Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

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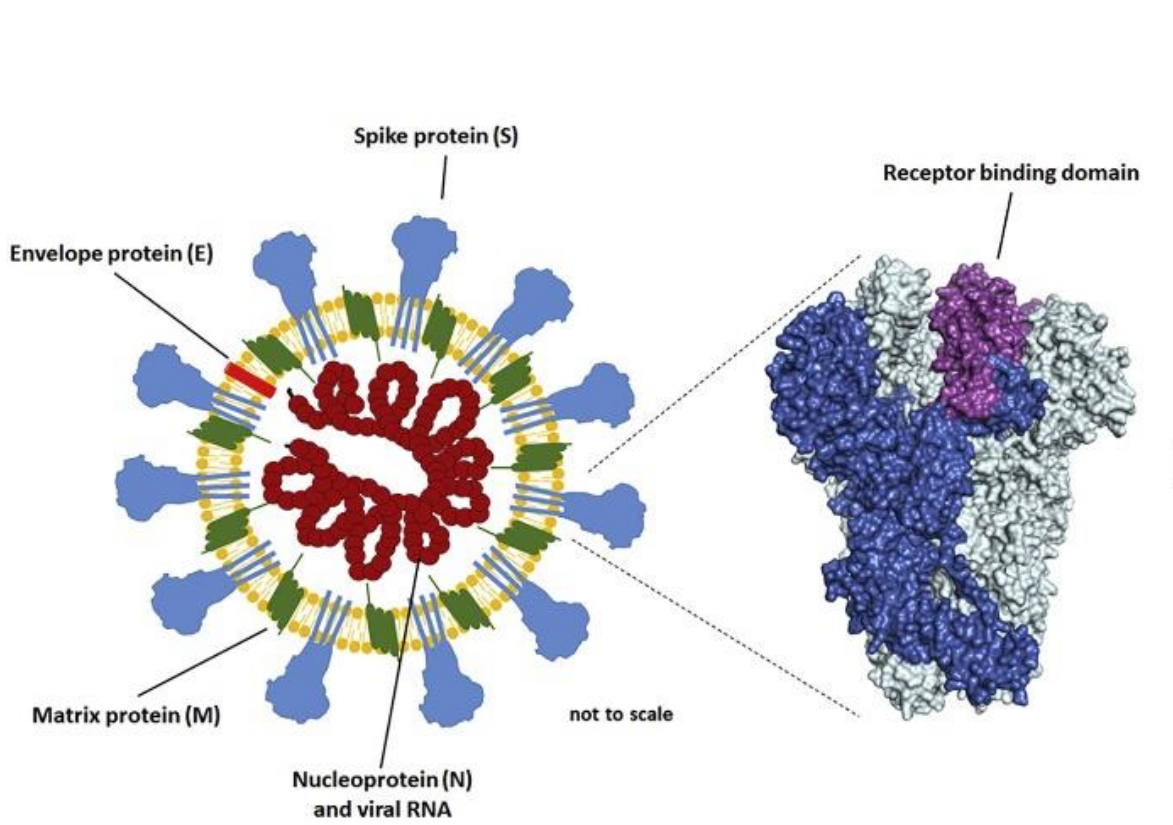
Background

- high transmission of SARS-CoV-2 (Zhu N. et al., *NEJM 2020*)
- 22% of the global population at increased risk of severe COVID-19 if infected (Andrew C. et al., *The Lancet Global Health 2020*)
- low anti-SARS-CoV-2 IgG seroprevalance in general population (Stringhini S. et al., *The Lancet 2020*)
- little effective terapy against SARS-CoV-2
- effective vaccine against SARS-CoV-2 urgently needed

