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Webinar

Stand on the Same Side Against Covid-19 – The Future Strategies Against an Unknown Enemy

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"STAND ON THE SAME SIDE" Videoconferences

https://www.covid19expertpanel.network

"Implementing a science-based lockdown exit strategy is essential to sustain containment of COVID-19. China's experience will be watched closely, as other countries start considering—and, in some cases, implementing—their own exit strategies"

The Lancet, Volume 395, Issue 10232, 18–24 April 2020, Pages 1305-1314

This phrase expresses the purpose of this program called "Stand on the Same Side against Covid-19" that takes advantage of the new and rapid digital technologies to put together several experts worldwide. It's a global space were many countries hit by SARS-COV-2 can share only scientific information in order to face the pandemic.

July, 7th 2020,
CHINA-EUROPE VIDEOCONFERENCE

"STAND ON THE SAME SIDE AGAINST COVID-19 – THE FUTURE STRATEGIES AGAINST AN UNKNOWN ENEMY"

Lorenzo Corbetta: Good morning, good afternoon or good evening, depending on where you are. My name is Lorenzo Corbetta. I am a professor of Respiratory Diseases in the University of Florence and director of the educational programme in Interventional Pulmonology. This is the fourth webinar on the educational project called Stand on the Same Side Against COVID-19, and now with the title 'The Future Strategies Against an Unknown Enemy.' Our aim today is to update you on the evolution of the pandemia and on evolution of the virus that we have called 'unknown enemy,' but maybe during the webinar we'll find out something more about it thanks to the presentation of Professor Duccio Cavalieri, Professor of Microbiology in the University of Florence. Then we will talk about the development of a vaccine for COVID-19 with Professor Bonanni, Director of Specialisation in Hygiene and Preventive Medicine of the University of Florence, and about clinical recommendations and clinical trials in progress with Professor Mohammed Munavvar, who is the current President of the British Thoracic Society and President of the European Association of Bronchology and Interventional Pulmonology.

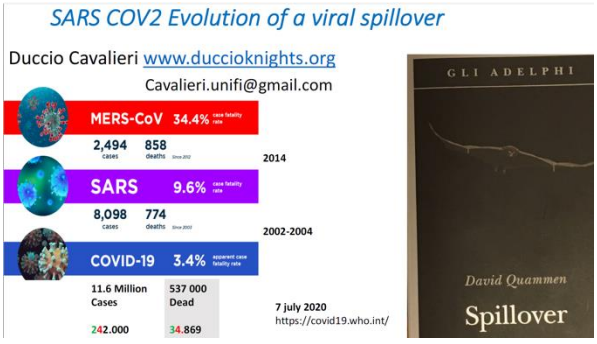
Furthermore, we have important guests from countries that are now still in full outbreak, the Professor Rendon, President of the Mexican Pulmonology Society, who is already attending the latest webinar with us, and another old friend from Brazil, Professor Cruz, Professor of Allergology and Pneumology at the Federal University of Bahia. Last but not least, we have the pleasure to have with us Dr Laura De Paoli, who represents a very influential body, the WHO, World Health Organisation, and she have been working for several international organizations to provide medical assistance worldwide, recently in Africa. Now it's my pleasure to introduce my mentor, Professor Leonardo Fabbri, who is a Professor of Respiratory and Internal Medicine in the University of Modena & Reggio Emilia, who will chair with me the webinar. Please, Professor Fabbri.

Leonardo Fabbri: Thank you Lorenzo, and thank you for organizing these very interesting seminars. I'd like to thank the speakers for supporting this initiative. Without further ado, I give it back to you to introduce the first one.

Lorenzo Corbetta: Okay. I introduce Professor Duccio Cavalieri, Professor of General Microbiology of the Department of Biology of the University of Florence, with the title, 'Evolution of a viral spillover.' Please, Professor Cavalieri.

Duccio Cavalieri: Thank you. So, I had the task here to try to make sense of where this virus came from and what are its dynamics. I've been trained in Harvard for six years in evolutionary biology and that's why my interest spreads through several kingdoms of microbes, from bacteria to yeasts and viruses. I have been studying specifically a yeast virus. It's called killer virus. It has some similarities with SARS-CoV-2, but kills yeasts not humans. So, in genomics the evolution of the genome it's a process that is basically constant, and since the times of Darwin we know that change is brought up by mutations that occur hypothetically randomly along the genome. The same maybe holds true for COVID-19. COVID-19 is not a complete novelty. We have had here in this life two previous emergencies, MERS-CoV with a 3.4 case fatality rate, 2,494 cases, 858 deaths, SARS, 8,000 cases, 774 deaths, and now COVID-19, 11.6 million cases, 537,000 dead, where the numbers below are Italy. 242 cases, 34,869 deaths. This data is as of yesterday.

A relevant point is that coronaviruses have passed through human evolution several times in the past. Probably we have met at least 40 different coronaviruses, and four of which have been associated to common cold. One actually at the end of the 19th Century which started in Russia was probably a coronavirus. Two of them came from mice, two of them came from bats. Bats are a perfect incubator for coronaviruses because they rarely develop the disease. They harbour the virus and they harbour large communities of viruses.



Today there are at least 61 different bat coronaviruses that can infect man and have been described in detail. Jumping species is a crucial mechanism for coronavirus evolution and survival. The virus is alive only in the host, and so bats provide the reservoir and evolution place. Interestingly, mutation rate in SARS-CoV is apparently low with respect to flu and HIV, but recombination between different coronavirus infecting the same host is indeed frequent. Some bat species can carry up to twelve different coronaviruses simultaneously.

This work has been made by a researcher from Wuhan, Zhengli, the 'Bat Woman,' and the work from the Ralph Baric Laboratory in University of North Carolina Chapel Hill. Interestingly, since the time of SARS, this review came out in 2007 and it's a summary of the conclusion of the SARS episode. The last author, Kwok Yung Yuen, said: 'The presence of a large reservoir of SARS-CoV-like viruses in horseshoe bats together with the culture of eating exotic mammals in southern China is a time bomb.' His words come from this review. 'The possibility of re-emergence of SARS and other novel viruses from animals or labs, and therefore the need for preparedness, should not be ignored.' I think we probably have not read this review carefully enough, because recently, as we all know, this is exactly what happened. This is the first paper that describes in detail the composition of the RNA viruses in the lungs, this is BAL, in the lungs of a patient, one of the first patients in Wuhan. As you see, the vast majority of the patient that was suffering from this disease, COVID-19, was actually SARS-CoV-2. From the first regional work published by the group of Zheng-Li Shi, we see that the author already suggests as the origin of this bat and puts at the basic of this, at 97% identity with the SARS-CoV-2, the coronavirus that we've come to know so well, RaTG13. Remember this name because this probably is the missing link, is the virus screen in the bat that differs from the one that infects the humans, but could be the backbone. It's the nearest neighbor to what we are seeing here. The differences between the bat virus and the human virus are substantial. So, indeed the potential origin and the nearest neighbor are bat viruses, but the differences are substantial. This is the paper from the Andersen group that suggests the natural origin of this virus and shows that this virus has unique traits, as we all know. The spike region is unique with respect to the other SARS and MERS.

The sequence of the spike with the binding sites to ACE2 is so diverse that in the early days for the whole month of January, February, the scientific community was doubting that actual ACE2 was the target for the binding. But then we know now that this is a degenerated site that is more efficient of the one from SARS for binding to ACE2. The second trait that we should all remember is relevant for the infectivity of the strain is the presence of a furin-like cleavage site that is absent in coronaviruses of the same clade. These two traits, in particular the second trait, have never been described in another coronavirus before, are unique to this virus that is attacking the humans, and probably this second trait that has been seen before in viruses like HIV-, the second trait, this furin splicing site, is, kind of, interesting because it's probably within the ability of this virus to escape the immune system. Now there are more than, today, 7,000 genomes of this virus sequenced, okay? The data I report here and which I'll talk during my presentation do a summary of what is known around 4,256 of those for which we have an almost complete assembly. We have a sequence of at least 85% of the sequence of the virus. Amongst these, we have 350 Italian genomes that are currently being published by the group of researchers from the Sacco Hospital in Milan and their collaborators. Immediately from the beginning, probably we have been exposed to two different strains of SARS-CoV-2. I know the definition of 'strain' within virus infection is quite peculiar because there is not a real boundary. As I have seen, 97% is the boundary between the nearest neighbour from the bat and what happens in humans, but these are the sequences extracted from the first 5,000 genomes. We see that there are two clades, one clade in which is predominant the Shanghai signature, and one clade in which is predominant the Wuhan signature.

What does it mean? This means that even if the virus mutates slowly, evolution occurs, and this is not something surprising. In fact, this paper that is accepted in Nature should come out in the next days. This preview of an accelerated article preview shows exactly this fact. You can discriminate, based on specific mutations, the two different clades. It's interesting this because there are several mutations, 80% of which are non-synonymous mutations. What it means that the virus mutates, mutations are not evenly distributed along the sequence. There are some regions that are enriched in non-synonymous mutations, so in mutations that lead to an amino acid change. The fact that they lead to an amino acid change means that the protein is changed. The big challenge is showing that there is a change in functions, and this we don't know, but you have to know at the moment that 198 recurrent mutations describe homoplastic sites. Four sites are mutated in more than fifteen patients of those that have been sequenced, and one site is mutated in over 40 patients. Why is this interesting? How can we use this information? We can use this information to track the flow of the virus. This is a paper published on PNAS. All of these papers have been heavily criticized. That's the way science goes. The applicability of network theory of evolution to the evolution of virus sequences is not trivial because you do not have the models of evolutionary theory that we have for yeast or for bacteria, but the applications of the nearest proxies suggest that we can track the virus that started from Wuhan, arrived in Shanghai, moved to Munich, arrived from Munich to Milan, and from Milan to Mexico City in 30 days for a precise set of mutations. This approach allows, let's say, to estimate the success rate of the entry of coronavirus into a country.

