UCI School of Medicine

CORONAVIRUSES AND VACCINES

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ENVIRONMENTAL VIROLOGY

- IT IS ESTIMATED THAT OVER THREE MILLION DIFFERENT VIRUS TYPES CAPABLE ON INFECTING VERTEBRATES EXIST IN NATURE
- TO INITIATE INFECTION VIRUSES MUST FIND AND ATTACH TO A SPECIFIC RECEPTOR LOCATED ON A CELL.
- THE VIRUS THEN MUST ENTER THE CELL AND EITHER PRODUCE NEW VIRUSES OR BECOME LATENT OR DORMANT
- AS VIRUSES REPLICATE THEY MAY DAMAGE THE CELL AND/OR INTERFERE WITH ITS FUNCTION
- VIRUSES ENTERING THE CELL ESPECIALLY WHEN REPLICATING ELICIT AN IMMUNE RESPONSE

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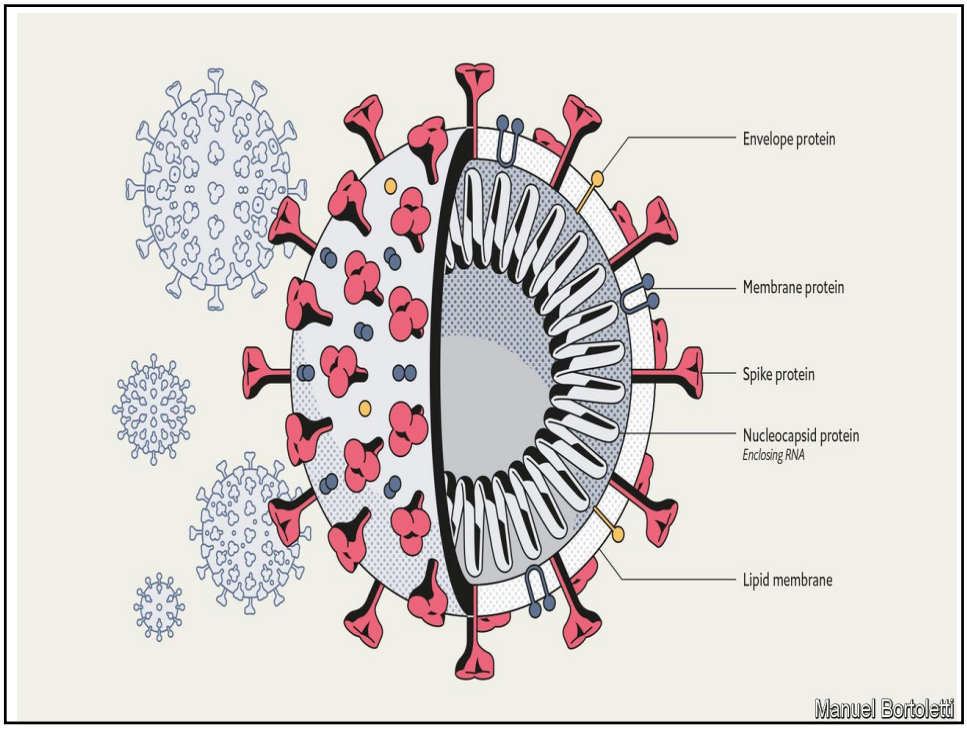

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MAJOR STRUCTURAL PROTEINS OF THE VIRUS

- SPIKE PROTEIN (S1/S2 PROTEIN)
- MATRIX PROTEIN (M PROTEIN)
- NUCLEOCAPSID PROTEIN (N PROTEIN)
- ENVELOPE (E PROTEIN)

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WHAT IS THE INFECTIOUS NUMBER OF PARTICLES

- SARS-CoV PROBABLY 100 PLUS PARTICLES
- MERS PROBABLY 1000 0R MORE
- SARS CoV-2 UNKNOWN PROBABLY 100+

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TRANSMISSION

- WE NOW UNDERSTAND AS MUCH AS 40% OF TRANSMISSION CAN OCCUR IN PRESYMPTOMATIC PATIENTS (I.E. TWO TO THREE DAYS BEFORE THEY BECOME ILL) OR, TOTALLY ASYMPTOMATIC PATIENTS WHO NEVER GET RECOGNIZABLE SYMPTOMS.
- NEW STUDY OF 1848 MARINE RECRUITS SHOWED AFTER INITIAL QUARANTINE, 16 TEST POSITIVE ON ARRIVAL AND ONLY ONE WITH SYMPTOMS. AFTER ARRIVAL AND SUBSEQUENT QUARANTINE 35 TEST POSITIVE 4 WITH SYMPTOMS.

