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Webinar

Stand on the Same Side Against Covid-19 - Diagnostic, Screening Tools and Pathways for Clinical and Preventive Purposes.

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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.

May, 19th 2020,
CHINA-EUROPE VIDEOCONFERENCE

"STAND ON THE SAME SIDE AGAINST COVID-19 - DIAGNOSTIC, SCREENING TOOLS AND PATHWAYS FOR CLINICAL AND PREVENTIVE PURPOSES"

Professor Corbetta: Good morning to our friends from Europe and America, and good afternoon or good night to our Chinese friends. Welcome to the second webinar of the project Stand On The Same Against COVID-19, that was started from the friendship with our Chinese colleagues to recommend, to take and to share with the Chinese colleague the experience to implement a science-based lockdown exit strategy. This project comes from years of collaboration with our colleague from Guangzhou and also other Chinese Universities. Now we have an agreement between our University of Florence and their University of Guangzhou.

The first webinar on preventing a second wave of COVID-19's outbreak was a big success of audience with 5,000 participants, and now is available the video recording and the transcription in the website of the project https://www.covid19expertpanel.network/.




This is an ideal graphic of an estimated picture of the diagnosis for COVID-19: https://jamanetwork.com/journals/jama/fullarticle/2765837. There are many, many questions that are open, and we will try to answer during this conference. Thank you to all the speakers and all the participants, and in particular to Professor Shiyue Li, thank you very much. Now I give theword to my friend Professor Li, please Professor Shiyue Li.

Professor Shiyue Li: Thank you very much, Professor Corbetta. Good morning, good afternoon to the European colleagues and good morning to the Latin American colleagues, and good evening to the Chinese colleagues. Welcome to the webinar. In this meeting we are focused on the diagnosis, screening tools and pathway for the clinical and prevention purpose. The main purpose is that we are still on the same side against the COVID-19: the Chinese colleagues, European colleagues and the other colleagues. Before the meeting, I would like to thank Professor Corbetta for organising it, doing a lot of things. Also thanks to the pharmaceutical company to support this meeting. Thank you so much. Next, I would like to call this meeting's host, Professor Jing Li from Guangzhou Institute of Respiratory Health. Please, Professor Li.

Professor Jing Li: In this webmeeting between Europe and China I'm so glad to introduce the first speaker, Professor Gian Maria Rossolini. He is the professor of microbiology and clinical microbiology at the Department of Experimental and Clinical Medicine of the University of Florence, and he's also the president of the degree course in the healthcare of University of Florence, and also the director of the microbiology and virology unit, and of the laboratory diagnostics of the surveys department, Careggi University Hospital. He's going to give us a talk on the topic of characteristics of COVID-19 and laboratory diagnosis. Now please, Professor Rossolini.

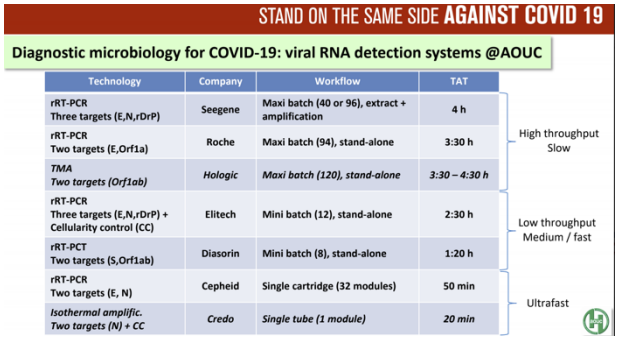
Professor Rossolini: So, I would like first of all to thank Professor Corbetta for inviting me to join this webinar, and to share with you our experience so far with the diagnosis of COVID-19 disease and condition and subsequent to infections. The purpose is just to present a brief overview of the diagnostic approaches that we are using and we have been using in our setting, in order to make some discussion according to different experiences. Well, so we have started in this field since three months, more or less, so it's a very early diagnostic work flow.

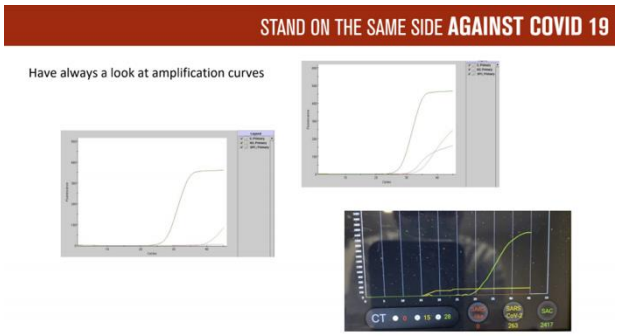
The issues that we now face for COVID-19 microbiological diagnosis are first of all related with confirming the suspect cases in order to decide whether they have to go in the COVID or not-COVID pathways inside of the hospitals, or if they should be isolated. We have also had to confirm viral clearance after infection, which is important to release patients and to take out the isolation from procedures. Then a very important issue, that I have seen it will be further discussed in other presentations in this webinar, is about the need for identification of infected subjects that are asymptomatic or that have unrelated disease but no COVID symptoms. Finally, there is another need with surveillance of the prevalence of infection, and with declaring a protection status after infection.

This part is still under debate, so I will mostly focus on the first three issues during this brief presentation. Just going through the confirmation of suspect cases and viral clearance, we have at least three different approaches. One is the molecular detection of viral RNA, which is the most common, the reference approach that all laboratories are now going for. There is the possibility of molecular detection of viral proteins, which is something under investigation that could be potentially useful in some settings.

Finally there is viral isolation, which of course is something of value for reference and for studying the viral biology but is not really feasible in routine diagnostic practice. In fact, so far, at least in our experience, the golden standard for the confirmed suspect cases is represented by the molecular detection of viral RNA using different molecular technologies. Currently in our laboratory we have implemented a number of different detection systems. This is something unusual for a diagnostic laboratory, because normally in a diagnostic laboratory you have to focus on a single diagnostic system in order to simplify and streamline the workload. This has not been the case for COVID, however. These are the different systems that we have in our laboratory.

The reason for having such a redundancy is mostly due to the shortage of reagents, in one case and to the different turnaround times that different systems provides. We have different maxi batch systems that can evaluate a large number of specimens in a batch and which provides results in a turnaround time of around four hours. Then we have some mini batch systems that are faster and can analyze around 10 specimens per time with a turnaround time of slightly more than one hour, or slightly more than two





hours. Finally, we have implemented two different ultra-fast systems that work with single cartridge and provide results in less than one hour. With the last system, which was very promising at the beginning, we however have not had a positive experience so far due to mostly false positive results, apparently false positive results. The last system, the isothermal amplification system, which provides results in 20 minutes, is currently in standby in our laboratory and other task laboratories due to these problems. So, quite a broad number of diagnostic systems for COVID. This is the current scenario, in order to address the requests and cope with the shortage of diagnostic reagents for COVID that we are experiencing due to the pandemic.

An issue that I would like to mention in this case is that even with the single cartridge systems, that could be proposed in a point of care format we have experienced that it is very important to look at the amplification cause and to look at the results. So, in our experience it is not possible to locate these systems in the emergency room or in clinical wards unless there is a technician from the lab that looks at the occurrence and experienced it personally from the lab that used to judge them. This is an example of positive curve, which is quite clear. No problem.

The reagents reported results as positive and with two targets, but this for instance is an example of a single target positive after the focus cycle, and the systems in this case reported it negative but the curve is convincing. So, we have reassessed it with another system and it was in fact positive even at low viral loads. This is an example of a false positive. A curve which is not really convincing, and in fact this was a false positive, and a system reported this result as a positive. So, a warning. Always have a look at amplification curve. Do not trust entirely only to the machine, which is at least in our experience important to care for. This picture has already been showed by Professor Corbetta.