This is the American example. This is a paper published by the group of Lemey, and they analysed the sequences and asked how many times the virus arrived in Washington State. They found a first aborted entry that was not successful around January 15, and the second successful entry on

February 15. The interesting thing of the model they built is that they could see that the first arrivals were not successful. The two arrivals that brought the virus into the US were one from Hubei to Seattle on February 13, and the second that brought the virus that probably expanded in Milan to New York City on February 20th. So, this allows us to follow the routes, and what we know now is that these two viruses were slightly different. These are not enormous differences, but were slightly different, and what we know now is that the exact two same differences that had been discovered in China were present in Milan, were present in Lodi and in Bergamo. This is the paper of the first published publication from an Italian group. It's the group of Stefanelli Paola, you recognise the name, Maria Rita Gismondo, Giovanni Rezza. They described the presence of two specific strains. Now here's the caveat of this story. Some of these papers, some of the research groups, are making claims that are currently hard to support. This paper here from Montefiori and Korber, it's a very interesting one but suggests that the spike mutation that we have seen being present in at least 25 of the genomes sequenced leads to a less transform to discriminate two forms of the virus, one that can be transmitted more efficiently and one that can be transmitted less efficiently. Now, the big issue with these assumptions is the sampling error. The paper I'm reporting you here just came out on Current Biology from the group of Sarah Otto, an excellent evolutionary biologist. (https://www.cell.com/current-biology/fulltext/S0960-9822(20)30847-2) What Sarah shows is that based on the genomic sampling over time, the substitution rate can be estimated. We can estimate one mutation per week during the movement of the virus in the world. We can see that the substitution rate is much less the one from influenza, and we can make assumptions on which will be the dynamics of the mutation using evolutionary theory.

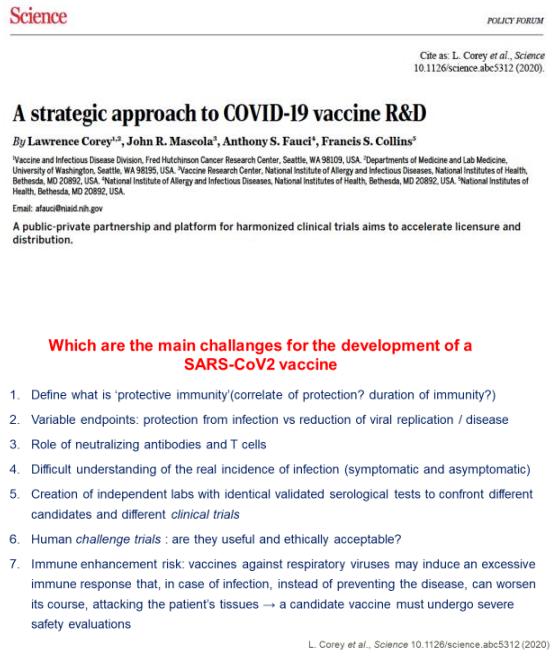
According to the models that Sarah Otto has developed, the mutation should increase transmission, reduce symptomatic fraction, increase the duration of the incubation phase, reduce virulence, and the models predicted that the lockdown period, the whole experience, will probably lead to the emergence of a second wave of the virus in mutated form in the fall, September, October. This model is supported mathematically in quite an interesting and convincing way, and this model draws a few fine lines about the searching for that mutation of SARS-CoV-2 and basically puts an important caveat. Currently, the lack of a neutral sampling strategy, so the fact that we have sequenced not really at random, but we have sequenced in areas where we were having hotspots of the virus is leading to a potential sampling error that makes it very hard to say whether one variant is associated to an increased rate of transmission or to an increased pathogenesis. But very likely the virus is dynamically changing.

This paper here shows very interestingly that we have not identified a single recurrent mutation convincingly associated with increased viral transmission, and we have to keep in mind that mutations could even make the virus worse. So, my suggestion to the audience is that when we look at the virus and its evolution, we should keep in mind what Dobzhansky said. 'Nothing in biology makes sense unless observed using evolution as a lens.' So, selection acts on the whole genome, on the genes of the virus, of the host, and of the other microbes that are carried by the host, but why there is no evidence currently of the outcome of SARS-CoV-2 adaptation? The analysis in the study of the rate of change of this virus is important to adjust and potentially drive the strategies for its containment and to make conclusions supported by evidence. Thank you.

Lorenzo Corbetta: Thank you very much, Duccio, for your very nice presentation. We will have many questions for you at the end of the other presentations, and for the audience, they could post the questions in the chat and we will respond later. Now I introduce Professor Paolo Bonanni with a presentation on perspectives for the development of a vaccine for COVID-19.

Paolo Bonanni: So, thank you Lorenzo for the invitation to join you in this very interesting webinar. My task is to give a perspective for the development of a vaccine for COVID-19, and you know that a lot is moving around this topic. I would suggest our colleagues to read this paper if they did not already read it. The authors are colleagues from the US, including Anthony Fauci, and in this paper we have some interesting perspective regarding the challenges for the development of a vaccine against COVID-19.

First one is define what is protected immunity. So, we would need to have a correlate of protection which we don't still have. Another point is how long the immunity could last, so the duration of immunity. The second point is we have variable endpoints for the evaluation of a vaccine. Are we speaking of protection from infection or of reduction of viral replication or reduction of the severity of the disease? These are different endpoints that should be considered separately. Then the role of neutralising antibodies and T cells. We have difficulties in understanding the real incidents of infection because we don't know exactly what the percentage of asymptomatic subjects is, compared to the symptomatic ones. We have a challenge in the potential creation of independent labs with identical validated serological tests to confront different candidates and different clinical trials. We



Science

POLICY FORUM

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A strategic approach to COVID-19 vaccine R&D

By **Lawrence Corey[1,2], John R. Mascola[3], Anthony S. Fauci[4], Francis S. Collins[5]**

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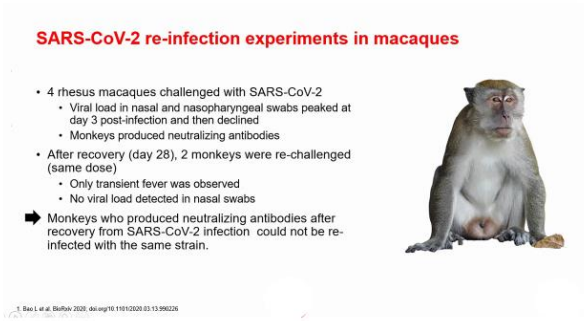
A public-private partnership and platform for harmonized clinical trials aims to accelerate licensure and distribution.

Which are the main challanges for the development of a SARS-CoV2 vaccine

1. Define what is 'protective immunity'(correlate of protection? duration of immunity?)
2. Variable endpoints: protection from infection vs reduction of viral replication / disease
3. Role of neutralizing antibodies and T cells
4. Difficult understanding of the real incidence of infection (symptomatic and asymptomatic)
5. Creation of independent labs with identical validated serological tests to confront different candidates and different *clinical trials*
6. Human *challenge trials* : are they useful and ethically acceptable?
7. Immune enhancement risk: vaccines against respiratory viruses may induce an excessive immune response that, in case of infection, instead of preventing the disease, can worsen its course, attacking the patient's tissues → a candidate vaccine must undergo severe safety evaluations

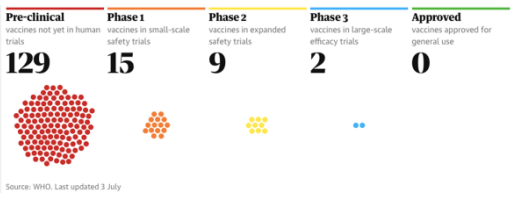
L. Corey *et al.*, *Science* 10.1126/science.abc5312 (2020)



should be able to compare the very many vaccines that are in development today to see what the comparative ability of each candidate is.

Then an ethical point, the human challenge trials, are they useful first of all, and are they ethically acceptable? The last point is the immune enhancement risk. We must remember that vaccines against respiratory virus may induce an excessive immune response that in case of infection, instead of preventing the disease, could worsen its course, attacking the patient tissue. So, a candidate vaccine must undergo severe safety evaluations. This is a mechanism of antibody mediated immune enhancement with an increase of growing inflammatory cycle times, but also the mechanisms of antibody-dependent enhancement where no neutralising antibodies could increase the potential for the virus to enter the target cells. For sure our target is the S protein, the spike protein of the coronavirus, where there are these three identical binding domains, all of which must bind to the host cell. Here we can see that when the virus needs to enter the cell there is this opening up of the spike with the receptor binding domain which can bind to the ACE2 receptor. If you look at the different vaccine trackers in the web you can find sometimes different numbers on the same day because it's very difficult to keep up with the many research groups that are working on this topic. Here you can see, this is from WHO, 129 pre-clinical studies, fifteen in phase one, nine in phase two, two in phase three, but none approved today. If you look at another tracked which is from the London School of Hygiene and Tropical Medicine you'll find different numbers. This is also very recent from yesterday, but what is amazing is the number of projects that are in the pre-clinical phase, but some of them then are progressing to the phase one, two or three before they get approved and licensed.

So, what are the possible approaches to a vaccine against COVID-19? One of the most advanced approaches is based on DNA and RNA-based vaccines.

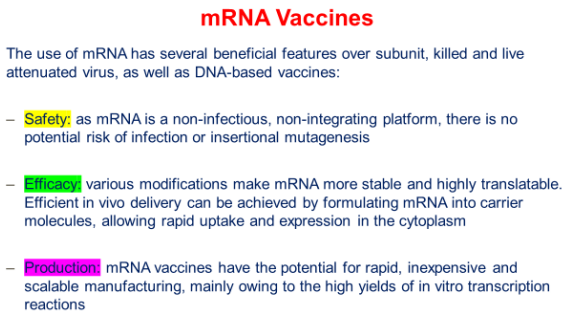


(https://www.nejm.org/doi/full/10.1056/NEJMp2005630)

Why an RNA vaccine? An RNA vaccine is probably very much scalable in a big way. How do they work? The mRNA, which is the coding for the spike protein, is encased into a live lipid code, then it's introduced into the cell, it goes into the cytoplasm and produces the spike proteins that are then released for the contact with the immune system. But there are also the DNA vaccines, which are introduced by an electroporation system and they must enter the nucleus and integrate into the nucleus and then produce mRNA to produce the spike proteins. So, what is the advantage of mRNA vaccines? The use of mRNA vaccines has several beneficial features over subunit, killed and live attenuated virus, as well as over DNA-based vaccines because safety is important and mRNA is a non-infectious, non-integrating platform. There is no potential risk for infection or insertional mutagenesis. Then the efficacy, because various modifications make mRNA more stable and highly translatable. There is an efficient in vivo delivery that can be achieved by formulating mRNA into carrier molecules, allowing rapid uptake and expression into the cytoplasm. The production also, I already mentioned this. MRNA vaccines have the potential for rapid, inexpensive and scalable manufacturing, mainly owing to the high yields of in vitro transcription reactions. We have two sub-types of mRNA vaccines. The first one is the simple mRNA, you introduce the mRNA which produces the spike proteins, but we have also some self-amplifying mRNAs. In this case not only the mRNA which is encoding for the spike proteins is introduced, but also some non-structural proteins that allow the self-amplification of mRNA, and so a higher production of spike proteins. There is already a vaccine with this characteristic developed by a college in London.

