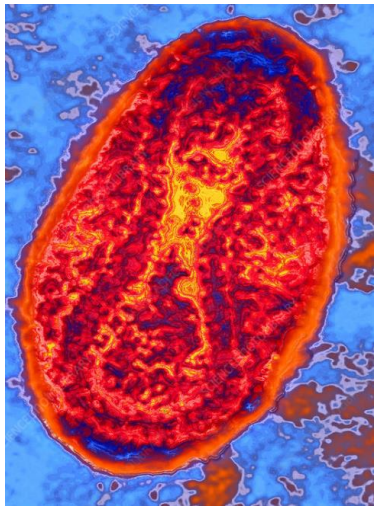
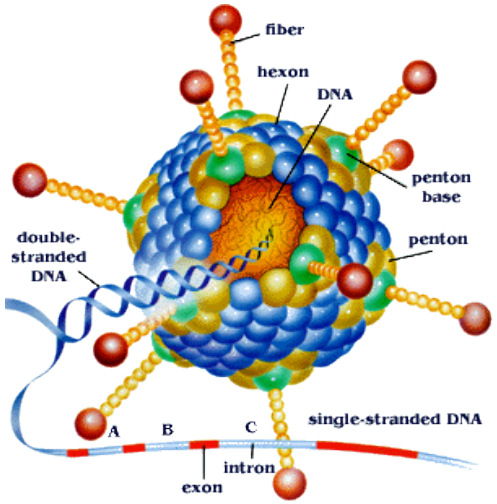
Viral Vectored Vaccines





Viral vectored vaccine platform technologies

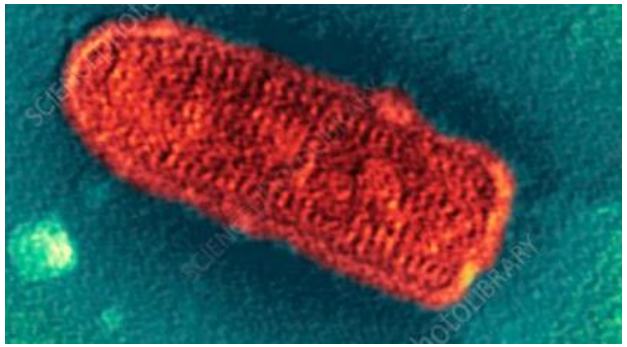
Sarah Gilbert

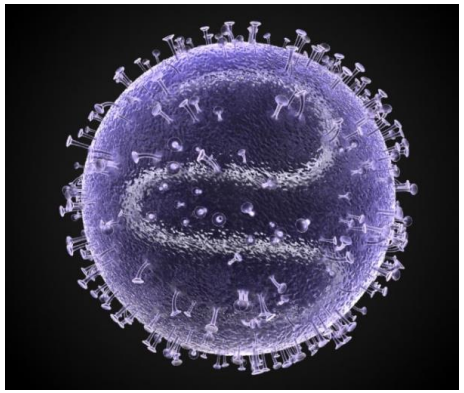
Jenner Institute

University of Oxford

Global Vaccine and Immunization Research Forum

February 2021





Viral vectored vaccines may be replication-deficient or replication competent

Replication-competent viral vectors include

- Vesicular Stomatitis Virus; licensed for Ebola
- Measles; in development for Chikungunya
- Cytomegalovirus; in development for HIV

Replication-deficient vectors include

- Modified Vaccinia virus Ankara (also NYVAC); licensed for Ebola
- Adenoviruses; licensed for Ebola and Covid

Viral vectors have often been employed in heterologous prime:boost regimens, along with other viral vectors, DNA, protein, or possibly in future RNA vaccines

- Advantages
  - No adjuvant required
  - Generally well tolerated
  - Excellent safety profile of replication-deficient vectors
  - Whole antigen expressed

- Disadvantages
  - Manufacturing may be complex; cell bank and virus seed stock required
  - Poxviruses require closed process
  - Anti-vector immunity – in practice has little effect for most

- Dependent on the viral vector
  - Low storage temperature/lyophilisation requirement
  - True platform technology or pseudotyped virus
  - Multiple antigens may be expressed