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IMMUNOLOGY

- ANTIBODIES AND CELL IMMUNITY DEVELOPS IN ALL, TO NEARLY ALL PATIENTS BEGINNING ABOUT THE EIGHTH DAY OF ILLNESS. NEUTRALIZING ANTIBODIES, ANTIBODIES TO THE RECEPTOR BINDING DOMAIN AND THE N PROTEIN HAVE BEEN FOUND.
- ASYMPTOMATIC INDIVIDUALS ALSO DEVELOP ANTIBODIES
- CELLULAR IMMUNITY DEVELOPS TO CORONAVIRUS PROTEINS INCLUDING S PROTEIN

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RELAPSE OR REINFECTION

- 26 CASES OF REINFECTION WITH SARS-CoV-2 WELL DOCUMENTED WORLDWIDE
- 3 REPORTED AND WELL DOCUMENTED IN US
- OTHER COUNTRIES REPORTING REINFECTIONS INCLUDING SOUTH KOREA, BELGIUM, NETHERLANDS, QUATAR, INDIA, ECQUADOR, SPAIN, SWEDEN,HONG KONG.

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ACCEPTED TREATMENTS

1. ANTIVIRAL: REMDESIVIR

Ref:
1. BIEGEL J, TOMASHEK K, DODD L ET AL. NEJM:2020;
DOI 10.1056/NEJm2007764
2. WANG Y, ZHANG D, DU G. ET Al. THE LANCET:2020;
10.1016SO140/6736(20)31022-9

2. ANTIINFLAMMATORY: DEXAMETHASONE :
for Patients with Oxygen Need or Mechanical Ventilation .

Ref:
1. THE RECOVERY COLLABORATIVE GROUP. NEJM:2020;
DOI/full/10/1056/NEJMoa2021436

3. IMMUNOTHERAPY:
Convalescent Plasma
Monoclonal Antibodies

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POTENTIAL TREATMENTS

- ANTI INFLAMMATORIES: (Cytokine Inhibitors, initial studies mixed results)
- INTERFERONS

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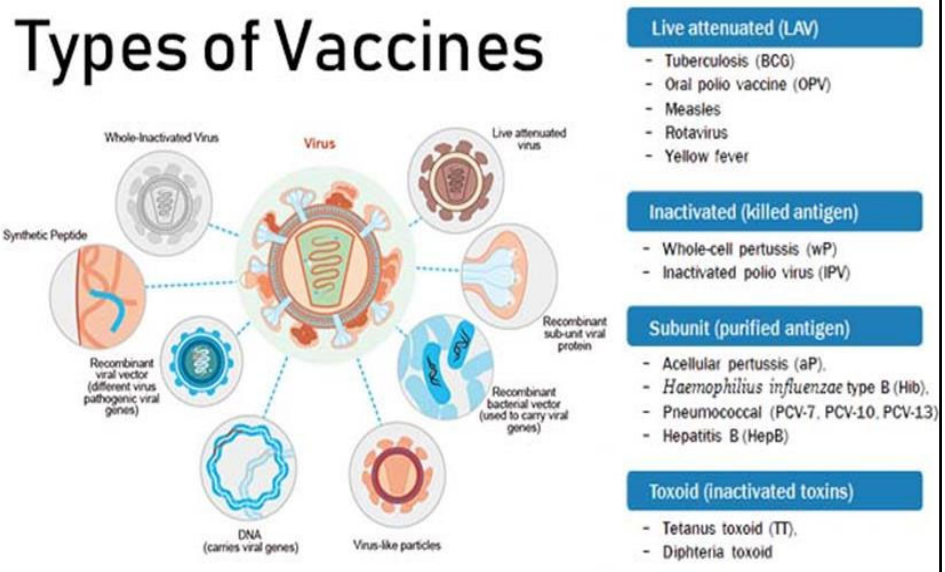

Figure 1 Schematic representation summarizing multiple approaches used for the development of vaccines against viral pathogens.