Then the most advanced RNA-based vaccines are these two. Of course I cannot mention all of them, but the most advanced are the ones from Moderna. This vaccine uses messenger mRNA to produce viral proteins. The American company is eyeing phase three trials in July and hopes to have vaccine doses ready for early 2021. Then there is another vaccine of some biotechs together with Pfizer, which have also been announced on July 1st that all the volunteers for phase 1/2 trial produced antibodies against SARS-CoV-2 with some moderate side effects. So, this warrants further studies that are going on at this time. So, this is the plan of the phase one study for Moderna, and here you see it's foreseen to end in September 2021.

The other one from Pfizer, they had several studies with many participants. You can see here 7,600 participants in this



mRNA1273 (RNA vaccine, Moderna)

Interventional	
Estimated Enrollment :	105 participants
Allocation:	Non-Randomized
Intervention Model:	Sequential Assignment
Masking:	None (Open Label)
Primary Purpose:	Prevention
Official Title:	Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults
Actual Study Start Date :	March 16, 2020
Estimated Primary Completion Date :	September 20, 2021
Estimated Study Completion Date :	September 20, 2021

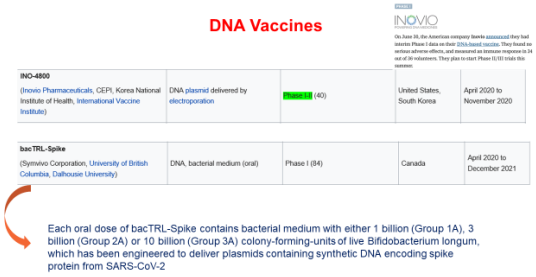
BNT 162 (RNA vaccine, Pfizer)

Interventional (Clinical Trial)	
Estimated Enrollment :	200 participants
Allocation:	Non-Randomized
Intervention Model:	Sequential Assignment
Masking:	None (Open Label)
Primary Purpose:	Treatment
Official Title:	A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of Four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-2019 Using Different Dosing Regimens in Healthy Adults
Actual Study Start Date :	April 23, 2020
Estimated Primary Completion Date :	August 2020
Estimated Study Completion Date :	August 2020

phase 1/2 randomised observer blind dose-finding study. Then again this is a dose escalation study, so it foresees to verify what is the right dosage of this vaccine. Let's turn to the DNA vaccines. DNA vaccines are also important because DNA is easy to manipulate, it can allow rapid design and construction of potential vaccines. Another advantage of DNA vaccines is that they are extremely stable, and so they could reduce the need for a cold chain and increase the production shelf life, which is important, for instance, for developing countries where the cold chain could not be assured in some instances.

There are some pre-clinical data of some of these vaccines. They are studied in rhesus macaques, 35 of them. They induced an important humoral and cellular immune response, including neutralising antibody titers comparable to those found in convalescent human and macaques infected with SARS-CoV-2. Following vaccination, the animals were challenged and it was possible to demonstrate that the level of viral presence had a very important reduction in median viral loads in bronchoalveolar lavage and nasal mucosa. There are other DNA vaccines, one is from Inovio. There is also an oral vaccine based on the DNA technology where there are billions of colony-forming units of Bifidobacterium longum, which has been engineered to deliver plasmics containing synthetic DNA, encoding spike proteins from SARS-CoV-2.

DNA Vaccines



INO-4800 (Inovio Pharmaceuticals, CEPI, Korea National Institute of Health, International Vaccine Institute)	DNA plasmid delivered by electroporation	Phase 1,2 (40)	United States, South Korea	April 2020 to November 2020
bacTRL-Spike (Symvivo Corporation, University of British Columbia, Dalhousie University)	DNA, bacterial medium (oral)	Phase I (84)	Canada	April 2020 to December 2021

Each oral dose of bacTRL-Spike contains bacterial medium with either 1 billion (Group 1A), 3 billion (Group 2A) or 10 billion (Group 3A) colony-forming-units of live Bifidobacterium longum, which has been engineered to deliver plasmids containing synthetic DNA encoding spike protein from SARS-CoV-2

Another type of vaccine that is under development now is the one based on viral DNA vector. This is a variation of the design of the expression plasmid, which are used to construct a DNA expression system that can amplify the level of RNA and protein expression as occurs in a live virus infection. The most popular ones are those based on adenoviruses, but anyway, there are around 25 groups that say that they are working on viral vector vaccines. The virus is like measles or adenoviruses that can be genetically engineered so that they can produce coronavirus proteins in the body. Then we can have replicating viral vectors such as with measles or also the vesicular dermatitis virus that was used recently to produce the first Ebola vaccine which was licensed, but also non-replicating viral vectors such as adenoviruses. In this case, booster shots can be needed to induce long-lasting immunity. So, the adenoviral vector is particularly useful if you want to get a CD8+ cytotoxic T lymphocyte response, because in this way the antigens that are carried by the adenoviral vectors can be presented to T cells via MHC class 1 molecules and this causes a robust CTL response.

So, in this way they can also, the intracellular virus could be killed. We have two important adenoviral-based vaccines presently underway, the Ad5 coronavirus produced by CanSino, a Chinese company, but also the vaccine based on the chimp adenovirus 5 developed by the University of Oxford. Here you can see that the pre-clinical studies of the vaccine developed by the University of Oxford showed to be able, under challenge, to reduce the possibility to have pneumonia in the macaques that were immunised compared to those who were control group. The other important data is that the nasal fluid, the ability of the vaccine to reduce the viral load is not as much important as is the bronchoalveolar fluid. So, there might be some doubts that this vaccine is able to avoid the disease but not the transmission of infection. So, we have here again phase 1/2 studies with different numbers, but also the vaccine from CanSino, from the Chinese company is very well studied. We have this phase two clinical trial to

Adenoviral vector

Ad5-nCoV (CanSino Biologics, Institute of Biotechnology of the Academy of Military Medical Sciences)	recombinant adenovirus type 5 vector	Phase II interventional trial for dosing and side effects (500)	China	March 2020 to December 2020
Ad5-nCoV (CanSino Biologics, Institute of Biotechnology of the Academy of Military Medical Sciences)	recombinant adenovirus type 5 vector	Phase I (108)	China	March 2020 to December 2020
ChAdOx1 nCoV-19 (University of Oxford)	adenovirus vector	Phase I-II, randomized, placebo-controlled, multiple sites (510)	United Kingdom	April 2020 to May 2021

Two adenoviral vector-based vaccines:

–Ad5-nCoV, CanSino

–ChAd5, University of Oxford

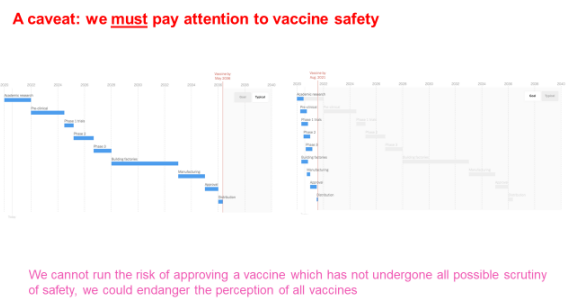
Adenovirus-based vaccine (University of Oxford)

Interventional	
Actual Enrollment :	1090 participants
Allocation:	Randomized
Intervention Model:	Sequential Assignment
Masking:	Single (Participant)
Primary Purpose:	Treatment
Official Title:	A Phase I/II Study to Determine Efficacy, Safety and Immunogenicity of the Candidate Coronavirus Disease (COVID-19) Vaccine ChAdOx1 nCoV-19 in UK Healthy Adult Volunteers
Actual Study Start Date :	April 23, 2020
Estimated Primary Completion Date :	May 2021
Estimated Study Completion Date :	May 2021

evaluate the safety and immunogenity of the recombinant novel coronavirus vaccine, and also this trial which is a dose escalating phase one clinical trial.

We have the first result of this study where they showed that giving a low dose, a medium dose or a high dose, they had 75 to 83% participants declaring they had the side effects, but they were not bad side effects, so there was no serious adverse event noted within 28 days post-vaccination. They also studied the ELISA antibodies and neutralising antibodies which increased significantly at day fourteen and peaked at 28 days post-vaccination. So, they are going on and should be one of the first groups to get a vaccine close to the license route.

So, they also have another study here. Then we turn to the other approach, which is the one of inactivated vaccines, and a vaccine which is advanced is the one from Sinovac, a private Chinese company. In June, the company announced its phase 1/2 trial on 743 volunteers, and they found no severe adverse events and produced an immune response. So, they are launching a phase three trial in Brazil in this month, in July. Then there is also the Wuhan Institute of Biological Products, the other vaccine. In June they are moving to a phase three trial, so they are in advanced phase. Again, we have data from the Sinovac vaccine on pre-clinical data showing that it's a good response and the possibility to work with this vaccine licensed are rather high at this moment. One of the last things I wanted to report is that some groups are also studying the possibility to use the MMR vaccine, the measles, mumps and rubella vaccine, for its potential to give cross-reactivity and cross-protection also for the COVID-19. We have the first subunit vaccine available today in clinical trials. This is very recent news that a first subunit vaccine underwent the first phase one study. Here it's a vaccine which has two different adjuvants. They are AS03 adjuvant, which was used also for the H1N1 pandemic vaccine in 2009, and also the CTG, the repeat of the cytosine and guanosine sequences that are a good adjuvant also for this kind vaccine. Then we also have the pathogen-specific artificial antigen-presenting cells, where genetically modified artificial antigen-presenting cells can express conserved domains of the viral structural proteins delivered by lentivirus vector, which are supposed to evoke the naïve T cells in the human body and lead to differentiation and proliferation. We also have autologous antigen-presenting cells that are charged with the antigen and re-infused in the nurses and doctors that will undergo this first study in China. Final considerations. I have rushed to show you what is going on on the vaccine studies, but we have to remember that usually a vaccine takes fifteen years to be developed, and so this is the timeline we would get a vaccine if we had a normal development. We would have a vaccine in May 2036. We are rushing, so one caveat is that we cannot run the risk of approving a vaccine which has not undergone all possible scrutiny of safety because we could endanger not only the COVID vaccine but also all vaccines that we are using today with exceptional results.