UNIVERSITY OF OXFORD

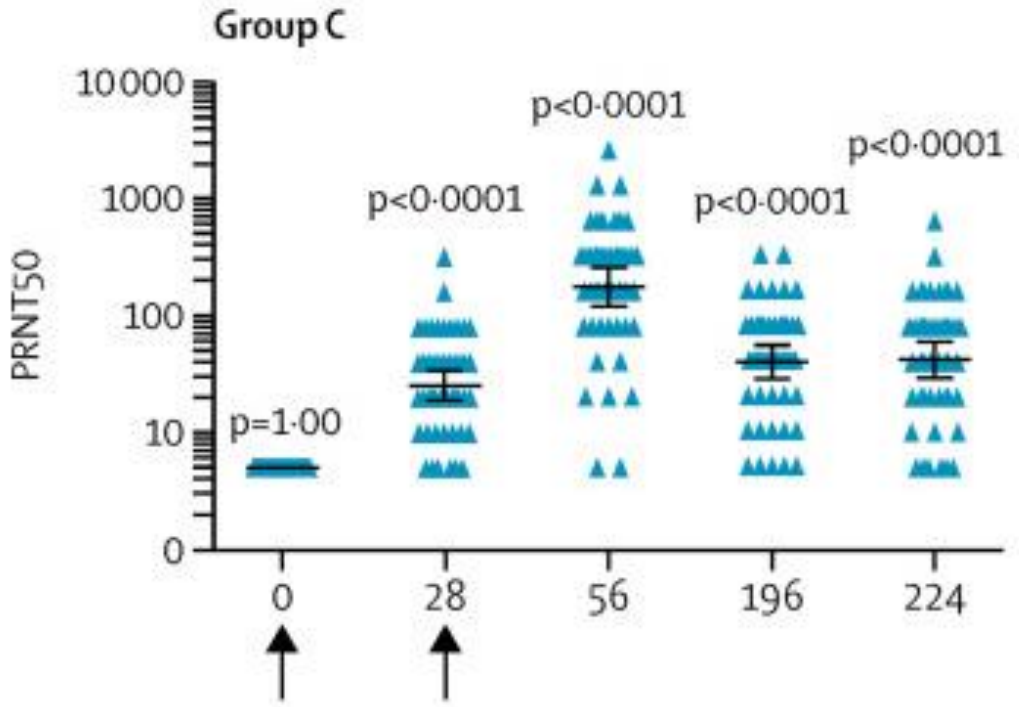
Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Henao-Restrepo et al., Lancet 2017

- 4539 contacts and contacts of contacts in 51 clusters randomly assigned to immediate vaccination
- 4557 contacts and contacts of contacts in 47 clusters randomly assigned to delayed vaccination
- **No cases of Ebola virus disease occurred 10 days** or more after randomisation among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases (7 clusters affected) among all eligible individuals in delayed clusters
- All vaccinees received one dose of 2×10^7 plaque-forming units of the rVSV-ZEBOV vaccine intramuscularly in the deltoid muscle
- Generally well tolerated, but greater reactogenicity in one Swiss phase I trial
- Vaccine requires ultra-low temp storage, manufacturing process not yet scalable

Measles-vectored Chikungunya vaccine

Developed by Themis, phase III planned
Dose of 5 x 10^5 $TCID_{50}$ chosen
Large scale measles vaccine manufacturing well established, typically lyophilised for refrigerated storage



Phase II study of 263 adults

Vaccine was well-tolerated, no SAEs

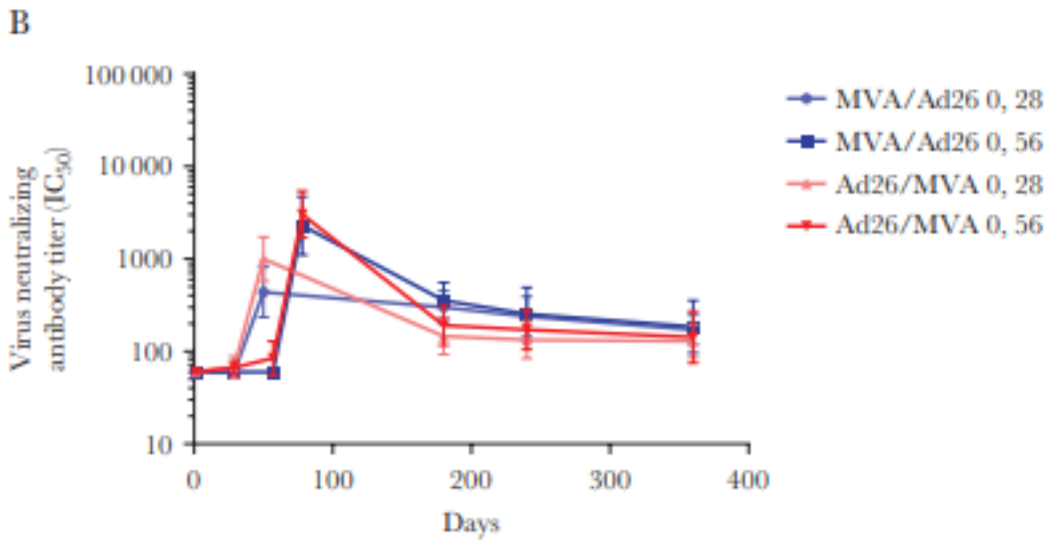
Neutralising antibodies against Chikungunya were induced after one dose and boosted by a second