COVID-19 vaccine development pipeline



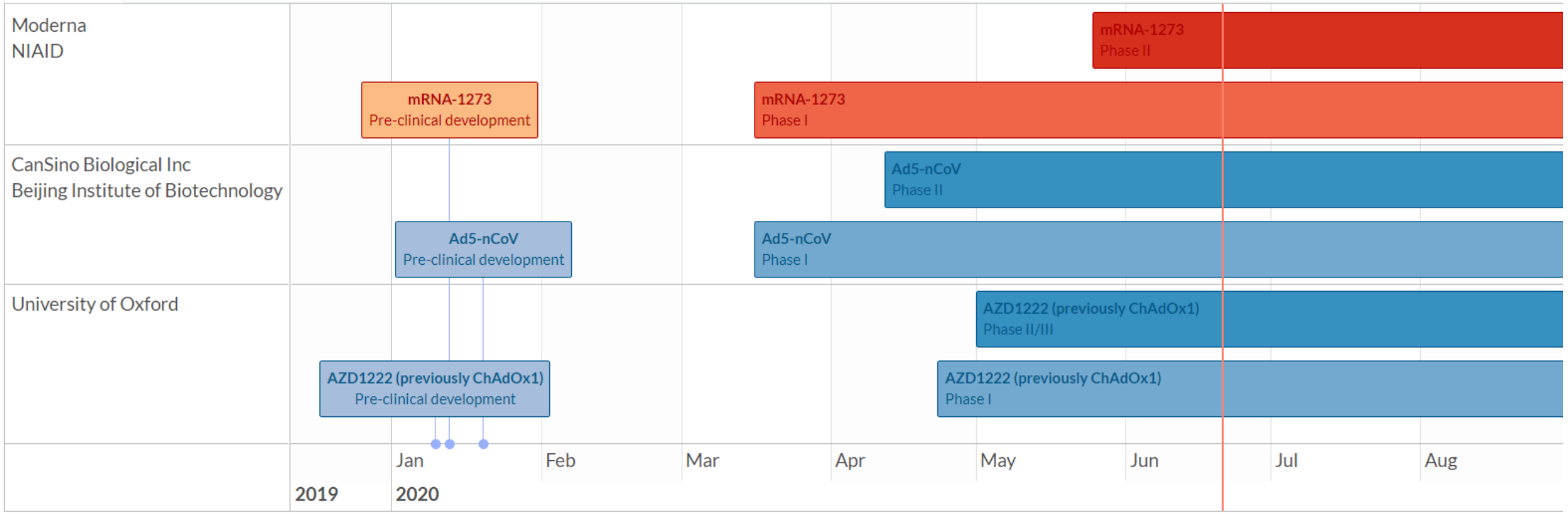
Current stage: Development of vaccine candidates and pre-clinical testing

194 vaccine candidates

RNA vaccines	21
DNA vaccines	12
Recombinant protein vaccines	59
Vectored vaccines	36
Inactivated vaccines	5
Live attenuated vaccines	3

Amanat F., et.al SARS-CoV-2 Vaccines: Status report. Immunity April 2020 https://doi.org/10.1016/j.immuni.2020.03.007

COVID-19 vaccine phase II/III



https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/

Methods

- Design:
  - Single-centre, open-label, non-randomised, phase I trial
  - Platform: non-replicating adenovirus type-5 (Ad5) vectored COVID-19 vaccine
  - Location: Wuhan, Hubei Province, China
- Paticipants: healthy volunteers
  - Age 18 – 60y
  - Negative IgM and IgG against SARS-CoV-2 and PCR
  - CT-Chest: no lungs lesions
- 3 Groups:
  - low dose ($5x10^{10}$ viral particles(VP)/ 0.5mL)
  - middle dose ($1x10^{11}$ VP/mL)
  - high dose ($1.5\ x10^{11}$ VP/1.5mL)
- Endpoints:
  - Adverse reactions within 7 and 28 days post-vaccination
  - Abnormal laboratory changes at day 7
  - Binding antibody and neutralising antibody responses, T-cell responses