With this I thank you for your attention and this is my address for any questions you want to address. Thank you very much.

Lorenzo Corbetta: Thank you very much Paolo. We will have many questions for you, and now we carry on with Professor Muhammed Munavvar, Consultant Chest Physician of the Hospitals of Preston (UK). His presentation will be an update on the current experience and plans for the future from the Thoracic Society's perspective. Thank you Mohammed.

Mohammed Munavvar: Thank you very much. It is indeed a pleasure and privilege to be here, to be able to speak and update you. I had given a similar presentation in the first event of your excellent series of webinars. What I am going to do basically is cover this topic with a very brief introduction, then an update about thoracic society-related statements and guidelines, a brief overview of clinical trials in the UK, some of which you will already read about, and then conclude this presentation. First of all, I don't have any conflict of interest. I work for Lancashire Teaching Hospitals, British Thoracic Society and EABIP, as you have already mentioned. The global incidence, just checked about an hour ago, as mentioned already with the first speaker, it has crossed unfortunately more than 11 million cases and more than half a million people have died. So, this unprecedented global pandemic has left a trail of devastation, despair and deep distress to a whole lot of people around the world, and it does not respect royalty or indeed position, as we have seen in the last few months. The UK data, again checked yesterday, was nearly 300,000 cases and unfortunately more than 44,000 people have passed away. The only good news is that although there was a peak in April, latter part of April and early May, we are starting to see a decline in the numbers and also in the number of deaths. So, what have we done as British Thoracic Society during this period? We have produced a great deal of guidance in relation to COVID and I'm going to take you through some of this guidance in the next few minutes of my presentation. We have set up a separate section in the British Thoracic Society. I don't know whether any of you had had the opportunity to visit, but it's something that we can share free downloads of a variety of information on COVID for the respiratory community.

Now we have started to move to this section, where we are trying to focus on how to resume services, and I'll touch upon this as well in the next few minutes. A whole lot more than 25 different statements have been produced at a record pace in the last three to four months, where they would have normally taken three to four years to put together all this guidance. A team of people have worked round the clock to produce guidance on various aspects of pulmonology, but also other

conditions such as venous thromboembolism, oxygen therapy, etc. So, essentially every aspect of respiratory medicine, how should the pulmonologist or how should we non-pulmonologists manage is what we are focused on. As I said, now we have not surprisingly found that a whole lot, thousands and thousands of patients who do not have COVID, who have non-COVID-related respiratory problems have suffered a great deal as a consequence of the pandemic because their care has been severely affected because appointments have been delayed, elective care has been affected, even semi-emergency care has sometimes been affected. So, we put together some documents on how to plan the resumption of these services, particularly lung function tests, how to do it safely step-by-step, because there have been very few lung function tests carried out during this period. Sleep physiology and sleep medicine, a crucial part because of its wide-ranging implications for the patient and the wider public. Procedures related-, how to resume procedures which I'll come to in a minute. Specific guidance has also been produced with regard to pulmonary rehabilitation and long-term ventilation services. And this is part three and then we're going to stretch to all the other respiratory services. We have also focused on guidance for healthcare professionals because I presume it's happening in your countries as well, where patients who are over 70 but also patients with respiratory illnesses and a variety of other illnesses, have been shielding during the lockdown period.

The other big tsunami that is going to hit us, or has already started to move towards us, is the large workload of post-COVID pneumonia patients. How do we systematically ensure that these patients are cared for in the weeks and months after they recover, fortunately, from COVID pneumonia. This has been divided into two sections, those who have had severe pneumonia and needed admission to an intensive care unit, or high-dependency unit and those who have had mild to moderate pneumonia. Patients in the severe category are given details of a helpline, this varies around the country and they are given a call or face-to-face consultation about four to six weeks following discharge from hospital. These patients then-, we have to do a systematic workup, look at-, consider new diagnoses of PE, liaise with localised CU team, post-COVID holistic assessment to pick up any new problems that developed as a consequence of COVID pneumonia. And twelve weeks after discharge, they have a thorough assessment, including full lung function test, where necessary a CT scan, other lung function tests, functional assessment such as a six minute walk test, consider an echocardiogram and where appropriate even repeat the CTPA required. And then we pick up a percentage, we think we'll pick up cases of interstitial lung disease, they'll go to the specialist interstitial lung disease and some may end up requiring attention from the pulmonary vascular disease specialist. In the milder category, we could relax a little bit more and have a more-, a less proactive approach but where necessary, on demand we can provide service but also twelve weeks post-discharge we will carry out an assessment initially to see how they are and then if necessary proceed to a more detailed systematic assessment as has happened in this category. All these documents are available in the British Thoracic Society website and are free to download and as you can see here from March to April to May, more than 100,000 people have-, 100,000 times it has been downloaded, each of these documents, to cover all these aspects.

Change in practice is also required, I'm just giving you an example from being an interventional pulmonologist like Lorenzo, giving an example of what is happening in the bronchoscopy suite but this applies to every procedure in the hospital, every visit to the hospital. So, the moment we receive a referral, we do an assessment remotely and then ask the patient to isolate. Ideally for fourteen days but of course in the lung cancer field or cancer field, that is not possible, every minute is crucial so, we ask them to isolate but continue with the diagnostic part. We are undergoing a PET-CT scan, a CT scan, have a COVID swab 24-48 hours in advance. What is becoming more widespread, is the availability of IGG antibody tests and then at that point we check and sometimes we need a repeat CT scan if they have not had a PET-CT scan. On the day, they will have a questionnaire done, potentially in the future they can have a point of care lateral flow assay, to check for antibody test, or even point of care swab to make it safe for those patients to undergo whatever procedure they need to. We cannot keep postponing procedures, so far we've postponed some of the elective procedures. And at the same time, we want to ensure that our staff are safe. How do we do that? We want to make sure by this pathway, that it's a green area, not a red area but a green area by admission and recovery. We want to ensure that everybody's wearing full PPE. Maybe we have to adapt the area, the environment as well with regard to negative pressure rooms or the whole room. The suite needs to be changed, the layout needs to be changed to have a separate dining area, separate exit or doffing area etc. Majority of procedures we try to do under general anaesthesia, as has been demonstrated by myself here with an EG tube. That is the closed circuit but sometimes and this applies also in the intensive care unit, where you have a sheet along with an EG tube and a T-piece but sometimes you have to carry out this procedure under local anaesthesia and sedation and a number of different devices have been put together imaginatively.

And one such is the slotted surgical mask or face mask, make a little incision and through that you introduce the bronchoscope while oxygenating the patient through the nasal cavity. A number of other boxes are available for this purpose as well. Moving on to the next major section that I want to spend a few minutes on, it is about research and therapeutic trials and when the pandemic hit us, the UK got involved in a number of studies. If you look worldwide and if you type into the US ClinicalTrials.gov, there are more than 2,000 studies underway currently in the COVID world and there have in fact been more than 27,000 publications. What happened in the UK very early on, it was decided that the government will pump in a great deal of money through the National Institute of Health Research into a variety of trials, everything from vaccines to epidemiology, to policy development and research and so on. And a previous speaker very nicely covered the vaccines and some of the couple of vaccines which are being developed here. A number of clinical trials were initiated, multi-centre clinical trials, so that we get proper randomised

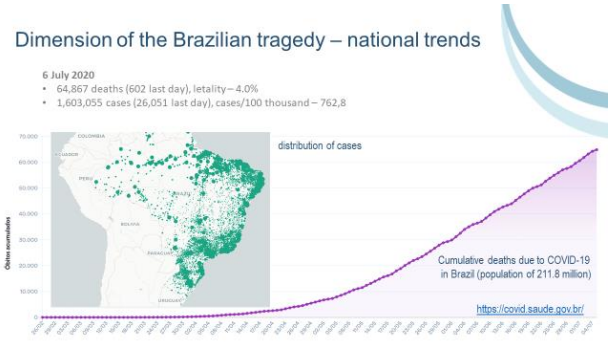
trials, with meaningful conclusions and one in particular I will touch upon in a minute. The trials are plasma transfusions, trials of vaccines and a variety of other areas as well. The Recovery trial is the biggest trial that was conducted in the UK, the randomised control trial and this was engineered from Oxford, a team, on a national basis. Almost every hospital in the UK was involved in this trial. Initially the trial design looked like this. You had five arms, two is to one, is to one, is to one, is to one, no additional treatment or HIV-, anti-HIV drug lopinavir/ritonavir, dexamethasone low dose, hydroxychloroquine, or azithromycin. Later on what was added was convalescent plasma or no additional treatment, another randomisation. In the second week, if the patients continued to deteriorate despite the initial intervention, then they were randomised to tocilizumab or no additional treatment when the cytokine storm was considered to be important.

So, what happened? That trial was started in-, end of March early April and first week of June, on the 5th of June, the data from more than 1,500 patients, 1,542 patients, in comparison with usual care in double that number. Hydroxychloroquine, it was found that there was no significant difference in the primary end point of 28-day mortality, between the hydroxychloroquine arm and the usual care. There was also no evidence of beneficial effects on hospital day duration or other outcomes. This indicated that there was no meaningful mortality benefit with hydroxychloroquine and therefore hydroxychloroquine arm was removed from the randomisation. And on the 16th June 2020, there was groundbreaking results from this trial and as you would have all seen, a total of more than 2,000 patients were randomised to receive dexamethasone 6mg, once daily for ten days and were compared with double that number of patients who were in usual care. And what it showed is that dexamethasone reduced deaths by one third in ventilated patients. For the first time, there was a medication that has proven beyond doubt to bring about mortality benefit in ventilated patients one third and in patients requiring oxygen, outside of the critical care unit, one fifth mortality benefit. Based on these results therefore, it was concluded that one death could be prevented by treatment of around eight ventilated patients with dexamethasone and around one death could be prevented in 25 patients requiring oxygen alone. Next came the results on the 29th June, remember dexamethasone was the 16th June. On the 29th June it was shown that lopinavir/ritonavir, the anti-HIV drugs, did not bring about any clinical benefit. Again, more than 5,400 patients and comparing it, more than 3,000 patients and it showed there was no mortality benefit and there was no evidence of beneficial effects on the risk of progression to mechanical ventilation or length of stay. So, anti-HIV drugs also have been removed from the recovery trial recently. That is a quick overview of what has been happening and I'd like to conclude by making the following points.