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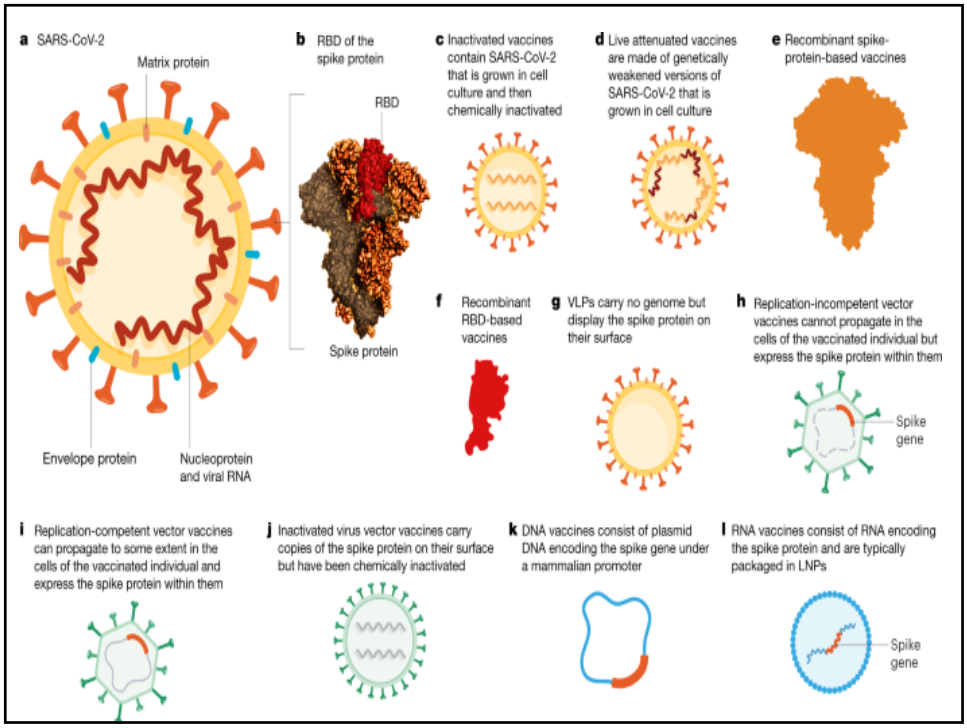

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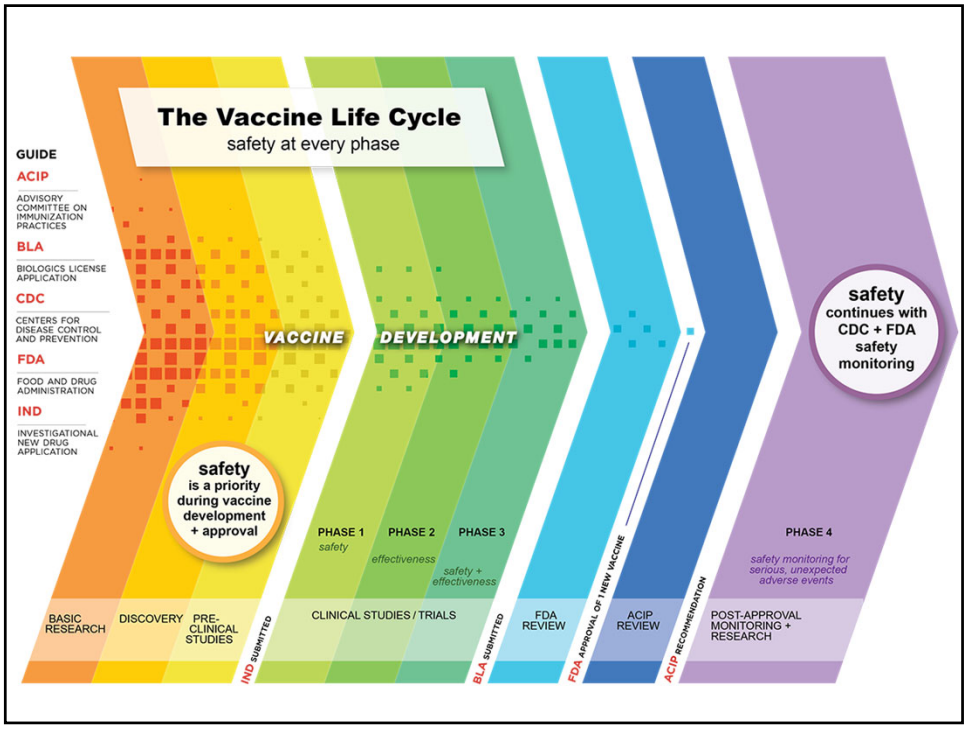