Results: Baseline characteristics

	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)
Age, years			
18–29	9 (25%)	12 (33%)	10 (28%)
30–39	13 (36%)	14 (39%)	15 (42%)
40–49	8 (22%)	3 (8%)	7 (19%)
50–60	6 (17%)	7 (19%)	4 (11%)
Mean age, years	37·2 (10·7)	36·3 (11·5)	35·5 (10·1)
Sex			
Male	18 (50%)	19 (53%)	18 (50%)
Female	18 (50%)	17 (47%)	18 (50%)
Mean body-mass index, kg/m²	23·3 (2·7)	23·9 (2·7)	24·1 (3·1)
Underlying diseases*			
Yes	1 (3%)	2 (6%)	4 (11%)
No	35 (97%)	34 (94%)	32 (89%)
Pre-existing adenovirus type-5 neutralising antibody			
Mean GMT	168·9 (13·9)	149·5 (10·5)	115·0 (13·4)
≤200, titre	16 (44%)	17 (47%)	20 (56%)
>200, titre	20 (56%)	19 (53%)	16 (44%)

Results: Adverse reactions

	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	Total (N=108)
All adverse reactions within 0–7 days				
Any	30 (83%)	30 (83%)	27 (75%)	87 (81%)
Grade 3	2 (6%)	2 (6%)	6 (17%)	10 (9%)
Injection site adverse reactions within 0–7 days				
Pain	17 (47%)	20 (56%)	21 (58%)	58 (54%)
Induration	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Redness	2 (6%)	1 (3%)	1 (3%)	4 (4%)
Swelling	4 (11%)	4 (11%)	0	8 (7%)
Itch	2 (6%)	3 (8%)	0	5 (5%)
Muscular weakness	0	0	1 (3%)	1 (1%)

Laboratory tests d7: no clinically significant abnormalities

	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	Total (N=108)
Overall adverse events within 0–28 days				
Any	31 (86%)	30 (83%)	27 (75%)	88 (81%)
Grade 3	2 (6%)	2 (6%)	6 (17%)	10 (9%)

	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	Total (N=108)
Systemic adverse reactions within 0–7 days				
Fever	15 (42%)	15 (42%)	20 (56%)	50 (46%)
Grade 3 fever	2 (6%)	2 (6%)	5 (14%)	9 (8%)
Headache	14 (39%)	11 (31%)	17 (47%)	42 (39%)
Fatigue	17 (47%)	14 (39%)	16 (44%)	47 (44%)
Grade 3 fatigue	0	0	2 (6%)	2 (2%)
Vomiting	1 (3%)	0	1 (3%)	2 (2%)
Diarrhoea	3 (8%)	4 (11%)	5 (14%)	12 (11%)
Muscle pain	7 (19%)	3 (8%)	8 (22%)	18 (17%)
Grade 3 muscle pain	0	0	1 (3%)	1 (1%)
Joint pain	2 (6%)	2 (6%)	5 (14%)	9 (8%)
Grade 3 joint pain	0	0	1 (3%)	1 (1%)
Throat pain	1 (3%)	3 (8%)	4 (11%)	8 (7%)
Cough	1 (3%)	2 (6%)	3 (8%)	6 (6%)
Nausea	2 (6%)	1 (3%)	3 (8%)	6 (6%)
Functional GI disorder	1 (3%)	0	0	1 (1%)
Dyspnoea	0	0	2 (6%)	2 (2%)
Grade 3 dyspnoea	0	0	1 (3%)	1 (1%)
Appetite impaired	6 (17%)	5 (14%)	6 (17%)	17 (16%)
Dizziness	1 (3%)	0	1 (3%)	2 (2%)
Mucosal abnormality	0	0	1 (3%)	1 (1%)
Pruritus	1 (3%)	1 (3%)	1 (3%)	3 (3%)