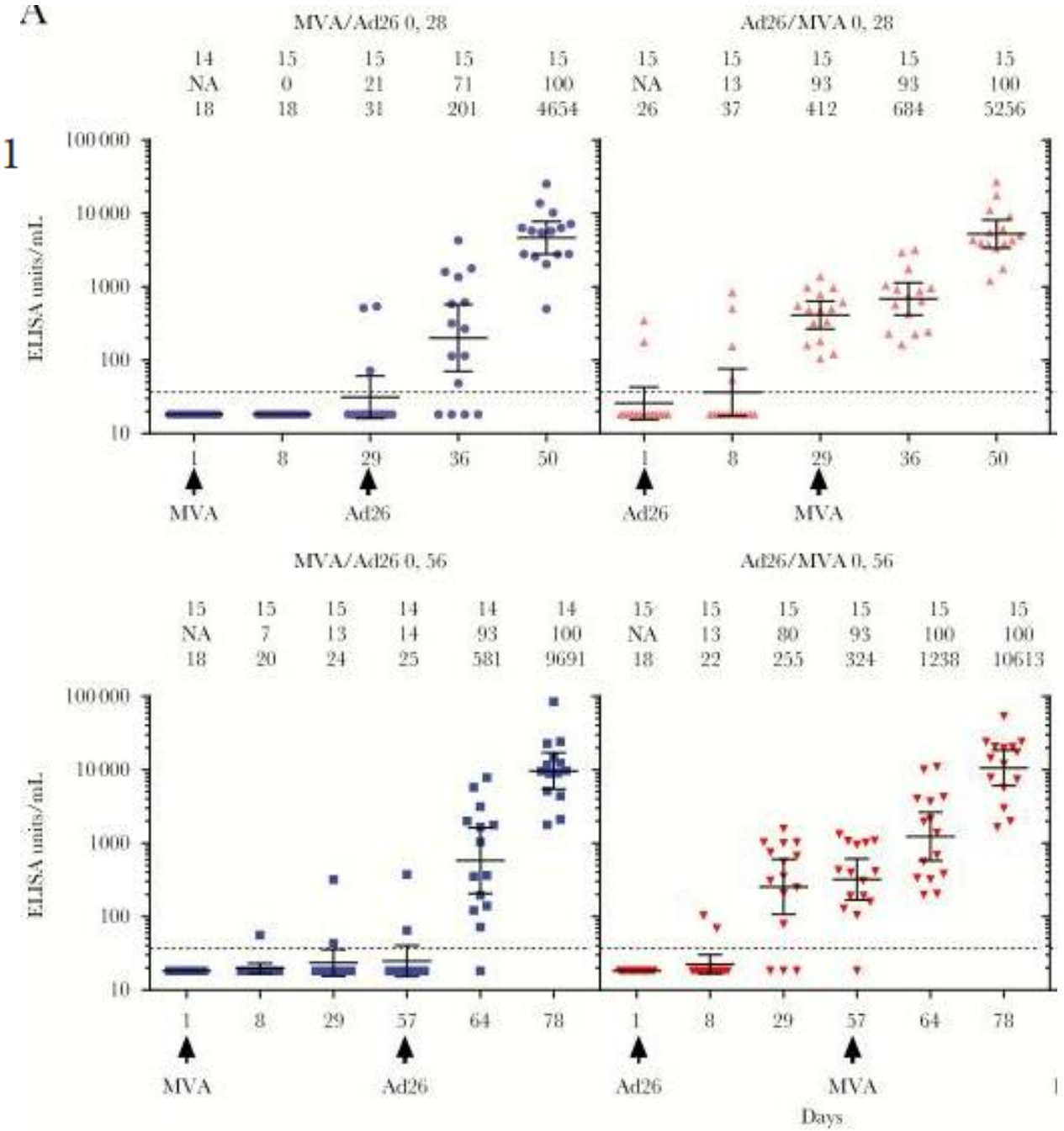
Vaccine was immunogenic after prior receipt of measles vaccine

