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MEETING REPORT

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TIPICO XI: report of the first series and podcast on infectious diseases and vaccines (aTIPICO)

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ABSTRACT

TIPiCO is an annual expert meeting and workshop on infectious diseases and vaccination. The edition of 2020 changed its name and format to aTIPiCO, the first series and podcasts on infectious diseases and vaccines. A total of 13 prestigious experts from different countries participated in this edition launched on the 26 November 2020. The state of the art of coronavirus disease-2019 (COVID-19) and the responsible pathogen, the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the options to tackle the pandemic situation were discussed in light of the knowledge in November 2020. Despite COVID-19, the status of other infectious diseases, including influenza infections, respiratory syncytial virus disease, human papillomavirus infection, measles, pertussis, tuberculosis, meningococcal disease, and pneumococcal disease, were also addressed. The essential lessons that can be learned from these diseases and their vaccines to use in the COVID-19 pandemic were also commented with the experts.

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Introduction

TIPICO is an expert meeting and workshop that aims to provide the most recent evidence in the field of infectious diseases and vaccination. In 2020, under the exceptional circumstances of the COVID-19 pandemic, the yearly edition of TIPiCO workshop changed its name and format to aTIPiCO, the first series and podcasts on infectious diseases and vaccines. Its premiere was on the 26 November 2020. A total of 13 prestigious experts from different countries conversed with the chairman Dr Federico Martinón-Torres. As usual, these series addressed current and trending issues in the field of infectious diseases and vaccination with a special focus in the current pandemic situation caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

The first three sessions addressed the most important aspects of coronavirus disease-2019 (COVID-19) such as the pathogen and the disease, the different screening tools to control the transmission and the vaccines. The other six sessions covered other important infectious diseases, most of them preventable by vaccination, including virus infections such as influenza, respiratory syncytial virus (RSV) disease, human papillomavirus (HPV) infection, or measles and bacterial infections like pertussis, tuberculosis (TB), meningococcal, and pneumococcal diseases. This edition also counted with a special session that provided a paleoanthropological perspective of infectious diseases.

In light of the knowledge and information available in November 2020, this report gathered what was discussed during aTIPiCO sessions about the state of the art of COVID-19 and the options to tackle the pandemic situation and about other important infections, despite COVID-19, and the essential lessons they can provide, based on the experience and research of the experts in the field.

What do we know about the SARS-CoV-2 virus and the COVID-19 pandemic and how can we tackle it?

Can omics help against COVID-19?

In this session, Dr Jose Gómez Rial, Dr Federico Martinón-Torres, and Dr Antonio Salas on behalf of the Genetics, Vaccines and

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Pediatric Infectious Diseases Research Group (GENVIP; Spain) from the *Instituto de Investigación Sanitaria* (IDIS; Spain) de Santiago and *Universidad de Santiago de Compostela* (USC; Spain) discussed and reviewed the state of the art of the SARS-CoV-2 in terms of disease, prevention, and physiopathology from a translational research perspective.

This session started talking about the SARS-CoV-2. A few weeks after the pathogen responsible of the COVID-19 was identified, the complete viral genome was published.[1] By November 2020, more than 170,000 genome sequences of SARS-CoV-2 were reported. The analysis of SARS-CoV-2 genomes has helped confirm its natural origin and take back the controversial ideas that supported the artificial variability of the SARS-CoV-2. Dr Salas explained that the origin of SARS-CoV-2 is natural because its genome presents a variability that typically corresponds to that of the natural virus. In addition, it has been possible to trace the variability to the root of the SARS-CoV-2 genome without detecting anything unusual in what should be a natural evolution of coronavirus.[2,3] Besides, sequencing more SARS-CoV-2 genomes provide information related to the phylodynamics of the virus and it will allow tracking the virus to establish a solid phylogeny of worldwide variation.[3]