Future, as far as COVID is concerned, one of the biggest things that has happened, is training and teaching has been severely affected by COVID because students, trainees, fellows, are not allowed into the COVID ward. We need to think outside the box and think of ways and means to provide the training, continue to provide the training and we are trying to evaluate a few different techniques, such as the use of 360 degree camera, the HoloLens and augmented reality and so on. The pandemic curve has indeed flattened and started a downward trend in many countries around the world. However, we can expect further low incidents with waves. It could also become endemic, therefore we need to remain vigilant, there is no room for complacency. Primary and secondary care services need to restructure and work collaboratively. I've spoken about post-COVID follow up and need to resume services. We cannot continue to ignore all those other patients who have non-COVID related conditions. We have seen a tremendous expansion of digital healthcare, telehealth, minimising face-to-face consults and this is here to stay and we've just got to expand on it and do it properly. Every patient who comes through for interaction in the hospital, will need to be isolated, tested, screened, prior to any interaction, any procedure in the hospital. We need to find novel methods, innovative approaches to ensure that this is speedy, accurate and effective. We're also looking at therapy remotely, example virtual pulmonary rehabilitation. We've already looked about and talked about the importance of research into therapy, vaccines and prophylaxis and this needs to be a collaborative, collective and consistent approach across the world. As I said in my first talk, nobody should think that they can be safe without making everybody else safe. Thank you very much indeed for your attention.

Leonardo Fabbri: Thank you very much Dr Mohammed Munavvar. And it's now my pleasure to introduce the next speaker, Professor Alvaro Cruz from the University of Salvador, Bahia. Alvaro is a professor of medicine, has contributed tremendously to the science and education in the field of asthma and allergic disease. Today he will address the topic of controlling the COVID-19 outbreak in Brazil. Is it possible? Alvaro, privileged to have you with us.

Alvaro Cruz: Thank you very much to you. I'm honoured to be part of this most relevant discussion with such distinguished chairs and speakers. I'm especially pleased by the title of the programme, 'standing on the same side'. This is exactly why I chose this title. 'Controlling COVID-19 outbreak in Brazil. Is it possible'? We are facing this combat regretfully completely divided. This is a dark side of Brazil that many of you know unfortunately. We have a minority living in good conditions and a lot in underprivileged neighbourhoods. This is the major split of inequalities in Brazil. The leaders should have been taking care of for a long time and trying to reduce this. Now we have another problem. This is my conflict of interest disclosure. My major links are with ProAr Foundation, Federal University of Bahia, the National Research Council in Europe that is developed to supervise me in Brazil. I divided this talk, brief talk, in four topics, the dimension of the Brazilian COVID-19 tragedy, the dangers of national division in fighting COVID-19, the strong response from the public health system and respiratory health as a global priority. You see the division of the Brazilian tragedy, the national trend in cumulative deaths to COVID-19. Over 60,000 deaths, 602 the last day, mortality of 4%.



Over 1,600,000 cases. And here you see the distribution of cases from the big cities at the seashore, towards the countryside in every state. And you see some white areas not affected by cases, it's because the population is scarcely distributed.

Now, some information from the City of Sao Paulo, the first one that was affected. The first case was somebody coming from Italy, as you know Sao Paolo has strong links with Italy. And what you see in this upper panel here, is an estimate of adherence to social distancing by anonymised geolocation monitoring Sao Paolo. You can see the numbers but they are all around 50%. So, it's social distancing that was in place that was happening in Sao Paolo, was never beyond 60%, it got up to 59% in the beginning and now it's around 47%.

I guess this is not enough, it's part of the reason that things are not well in Brazil. Some information which is important for coronary physicians, comorbidities amongst subjects dying with COVID in Sao Paolo. This is an estimate by May 23rd, over 6,000 cases, 10% of them had lung disease, some sort of lung disease, and 3.4% had asthma. Asthma was not a lung disease but this problem of reporting comorbidity, especially the respiratory comorbidity, is a problem all over the world. An underscore of the fact that many chronic lung disease such as asthma and COPD are under-diagnosed, under-recognised. Now, some good news. Despite all of the problems we have and I will show you some of the background of the problems but now some good news. The numbers of deaths per day in Brazil in your upper left, apparently it's reaching a plateau and perhaps a trend to decline. The same you'll see here in the number of deaths per day in the state of Sao Paolo, a plateau and in the city of Salvador in the left lower graph where I live, there also seems to be a trend, or plateau or even decline. And the same happens in the city of Sao Paolo. There is certainly a plateau and perhaps a trend to decline. This is an interesting paper published recently from the US, that studied the association between mobility patterns and COVID-19 transmission in the USA, using a mathematical modelling study, in which they calculate the daily mobility information derived from aggregated and anonymised mobile phone data, as it was done in Sao Paolo. And what they have shown, is that the mobility patterns dropped by 35 to 63%, relative to the normal conditions, very similar to Sao Paolo as I mentioned. Mobility patterns are strongly correlated with decreased COVID-19 case growth rates for the most affected counties in the USA. They observe now, that individuals apparently anticipated public health directives where social distancing was adopted despite a mixed political message. Again a similarity with our situation in Brazil.

Now, I wish to share with you some facts. I will try to abstain from making judgements. The dangers of national division in fighting COVID-19. We'll see here some of the President's-, Jair Bolsonaro's recent statements and action. He has said in a national TV broadcast, that COVID-19 is just a bit of flu, that the priority should be for economic activity, this has been always behind his statements and he attempted to fight states and municipalities when they tried to promote social distancing. There was no real lockdown in Brazil in any major area and he said there was no need for social distancing because this would be bad for the economy. Then due to this, the first Minister of Health was fired, who was doing a very good job at the time. Then, he often took part in demonstrations with no mask, as you see in the picture. He ordered massive production of hydroxychloroquine in Brazil and due to this reason, the second of Minister of Health resigned because he didn't agree with using this bribery with no scientific basis. And the Ministry of Health has been led by a general so far. Another quote from President Bolsonaro, when he was asked about increasing numbers of deaths, he said, 'And so what, I make no miracles,' and he has attributed the responsibility to the governors and mayors. Then he said, 'Those from the right take chloroquine. The lefties take Tubaina which is a popular soft drink,' making a joke about the political divides on medical matters, that has been unbelievable. But a strong response has been set up in Brazil. We have universal public health coverage from the constitution of 1988, it's far from ideal but it's there. It's one of the largest countries in the world in terms of population and you see as universal public health, by law everybody is covered. There was an emergency cash transfer to the undeserved and informal workers from the federal government, which was a law passed in agreement with the congress. There was support to employers and workers to avoid massive unemployment.

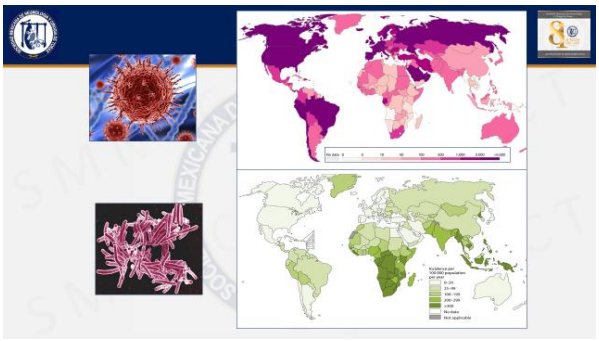
There were various aids from municipalities and states, direct involvement of many governors and mayors with the policy to combat COVID. There were shelters for subjects with COVID-19 and the war hospitals and ICU beds with ventilators built. Some other examples of a good response throughout Brazil, Sao Paolo University Hospital complex offered 1,000 beds exclusively to COVID-19, including 300 ICU beds. There was a network developed in my university in collaboration with the FIOCRUZ, Foundation through the Ministry of Health, and a centre for big data called CIDACS, to analyse date and publish trends, daily updated from more than 5000 municipalities in all states of the country. We set up a tele-coronavirus hotline, in Bahia my state to help guide people on whether they should go to the health service. The state of Bahia and the city of Salvador are building COVID war hospitals and shelters. There was the SOS Favela in Rio trying to watch what happens in other certain populations. These are only a few of many good initiatives. Another thing that is worth mentioning, is the rapid generation of knowledge and I bring two examples here. A report from minimally invasive autopsies of COVID showing and confirming that it's

a systemic disease with major events in the lungs and involvement of various organs and tissues. The pulmonary changes are the result of severe epithelial injury, with microthrombotic vascular phenomena. You see here, in patients with diffused alveolar damage in fatal COVID-19, fibrinous microthrombotic in small sized pulmonary arterioles observed in eight out of ten patients. My colleagues, I wish to bring you to this broader scenario of respiratory disease. As you see here, COPD is responsible for 5.72% of the deaths globally. Lower respiratory infection, 5%. Lung cancer, tuberculosis, asthma, interstitial lung disease, the major respiratory disease were responsible, the cause of 16.92% of all deaths in 2017. It's going to be much more this year. The dimension of the Brazilian COVID-19 tragedy is 63,000 deaths already.

There is national division which leads to major weak flanks in many fronts, regretfully. A strong response from the public health system has prevailed however in states and municipalities and respiratory disease are the leading cause of deaths globally. Some thoughts to share with you. Health specific hospital beds and ventilators are not enough to solve the problem. Social distancing has to be taken seriously from the beginning of the fight. Collaboration is key to planning strategically and preparedness. Capacity for research, surveillance and manufacturing essential products is crucial. WHO is vital for global health security co-ordination and response. Respiratory infections are a major threat to mankind. Cannons and bombs are useless to fight it but science, solidarity and sharing knowledge, work. Political leaders must engage with health authorities, not fight them and health is the most precious asset one has. Health problems respect no border and everyone must be cared for to protect all. And top priority has to be given to protect respiratory health, hopefully in a cleaner and greener role. Thank you very much.