Safety and Immunogenicity of a 2-Dose Heterologous Vaccination Regimen With Ad26.ZEBOV and MVA-BN-Filo Ebola Vaccines: 12-Month Data From a Phase 1 Randomized Clinical Trial in Uganda and Tanzania

Zacchaeus Anywaine,[1,a] Hilary Whitworth,[2,3,a] Pontiano Kaleebu,[1] George Praygod,[4] Georgi Shukarev,[6] Daniela Manno,[2] Saidi Kapiga,[2,3] Heiner Grosskurth,[2,3] Samuel Kalluvya,[5] Viki Bockstal,[6] Dickson Anumendem,[6] Kerstin Luhn,[6] Cynthia Robinson,[6] Macaya Douoguih,[6] and Deborah Watson-Jones[2,3]

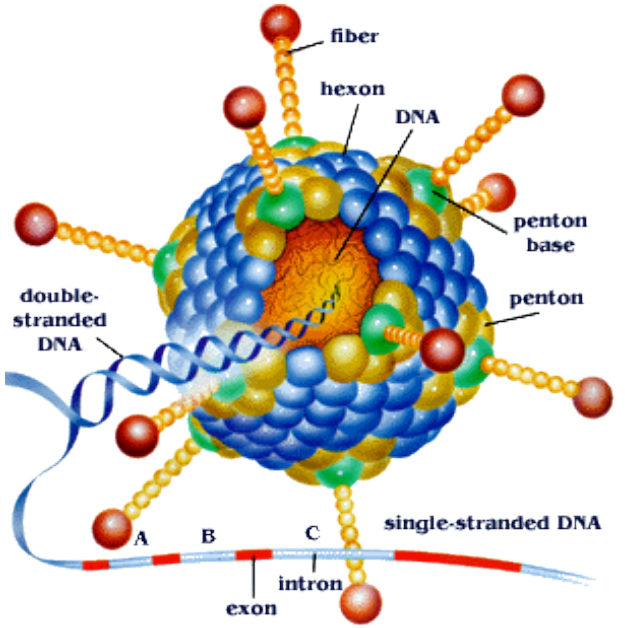
Vaccines were well tolerated and immunogenic
EU marketing authorisation granted
Phase III efficacy not possible, so licensed based on clinical safety and immunogenicity, plus non-human primate efficacy



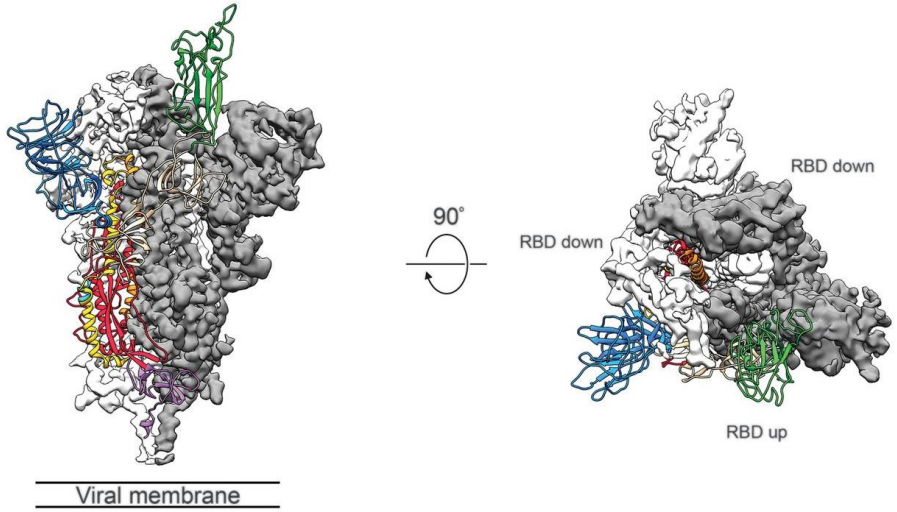


ChAdOx1 nCoV-19/AZD1222: The technology

- Non-replicating simian adenoviral vectored vaccine expressing nCoV-19 Spike
- Non-replicating due to E1 (and E3) gene deletion
- Simian adenovirus avoids issues with pre-existing immunity to human adenoviruses
- Vaccine antigen encoded in the viral genome - not a structural part of the virion
- Induces strong B and T cell responses after single vaccination