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VACCINE TRIALS

- PHASE I:

  USUALLY ABOUT FIFTY PATIENTS TO DETERMINE IF THE CANDIDATE ELICTS AN IMMUNE RESPONSE AND TO GENERATE SOME DATA ON DOSING

- PHASE II:

  USUALLY SEVERAL HUNDRED PATIENTS TO CONFIRM DOSING AS MEASURED BY IMMUNE RESPONSE AND TO CHECK FOR ADVERSE EFFECTS

- PHASE III:

  30,000 OR MORE PATIENTS TO SEE IF THE VACCINE CAN PREVENT INFECTION AS WELL AS TO MONITOR TOXICITY

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FDA VACCINE REQUIREMENTS

- EVIDENCE OF THE VACCINE EFFECTIVENESS
- AT LEAST FIVE SEVERE CASES IN THE CONTROL GROUP
- EVIDENCE THE VACCINE IS SAFE
- AT LEAST TWO MONTHS SINCE LAST IMMUNIZATION TO MAXIMIZE OPPORTUNITIES TO DETECT ADVERSE REACTIONS

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VACCINES

- 200 CANDIDATES AT LEAST 36 IN CLINICAL TRIALS AND 140 IN PRECLINICAL TRIALS
- 18 IN PHASE 1 TRIALS
- 12 IN PHASE 2 TRIALS
- 6 IN PHASE 3 TRIALS
- 1 APPROVED SPECIAL CIRCUMSTANCES
- VACCINE TYPES
- GENE BASED
- NON REPLICATING MODIFIED VIRUSES
- REPLICATING MODIFIED VIRUSES
- PROTEIN BASED VIRUSES
- ATTENUATED VIRUSES
- INACTIVATED VIRUSES

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VACCINES

- GENETICALLY BASED VACCINES
- MODERNA (mRNA)*
- PFIZER/BioNTech (mRNA)*
- INOVIO (DNA)**
- OTHERS
  - IMPERIAL COLLEGE LONDON (mRNA)
  - ARCTURUS (mRNA) SINGAPORE
  - CureVac (mRNA) GERMANY
  - SANOFI (mRNA) FRANCE
  - ZYDUS (DNA) INDIA
  - AnGen (DNA) JAPAN

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RNA VACCINES

- DEVELOPED AND MANUFACTURED RAPIDLY.
- CAN BE AMPLIFYING OR NON AMPLIFYING.
- REQUIRES CERTAIN RNA MODIFICATIONS TO STABILIZE THE RNA.
- CAN BE GIVEN REPEATEDLY
- LOW RISK OF ANTIBODIES TO THE VACCINE
- DO NOT ENTER NUCLEUS
- CAN BE TEMPERATURE SENSITIVE
- LIMITED EXPERIENCE WITH MASS VACCINATIONS
- IN TRIALS: Cure Vac, Arcturus, Sanofi

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DNA

- PLASMID DNA
- CAN BE PRODUCED IN E COLI
- ARE STABLE
- POOR IMMUNOGENS
- EASILY DEGRADED BY HOST ENZYMES
- REQUIRE SPECIAL EQUIPMENT TO INJECT
- FOUR IN TRIAL