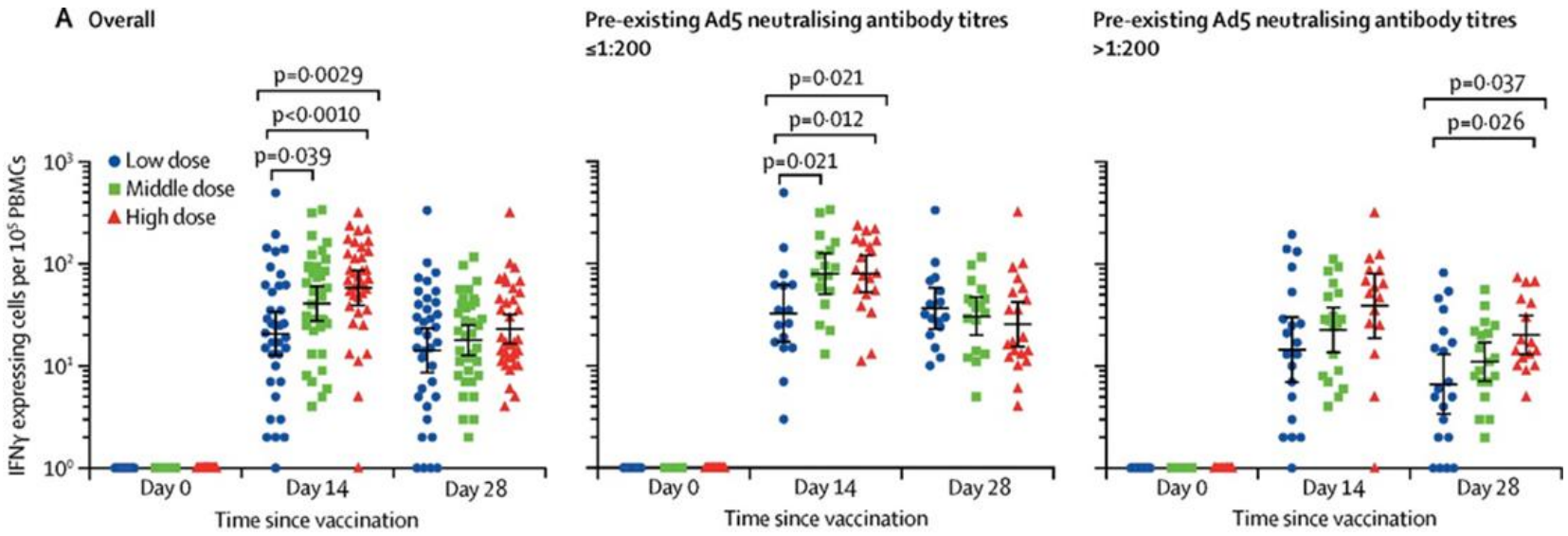
Specific antibody responses

	Day 14				Day 28			
	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value	Low dose group (n=36)	Middle dose group (n=36)	High dose group (n=36)	p value
ELISA antibodies to the receptor binding domain								
GMT	76·5 (44·3–132·0)	91·2 (55·9–148·7)	132·6 (80·7–218·0)	0·29	615·8 (405·4–935·5)	806·0 (528·2–1229·9)	1445·8 (935·5–2234·5)	0·016
≥4-fold increase	16 (44%)	18 (50%)	22 (61%)	0·35	35 (97%)	34 (94%)	36 (100%)	0·77
Neutralising antibodies to live SARS-CoV-2								
GMT	8·2 (5·8–11·5)	9·6 (6·6–14·1)	12·7 (8·5–19·0)	0·24	14·5 (9·6–21·8)	16·2 (10·4–25·2)	34·0 (22·6–50·1)	0·0082
≥4-fold increase	10 (28%)	11 (31%)	15 (42%)	0·42	18 (50%)	18 (50%)	27 (75%)	0·046

Multivariable analysis†

Intercept	0·65	0·17		
Middle dose	-0·06	0·91	0·94	0·33, 2·67
High dose	1·02	0·074	2·76	0·91, 8·44
Age	0·68	0·011	3·88	1·37, 11·01
Sex	-0·32	0·17	0·53	0·21, 1·31
Pre-existing Ad5 antibodies (>200)	-1·67	0·0003	0·19	0·08, 0·47

Specific T-cell response (ELISpot)



Positive responders 83-97%

15/20 (75%)