I wanted just to refer to this, which is an ideal and schematic representation of virological parameters in COVID infections, just to mention that while PCR positivity tends to remain positive for weeks, in some cases, after clinical recovery. In late-stage it may be seen that positivity is present in lower respiratory tract specimens, rather than in nasopharyngeal swabs. So, we may have different results depending on the different specimens that we test. It's also still partially unclear if in this late stage the subject is still infecting or not. According to this picture
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa449/5821311
virus isolation is only possible during the first days, but this result has been reported after investigation of, so far to my best

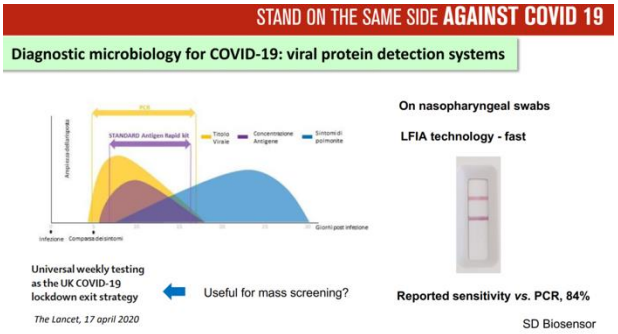
knowledge, only nine cases of patients. I think that this is still a grey zone and we have to understand if really in these circumstances the patient is infectious or not. Virus is not routinely searched for and normally not detected in bloods, but there was this very interesting report that appeared recently on clinical infectious disease which correlated the presence of RNAemia with the severity of disease and even with the IL-6 levels. So, this might be just an indicator and marker for the severity of disease.

We normally do not routinely search virus in serum, but this is something that could be considered according to the experiences of this COVID. Another interesting perspective could be that of looking for viral proteins in nasopharyngeal swabs. There is a commercial system that has recently been proposed, which suggests that we could look for antigen, viral antigen, in nasopharyngeal swabs during the early phases of infections.

The system is based on lateral flow immunoassay technology, so it provides results in a very short time frame of around 10 minutes. The susceptibility, the reported sensitivity was 84% in terms of comparison of PCR in symptomatic patients. This could be something of interest. We are planning clinical investigation on this, but we have no direct experience. What I would like to underscore, however, is that this system could be useful for mass screening and for screening of asymptomatic patients as well. Very recently in The Lancet a proposal just appeared for the UK exit strategy from the lockdown by using the type of screening, for mass screening for people.

Finally, a comment on the antibody response. There have been a number of papers studying the production of different classes of immunoglobulins against viral antigens after infection. I just picked up this one, which was quite recent, just to underscore a few issues:
https://www.nature.com/articles/s41591-020-0897-1
For instance, antibodies can be detected quite early after the symptoms' onset. In these cases, both the IgM and IgG tend to appear at the same time. In some cases, there is an early appearance of IgG, in other cases of IgM, but the title of IgG tends to be higher than that of IgM and the positivity also tends to be higher. So, in our experience in fact that the IgG were more reliable as a serological marker for infection than IgM, probably because the systems that we currently use for IgM are less reliable than for IgG. This is at least our experience. So, serological testing, considering these results, could be useful and helpful in some cases for diagnosis of PCR-negative patients. These are not very common, but in our experience it may occur patients who present a picture that is suggestive of COVID-19 infection but nasopharyngeal swabs repeated testing is negative, and the patient is not so ill that we can do BAL testing. At least in two cases we have experienced positivity. This is an example of how serology could be even helpful for diagnosis in some cases.

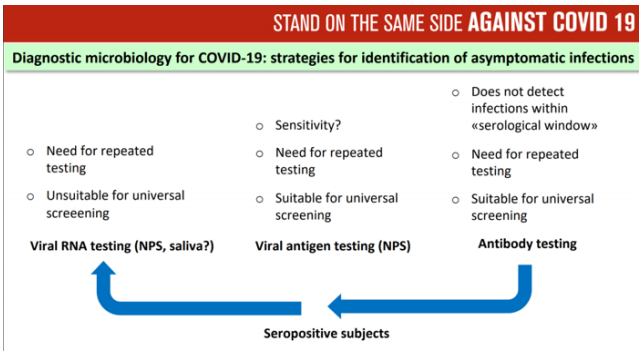
The other interest for serology, at least in our experience, is that of using serology for identification of asymptomatic infections. Also the authors of this paper just suggest this as a possibility. In fact, for identification of asymptomatic infections, there are at least three different strategies that can considered. One is that of viral testing in swab or saliva, but

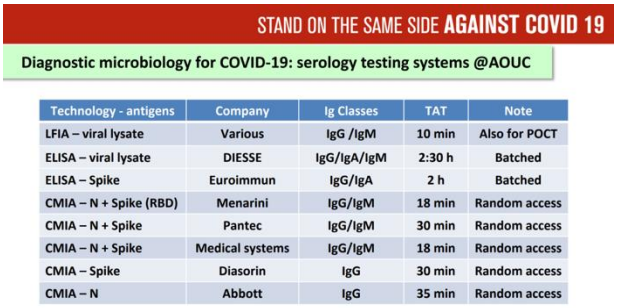


this of course is unsuitable for universal screening, at least for now, because of the complexity of costs and of the shortage of reagents. In this case, of course, it should be performed a repeated testing at very short intervals considering that we have a picture of the current situation. The second strategy is that of looking for viral antigens. We have already mentioned this before. In this case, this system could be suitable for mass screening, for universal screening. Again there is a need for repeated testing, and the question mark open in my opinion here is the sensitivity of the system. So, we have seen that the producer report for this test has sensitivity of 84% but in symptomatic patients. So, we have no information, to my best knowledge, of the sensitivity of this system on asymptomatic carriers. So, if any of you have some information I would be grateful to know some more information about this.

The third strategy, which is the one that we have adopted in our setting, is just to screen for antibodies and then on seropositive subjects to confirm viral testing by molecular testing. This is suitable for universal screening. Again, there is a need for a repeated testing at intervals that may depend on the local epidemiology. The problem is the serological window. In our experience, I will report just as an example, the results in our hospital. We have tested more than 5,000 asymptomatic healthcare workers with no history of contact with COVID patients. Of these, we have found around 5% of seropositivity for IgG or IgM, and of these we found that eventually 20, so 7% of the positive which are PCR-positive for viral RNA and so could be classified as asymptomatic carriers. Currently in our laboratory we are testing and using a number of different testing symptoms for serology. Apart from the lateral flow rapid tests which works with viral lysates, there are some ELISA tests that work in batches and some chemiluminescent assays. We are testing with a collection of serums from different types of specimens to compare, and we are making some experience about that.

I would be happy to share our preliminary experiences with





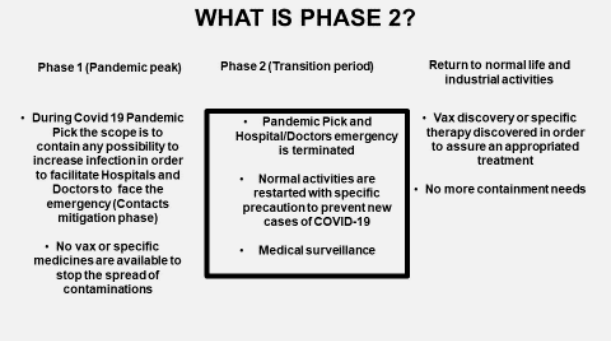
Technology - antigens	Company	Ig Classes	TAT	Note
LFIA – viral lysate	Various	IgG /IgM	10 min	Also for POCT
ELISA – viral lysate	DIESSE	IgG/IgA/IgM	2:30 h	Batched
ELISA – Spike	Euroimmun	IgG/IgA	2 h	Batched
CMIA – N + Spike (RBD)	Menarini	IgG/IgM	18 min	Random access
CMIA – N + Spike	Pantec	IgG/IgM	30 min	Random access
CMIA – N + Spike	Medical systems	IgG/IgM	18 min	Random access
CMIA – Spike	Diasorin	IgG	30 min	Random access
CMIA – N	Abbott	IgG	35 min	Random access

you if you wish. Finally, just to finish, which are in my opinion the open issues in diagnostic microbiology for COVID-19. One is that currently sustainability of molecular testing due to the global shortage of reagents. It has been really a big problem, I don't know if it's the same in your cities but at least in our country from the beginning of the pandemic until now, and even more with the reopening, there will be a shortage of these types of reagents. Then there is to clear which is the relationship between viral shedding versus the infectivity. So, all those cases that are clinically recovered and that retain positivity for a single viral target, for instance the N. Normally it's the N gene if the subject is infected or not. Then there is the development of reliable molecular testing for viral quantification, because so far the systems that we have had are not quantitative, are qualitative. We can have some kind of judgement by cities, but of course this is not precise quantification of the viral load. Then the nature and the threshold of protective antibodies still is a matter of debate. Of course it would be very interesting to further know and gather information as soon as we have more knowledge about this.