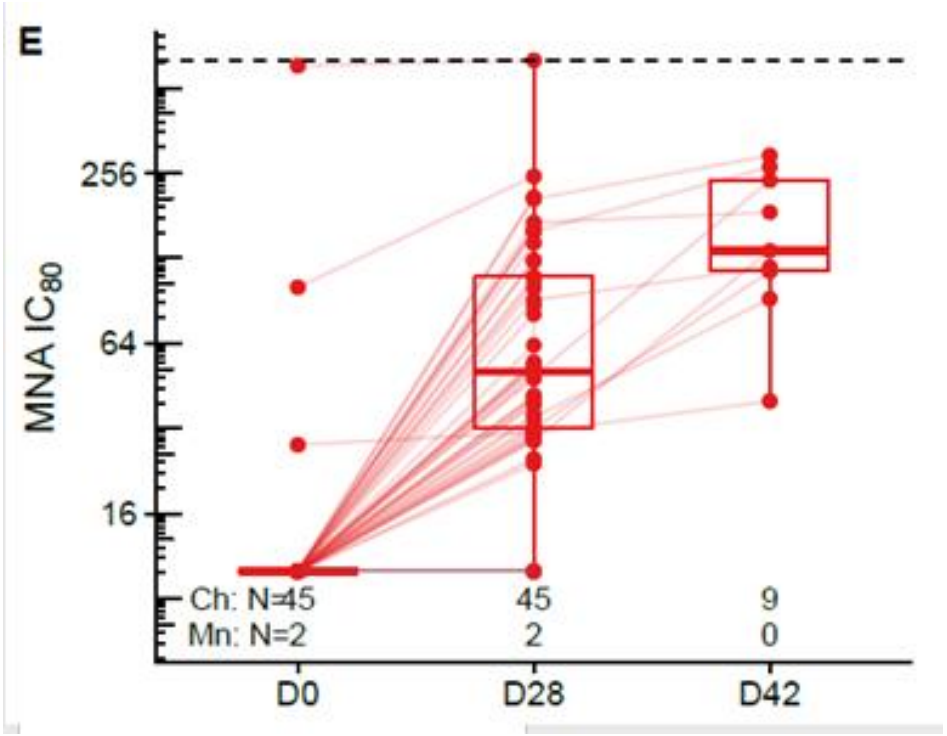
- Prior to April 2020, 12 phase I studies, 330 subjects vaccinated
  - ChAds in trials totalling over 6000 subjects of all ages
  - Consistent safety profile and strong immunogenicity after one dose
  - ChAdOx1 MERS protective in NHPs, now in Phase I trials in UK and KSA