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PFIZER BioNTech 162b2

- AT LEAST 43,538 ENROLLED IN PHASE III TRIALS
- AT LEAST 38,955 HAVE RECEIVED TWO DOSES 21 DAYS APART
- REQUIRES -94 DEGREES FARENHEIT STORAGE
- ENCODES OPTIMIZED FULL LENGTH SPIKE GLYCOPROTEIN
- INDUCES BOTH NEUTRALIZING ANTIBODIES AND DELAYED HYPERSENSITIVITY
- EARLY ANALYSIS SUGGESTS AT LEAST 95% EFFECTIVENESS:
  - 170 CONFIRMED CASES; 162 IN PLACEBO GROUP
  - 11 SEVERE CASES (after first dose); 10 IN PLACEBO GROUP, ONE IN VACCINEE
  - NO SERIOUS ADVERSE EFFECTS SO FAR
- NO SUBSIDIES BUT CONTRACT FOR 100 MILLION DOSES ($1.95 BILLION)
- EUA PENDING

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MODERNA mRNA 1273 VACCINE

- ENROLLED 30,420 PATIENTS IN PHASE III
- RNA CODES FOR PREFUSION SPIKE PROTEIN
- TRIAL TWO DOSES 28 DAYS APART
- REQUIRES COLD STORAGE AT -4 DEGREES FARENHEIT
- KNOWN FROM PHASES I AND II TO INDUCE NEUTRALIZING ANTIBODIES AND DELAYED TYPE HYPERSENSITIVTY
- RESULTS REPORTED FOR PHASE III 95% EFFECTIVE:

SYMPTOMATIC COVID IN 185 PLACEBO RECIPIENTS AND 11 VACCINEES.

SEVERE COVID IN 30 RECIPIENTS NONE IN VACCINEES. ONE DEATH IN PLACEBO RECIPIENT

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ADVERSE EFFECTS AFTER RNA VACCINES

- LOCAL: INJECTION SITE PAIN, ERYTHEMA,
- SWELLING
- SYSTEMIC
- FATIGUE
- FEVER, CHILLS
- HEADACHES
- MYALGIAS, ARTHRALGIAS
- ANAPHYLAXSIS POSSIBLE

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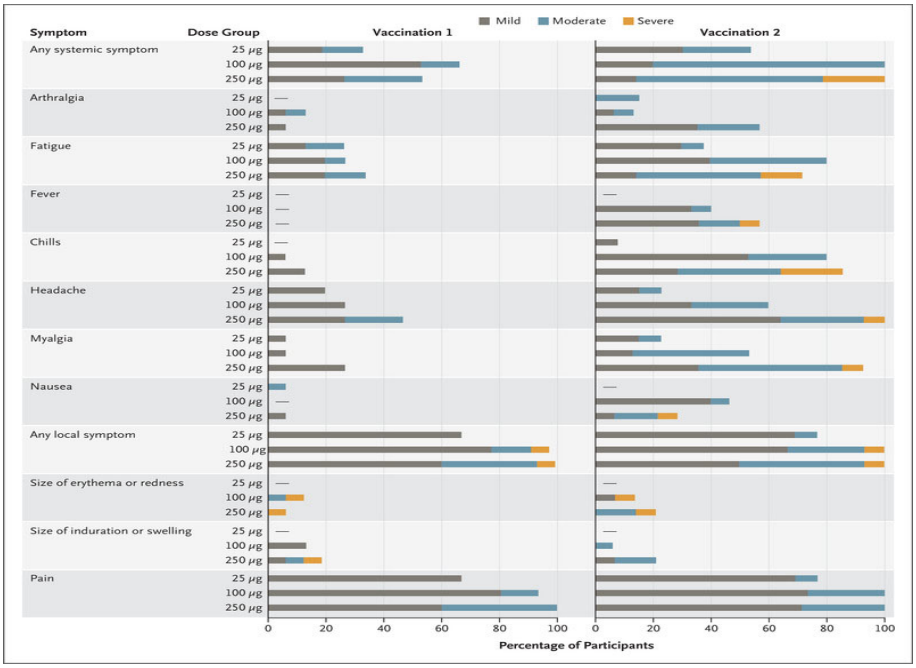