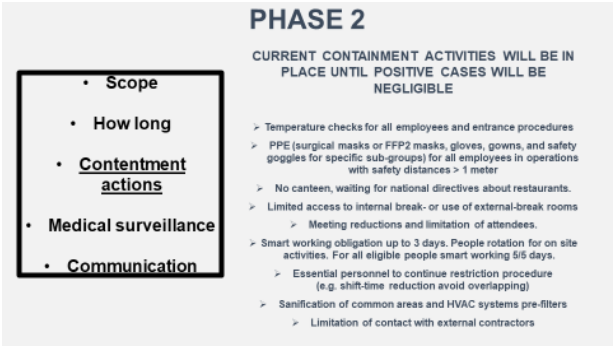
Finally, something that we have to face is that COVID patients unfortunately may have bacteria and fungal co-infections, and this is not uncommon as originally reported. We have to, of course, contextualise the analysis of these types of infections together with COVID. I will stop here and will be happy to take your questions. Thank you very much for your attention.

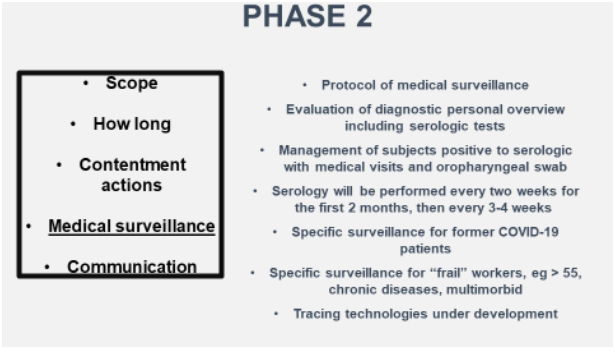
Professor Jing Li: The issue after all the speakers are finished their talks, and this is a very useful and practical talk on how to diagnose the virus, SARS-CoV-2 from the virus including RNA detection, viral protein protection systems, and viral isolation. Also including the serological testing for the antibody IgG and IgM measurement, and also their clinical implication. Thank you, Professor Rossolini. Very practical talk. Then we move into the second one, Professor Leonardo Fabbri. He's a professor of respiratory and internal medicine, University of Modena and Reggio Emilia. Also he is the eminent scholar of the respiratory and internal medicine of University of Ferrara. He's going to give us the talk with the topic of the reality of restarting industrial activities after the lockdown. Let's welcome Professor Fabbri.

Professor Fabbri: Good afternoon. Thank you, Doctor Li and Corbetta. Thank you very much for this invitation to contribute to this interesting webinar. My name is Leonardo



Fabbri. I am a clinician, but recently I have been asked to plan the screening of 1,200 employees of a company that stopped during the pandemic in Italy. I will go with you through the process of restarting an industrial activity during (as it is called here) Phase 2, it occurs when the pandemic peak is over and the hospital and doctors' emergency is terminated. It's what is going on in Italy these days. It's not really terminated, but the situation is much improved and as a consequence both the national and the regional government approved the application to restart industrial activity with very meticulous, specific precautions, and obviously proposing a medical surveillance. The scope of Phase 2 is to run business under specific conditions. You have limited industrial activity, you have limitation in transportation and travel. I won't go into the details, because I think you know this from the newspapers. There is a risk of a rebound pyramid, so that everybody is very careful in detecting this danger. Due to the political organization of the country that is run by the national government and by the regional government, there is not heterogeneity of intervention. More importantly, we don't have epidemiological data, so we don't know the denominator of the infection. By not knowing that, we get into the issue that was touched by Professor Rossolini, that is the





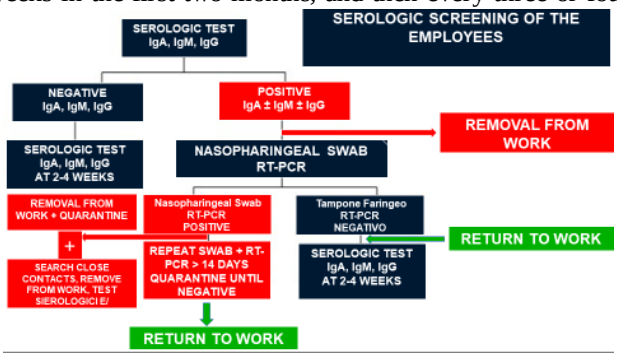
asymptomatic subject. The Phase 2 transition period started last 4th of May, and every week we have a progressive release of restrictions.

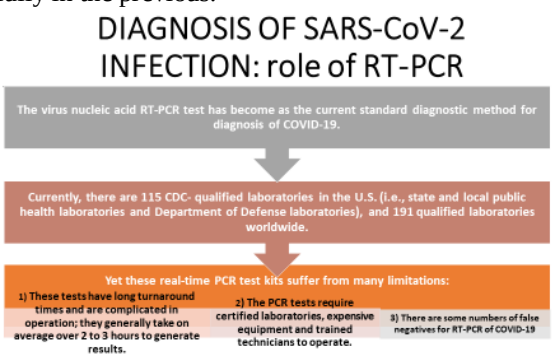
It's tightly monitored, this Phase 2, and already we had three or four micro-epidemics. Not in industrial settings, mainly in nursing homes or hospitals. With micro-epidemics they need to establish stricter conditions, but the end of the Phase 2, the real end of the Phase 2, while it has run for 31st July 2020, will obviously be only when we will have a vaccine and we will be able to work with the presence of SARS-CoV-2 without the risk of ending up in the emergency room. I list very quickly the current containment options that are logic. First, no worker with COVID symptomatic or suspicious symptomatic or subjects at risk because of close contact with COVID are admitted at work. That's before even starting. They have under their own legal responsibility to stay home and to be investigated by the local GP and the local authorities. When the workers get to work there is a temperature check, and daily or monthly they are given protection equipment, personal protection equipment, a surgical mask for those who can respect the social distance of 1m, and a more sophisticated protective mask for those who cannot respect the distance of 1m. All the internal gathering places are either closed or restricted, like canteen meetings, and a large part of the administrative work is done as home working obligatory and progressively, at least it's three days per week now. Some people's it's four of five days.

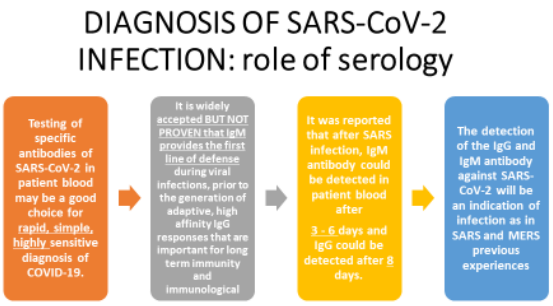
Sanification, of course there are areas within the company where they are protected so whenever it happens that a worker claims symptoms at work can be confined and then transported safely to the local medical facilities. There are very tight limitations of contact with external contractors. The medical surveillance, there is a very meticulous, is planned with the so-called occupational doctor that here is called a “medico competente”, who is in charge. Usually they have visit every year, but of course during this period these controls are intensified. The issue of the serologic test that will be the focus of my next part of the presentation, it's very much debated. It has been implemented. We have just started, but just to give you an example, the Ferrari company that is in my town already started the serologic testing and including the PCR for those who are positive to the serologic testing. I'll show you some examples. There is a precise algorithm that I would like actually to discuss at the end, hopefully with your feedback, on what to do when you have a positive test. The serology will be performed every two weeks in the first two months, and then every three or four weeks depending on the outcome.