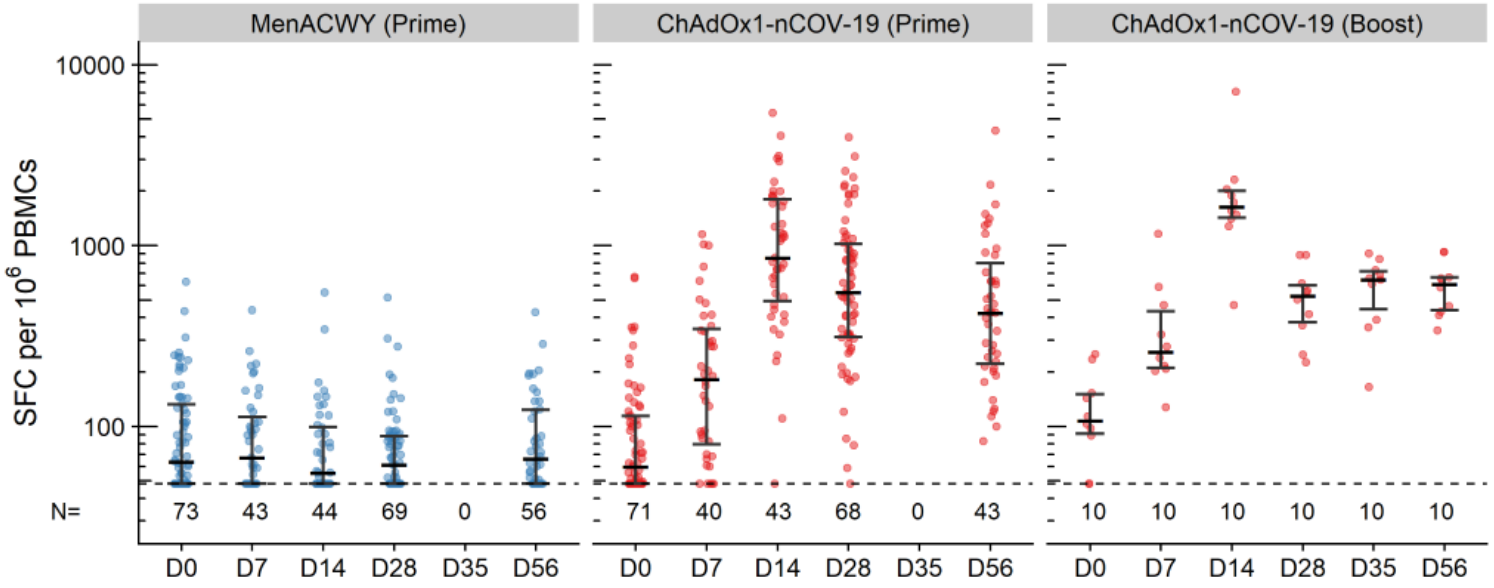


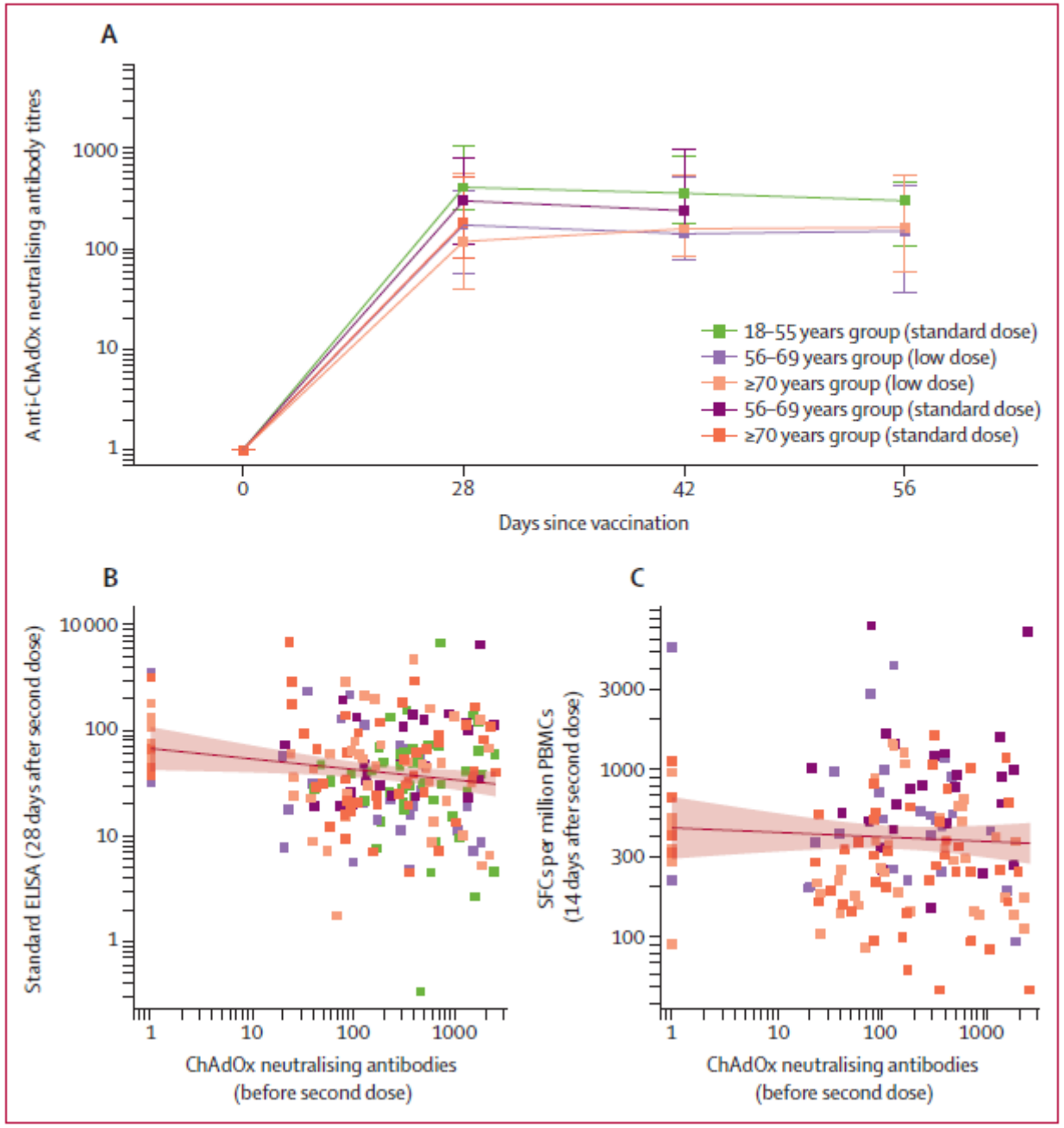
ChAdOx1 nCoV-19 AZD1222: Phase I

Country	Population	Recruitment
UK	18-55	1077

Started 23rd April 2020







ChAdOx1: negligible effect of anti-vector immunity even when second dose is given at 28 days
Ramasamy et al., Lancet 2020

Efficacy of ChAdOx1 nCoV-19/AZD1222 against mild symptomatic PCR-confirmed COVID-19 after a single dose

Symptomatic COVID-19 Cases > 21 days after a single SD dose	N cases	ChAdOx1 nCoV-19	Control	Vaccine Efficacy (95% CI)
Time since first standard dose				
22 to 30 days	37	7/ 9257	30/ 9237	77% (47%, 90%)
31 to 60 days	28	6/ 7147	22/ 7110	73% (33%, 89%)
61 to 90 days	23	4/ 2883	19/ 2974	78% (36%, 93%)
90 to 120 days	10	4/ 1368	6/ 1404	32% (-142%, 81%)
22 to 90 days	**88**	**17**	**71**	**76% (59%, 86%)**

Johnson & Johnson report 72% effective against moderate to severe covid in the US, 66% in Latin America and 57% in South Africa, 28 days after a single dose vaccination. Efficacy against mild disease not yet reported.

Interval between two standard doses

Symptomatic COVID-19 Cases > 14 days after second dose	N cases	ChAdOx1 nCoV-19	Control	Vaccine Efficacy (95% CI)
Time between first and second dose SD/SD				
< 6 weeks	111	35/3900 (0.9%)	76/3860 (2.0%)	54.9% (32.7%, 69.7%)
6-8 weeks	64	20/1103 (1.8%)	44/1004 (4.4%)	59.9% (32.1%, 76.4%)*
9-11 weeks	43	11/905 (1.2%)	32/957 (3.3%)	63.7% (28.0%, 81.7%)¥
≥12 weeks	53	8/1293 (0.6%)	45/1356 (3.3%)	82.4% (62.7%, 91.7%)†

In the UK the recommendation is for 12 weeks between doses.
Now in use for adults over 18, with trials underway in HIV +ve, in children, and planned for maternal immunisation

Efficacy against mild disease caused by B.1.1.7 only slightly reduced
Overall two thirds reduction in cases, including asymptomatic, with reduction in viral load and duration of PCR positivity in those who became infected after vaccination