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VACCINES

- VIRAL VECTOR VACCINES
- REPLICATION DEFECTIVE VIRUSES
- OXFORD/ASTRA ZENECA (CHIMP ADENO)*
- JOHNSON AND JOHNSON (ADENO 26)
- CanSino BIOLOGICS (ADENO 5) CHINESE***
- GAMELEYA (ADENO 26 AND 5) RUSSIAN
- REPLICATING VIRUSES
- MERCK (VSV)
- MERCK AND THEMIS BIOSCI (MEASLES)
- VaxArt (ORAL RECOMBINANT ADENO)

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REPLICATION DEFECTIVE VACCINES

- EXPERIENCED METHOD
- UNNECESSARY TO HANDLE LIVE VIRUS
- GOOD IMMUNE STIMULATION
- MAY BE PARTAILLY NEUTRALIZED BY EXISTING ANTIBODY

ENGINEERED TO EXPRESS SARS-CoV-2 PROTEINS
INCLUDE VACCINES BY ASTRA/ZENECA, Janssen, CAN SINO, GAMALEYA, REITHERA
CAN USE ADENOVIRUSES, VACCINIA, ETC

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OXFORD ASTRA/ZENECA AZD 1222

- CHIMPANZEE ADENOVIRUS
- CODES FOR SPIKE PROTEIN
- REPLICATION DEFECTIVE IN HUMANS
- IN PRECLINICAL AND PHASE I/II STUDIES GOT NEUTRALIZING ANTIBODY AND CELL MEDIATED IMMUNE RESPONSE
- EXPECTING 30,000 US ENROLLEES BUT STUDIES BEING DONE IN UNITED KINGDOM, BRAZIL SOUTH AFRICA AND JAPAN. LIKELY COMPLETED BY DECEMBER.
- WAS ON HOLD FOR UNEXPLAINED ILLNESS BUT NOW REOPENED
- CONTRACTS WORLDWIDE FOR 2.1 BILLION DOSES

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AZD 1222 SAFETY AND EFFICACY

- INTERIM ANALYSIS JANUARY 2021
- STUDIES IN BRAZIL, SOUTH AFRICA AND UK
- 23,848 PATIENTS AND 11,636 ANALYZED
- VACCINE EFFICACY WITH TWO STANDARD DOSES WAS 62.1% BUT WITH A SUBSET WHO RECEIVED HALF A DOSE AT THE FIRST VISIT AND A FULL DOSE AT THE SECOND VISIT IT WAS 90% Combined efficacy 70.4%. (30 cases in vaccinees and 101 in control group)
- 10 CASES HOSPITALIZED ALL IN CONTROLS
- CONTROL GROUP (meningococcal vaccine)
- Dose now 3.5 to 6.5 x10 billion viral particles
- 3 cases transverse myelitis considered not vaccine related

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How some of the Covid-19 vaccines compare

Company	Type	Doses	How effective*	Storage	Cost per dose
Oxford Uni-AstraZeneca	Viral vector (genetically modified virus)	x2	62-90%	Regular fridge temperature	£3 ($4)
Moderna	RNA (part of virus genetic code)	x2	95%	-20C up to 6 months	£25 ($33)
Pfizer-BioNTech	RNA	x2	95%	-70C	£15 ($20)

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JOHNSON AND JOHNSON/JANSSEN

- ADENOVIRUS 26 VACCINE EXPRESSES SPIKE PROTEIN
- SAME TECHNOLOGY USED FOR EBOLA VIRUS VACCINE
- GOOD PRECLINICAL RESULTS IN ANIMALS
- MAYBE ONLY SINGLE DOSE VACCINE
- INITIAL STUDIES SHOW GOOD NEUTRALIZING ANTIBODIES IN 92% RECIPIENTS IN PHASE I/II STUDIES
- PHASE III STUDIES BEGAN SEPT 23.
- BRIEF HOLD FOR SAFETY BUT PETITION TO RESUME OCT 23
- ENROLLING 60,000 PATIENTS PHASE III
- WILL PROVIDE 1 BILLION DOSES 2021

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REPLICATION COMPETENT VACCINES

- ATTENUATED VIRUSES ENGINEERED TO EXPRESS TRANSGENE
- TRIGGERS ROBUST IMMUNE RESPONSE
- NEED TO HANDLE LIVE VIRUS.
- CAN BE GIVEN INTRANASALLY
- Merck, Beijing Wantai Biological Pharmacy

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MERCK VACCINES

- THESE WILL BE LIVE REPLICATING VACCINES USING EITHER MODIFIED VESICULAR STOMATITS VIRUS OR MEASLES VIRUS TO CARRY SARS-CoV-2 ANTIGENS.
- VSV VACCINE SUCCESSFULLY USED FOR EBOLA VIRUS.