The numbers presented in the previous presentation are very encouraging, because health personnel is positive in that kind of range, 5%, and only 5% of the 5%, only 20% is positive to the molecular testing. Those numbers are reasonable during this period. There are two aspects of the prevention at work that have been very strongly emphasysed. First, there must be a specific programme for fragile workers, defined as workers of more than 55 and/or with multi-morbidity or chronic diseases. Just to give you an example, chronic leukaemia, lymphoma, people treated with immuno-suppressants or transplanted people have to undergo a specific control. In order to answer the question of the epidemiology of COVID-19 in Italy, the tracing technology is under development. It will be developed at the national level, but it will be made available also at the company level. This is the algorithm that we plan. I hope you see the pointer. We start with the serologic test for everybody. We recently were asked to include the IgA, even if I agree with the previous presentation that the data is really non-existent, particularly in our population. Now, let me underline once again what these serologic tests are performing onto people who are asymptomatic. So, all the people are by definition asymptomatic.

If they are negative, then they repeat the test every two weeks for two months and then every month. If they are positive, first they are removed from work safely right away. Actually, we are trying to abolish this step by having the communication of the positive result directly to the worker via telephone or email so that he get the procedure to follow in case of positivity without getting into the workplace or without meeting the doctor in person. The subject will undergo PCR, nasopharingeal swab for PCR. If the PCR will be negative, then he will go back to work and to the regular screening serologic test. If the PCR is positive, then he will go into the quarantine and followed by the general practitioner, and he will be allowed to come back only when, you will see the criteria at the end but basically you have two PCR negative within 48 hours and asymptomatic for more than five days. When we get the positive PCR, we also remove the subject from the contact at work. We remove the subject again. We keep the subject far from work, but also we search for the close contact at work: if they hear the negative test they will keep going with the regular serologic test. If they are positive then we go to the PCR and removal from work as well. Now, the diagnosis, I won't go through it, has been described very carefully in the previous.







Particularly I like to think that there are some false negative PCR in patient, false negative, in patients that are in the virus.

This is a danger. This has been reported a few days ago, the 14th of May. The proportion, of course, diminishes with time from onset of symptoms, but I think that the serologic test may complement the molecular test to make the diagnosis. The alternative is the serology and the rapid tests.

I think that they are not reliable and they are not taking into consideration. There is some evidence that the IgM actually occur further before the IgG, so when we started to design this strategy we considered to have the IgM as a pre-symptomatic, pre-viral infection in our early detection of viral infection. I'll show you the data:
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa344/5812996
There is not much evidence of that. Eventually we agreed with the previous proposals that any of the three of the two, IgM and IgG, possibly the IgA, we have to make experience positive will activate the cascade that brings to the molecular taste testing (ph 42.30). Here is a study that reported the median duration of IgM and IgA. Antibody detection, five days since symptoms start, whereas the IgG was detected at 14. If you look at the same paper, you can see that there is very much overlap. I don't think we can distinguish the early phase depending on the type of antibody.

The outline that also Professor Corbetta showed suggests that the antibodies may not only be helpful for the screening but also for the diagnosis of disease when the PCR become negative after the disease. Let me underline, before I close, that the purpose of screening, of serology in these conditions, in industrial conditions, is just for screening. It's not for diagnosis. The purpose of this exercise is to identify people that potentially are carriers of the virus, to identify them and to obviously protect the individual but also to protect the subjects that are close contacts to prevent micro-epidemic. Again, the time course of the antibodies, we have already said that.

This is the algorithm that I would like you to comment on at the end and give me any suggestions, because we have 10 more days before we start and if you have suggestions or experience in this field I will be delighted to take them on board and adapt the protocol according to your suggestions.
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa179/5758073
Now, this is the afebrile removal from work of the subject that I mentioned to you. He must be afebrile and for more than 48 hours, two negative tests, six days with no symptoms excluding other diagnosis, contacts.

There is a meticulous cascade to prevent exposure at work. Eventually, I underline the importance of education. The communication, that all the personnel has to be educated on the nature of the disease, on the risk. We are much more worried of the potential infections outside of the workplace, because in the workplace all the technology that prevents from getting the infection that you know, they are familiar, they are released by the government, are followed. The problem is when they are at home, where some relatives may be sick, and transportation. People are now encouraged to use private transportation, not public transportation, because the public transportation first is very limited and second is a unique opportunity to get in touch with people. With this I am finished, and I thank you very much for your attention and for the opportunity to present this plan.

Professor Jing Li: Thank you, Dr. Fabbri, for your very fantastic talk on the importance of how to screen the asymptomatic people using the serologic test. Also you point out the very significant differences between the screening test and diagnostic test, and also the last one, how to educate and also the communication between people. Okay, thank you very much.

Professor Corbetta: Okay. It's a real pleasure to introduce Professor Li Jing. Professor Li Jing is professor of medicine and doctoral supervisor at the the First Affiliated Hospital of Guangzhou Medical University. She is the director of the Department of Allergy and Clinical Immunology, of the Guangzhou Institute, and specially appointed professor at the Loma Linda University in the United States, and a member of the European Academy of Allergology ERS and CSA (ph 48.03). The title of her presentation is longitude in hematologic and immunologic variations associated with the progression of COVID-19 patients. Please, Professor Li Jing.

Professor Jing Li: Yes. Thank you very much for inviting me to give this very brief presentation on the study we just published. It's a very nice study, because we look at the longitude and we look at the hematology and immunology variation, and we make the association with the progression of the COVID-19 patients. From the contact of the virus, some people develop symptoms because of the immune systems then they make some actions against the virus infection. They will develop some systems systemically and locally, especially the symptoms in respiratory system. When you're looking at the response of the immune system, we can come up with different outcomes. On one side, mild and moderate patients, they have some light or normal or balanced immune response. They will get the outcome of minor symptoms and minor damage, the patient get recovery from the disease. On the other side, some patients have an imbalance of their immune response. Some of the turbulence happens. Then they have the outcome of severe symptoms and multiple organ failure, and also tissue damage, then have fatality outcome.

We point out that a little is known about how different lymphocytes subsets and the dynamic change in the immuno-

related biomarkers differ during different prognosis and outcome of COVID-19 patients. The purpose of our study is to address the dynamic change of all these kinds of biomarkers during the time of the disease. (Jing Li, JACI in press)

This is a retrospective study, including 548 COVID-19 patients in-hospital, and also it is a cross-session and also a longitudinal study, and we compare all the immunology and haematology biomarkers. Then we kind of get the association between these biomarkers, and the different severity and outcome of the patients. You can see we have majority of them, they are mild and moderate patients, and 155 patients with severe of the degree. Also we have 48 patients with critical situations. Now you can see actually from this different severity of patients, in mild/moderate patients we have very little of them they have fatal outcome. Also in the very severe degree of the disease, like critical situation, we have some degree of survival. This is very interesting, that different mechanism on baseline that may be associated with the survive and non-survive outcome.

Then on the admission of the hospital, we can see the survivor and non-survivor, they have a very significant difference in terms of the haematology indexes like leukocytes and neutrophils. They have a very significant higher level in the non-survivor compared with the survivors. However, the lymphocytes, eosinophils and basophils have a very significant lower level in the non-survivor compared with the survivors. Also you can see the other ratio indexes in terms of NLR and PLR. We have a significant increase in this ratio in the non-survivors. So, just on the admission they have significant differences between the two outcome groups. In terms of the T cell subsets level, you can see the dramatic loss of CD4 and CD8, and also the T lymphocyte size in very severe and non-survivor patients. CD4 and CD8 ratio didn't change much among the disease survivor. However the CD4 over CD8 ratio increase in non-survivors indicates the greater loss of CD8 T cells might lead to the fatal outcome in our patients. Regarding the other infectious related parameters, such as SAA, CRP, ferritin, and D-dimer, we can see some significant increase in the non-survivors when compared with the survivors on the admission of the hospital. Also, IL-6, the level of IL-6 and PCT also increases significantly in this group of patients as well.

