**Note: Ad5 seroprevalence in NA is ~30% whereas AD26 seroprevalence is ~10%.**

# ChAd Immunogenicity and Safety Data: AstraZeneca/Univ Ox

**Folegatti et al Lancet Phase 1/2 NCT04324606**

Population**:** Phase 1/2 trial of 543 healthy adults 18-55 with no history of COVID, compared to meningococcal conjugate vaccine (MenACWY) as control (n=543). (median age: 35, majority white). 10 participants received a second dose on day 28.

Safety: ***Serious Concerns***

- Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group (67% vs 38%) and many were reduced by use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise (all p<0·05).
- Protocol amendment at 2/5 sites allowed prophylactic administration of paracetamol before vaccination.
- **Phase 3 studies stopped due to reporting of at least one participant with transverse myelitis, as of Sept 28 US arm still stopped**

Immunogenicity ***Dose-number dependant responses***

- All participants that received one dose had binding and neutralizing within the range of convalescent plasma.
- Individuals with two doses got higher responses, still within the range of convalescent plasma. Two dose group may have increase durability of response.

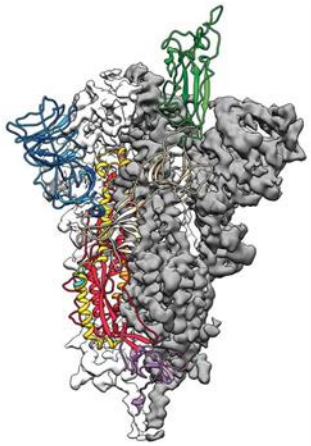
Effect of Vector Immunity: ***Ad pre-immunity***

- 1% of participants had high titre of vector-neutralizing antibodies, antibodies detected in further 18% of ~100 participants.
- Found no relationship between pre-existing immunity and levels of binding antibodies

# Protein-based

# Protein-based Vaccines: Mechanism of Action

***SARS-COV-2 Spike***



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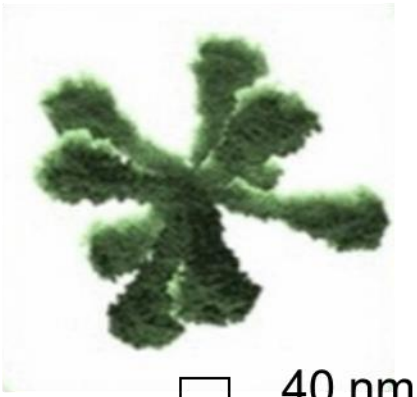
***Adjuvant***

Matrix M is a nanoparticle composed of saponins, cholesterol and lipids

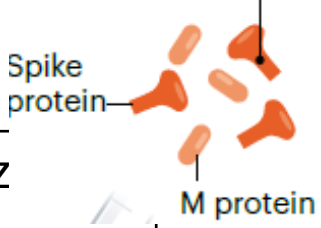
***Vaccine Nanoparticle***



40 nm

- **Humoral Immunity**
  (antibodies)
- **Cellular Immunity**
  (CD8 and CD4 T Cells)

# Subunit Protein Vaccine Platform:




| | |
|---|---|
| Advantages: | • Platform has been used in previously authoriz vaccines<br>• Fast design and relatively rapid production possible |
| Disadvantages: | • Antigens are less immunogenic and may need an adjuvant |

| Organizations | Platform | Stage of Development |
|---|---|---|
| Novavax (USA/Australia) | NVX-CoV2373: Nanoparticle of recombinant full length SARS-CoV-2 Spike protein (S) in prefusion state with Matrix M adjuvant | • Phase 1/2 in US and UK<br>• Phase 2 in South Africa<br>• Phase 3 in UK |
| Sanofi/GSK collaboration (France, US) | Recombinant trimeric SARS-CoV-2 Spike protein (S) in a baculovirus expression system in SF9 insect cells plus GSK adjuvant. | • Phase 1/2 in US |

# Novavax Vaccine Candidate:

**Keech et al for Phase 1 NCT04368988**

Vaccine: Two doses IM of the FL spike protein subunit vaccine candidate from Novavax given IM with and without Matrix-M1 adjuvant 21 days apart compared to placebo (average age: 30)

Population: 131 healthy, non-pregnant adults with no-comorbid conditions.

Safety: **Dose and Adjuvant Dependant Reactogenicity**

- Two participants had severe events following first vaccination and eight participants following second vaccination
- More frequent in second dose and in adjuvant group, headache, fatigue, and myalgia were the most common

Immunogenicity: **Very strong Immune Responses**

- elicited robust immune responses (IgG and neutralization) **four-fold higher** than the mean observed in COVID-19 convalescent serum

# Key Messages:

- Novel technology, not previously used in vaccines authorized to be used in humans, represents the front runners of COVID-19 vaccines in development.
- All vaccines to be used in Canada, regardless of platform, will need to be authorized for use by experts at Health Canada

*Based on very limited data:*

- All vaccine platforms covered here induce **humoral and cellular responses** in the majority of vaccine recipients
  - Protein-based vaccine (Novavax) induced very high humoral immune responses
- These responses may be **limited by pre-existing immunity and age**
  - Adenovirus –based vaccine: Pre-existing immunity to vector (observed for Ad5 and ChAd, unknown for Ad26) which may be related to age
- Some platforms may be more **reactogenic** than others

***To understand the benefits and risks of this platform, we await phase 3 clinical trial results (late 2020 and 2021).***

# QUESTIONS?