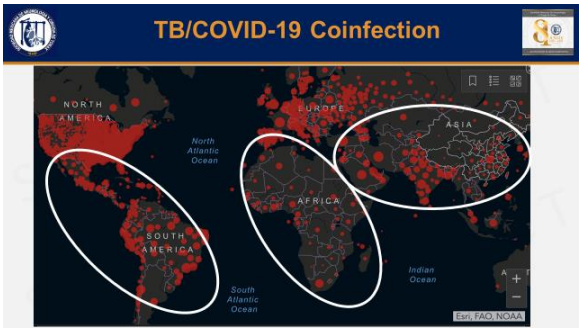
Leonardo Fabbri: Thank you very much Professor Cruz for your nice presentation. We now move to the next presentation by Professor Adrian Rendon from Nuevo Leon. Professor Rendon is also President of the Mexican Pulmonary Society and today he will address the issue of the coexistence of two pandemics, TB and COVID-19. Professor Rendon.

Luis Adrian Rendon: Thank you. Okay. I live in a country, that is endemic for tuberculosis and now it's suffering the severe attack of COVID. So, I may speak a little bit about the coexistence of these two pandemics. I'm a member of the Green Light Committee from the World Health Organization, actually for PAHO, the branch for the Americas. Here, in these two maps, you can see the global distribution of COVID. Here, the darker the worse and the TB distribution. I put these two maps together because it seems that COVID territories respect tuberculosis territories but we will see later that this is not true, actually the opposite. The WHO report, averages about 10 million new cases of tuberculosis, incident cases and for COVID just in seven months we have overpassed that number with 11.5 million. About deaths, tuberculosis is in the top ten cause of death,



tuberculosis is the number one infection, leading counts of deaths from an infection, with 1.5 million cases a year. But in just seven months, COVID is reaching more than half a million and if it was a race, maybe COVID is going to win this race if things are going on as we are seeing. Early this year before TB Day, the WHO launched this information note, before TB Day because there was some concern and they were pointing out two main questions. Number one, are people with TB likely to be at increased risk of COVID infection, illness and death. The main concern at that time was that the TB patients would suffer in their treatment because of the pandemic. We didn't know too much about the coexistence of the two infections, actually we don't know yet about that. And the second question was, 'Can we maintain and support the essential services for TB as prevention, diagnosis and treatment.' For prevention, it was clear that we have to limit the transmission of TB to COVID patients and COVID patients to TB because they may have similar clinical presentation, they can share some symptoms and they are often in the same places. If we were doing well with the respiratory protection measures, we shouldn't be worried, but we know that all around the world we were suffering from TB outbreaks among healthcare workers.

So, bilateral transmission is a real risk. For diagnosis, we have the proposal that all the TB patients and COVID patients at the moment with suspect cases, should have available the two tests, the one for TB and the one for COVID. But on the field, those two problems work independently and there is a real concern about biosafety. Nobody wants to test for TB if they are not sure the patient is not a COVID case. For treatment and care, most of the TB programmes have very specialised staff, including the physicians, immunologists, nurses and whatever was needed and they were supposed to be a group that could help in the COVID pandemic, sharing their expertise. But what happened in real life, is that expertise was transferred to COVID programmes, leaving alone the TB programmes. What about the coexistence of TB and COVID.

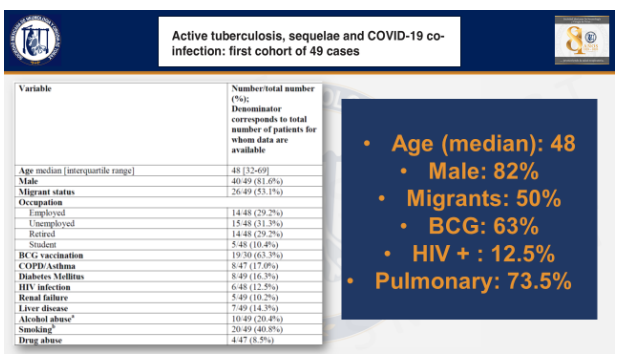


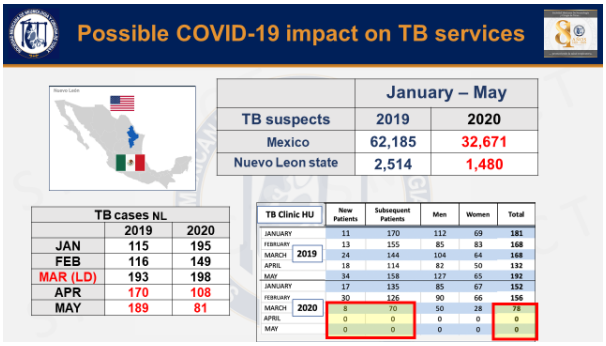
What do we know now, we don't know too much. Now, I'm using this map to point out the endemic regions for tuberculosis. The red dots are COVID and you can see that COVID is anywhere.

It seems that there are more COVID on the industrialized countries but we can see the numbers, we can see that this is different because of the magnification in the map. Actually you can see here, we just listened to the case of Brazil, I can tell you about the case in Mexico. Mexico, Brazil and Peru, are the three countries in Latin America with more TB cases and they are also the three countries with more COVID cases. So, they don't respect each other, they are together. I'm going to present this case briefly. The coexistence of cases with TB and COVID, there are not too many. These cases, are cases in my institution. It was a young physician, a female who presented with a classical, clinical picture of pleural tuberculosis that was confirmed by culture. The patient was put on regular treatment, standard treatment. She returned to work and when she was in the hospital they performed screening for COVID on all the healthcare workers and she resulted positive. She was on six months of TB therapy, she has no symptoms and the chest X-ray taken at that time didn't show any findings suggestive of COVID. Currently the patient is doing well, she's continuing the TB treatment and she didn't receive any COVID treatment.

This is the first cohort report, of the coexistence of the two diseases, tuberculosis and COVID. They collected patients from Russia, from Europe and from Brazil and they put together 49 cases. The median age was 48 years old, most of them were male, half of them were migrants, BCG has been applied in 63% of those cases. A minority was HIV positive and most of the cases were pulmonary tuberculosis. For the COVID presentation, 90% of the patients were symptomatic and 48% had COVID pneumonia. Regarding the time for the diagnostic, TB was diagnosed first in half of the patients, COVID first in almost 30% of the patients and the diagnosis was simultaneous in the same week in 88%.

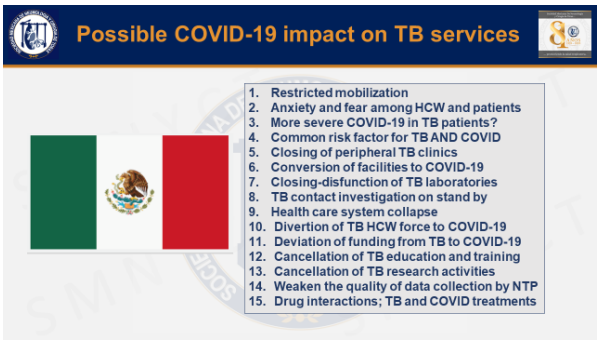
The second paper is a kind of continuation of the previous one. They put together the 49 patients they already had, plus twenty more from Italy. They had a total number of 69 patients and they look at mortality in this group and mortality was 11%. The risk factors they found, were the same we already know for COVID, the elderly population with comorbidities. They found less mortality in migrants and we can guess that one of the considered reasons was the younger population. This is a new paper that we are participating in, it was just submitted. This is a global study that includes all





the continents in the world and we are looking at the impact of COVID on TB services. We are comparing the study of statistics, the TB statistics from February to May 2019, to the same period 2020. I wasn't allowed to present the results but I wanted to give you some numbers from my institution. What is the possible impact of COVID on TB services? This is a short list, a summary list of those. Shortage of supplies because of lack of mobilization and for the patients that are not going to the clinics, so we are suffering from inadequate follow-up with the patients. There is also a lack of services for TB, the small periphery clinics have been closed. There is a lack of TB experts because they are working with COVID, so that counts as poor quality of TB care. Also, the money is moving to COVID, the TB programmes were not prepared for it. We may guess what is the role on the severity of the two diseases when they are together. If one has got TB and they've got COVID, it's going to be a more severe case and the opposite is also true? In the case I just presented to you, it didn't happen, it was a priority here for a permanent TB infection and the COVID was an asymptomatic case. And what about the drug interactions. We don't know how to treat COVID yet but we're using many drugs, often labelled, and the MDR patients, XDR patients, using a lot drugs that can have very dangerous interactions with those drugs that we shouldn't' be using as we are. All of these issues lead to less TB diagnosis, delay in TB diagnosis, so we are expecting to have more TB cases there in the community but we're not aware of them. All of this is happening in my country, in Mexico. I've seen that and I can tell you that we are suffering from all of this and maybe in some countries like Brazil, they have the same situation. Here I'm going to show you some numbers that I have from Mexico and from my state, Nuevo Leon, which is very close to the border with the United States. This is last year, this is the current year, the period January to May. On this year, TB suspects, we have more than 60,000 and in the same period we have about half.

We've decreased the number of TB suspects that we're studying and the same happened in my state. What about the TB cases diagnosed in my state. This is last year, this is current year. Over January and February, we were having an increasing number of TB cases, we were doing well but then the lockdown started in March and you can see that after that the number of diagnoses decreased a lot. And the worst scenario happened in my hospital. Our TB clinic was closed with the lockdown because of safety reasons, you had more than two months, actually three now, because we haven't diagnosed any TB cases.



Those cases are there but we haven't diagnosed them. The WHO was expecting to reach the milestone for 2025 through the strategy, End TB elimination. This is the curve that they expect, this is what really was happening until 2019, this is for incidents and this is for deaths. When the pandemic hit this program, we can say that the expected is very difficult to reach for incidents and for deaths and maybe we should expect a resurgence of TB. We must be prepared to have many more TB cases, many more viral-resistant cases and also many more TB deaths and we need a damage control plan to deal with that. COVID is supposed to stay, it's very probably going to stay. TB wasn't really there. TB is going to stay and actually is going to be a stronger pandemic. Thank you very much for your attention.

Lorenzo Corbetta: Thank you very much, it is very interesting this correlation between TB and COVID and maybe Professor Laura De Paoli will talk about it in her presentation. I introduce Laura De Paoli who is the Platform Co-ordinator of WHO Europe and she will talk about the resurgences after COVID-19 in Europe. Please Laura.