This is the longitudinal dynamic change of the haematology and immunology indexes, they show different patterns. The first pattern, you can see the eosinophils and the lymphocytes and the platelets. The empty group shows the survivor patients, and solid group represent the non-survivor. You can see a significant continual upward trend in the survivor patients, regardless of their severity, but the downward or on the very low level, or even continued to decrease in their levels in the non-survivor patients. Pattern three, we have no clear patterns. There is no difference between survivor and non-survivor patients but in some of the parameters, like this group, there is a very large amount of the biomarkers, they maintain a significant lower level and show a slightly downward trend in the survivor. Neutrophils to lymphocytes ratio are six and some other parameter related to the infectious also show these patterns. So, you can see different groups of the parameters, they show different trends in the level between the survivors and non-survivors. This is some more of the cell to cell and index interaction network.

We can see on admission non-survivors and survivors. You can see interaction amount, haematology and immunology cells in both survivor and non-survivors. On the admission, the cell to cell interaction and the interaction between the indexes have a very strong relationship in the non-survivors and survivors, but with different patterns. Indicate immunology profile associated with host antiviral defence vary in different studies. When we see the interaction in our patient at the end of the hospitalization, comparing the subsiding of the cell to cell interaction in the survivors you can see very light interaction between these indexes. Our non-survivors still have a very strong interaction between cells and the indexes, and these suggest higher virus load plus inflammatory turbulence might contribute to the mortality of this group of patients. This is the principal component analysis for immunology cells and biomarkers, and you can see from the colour we can separate the patients between the survivors and non-survivors, and also on the admission and at the end of the hospitalization. The top three positives to contribute to index on admission are lymphocytes, CD4+ T cell and CDA+ T cell. At the end of the hospital are the platelets, lymphocytes and eosinophils.

Top three negatively-contributing indices include CRP, ferritin, and SAA. This is very interesting to us. We have also done some predictive factor for the fatal outcome for the survival curve, and when you see different haematology and immunology parameters you can see the eosinophils count, platelet count, and the differences of the eosinophils count between the end hospitalisation. On admission there are also lymphocyte differences. You can see eosinophils difference and platelet differences and also other parameters' differences. If you have lower level, or the differences of these parameters getting higher, you have lower survival rate in this group of patients. We can see some of the parameters, they have negative contribution, and some of them they have positive contribution to the progression of our patients. The last one, we have a summary of this immunology and haematology indexes. On the admission of the hospitalization, we can see some of our patients, they demonstrate normal level of all these parameters. Some of them they have significant increase in the neutrophils and and infectious parameters.

Also, some of our patients have very low level of lymphocytes, platelets, and eosinophils, even at the beginning of the disease when they are admitted to the hospital and we will monitor their change of this immunology and haematology parameter. If your level recovers to normal range, the ending is recovery and you will be discharged from the hospital, but if you keep higher for the eosinophils or the inflammatory parameters, then maybe you'll end up deceased. Also, the lymphocytes, platelets and eosinophils, also if you have the very low level or keep in this very low level, maybe the outcome was not good. So, we have this conclusion of outer interaction among immunology and haematology indices indicate impaired immune response in the COVID-19 patient.

Restored lymphocytes, eosinophils and platelets could predict recovery. Progressive increases in neutrophils and cytokine level were associated with mortality. I would like to thank the leaders of our study, professor Nanshan Zhong and Shiyue Li, and also, we would thank all the participant hospitals around our country. Thank you very much.

Lorenzo Corbetta: Thank you very much, professor Li Jing. Very interesting and this is a very important experience in case of future outbreaks to prevent and to recognise the severe patients. Please.

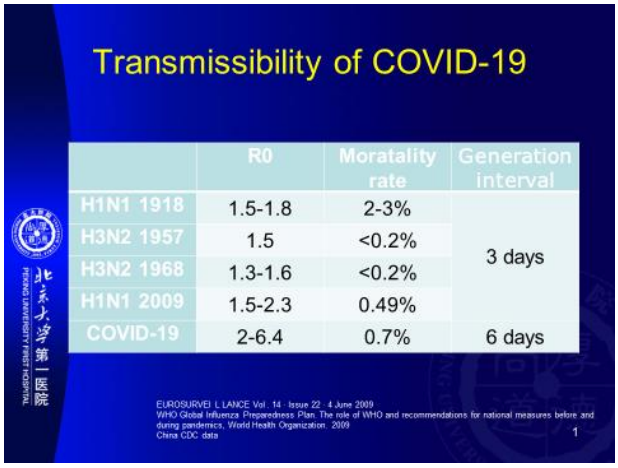
Jing Li: I will continue to host the later section and the next speaker, we'll come to the famous professor of bronchoscopy therapy, professor Wang Guangfa, and he is the national consultant committee of the public health, and member of the national committee of public health and sanitation in emergency, and also, he has a lot of titles in the national and international society of bronchoscopy, and he also works closely with a lot of chest physicians in the fighting of Covid-19 in China. He's going to give us a talk of the asymptomatic Covid-19, a real risk. Now, please, professor Wang.

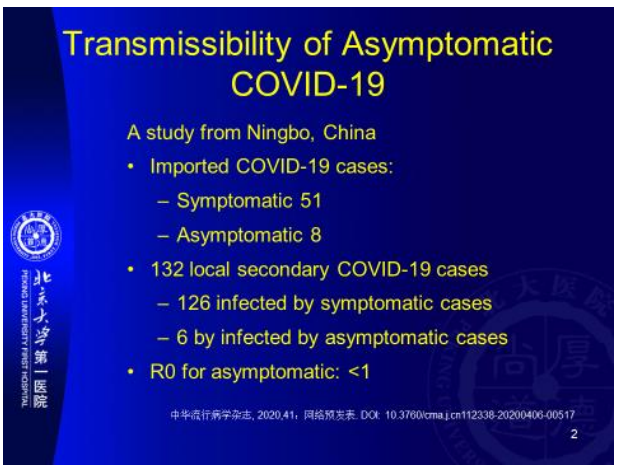
Guangfa Wang: Good afternoon, and good evening ladies and gentleman. It's my pleasure to join the webinar and to communicate with our European colleagues and to share with our experience on Covid-19. So, I would like to talk about asymptomatic Covid-19. Is it a real challenge or a real risk? So, I have no disclosure about my presentation. So, Covid-19 occurred in China in early this year. So, in a very short time, it spread all over China, and even out of China. So, with restrective measures the containment of the disease succeeded. This is the epidemic curve of Covid-19 in China.

The most dominant measure is the lockdown of Wuhan. After one week of the lockdown in Wuhan, the epidemic curve changed and it went down. Right now in China there are only a few local Covid-19 patients. Most are coming from abroad: we still are facing a high pressure from the importation of Covid-19 cases. So, retrospectively, the success of Covid-19 containment in China are visible. We adopted a different, very successful measures, including individual measures, case isolation and management, close contact quarantine, suspension of public gatherings, and mobility restrictions. So, right now, these measures are very, very successful. Now, we are facing a new stage. So, everybody is talking about the restart of the economy and work and other social activities. So, for clinical practice in the management of Covid-19, we emphasize the early detection, early reporting, early isolation and early treatment.

This is also very successful in China, but we are facing a high pressure from the rebound of Covid-19 because we have some cases from importation. So, another risk, I think, is asymptomatic Covid-19 cases. So, here is a study from Nanjing, China. They have reported 24 cases with asymptomatic infection: they are collected from the screening of close contacts. So, five cases developed symptoms during hospitalization. Twelve showed a typical chest CT scan of Covid-19. Five showed a typical presentation as stripe shadowing in the lungs. Only seven cases showed a normal CT scan and had no symptoms during hospitalization. So, for these cases, these seven cases, the median age is only fourteen. So, they are a young group. So, that is the report from Nanjing. So, here is some report from South Korea. So, they have retrospective analysis from over 200 Covid-19 mild cases. About 20% were asymptomatic until admission. So, I think most of them were developed symptomatic. So, I don't think they are all symptomatic cases. Similarly in the United States, in a nursing facility, so this facility experienced an outbreak of Covid-19, 23 residents in the facility have a positive PCR. Ten had symptoms on the date of testing, and thirteen were asymptomatic, but among the thirteen asymptomatic cases, ten ones had developed symptoms. So, that means only three were real asymptomatic cases. So, what is the instance of asymptomatic Covid-19? Different studies at different rates, but I think most of the studies include Covid-19 patients during incubation period. So, most of the patients will develop the symptoms.

