Vaccini e COVID-19: lo stato dell’arte.
Certezze e dubbi
Hartenian E, Nandakumar D, Lari A, Ly M, Tucker JM, Glaunsinger BA. The molecular virology of coronaviruses. The journal of biological chemistry. 2020;295(37):12910–12934 Figure 1, summarizing the replication cycle of coronaviruses like SARS-CoV-2.
The high infectivity of SARS-CoV-2 and rapid rise of number of patients is explained by the lack of pre-existing immunity to a virus never encountered before
before

minutes

hours

two weeks
La MEMORIA IMMUNOLOGICA è la proprietà del sistema immunitario
di riconoscere e neutralizzare patogeni noti
Per questo la memoria immunologica prevenne l’infezione e la malattia

I vaccini funzionano perché generano la memoria immunologica
VACCINO

IMMUNITÀ DI GREGGE

= IMMUNITÀ SOLIDALE
Se la percentuale di persone vaccinate è alta la malattia non si diffonde. Sono protetti anche gli individui che non possono vaccinarsi.
The clinical presentation of patients with SARS-CoV-2 infection ranges from lack of symptoms to COVID-19 with mild upper respiratory tract illness, or severe respiratory distress and multi-organ failure requiring intensive care unit admission and mechanical ventilation.

The variability of disease severity suggests that the individual immune response to the virus plays a most important role in determining the clinical course.
Hypothesis: Infection tolerance

Viral infection

Inflammation
Antiviral effect

Resource for comparative genomics and bat immunology

Expansion and diversification of bat immune genes

NKG2 genes
Type I IFNs
MHC class I

Complex and inhibitory signaling potential in bat NK cells

- High baseline expression of inhibitory receptors

Cytotoxicity

Inflammatory cytokines

NK cell

DAP10

CELL. 2018 https://doi.org/10.1016/j.cell.2018.03.070
Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

Auto-antibodies against type I IFNs in patients with life-threatening COVID-19
CROSS-REACTIVE OR NATURAL ANTIBODIES?

doi: https://doi.org/10.1101/2020.05.11.20098459
Loss of Bcl-6-Expressing T Follicular Helper Cells and Germinal Centers in COVID-19

Cell 183, 1–15, October 1, 2020
**Data scientist explains dangers of trying for herd immunity**

Dr. Chris Murray, Director at the University of Washington’s Institute for Health Metrics and Evaluation, explains why it's dangerous to try for herd immunity from coronavirus as the pandemic rages on. *Source: CNN*

<table>
<thead>
<tr>
<th>Herd Immunity</th>
<th>Global Deaths</th>
<th>U.S. Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>40%</td>
<td>10,446,745</td>
<td>815,150</td>
</tr>
<tr>
<td>45%</td>
<td>11,752,588</td>
<td>917,044</td>
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<tr>
<td>50%</td>
<td>13,058,431</td>
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<tr>
<td>55%</td>
<td>14,364,274</td>
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<td>60%</td>
<td>15,670,117</td>
<td>1,222,725</td>
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</table>

**CNN Global Town Hall**

NEW DATA SHOWS DANGERS OF TRYING FOR HERD IMMUNITY

*Source: The Institute for Health Metrics and Evaluation at the University of Washington*
319 treatments and 236 vaccines
Effectiveness of convalescent plasma therapy in severe COVID-19 patients
9490–9496 | PNAS | April 28, 2020 | vol. 117 | no. 17

Screen convalescent patients

Neutralizing antibody concentration >1:640

200 ml /recipient
Chest CTs of two patients.

Kai Duan et al. PNAS 2020;117:17:9490-9496
Antibody-mediated viral neutralization

SARS-CoV-2

Neutralizing Antibody

ACE2

Host cell

Antibody-dependent enhancement

Non-neutralizing Antibody

Facilitate virus entry

Infection of target cell

Antibody-mediated immune enhancement

Non-neutralizing antibody

Activating FcγR

Endosome

Pro-inflammatory cytokines

Anti-inflammatory cytokines

Adapted from: Iwasaki A, Yang Y. Nature Rev Immunol 2020, doi.org/10.1038/s41577-020-0321-6
Identification of neutralizing human monoclonal antibodies from Italian Covid-19 convalescent patients