Laura De Paoli: Thank you very much indeed and good morning and good afternoon to everybody. Thank you for inviting me here Lorenzo, we've known each other for a long time. Okay, so this is a Situation Report of resurgences in EURO Countries. So, my name is Laura De Paoli, I'm the coordinator of the COVID-19 platform at WHO EURO at the moment in Copenhagen, at the moment I'm working from home. So, just a few words on the WHO structure. So, we all know that the headquarters are in Geneva, where there is the making of policy, protocols and there are experts on a number of businesses. And, then we have the regions. The regions are coordinating entities and also support of countries. Also, they do have experts there as well. So, there are six regions, AFRO, which is mainly the African continent, but countries can actually choose where they belong. So, we have Sudan, for instance, which is an African country, also Northern African countries, but Sudan is not really a Northern African country, which are actually they are affiliated to EMRO, which is Eastern Mediterranean Region. So, there are social, cultural, political and religious regions for belonging to a region rather than another one. So, for instance, Sudan belongs to EMRO because EMRO is a collection of Islamic countries and Sudan is mainly an Islamic country. EURO, which is the region I am working for, for instance, contains countries which don't belong to the European continent, but they are Central Asian countries, we'll see after. Then, there is PAHO, I think, and my colleagues from America, South America can tell me if I'm wrong, so it's Pan-American Health Organisation which is affiliated to WHO and I believe PAHO comprehends the whole of American countries. And, then we have SEARO, which is South-East Asian Region and WIRRO which is Western Pacific.

So, a very quick overview of the countries which belong to WHO EURO, which is 50 different countries and as you can see, I actually highlighted them in red, one is Azerbaijan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, Uzbekistan, which are not really considered normally, geographically, European countries.

Now, a very quick overview of the Sit Rep of which I'll give you a bit of a wrap up. We have over 200,000 deaths now in the EURO region. Since a few weeks, the number of new cases is no longer decreasing but has reached a plateau and is fluctuating at a relatively stable rate. And, we see small increases week by week, or small decreases. At this rate, we are seeing over half a million new cases per month, a very significant number of cases and this is happening at a crucial moment where countries are about one or two months from having lifted their lockdown measures. The picture is very mixed. In Western Europe, we still see countries where there is a stable decrease of cases, but in the Balkan region, Eastern Europe, the Caucasus and Central Asia, we see very significant increasing trends and in some cases, community transmission, which is the blanket transmission, which was not seen in early months. In Central Asia, numbers have been kept low in the early months and then with the lifting of

containment measures, we see the health system of those countries struggling, with hospitals overwhelmed by the increasing number of patients. We see localized outbreaks which are explosive and have the potential to see new community transmission. What we also see, in some countries, is very prompt action and reintroduction of localized widespread measures to control those outbreaks. And, these outbreaks in school settings as we see in countries, such as Asia. You know, the countries we see localized outbreaks, in specific sectors of society, for instance, food processing factories. Lately, we saw an outbreak in a slaughterhouse in Westphalia, West Germany, where the cold surfaces promoted the stability of the virus and the outbreak.

Other important factors are who is working in those factories, are they migrant groups, do they live in overcrowded settings, which is a facilitating situation for spreading the virus? Other outbreaks have happened in coal mines as in Poland, where there are specific environmental factors, there's lack of ventilation that facilitates the transmission of the virus in confined settings. These localized outbreaks must be kept under control, otherwise they can easily spread out to community transmission. WHO, obviously, recommendation includes the three Ts, testing, tracing, and obviously, treating. And, localized isolation, it's important to know that isolation is not only for individuals who test positive or are suspect, but also of the very place where the outbreak has taken place. For instance, the factories and the mines. Over the summer months, we will be able to take action while the situation is under control, in a number of European countries. The situation will become far more encompassing in Autumn as the influenza virus will start circulating in the region and the complexity of managing two respiratory viruses at the same time, with similar symptoms, will be a major public health issue, that will require a multi-sector approach with agencies at community level. There is a specific importance in this situation of recommending influenza vaccination at a political level. About the influenza vaccine, we will see a shortage of vaccines, unfortunately, due to the very situation we find ourselves in with the pandemic. There is not a specific WHO recommendation for pneumococcus vaccination or BCG vaccination, which has been suggested in many instances by different sources over these past few months. About BCG vaccination, we have seen observational studies in mice and humans suggesting a protection against COVID-19.

But we need hard evidence in the form of a randomized control trial which has been now carried out over the last few months and now we are waiting for results which should be coming by the end of October, at the latest, the end of the year. Now, I would like to show you the, how do you get out here. Share, and then share again. I would like to show you very quickly because I know, that's it. Can you see the situation report? Can you see the coronavirus disease? So, this is the Sit Rep that WHO Geneva publishes every night after 9:00PM, more or less. And it's a daily report, they close gates around 10.30 in the morning, so this is the one of yesterday, the Sit Rep of yesterday until 10.30. So, here we have a map that shows where the most cases have happened yesterday. So, happened in the last seven days, so this is United States, Brazil, unfortunately, India and then we have Russia and also Saudi Arabia, Iran and Iraq, also and then Egypt and South Africa, in Africa, you can see that Africa is actually not terribly touched by the virus. Here, we have a graph that shows the new cases per day and here we have the Western Pacific, where China, Japan, South Korea are, we can see they are the very first to spike up and then there are still cases but they're under control, now lately there have been, maybe a few more cases. Now, there is South East Asia, now this is India probably carrying out the line towards the up, but again, we don't see the spike that we saw here in Europe, this is Europe and we see in America, it's quite a linear arithmetic line. Then, we see Europe here in orange, so we see the exponential curve here and then the plateau and then now, a bit of descent. And, now we have reached a second plateau, with as I said, some countries in Western Europe have a downwards curve at the moment, but in the Eastern European countries, Balkans and Central Asia, we have cases going up, we'll see it in a second. Then, we have Eastern Mediterranean which is receding but again, it's not exponential.

We see America which is definitely exponential right now. And, Africa, again, I worked in Africa until a couple of months ago and we could see that the cases just didn't have at all that spiky tend that we saw in Europe. So, is it the heat, is it the BCG vaccination, or most African countries have a policy whereby children from zero to six months of age are vaccinated with a BCG vaccine to avoid military TB in infants. So, now we go down through the countries. Again, we have South Africa, which is very high for an African country. We have many cases, 8,773 new cases yesterday, so it's a very high number. And, then we have Nigeria with 190, now South Africa is about 50 million people, inhabitants, Nigeria, I think 190 plus million people and you can see that the number of cases are not very high. Some people say, do they find them all, are they able to identify them to diagnose them, now, being COVID, I'm sure you will agree with me, particularly in Africa, where I worked for many, many years, it's actually a city disease. It expands particularly in capitals or where there is a lot of incoming people, particularly from Europe, or from other countries where the incidence and the prevalence is higher. So, and then we have the Americas, with the United States as well all know, 57,000, the new cases of yesterday, Brazil, 37,900, so Brazil is also still going up and then Chile, Mexico and Columbia are quite high, considering, well Mexico is a very populated country, but the other countries are not as populated. Then, Easter Mediterranean, Iran, still very high, Iran was one of the first countries to be hit in the Eastern Mediterranean region. Then, we have Pakistan, one of the countries that should belong to South East Asia, but is with Eastern Mediterranean for the reasons that I spoke about before and Saudi Arabia, they have seen a very high number of new cases. Egypt as well and Iraq as well, we saw it before.

And, then we come to Europe, so the Russian Federation is by far the one with highest number of new cases and also the highest number, in Europe, of total cases, but keeping the number of the total number of deaths, not very high compared, for instance, to the UK, where we have a much lower number

of total cases, but a much higher number of total deaths. Now, these are official numbers, so we can believe them or not, but these are the official numbers that we do have. And, then we have Spain, we have Italy, which is on the coming down, fortunately. The UK has reached a plateau and it's now on the descending curve. It took it a while and it's due to the political choices really, the policies that weren't put in the place, the policies of lockdown, use of mask etcetera, were put in place much earlier in continental Europe and particularly Western Europe and they weren't put in place, or they were put in place very loosely in the UK. Turkey is still very high. Germany, after seeing a resurgence a few weeks ago due to what I was talking about, this resurgence in positive cases, over 600 positive cases in Westphalia in this factory, meat processing factory, where they went up to 700 and 800, now it's on the coming down again. Then, I just wanted to show you in Eastern Europe, with Israel as well, with quite a high number of new cases, considering the number of inhabitants and that's due to the resurgence we were talking about. And, then, I just wanted to show you what we were talking about. Eastern Europe, for the number, when we compare the total numbers, for instance, of Ukraine, which is 49,000, with the number yesterday of new cases, 1,366, there is a disproportion. We can see it's a very high number of new cases, so that's why we see Europe being on a plateau again, which is not really going down, because in Eastern Europe, as we said, Balkan and Central Asian countries, we see the curve going up still and it's the same for Kazakhstan, again a disproportion between the total cases and yesterday's new cases, which is very high.

So, the recommendations, immediate action in testing and contact tracing and isolation when we find ourselves facing localized outbreaks and time is of upmost importance. Strengthening of influenza vaccination policy, influenza vaccination noting particularly for at risk groups and BCG vaccination or second dose is not yet recommended, awaiting results of randomized control trials. Thank you.

Lorenzo Corbetta: Thank you very much Laura. We have concluded the presentation so we can open the discussion, if somebody of the faculty has some questions, please.

Mohammed Munavvar: Well, Lorenzo, if I may start. This is a question to the last speaker, Laura De Paoli, if you don't mind. Very interesting data that you presented, with regard to the African scenario, or generally even otherwise, one of the things that is missing in the data is the denominator, which is the number of tests which were carried out in each place. Because, what would be very useful, is a percentage of positive tests and secondly, also to get to know, another surrogate marker, is the number of excess deaths in that particular area compared to, say, last year. I just wondered whether you want to comment on those two points.

Laura De Paoli: No, unfortunately we should have that, we don't have that in the Sit Rep of COVID, we should have more studies about there, to be honest with you, I have actually come across anything. The problem is, when we do our meeting, we have people presenting, but of course, being in Europe now, I'm only seeing people presenting about Europe. And, basically, what they're presenting, the platform is formed by WHO, UN agencies, they're all UN agencies operating in Europe and they are cross movement. So, we have people presenting on their work, what they do in the country, but we don't tend to have very scientific presentations, unfortunately and this is something I'm actually trying to work on, trying to invite people from academia to present more scientific work. It's basically, a forum formed by managers and so, we don't have enough scientific leverage on that and I wish we had more. I am not able to answer the question, unfortunately.