So, I don't think it is real asymptomatic Covid-19. So, we have retrospected our 30,000 Covid-19 cases from out of Wuhan in China. Only twenty cases were real asymptomatic, because they are asymptomatic before and during hospitalization. So, it is not in the incubation period. The instance in terms of age was quite different. For younger cases 1.36%: his population have the highest asymptomatic Covid-19 cases. For older patients, the instance rate is very, very low. So, all the asymptomatic Covid-19 cases do not have





comorbidities, there is no death - it seems that asymptomatic Covid-19 cases will have a good prognosis.

So, how about the transmissibility of Covid-19? As we know, Covid-19, the R0, the reproduction number is about three. That means one patient can produce three patients. So, it is higher than seasonal influenza. So, that means the transmissibility of Covid-19 is higher than seasonal influenza.

Also, the generation interval is longer than influenza. So, it seems that the speed of transmission of Covid-19 is almost similar to seasonal influenza. How about transmissibility of asymptomatic Covid-19? So, there are only a few studies dealing with this issue. Here a study from Ningbo, China: this study is published in a Chinese journal, so perhaps our foreign colleagues have not read the paper. So, this city has reported imported Covid-19 cases, the total is 59. Among them, 51 are symptomatic. Only eight are asymptomatic. So, these imported cases produce totally 132 local secondary cases. So, among them, most of the secondary cases are caused by symptomatic patients.

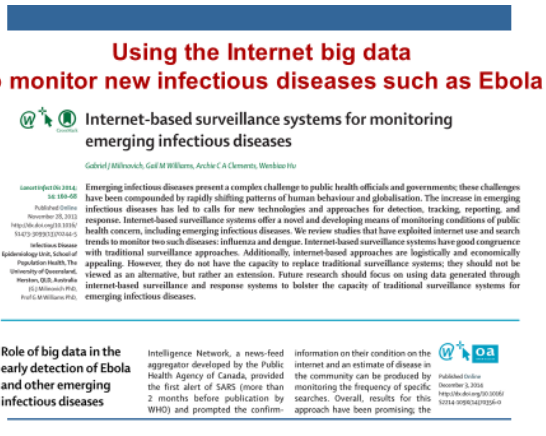
So, 126, but only 6 are infected by asymptomatic cases. Here we can calculate the R0 for asymptomatic cases. So, 6/8. So, only less than one. If we just look at R0 asymptomatic cases it's not a problem, because for a transmissible disease, if R0 is less than one, the transmission of the disease will spontaneously stop, but we should not look at it as safe, because an asymptomatic case can produce symptomatic cases. The symptomatic case R0 is three. So, the risk or the challenge of asymptomatic cases is they can produce symptomatic cases and can cause a persistent community transmission of Covid-19. That is real. So, it is very important to find an asymptomatic case, and also, the prognosis of asymptomatic cases is very good. There is no death. Also, the transmissibility is very low, but as it can cause symptomatic cases, then symptomatic cases can arise a large epidemic of Covid-19. So, maybe we will do our best to find asymptomatic cases. So, how do we find these cases? So, I think two strategies can be used. One is population screening, but for a community, for a city, or for a whole country the price is very, very expensive. I don't think it is acceptable by the government. Another strategy is tracing among close contacts. So, when you find a symptomatic case, then you should try to find all the close contacts, and among the close contacts, you can screen the asymptomatic cases. So, I think that this strategy is rational and feasible. So, it can be accepted by the government.

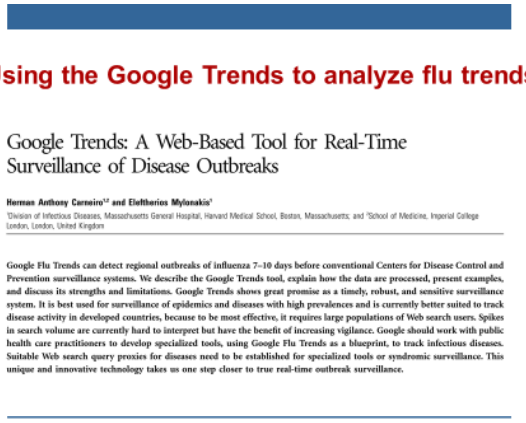
So, in summary to my slide, asymptomatic Covid-19 cases can be seen frequently, but the definition may be different with different incidence. The incidence of real Covid-19 is rare. It is not a popular phenotype. Most of the asymptomatic cases are younger, and without comorbidities. So, the prognosis of asymptomatic cases is very good. The transmissibility of asymptomatic cases is lower, but can produce symptomatic cases. That is a big challenge for us. So, we should keep high alert on the risk of transmission caused by asymptomatic cases, and try to trace these cases among close contacts, so that is very important for, in the future, the containment of Covid-19 in the world. Thank you for your attention. So, thanks, doctor Corbetta and doctor Shiyue Li and doctor Jing Li for inviting me to join the webinar. So, I think it is a good opportunity for us to communicate with each other and to learn from each other, and in the future we can find more opportunities to collaborate with each other. So, I think the world will benefit from our collaboration. Thank you for your attention.

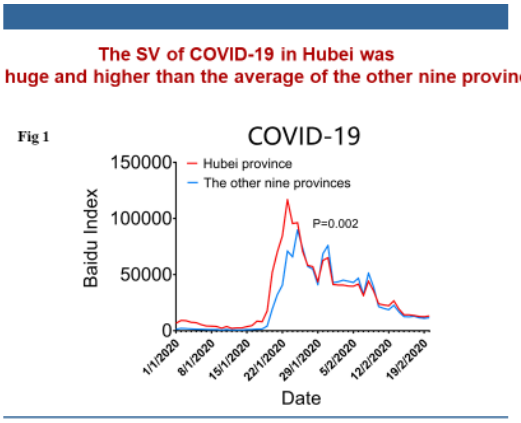
Jing Li: Very insightful talk on the thinking and pointing out some important points on the finding of prevention and tracing the asymptomatic patients with Covid-19. Very, very insightful talk. Thank you, professor Wang. Now, we move to the last speaker, professor Qintai Yang. He's my good friend, and he is the associate dean of the Third Affiliated Hospital of Sun Yat-sen University in China. He's also the director of the department of allergy at the Third Affiliated Hospital of Sun Yat-sen University. Also, the associate director of the department of Otorhinolaryngology, head and neck surgery of the Third Affiliated Hospital of the Sun Yat-sen University. He's going to give us a very interesting talk on what have we learned from big data analysis on Covid-19 symptoms. Now, please professor Yang.

Qintai Yang: Okay. Ladies and gentlemen, good afternoon and good evening. Okay. I'm honoured to have the opportunity to speak at this meeting. The topic I'm is what have we learned from big data analysis on Covid-19 symptoms? First of all, let me introduce a book called 'Everybody lies'. Everyone often lied to make themselves look better.