BioRXiv
doi:https://doi.org/10.1101/2020.05.05.078154
PHASE 1: Isolation of S-protein Specific mAbs

Patient Enrollment
14 Covid-19 Convalescent Patients

14 Days Incubation
CD40L feeder cells, IL-2 and IL-21 mAbs production

Single Cell Sorting
Post- Incubation
4,277 S-protein+ MBCs

S-protein ELISA

1,731 S-protein Specific mAbs

PHASE 2: Identification of Extremely Potent nAbs

Live Virus Neutralization Assay
Neutralizing mAb Non-Neutralizing mAb
Protected Vero E6 Cytopathic Effect on Vero E6

453 Neutralizing Antibodies

Characterization of Neutralizing mAbs

4 Groups of nAbs
Siena, 14 ottobre 2020 – Il Monoclonal Antibody Discovery (MAD) Lab di Fondazione Toscana Life Sciences annuncia la scelta dell’anticorpo monoclonale (MAD0004J08) che si è dimostrato più potente contro il virus e che sarà testato nelle prove cliniche il cui avvio è atteso per fine 2020. Una decisione scaturita dall’attuale fase di sviluppo e produzione dei tre anticorpi migliori (selezionati a luglio scorso) e che valuta sia la capacità dell’anticorpo di legare la proteina spike e di inattivare il virus, sia la resa da un punto di vista dello sviluppo e produzione della terapia contro coronavirus SARS-CoV-2 (Progetto MAbCo19).

A marzo arriveranno gli anticorpi monoclonali in grado non solo di curare in modo efficace i malati di Covid-19 ma anche di prevenire l’infezione nelle persone sane.
A NEW ALLIANCE TO FIGHT COVID-19

174 VACCINE CANDIDATE IN DEVELOPMENT
WEAKENED VIRUS
Viruses are weakened by being passed through animal or human cells until they gain mutations that limit their ability to cause disease.
E.g. Codagenix vaccine.

INACTIVATED VIRUS
Virus is inactivated using chemicals or heat.
E.g. Sinovac Biotech in Beijing has begun testing an inactivated version of SARS-CoV-2 in humans.

LEZIONE 5 | UPDATE SU COVID-19: QUALI SONO LE NOVITÀ SU TERAPIA E VACCINI

R. Carsetti

VIRAL VECTORS VACCINES

Replicating viral vector (such as measles)

Coronavirus spike gene

Viruses such as measles or adenovirus are weakened so they cannot cause disease, and are genetically modified to produce SARS-CoV-2 proteins

Non-replicating viral vector (such as adenovirus)

Virus replicates

Cell

APC
LEZIONE 5 | UPDATE SU COVID-19: QUALI SONO LE NOVITÀ SU TERAPIA E VACCINI

R. Carsetti

PROTEIN-BASED VACCINES

Protein subunits
Virus peptides are directly used with/without an adjuvant e.g. Spike proteins

VLP
Mimics the structure of SARS-CoV-2 but lack genetic material

LEZIONE 5 | UPDATE SU COVID-19: QUALI SONO LE NOVITÀ SU TERAPIA E VACCINI

R. Carsetti

NUCLEIC ACID VACCINES

The DNA or RNA encoding a viral peptide that promotes an immune response is inserted into human cells, which then produce large quantities of the specific DNA or RNA.

At least 20 teams are currently trying to develop a DNA- or RNA-based vaccines against SARS-CoV-2.
http://dx.doi.org/10.1016/j.molimm.2013.02.008
LEZIONE 5 | UPDATE SU COVID-19: QUALI SONO LE NOVITÀ SU TERAPIA E VACCINI

R. Carsetti

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Discovery and Target Validation
Preclinical Stage
Manufacturing Development
Initial bioprocess, formulation, and analytics

Phase I
Safety

Phase II
Safety and immunogenicity

Phase III
Safety, efficacy, and regulatory approval

Regulatory Review

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Translational medicine entry
Clinical Assay Optimization (antibody)
Dose Regimen Selection
Innovative Clinical Trials
Large sample size needed for safety and efficacy evaluation