Duccio Cavalieri: I have another question on a similar trend. If you look at the crude epidemiological models, that have been proposed for SARS-COV-2, Africa is not the only exception, there are several countries where the models do not behave as they should, I mean, as they hypothesized to and I have been collaborating with Mohammed there, and the group from University for years on innate immunity activation. So, I was wondering whether anyone has overlayed the data on vaccination in general and the rate of SARS-COV-2 cases, because I find the BCG hypothesis fascinating, but not sufficient to explain the differences also between the different African countries. And, the other question, several data just published by Harvard and other universities that show the crucial role of UV and transmission of the virus on micro-particles that could be limited thanks to UV radiation, why it could be enhanced in conditions where there's a lot of fog and I'm thinking about several areas where the numbers were very high. So, let's say, I know you don't have an answer, but it's more for a discussion point, I have looked into the mathematics of the epidemiological models and they basically ignore, like, with the theory of the black box, to put numbers that control for the environmental factors and for the variability of the virus. So, in basically all the models, the virus is like a black box, you know, it's given as constant and in my opinion, delving into those variables could be maybe possible by looking into details on the data that we derive from Africa or other countries where things are unclear. But, as I said, it's true that we would need more samples, more stops, more analysis of the action presence of the virus throughout the world. But, it was an excellent presentation.

Laura De Paoli: You're welcome, thank you. Yes, it is for sure, it's a multifactorial situations, so we have the heat, also, well correct me if I'm wrong, I'm not actually a specialist, but we know that at 70 degrees, the virus is denatured, so maybe, now, I was in Central African Republic and there was, not a constant temperature, but for a good part of the day, we were over 40 degrees centigrade, so that must have a degree of importance. For instance, in South Africa, we have cold winters, I lived in South Africa for a long time and I know that in Cape Town it gets as cold as in Europe over the winter. So, for sure, climate plays a role, I agree with you, mostly likely as you said, the micro-particles with the fog, pollution, in Africa we don't have that. And also with vaccination, because also at some stage, also the polio vaccination, anti-polio vaccination was put on the table of discussion as a possible

protection factor, because they switch the innate immunity on, basically, there is a modulation of T cells. So, it is probably multi-factorial, the thing is that just as well, in Africa, we don't have as many cases as we had in Europe, for instance, because in Africa, like in Central Africa, we didn't have any ICU beds, we had only a few ventilators, they belonged to some NGOs that worked in surgical units, so they needed the ventilators for the operations. We have very few oxygen concentrators, so fortunately, there is this situation of non increased exponential line in the number of cases, otherwise all of Africa will be wiped out, or a number of African people will be wiped out. We all know that the trend of an epidemic is towards a benign, it goes towards a benign outcome, the bell curve show that, but still we could have an extremely high mortality, if we had the conditions, whatever they are, that we had in Europe and the States, for instance.

We should find out about BCG very soon, because by the end of the year we should have the results of the BRACE study and I'm really hoping that there is something good coming out of that. And, there is no harm in vaccinating people, I don't know why WHO didn't put, okay, we have a policy of non-recommendation of BCG vaccination against COVID-19, but as it has been shown, the BCG vaccination operates such a good protection against a number of bacteria and viruses, or in general, also, inflammatory diseases of the respiratory system that why not have it, you know, like everybody. I had it, so I felt quite secure, a bit safer. I actually feel quite safe because I had it.

Lorenzo Corbetta: Professor Fabbri, have you any questions?

Leonardo Fabbri: Not really. I was intrigued by the presentation on tuberculosis and COVID-19 and obviously, it's a very relevant epidemiological and clinical issue, but it's also a stimulating immunologic open question, because one of the predictive factors of worse outcome in COVID is lymphopenia, whereas in tuberculosis, you have specific expansion of lymphocytes, particularly lymphocytes and I wondered whether in some cases, there might be actually a sort of protective effect of tuberculosis with respect to COVID, but it's just an immunologic question. I wondered whether Professor Rendon may make comment to that.

Luis Adrian Rendon: We may argue and we may verse against and in favor of theories, because talking about BCG, BCG is supplied to all newborns in Latin American, in many countries in Asia and in Africa and with all that, everything starts in China, BCG is supplied there, in India, BCG is supplied, they've had many cases. In Latin America, BCG is supplied and we are so far in a whirlwind pandemic, so if we have any kind of potential, we would expect less cases. Let's say that BCG doesn't protect against infection, but protects against severe forms of COVID, we are having a daily pandemic in Latin America, so you may guess against BCG, just because of the numbers. But, for instance, in my case, the case I present, there was a young physician, with BCG who has a primary TB infection and then got COVID with no symptoms. Was that because of the BCG primary infection, I mean the BCG vaccination or because of the TB primary infection that protected her from severe forms, we don't know, we are just arguing about that. But, anyway, if we think that BCG is good, well BCG is already played in most of these countries, so the people are already protected, they need that protection, we may argue about getting a second shot from BCG, nobody knows about that and I wondered if these studies that are being performed right now are going to give us that answer. Because, it's going to be very difficult to control many ambient factors for that. And, my main worry about Latin tuberculosis, that is highly prevalent in countries like mine, is when people got COVID a severe form and get dexamethasone or another kind of immunosuppressive therapy, they are in danger to have a reactivation of Latin TB. We should worry about that and we should be aware of that, it's going to be a great problem.

Lorenzo Corbetta: Thank you. I have one question from China, we have 2,000 people connected with us from China now and the question is about the vaccine for Professor Bonanni. They say, we all care when the vaccine will launch, could the speaker estimate the launch month? They are waiting for the vaccine. We are all waiting for the vaccine.

Paola Bonanni: This is an extremely difficult question, because we are all waiting for the vaccine to be available but we really do not know when it will be and which vaccine, because you have seen from my presentation that there are several candidates, some people who are developing the vaccine are also claiming that we might have a vaccine available in the next few months, maybe, some say that it might be the end of the year. But, I'm not sure on which data this is relying, because you have seen that most of the phase one, two and we need phase three studies of course, before launching a vaccine, there are at present one, two and a couple of studies in phase three. The others are in phase two, all companies and biotechs are rushing to get the vaccine, but actually, I would like to stress once more what I reported in my final slide. We must be very careful, because if we fail on safety on this vaccine, it might be an enormous danger for the credibility of all vaccines, because we have to consider that we have the problem of immune enhancement and that problem does not seem to be very heavy up to now for the studies we have seen up to date, but it's still a problem to solve and to exclude. And, the other thing is that we are squeezing research, pre-clinical research, clinical research, which usually lasts for seven, ten, twelve years into one year and we must be aware that we shouldn't be so anxious of having a vaccine if we are not sure that the vaccine is totally safe. I'm telling this, I am a vaccine lover, I define myself, because I'm working almost exclusively on vaccines and I love vaccines, they have improved the health of mankind in a way that is not comparable to any other measure or therapeutical preventative, but I am also conscious that we must preserve the reputation of vaccines. So, we need to be really very sure that if the vaccine is put on the market it is for sure, first of all, safe and of course it should be also effective. But, I don't want to give false messages, saying, oh we will have it in

December, or January, I don't know actually but I hope that when we start, we have a good vaccine.

Lorenzo Corbetta: We will have another video conference in September for updating. I have, maybe the last question, for Duccio Cavalieri The question is, are there countries who exhibited only one strain of the virus and does this explain the different incidence found in Africa?

Duccio Cavalieri: No one knows. I mean, I don't have an answer for this question and it is true that the variance of the virus is something expected, there's nothing unexpected on the fact that the virus evolves. In virology, the definition of mutation has an interesting meaning, because there is genetic mutation and then there is a mutation sensed as usually a change in the virus phenotype, okay. There are indeed changes in the virus phenotypes, so far the two viruses described in China have a different phenotype. It's hard to say whether one is better and one is worse, apparently both viruses have been travelling and they have been all apparently, the most of them have been travelling via Munich, or Germany. So, Germany has been one of the hubs, because it's a commercial hub. So, the other reason why in Africa, potentially, there has been less of an explosion, it could be that the travelling of the virus has been less efficient, because maybe transport means have been less efficient and so, I think that mapping the evolution of these viruses is important for one reason. The theory behind the assessment of evolution of viral infection is quite complex and not necessarily seen from only one perspective. The naïve point of view says that the virus should attenuate, okay, which is what we usually expect, but the point is that viruses that can jump very rapidly from one host to another, so viruses that have a high rate of diffusion can escape this general theory, because they can basically get to the second host, when basically, irrespective of the fact that the first host is dead or alive. For sure, one of the tendencies will be to expand the phase where the individual has the virus, can transmit the virus, but the disease does not manifest, so the symptoms are not there and this is what the model that I showed is telling us, okay. I think, in general, that the summer would be a bottle neck and this is because this is the lesson we've learned from the Spanish flu, if you read through the history of viruses, summers have always been a bottle neck.

And, I think, the reason why they are a bottle neck is exactly related to the main factor, the transmission, how easy and how fast, what is the transmission rate. That number, 3.5 is not the same throughout the entire year, sometimes it's probably five, sometimes it's 3.5 and it could be two. And, from that number depends the attenuation, because when that number goes down, in theory, the virus should decrease it's pathogenicity, it should become less aggressive, because it has to survive within the same host for longer. But, this is all to see, we have to see what will really happen. But, I don't know how many viruses go through Africa and this points out the fact that we should expand enormously the potential of sequencing the virus, rather than simply detecting the presence by means of real time PCR. Currently, I work in a laboratory that has the last level of sequencing facilities, we are hoping to sequence the strains from Tuscany. Sequencing has almost the same cost of doing the real time PCR test. We could boil down to maybe twice as much, but the amount of information that you get is significantly higher, so I hope that what is happening to us will lead to a technological leap that will allow us to change completely the way we look at viruses and we understand their movements.

Lorenzo Corbetta: Thank you, very clear. We have to conclude if the chairman wants to say something, Leonardo?

Leonardo Fabbri: Thank you Lorenzo, thank you once again for organizing this initiative, I think we had a fantastic overview, very informative and very clear presentations. I'd like to thank all the speakers for putting so much work on these and I wish all of them to keep going with enthusiasm, but at the same time to protect themselves in their local situation. Thank you very much, once again for the privilege to co-chair with you this session, Lorenzo, thank you.

Lorenzo Corbetta: Thank you all, thank you for your presentations and see you all soon in another video conference with some updates on your studies. Thank you very much and thank you to all the attendees. Thank you, bye.