They're real when faced with an Internet search engine, because they're not admitting to people face to face at the time, and the search content in their accurate need. Therefore, the search engine is also not a data truth serum . Nowadays, the most popular search engine is mainly Google outside of China. Baidu in China. There are 854 million web users in China, more than 90% of them use the Baidu search engine. As we know, searching online before visiting a doctor has become a habit of patient and their families in China. Therefore, the search data of Baidu will affect the real needs of the people. The amount of data it generates is large enough to be spread the trend. Some studies indicate that the search volume of symptom key words was highly correlated with the symptom of patients. It could reflect a real trend of public demand. For example, use the Google Trends to analyze the flu trend accurately. For example, use the Internet big data to

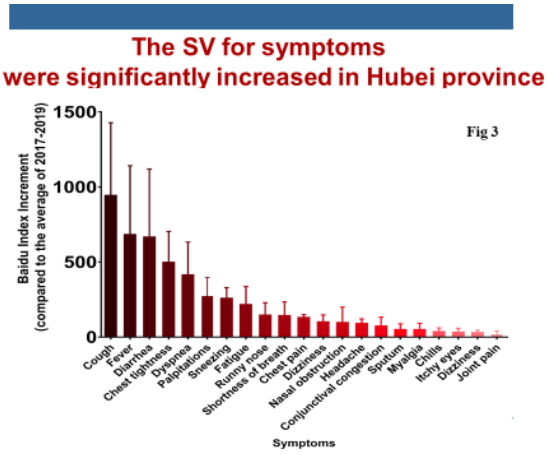


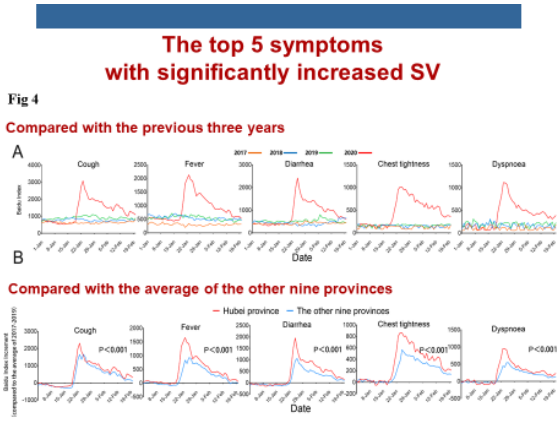




monitor new infectious diseases, such as Ebola, and use the Baidu index to analyse AIDS and flu in China. The Baidu Index is a data-sharing platform based on the Baidu search data of users.

Google Trends is the equivalent to Baidu in China. It could provide search data for many key words. In our study, first of all, we determined the total of ten provinces of the total confirmed cases nationwide, also after February 20 and the tenth number of the daily newly confirmed and suspected cases through the data released by the China CDC. Secondly, we searched key words in mandarin on the Baidu index to obtain the search volume, as shown in the table from January 1 to February 20 each year from 2017 and 2020. Geographically, in the ten provinces, different key words were combined. Finally, the data from 2020 was compared with those of the previous three years. The data from Hubei province was compared with the average of the other nine provinces. In our results, it showed that from January 1 to February 20, compared with the average of the other nine provinces, the people in Hubei was more concerned about Covid-19. The curve began to increase sharply on January 20, with the peak on January 23, and gradually fell back. On the other hand, compared with the average of the other nine provinces, Hubei did not have a significant search volume for diseases such as COPD, rhinitis, gastroenteritis and CHD. Moreover, the search volume of this disease in Hubei province was even lower than those in the other nine provinces. From January 20 to February 20, compared with the average search volume in the previous three years, the average daily search volume in Hubei province for symptoms increased significantly.





Figures:
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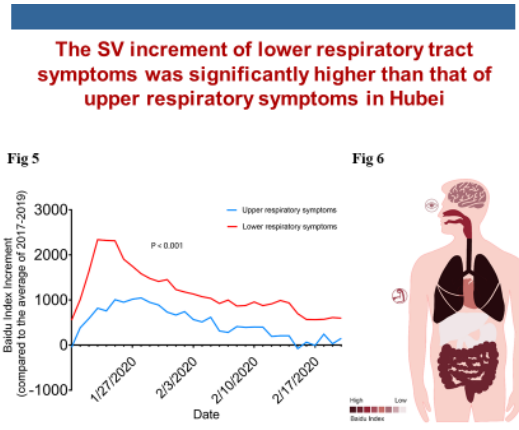
The top symptom with the significantly increased search volume was cough, fever, diarrhoea, chest tightness and dyspnoea. Look at this picture: figure A compared with the previous three years. It's a significant increase, and figure B compared with the average of the other nine provinces, it's significantly increased. Interestingly, we found that the search volume increment of lower respiratory tract symptoms was significantly higher than upper respiratory symptoms in Hubei.

According to the Baidu Index increment, the symptom of organ infection of the SARS-CoV-2 includes the respiratory system, digestive system, circulatory system and locomotion system and nervous system and eyes. According to the Spearman correlation analysis, the curve of newly confirmed and suspected cases was closely correlated to the curve of the Baidu Index. What's more, we constructed a distributed lag model to analyze the lag, the effect between Baidu Index and the number of confirmed and suspected cases. The result of



the distributed lag model, this indicated that in fact, people who searched for related symptoms on the Internet may start to see the doctor, become suspected cases in two or three days later, and be confirmed in about three days later. It was confirmed by the National Health Commission that the national average time from the onset to confirmation was 4.95 days. So, conclusion, during the epidemic, the total search volume increment of the low respiratory system was higher than of the upper respiratory system The search volume of diarrhoea also increased significantly. It warned us to pay attention to not only the symptoms of the lower respiratory tract, but also the gastrointestinal system, especially diarrhoea in patients with Covid-19. The Internet search behaviour has a positive correlation with the number of newly confirmed and suspected cases, suggesting that big data has an important role in the early warning of infectious diseases. In short, the Internet big data contributed to the recognition, monitoring, prevention and control of the new disease. The Internet big data contributed to analyzing the symptom characteristics of Covid-19. The Internet big data contributed to predict and warning potential patients with Covid-19. That's all. Thank you for your attention.

Jing Li: Thank you, professor Yang. Your talk is very different from all of us, very interesting thinking on the big data from the Internet. Two of the very powerful engines, Google and Baidu in China and about the appearance of the symptoms, the type of the symptoms and the cases using the big data search. Very, very interesting job. Okay. Thank you very much. Then, I think I've finished with my job of hosting the scientific section then. I am passing the host to professor Corbetta to host the discussion section.

Lorenzo Corbetta: Thank you very much for your work. There is one question for professor Fabbri. The question is "should you consider testing the employee twice a week apart, since IgG may take up to eight days to be detected?"

Leonardo Fabbri: Yes. In fact, we discussed the frequency of testing. The issue, once again, is the cost, because, you know, every time it's not only just the test itself, but you have to move the people and so on, but let me tell you that the data that professor Rossolini presented earlier on the 5,500 health employees of Careggi in Florence that were tested and only 5% were positive, and of the 5%, only 20% were also PCR positive. I think that it gives you the perspective of a very limited number of asymptomatic, true positive patients. The last presentation also, the one before the last, actually showed that the number of asymptomatic positives is very limited, and what is also reassuring is that they are not actually very contagious. So, to make a long story short, I think that the compromise of fifteen days was a good compromise, because you can fall anywhere between zero and 30. So, it's a small risk the one that you take by just doing every fifteen days, because then, you repeat it every fifteen days, you know? The contacts or the infection can occur any time during that period. I think that is already very generous by the company to pay for this surveillance, because with all the uncertainties we have about the meaning of the antibodies, I think it's a lot of investment to put a regular programme of twice-a-month control.

Lorenzo Corbetta: Thank you very much. Other comments about this topic, this question? If not, I have a question for professor Li Jing about the immunological topic. The question is, "is there any reactivity between antibodies for SARS-CoV-2 and other corona viruses"?

Leonardo Fabbri: If I may come in, this is Leo Fabbri speaking, yes, indeed because of the homology between SARS-CoV-2 and SARS-CoV, there is some cross-reactivity, but the number of SARS-CoV positive in China must be very small, minute. They have been exposed, you know, many, many years ago, and I don't think that is confirming, but the possibility is actually there.
I have a question, if I may ask. Professor Guangfa, a question for you. I very much enjoyed your presentation, very useful, because I know how difficult it must have been for you to find out the asymptomatic positive people, because either you do a general population or it's difficult to find them. Having said that, are you aware of any ongoing study in China where you have a large group of asymptomatic subjects that are regularly followed epidemiologically to see those who become positive to the antibodies and then to the virus, to see the natural history of the disease? Are there any epidemiological study going on in China?

Guangfa Wang: Yes. So, as of now, there is a study, so focusing on asymptomatic cases led by doctor Gao Fu, the chairman of the Chinese CDC. So, the study is just at the very beginning. It doesn't have any results yet, but I think in China we are facing some difficulty to collect enough cases, because only a few imported cases and also, recently, the various community outbreaks in a small city in the north of China. So, currently only 40 cases. So, perhaps in the future we can do some collaboration. If you want, I can talk with doctor Gao Fu, so thank you.