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PROTEIN VACCINES

PROTEIN BASED

- NOVAVAX
- OTHERS
  - ANHUI ZHIFEI LONGCOM (CHINA)
  - CLOVIS PHARMACEUTICALS
  - VAXINE (AUSTRALIAN)
  - MEDICAGO/DYNAVAX (CANADIAN)
  - UNIVERSITY OF QUEENSLAND (AUSTRALIAN)
  - KENTUCKY BIOPROCESSING
  - BAYLOR/TEXAS CHILDRENS
  - UNIVERSITY OF PITTSBURG
  - SANOFI (FRENCH)

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PROTEIN BASED VACCINE

- GOOD SAFETY PROFILE
- COST EFFCTIVE
- REQUIRE USE OF ADJUVANTS
- CAN GET GOOD IMMUNE RESPONSE
- EXAMPLE Hepatitis b vaccine

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NOVAVAX – NVX CoV 2373

- STABLE PREFUSION SPIKE PROTEIN
- USED AN INSECT VIRUS, BACULOVIRUS, IN ARMY WORM MOTH CELLS.
- PROTEIN IS HARVESTED FROM CELLS , MIXED WITH A SOAP LIKE PARTICLE WHICH EMBEDS THE PROTEIN AND ADJUVANT (SAPONIN LIKE) IS ADDED
- EXCELLENT IN PRECLINICAL STUDIES
- PHASE I AND II TRIALS SHOWED EXCELLENT NEUTRALIZING ANTIBODIES
- TWO DOSES BUT VERY STABLE AT REFRIGERATOR TEMPS
- PHASE III TO BEGIN NOW IN US BUT ALREADY ONGOING IN UNITED KINGDOM

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VACCINES

- WHOLE VIRUS VACCINES
  - SinoPharm (CHINESE)*
  - SINOVAC (CHINESE)*
  - INSTITUTE OF MEDICAL BIOLOGY(CHINESE)
  - BHARAT (INDIA)
  - ? (NORTH KOREA)
- REPROCESSED VACCINES
  - BCG

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INACTIVATED VACCINES

- TEND TO PRODUCE WEAKER IMMUNE RESPONSE
- USUALLY NEED ADJUVANT
- EXAMPLE INACTIVATED POLIO VACCINE

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WHOLE KILLED VIRUS

- BEING TESTED IN CHINA
- SINOVAC (50-78% EFFECTIVE)
- SINOPHARM (79 TO 86% EFFECTIVE)
- ADVANTAGES
- EXPERIENCED METHOD
- UNNECESSARY TO HANDLE LIVE VIRUS
- TEND TO PRODUCE WEAKER RESPONSE

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CONTRAINDICATIONS AND PRECAUTIONS

- SEVERE ALLERGIC REACTION AFTER A PREVIOUS DOSE OF AN mRNA VACCINE OR ANY OF IT'S COMPONENTS
- IMMEDIATE ALLERGIC REACTION OF ANY SEVERITY TO PREVIOUS DOSE OF mRNA OR ANY OF ITS COMPONENTS
- IMMEDIATE REACTION TO POLYSORBATE DUE TO POTENTIAL CROSS REACTION TO PEG

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EFFECT OF SARS-CoV-2 VARIANTS

- SO FAR AND BECAUSE ADMISTRATION OF THE VACCINE INDUCES A FAMILY OF ANTIBODIES DIRECTED AT DIFFERENT SITES IN THE SPIKE PROTEIN THE VACCINE IS LIKELY TO HAVE SOME BENEFIT EVEN FOR SARS-CoV-2 VARIANTS

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QUESTIONS AND ANSWERS

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