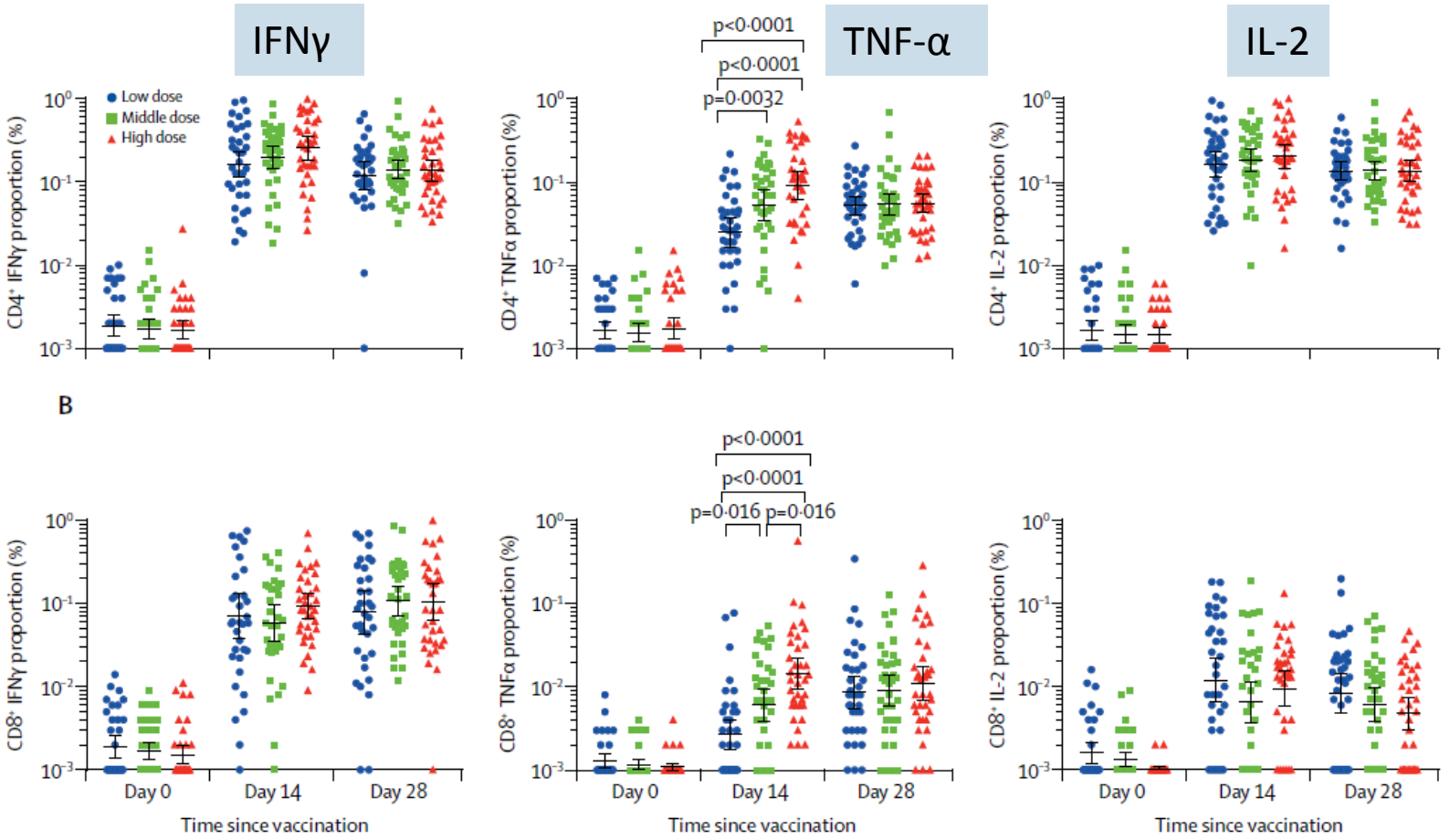
15/16 (94%)

18/19 (95%)

Cytokines secretion from $CD4^+$ and $CD8^+$ T cells

CD4+ T cells

CD8+ T cells



Discussion

- 75–83% of participants in three groups reported at least one adverse reaction by day 7
- Ad5 vectored COVID-19 vaccine was immunogenic in healthy adults
  - T-cell responses peaked at day 14
  - Antibody titers peaked at day 28
- Correlation of T-cell and Antibody responses and protection against COVID-19 remains unclear
- Pre-existing anti-Ad5 immunity and older age could diminish T-cell and antibody responses
- Concerns regarding HIV-1 aquisition risk and Ad5 vectored vaccine
- Phase II Trial: low dose vs. middle dose vaccine ongoing