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3–8 Yr
2–10 Yr
1–2 Yr

July 14, 2020 DOI: 10.1056/NEJMe2025111
<table>
<thead>
<tr>
<th>Developer / Researcher</th>
<th>Treatment vs. Vaccine</th>
<th>Product Category</th>
<th>Stage of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beijing Institute of Biological Products/ Sinopharm</td>
<td>Vaccine</td>
<td>Inactivated virus</td>
<td>Phase III</td>
</tr>
<tr>
<td>Wuhan Institute of Biological Products/ Sinopharm</td>
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<td>Inactivated virus</td>
<td>Phase III</td>
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<tr>
<td>Sinovac/ Instituto Butantan/ Bio Farma</td>
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<td>Inactivated virus</td>
<td>Phase III</td>
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<td>Non-replicating viral</td>
<td>Phase III</td>
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<td>Phase III</td>
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<td>University of Oxford, Oxford Biomedical, Vaccines Manufacturer/ Imperial Innovations</td>
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<td>Non-replicating viral</td>
<td>Phase III</td>
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<tr>
<td>Gamaleya Research Institute</td>
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<td>Non-replicating viral</td>
<td>Phase III</td>
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<td>Moderna/ NIAID/ Lonza/ Catalent/ Rovi/ Medidata/ BIOQUAL</td>
<td>Vaccine</td>
<td>RNA-based vaccine</td>
<td>Phase III</td>
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<tr>
<td>BioNTech/ Pfizer/ Fosun Pharma/ Rentschler Biopharma</td>
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<td>RNA-based vaccine</td>
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<td>Vaccine</td>
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<td>Phase II</td>
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<td>Protein subunit</td>
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<td>CureVac</td>
<td>Vaccine</td>
<td>RNA-based vaccine</td>
<td>Phase II</td>
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<td>Vaccine</td>
<td>DNA-based</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>Zydus Cadila Healthcare Limited</td>
<td>Vaccine</td>
<td>DNA-based</td>
<td>Phase I/II</td>
</tr>
</tbody>
</table>

540 records
PFIZER AND BIONTECH CONCLUDE PHASE 3 STUDY OF COVID-19 VACCINE CANDIDATE, MEETING ALL PRIMARY EFFICACY ENDPOINTS

Wednesday, November 18, 2020 - 06:59am

- 95% effective against COVID-19 beginning 28 days after the first dose;
- 170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group
- Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%
- Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved
- well tolerated across all populations (fatigue 3.8% and headache 2.0%)

Companies plan to submit within days to the FDA for EUA and share data with other regulatory agencies around the globe
The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021
Pfizer is confident in its vast experience, expertise and existing cold-chain infrastructure to distribute the vaccine around the world
- 94.5% efficacy. The COVE study, enrolled more than 30,000 participants in the U.S.
- 95 COVID-19 cases, of which 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.5% (p <0.0001).
- A secondary endpoint analyzed severe cases of COVID-19 and included 11 severe cases (as defined in the study protocol) in this first interim analysis. All 11 cases occurred in the placebo group and none in the mRNA-1273 vaccinated group.
- The interim analysis included a concurrent review of the available Phase 3 COVE study safety data by the DSMB, which did not report any significant safety concerns
- Based on these interim safety and efficacy data, Moderna intends to submit for an Emergency Use Authorization (EUA) with the U.S. Food and Drug Administration (FDA) in the coming weeks and anticipates having the EUA informed by the final safety and efficacy data (with a median duration of at least 2 months). Moderna also plans to submit applications for authorizations to global regulatory agencies.
Accelerating Development of SARS-CoV-2 Vaccines
— The Role for Controlled Human Infection Models (CHIM)

September 3, 2020
DOI: 10.1056/NEJMp2020076
Innovation for Pandemics
• Bill Gates,
DOI: 10.1056/NEJMp1806283

Coalition for
Epidemic Preparedness Innovations (CEPI)

Institute for Disease Modeling
The impact of vaccines

For 99.99% of the history of mankind, life-expectancy has been < 30 years

55 life-years gained from 1700
35 life-years gained from 1900

TIME “This Baby Could Live To Be 142 Years Old - Dispatches from the Frontiers of Longevity" (February 2015).