Leonardo Fabbri: Thank you. One question for professor Li. I mean, I very much enjoyed your presentation showing the biomarker of survivals versus non survivals. From your experience, and from your review of the literature, two questions. One is if you had to select one biomarker that predicts the fast development of severity in a hospitalized

patient, you know, the clinical experience that we have is that we admit 100 patients and only ten for unknown reasons, within one day or two develop respiratory failure and they get into the ICU. Now, the question to you is any marker among those that you measure that you believe can predict this risk to identify before the respiratory failure the subjects who are going to develop the respiratory failure?

Jing Li: Yes. A very good question. If you want me to point out one I think that it's most important to predict the prognosis of the disease in terms of immunology parameters, I will give you the cytokine of IL-6.

Leonardo Fabbri: Okay. Thank you.

Jing Li: It represents mostly the cytokine storm in the progression. It is a representative cytokine, but you need to have a dynamic measurement of these parameters to see whether they are continuing to increase, or they keep in the lower level. If they continue increasing, that is dangerous for the prognosis of the patient of the disease, a bad outcome.

Leonardo Fabbri: Thank you. Finally, if I may, one question to professor Qintai is you nicely showed that the upper respiratory symptoms were prevailing in the Wuhan region. Are you suggesting that Covid-19 can be clinically distinguished from other viral infection of the respiratory tract by having predominant lower respiratory symptoms compared to upper respiratory symptoms? It clinically looks like that. I mean, when you have influenza, mostly you have upper airway abnormalities. When you have Covid, you have lower airway, because you have a cough, but also dyspnoea.

Jing Li: Yes. Professor Yang, that means the difference of the symptoms when you compare Covid-19 and other upper airway tract infections/disease, the symptoms are different that you collected from the big data from the Internet.

Qintai Yang: From the Internet big data it's very difficult to tell, but flu symptoms and Covid symptoms are difficult to tell apart, but we can do it from the Internet. They're similar, the symptoms are similar.

Guangfa Wang: Can I have some questions? So, one to doctor Yang, the other one to doctor Li. So, the first question is to doctor Yang. So, you did a very good study. So, big data can reveal a lot of details. So, maybe we can expect the trends of something. Your study, can you say that from big data, we can prospect the early patterns of Covid-19 or other contagious diseases? So, if your big data can have such a prospective alert, perhaps we should add big data analysis to our disease control system. So, that is the question to doctor Yang. I will ask the next question later. So, please.

Qintai Yang: Thank you for your question. In the big data is a trend. I do think that big data can gradually influence our understanding of Covid-19, but big data can help us under the Covid-19 from the non-medical medicine. As we note, searching online before visiting a doctor has become a habit of the patient and their families in China. Therefore, the search data of the Baidu can show the real need of the people. The big data you generate is large enough to present a trend. So, we can predict it. It's a real situation, and really what we search. So, it will be enough to represent a trend, so that you can predict and face disease. So, I think so.

Guangfa Wang: So, for my contact there are people, many, many people very nervous to the epidemic of Covid-19. Even there is no disease, infection, so he or she thought, 'I was infected by Covid-19, and I will be dead.' So, they are searching a lot of help. So, including searching from Baidu or Google, but if nobody knows the epidemic of Covid-19, so can the big data about search volume reflect the epidemic, or the early stage of an epidemic of a disease?

Qintai Yang: Yes. Maybe your symptom is right. There are some limitations in our study from the big data. So, such a difference in the number of the Internet use and difference in the age of the Internet use. So, our study has a lot of limitations.

Guangfa Wang: So, another question to doctor Li Jing. So, you did a very good job, and very good research. So, from your study, I observed that eosinophils count can predict the death of the patient. So, what is the explanation of the phenomenon?

Jing Li: Good question. Very good question. Yes, because when we wrote the article, we searched a lot of other literature about the virus infection, the effect of a virus infection on the haematologic change, especially on eosinophils. We explained that the decrease of the eosinophils may be the reaction or reflex of the body against the virus infection, the severe virus infection, or the attack or the high intensity of the body response of the attack, like if somebody experienced a very high tension work or high intensity of swimming training, or some severe virus infection. They express the decrease of eosinophils. Yes. This is the general response of the immune system. Yes, but the detailed mechanism on why the decreasing of eosinophils in such a scenario, I think we need to further study. Yes. Thank you.

Lorenzo Corbetta: May I? A question for all of you. What is the role of CT scan for the identification of the patient with Covid-19, especially patients with symptoms but negative swab. Question for professor Shiyue Li, for example.

Shiyue Li: Okay. Yes. I think based on clinical experience, I think, as we all know, that the sensitivity of the RNA tests is just maybe 50%. So, the sensitivity is a little bit low, so, for a one-time test. So, I think also at the beginning of the outbreak of the Covid-19 in China, there are some limitations of the RNA test. CT scan is very convenient in the hospital. So, based on Chinese doctors' experience, the sensitivity of the CT image is quite sensitive. It's more than, based on the literature, about 95%. It's more sensitive than the RNA, but I don't think it's the golden standard now for the diagnosis. It should be combined with the RNA test. I think combined, this CT scan and RNA test, it's good for the clinical practice. This

is my opinion.

Lorenzo Corbetta: Thank you. You performed many bronchoalveolar lavages and bronchoscopies?

Shiyue Li: Yes. You know, in terms of the sample, the nasal swab is a little bit better than the throat swab and sputum is better than the nasal swab. I saw a literature that a biopsy through the bronchoscopy is about 60% of the time, is it, yes, for the RNA test.

Guangfa Wang: My answer to the first question is that so I think a CT scan is more sensitive and very rapid. So, for screening or for the examination of Covid-19 patients, but I think the specificity would be a problem. On recent weeks, we have at least two patients: the CT scan is very, very similar to Covid-19, but there is no epidemiological history, PCR of novel coronavirus are negative several times. So, at last, this patient has got, like another one, other immuno-disease. So, I think the diagnosis of Covid-19 should not really only on CT scan. So, in China, as we have experienced a reasonable time; in that time, a lot of patients come out and the capacity for current virus tests is very limited. But they need the official diagnosis and confirmation. So, if they are confirmed, so several patients can stay in one room, but if they are not confirmed cases, only suspected cases, one patient, one room to avoid cross infection. So, at that time, in Wuhan and Hubei a new diagnosis criteria have been put out. That is, a clinically diagnosed case. So, that means the patient had epidemiological history and a positive CT scan. So, although the guideline emphasized the features of Covid-19, but on the first day of the application of the new criteria, so over 13,000 new cases appeared. So, then right now, we have a retrospective analysis to the clinically diagnosed cases. We observed the hospital-acquired infection is much higher, almost more than fifteen times higher than confirmed cases.

So, I worried about, so these clinically diagnosed cases are not really Covid-19. So, it may be other pneumonia. So, back when they were classified as Covid-19 patients, they were staying with others in the one room. So, then cross infection happened. So, that is a problem. So, I think in the future, we should not emphasize the CT value on confirming the diagnosis of Covid-19, but if you want to find suspected cases, so that is a good tool. Why China selected CT, so for only one week they used these criteria? So, one reason is that we had many, many cases. The other reason is that the positive range of throat swabs is lower, very low. So, it has been recorded as 30% to 50% of confirmed cases. So, it is very low. So, we need a quality control. Another issue about bronchoscopy and bronchial lavage. At the early stage of the Wuhan Covid-19 epidemic, we observed the lavage has highest possibility to reach of Covid-19 than PCR, but when doing bronchoscopy, so we were risking a much higher risk for cross infection, especially for healthcare workers. In China, we do not encourage doctors to do bronchoalveolar lavage for the diagnosis, just for the diagnosis of Covid-19.

Lorenzo Corbetta: Okay. Thank you very much all. Thank you and I invite you to the next webinar that will be held on May 29th on the clinical management of Covid-19 and will be led by some Chinese presenters, like Bin Cao, professor Li Jing again and Italian professors, expert in immunology and in coagulation and an Italian doctor who is working in London, very expert in intensive care. So, thank you very much for your presentation, and see you soon. See you on 29th May. Thank you.