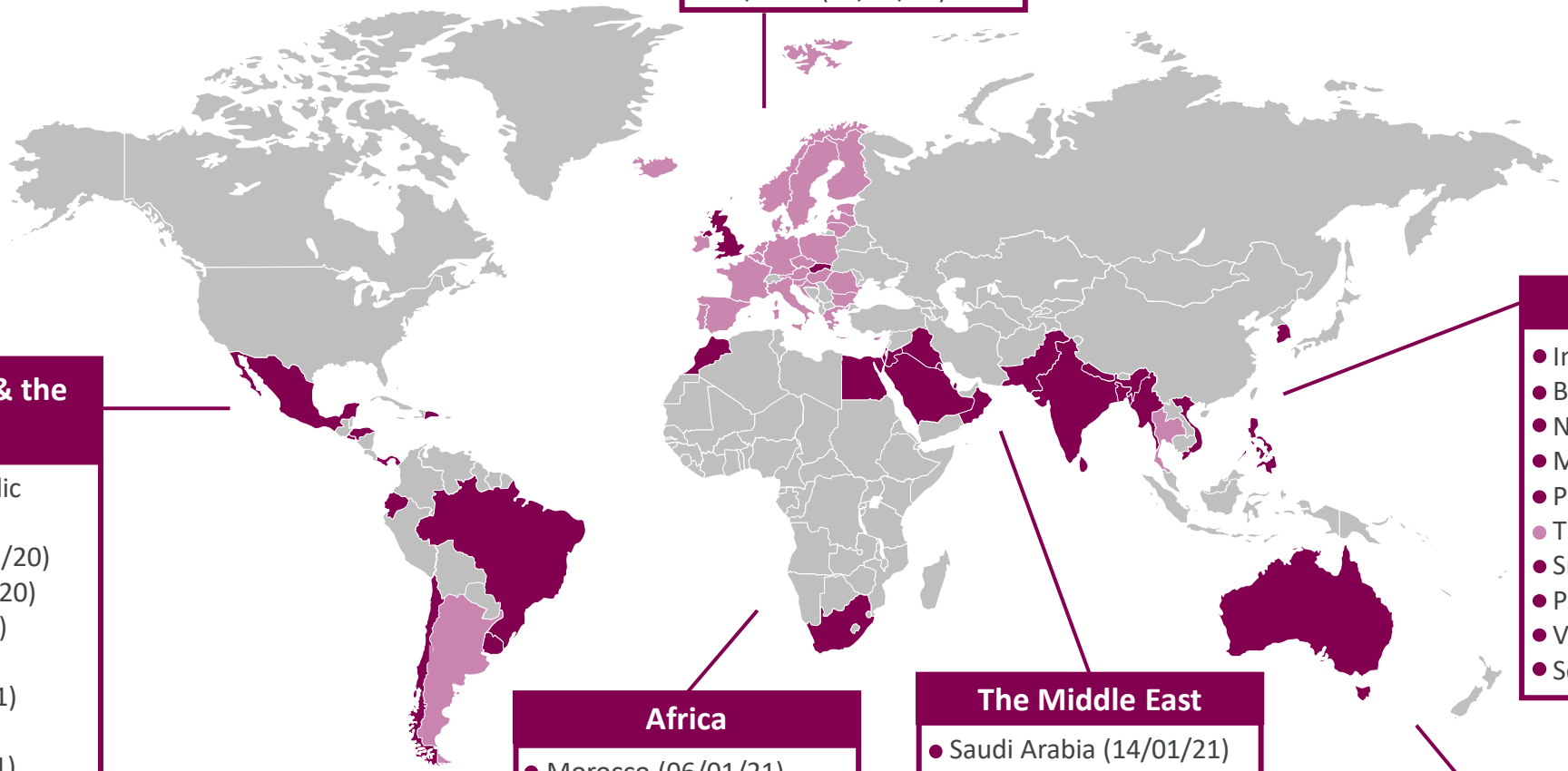
UK approval and policy

- 2 doses 3 months apart
  - Booster antibody response is 2.5-3.0x higher with 2nd dose
  - Trend to higher efficacy with second dose
- Protection 76% from 3 weeks after first dose until the second dose
- No hospitalisations or severe disease from 21 days post first dose

[Public Assessment Report (publishing.service.gov.uk)]

AZD1222: Regulatory status updates

- Conditional marketing authorisation
- Emergency use authorisation



Europe
- UK (29/12/20)
- Hungary (21/01/21)
- EU/EMA (29/01/21)

Latin America & the Caribbean
- Dominican Republic (30/12/20)
- El Salvador (30/12/20)
- Argentina (30/12/20)
- Mexico (04/01/21)
- Brazil (17/01/21)
- Ecuador (23/01/21)
- Chile (27/01/21)
- Panama (05/02/21)
- Honduras (unknown)
- Uruguay (11/02/21)

Africa
- Morocco (06/01/21)
- South Africa (22/01/21)
- Egypt (01/02/21)

The Middle East
- Saudi Arabia (14/01/21)
- Iraq (19/01/21)
- Bahrain (24/01/21)
- Kuwait (31/01/21)
- Oman (unknown)
- Palestine (unknown)
- Jordan (16/02/21)

Asia
- India (03/01/21)
- Bangladesh (07/01/21)
- Nepal (15/01/21)
- Myanmar (20/01/21)
- Pakistan (21/01/21)
- Thailand (22/01/21)
- Sri Lanka (22/01/21)
- Philippines (28/01/21)
- Vietnam (30/01/21)
- South Korea (10/02/21)

Oceania
- Australia (16/02/21)

EMA, European Medicine Agency; EU, European Union; UK, United Kingdom