In terms of the variability of the SARS-CoV-2, Dr Salas quantified and compared the mutation capacity of the virus with other viruses. SARS-CoV-2 mutates almost constantly in the host with a mutation rate of about 10^{-6} per replication cycle. Considering that a cycle lasts 10 hours (as inferred from other β-coronavirus), and there are roughly 10^3 cycles per year, it can be said that the virus mutates about 10^{-3} mutations/site/year, meaning once every 2 weeks or 24–28 times a year. This fits with the substitution rate obtained in evolutionary studies.[3] Comparing with other viruses, the substitution rate of the SARS-CoV-2 is not as different as the one in the human immunodeficiency virus (HIV) or influenza virus when normalized by their genome size: the substitution rate of the SARS-CoV-2 is less than half that of what the influenza virus does when considering their genome sizes. Moreover, despite its mechanisms of reparation, the coronavirus accumulates considerable variability per year due to its size (e.g. it is more than twice that of influenza virus and three times that of HIV). In November 2020, more than 20,000 mutations of the virus were known, but a vast majority has already disappeared. In Dr Salas' opinion, it was still too early to determine the impact of the virus variability on the design or efficacy of the vaccine. It is noteworthy that there are no ultra-conserved elements neither hypermutation spots in the whole genome. Therefore, although the variations are few numerically in the percentage of variation between each strain (>1%), the fact that the mutations can happen along the entire extension of the viral genome might be a problem. According to Dr Salas, in the gene that encodes the spike protein, the target of most the vaccine candidates against COVID-19, a bit more conserved spots have been identified.

Looking for the more advantageous strains, Dr Salas mentioned the A2 strain (using nomenclature from Gómez-Carballa *et al.*, 2020[3]) which contains a mutation at protein position 614 (D614G). This strain emerged at the beginning of the pandemic in the North of Italy and spread throughout the world.[3] Together with a strain that initially emerged in China, they have been the most successful strains. Regarding the idea that this mutation could provide the virus with diffusion facilities, Dr Salas relativized this hypothesis because other mechanisms are also compatible with the epidemiological evolution of this mutation; as for instance the role of super-spreading in the pandemic.[4] Thereby, the success of this mutation might have been strongly conditioned by the action of the genetic drift and not on the capability of the virus to successfully spread. The super-spreading phenomenon starts with a person that infects a significant number of individuals and after the incubation period they become an epidemic outbreak with a high basal number of infected people. This phenomenon has occurred everywhere around the world.[3] Although the role of the super-spreaders in the transmission has been identified from studying the virus, the specific characteristics of the host are not yet defined neither the contextual factors that may be involved in facilitating the transmission.

It is noteworthy that the asymptomatic-infected subjects are not more infectious than other infected patients, therefore restricted contact measures as social distance and use of mask should be enough to control the transmission from this group. According to epidemiological data, those who are the most contagious within a household are those who have more symptoms. The odds ratios also indicate a higher risk of being more infectious associated with more symptoms. In this line, Dr Martinón-Torres pointed out that although children are infected the same as adults, they have a differential role in the transmission chain, because they are more efficient in resolving the infection due to the plasticity of their innate system. Low levels of humoral response and antibodies against SARS-CoV-2 in infected children indicate that the infection is resolved with the innate immune response, without generating a specific response. Unlike adults, children have a robust innate immune system due to the continuous exposition to new agents and at the same time, it is well trained by the vaccines received as part of the child vaccination program. These factors help the immune system to be highly effective in stopping the virus from replicating.

The speakers also discussed about the importance of the identification of infected subjects, independently of symptoms by using the appropriate screening test. They agreed that the identification of asymptomatic individuals is not so trivial because it is a complicated task, and it is unclear the role they play and the impact they have on the pandemic. However, infected patients must be detected early and treated promptly, especially those who are symptomatic. For that, the use of self-use antigenic tests, despite being less sensitive than diagnostic tests, should be sensitive enough to detect positive subjects on time and help in the control of the transmission.

As the speakers mentioned, screening certain transcriptomics biomarkers of gene expression can be used as an approach to detect individuals with subclinical infections.[5] This type of screening could indicate if a person is infected before the incubation phase takes place. This option might be possible as several biomarkers are probably known, however, according to Dr Salas, it should be implemented in a quick device and be cost-effective for the general population.

In terms of the immune response against SARS-CoV-2, Dr Gómez pointed out that SARS-CoV-2 as other coronaviruses is able to manipulate the immune response. Three levels of immune response against SARS-CoV-2 have been described: asymptomatic, normal and exaggerated immune

response. This last one occurs in severe COVID-19, and the pathology is determined, not by a direct cytopathic effect of the virus, but by an over-response of the immune system as a systemic hyperinflammation, known as storm of cytokines.[6] In an asymptomatic individual, when the virus infects the cells, the interferon (IFN), as part of the innate immune system, is released to active and coordinate an immune response against the virus. However, in severe cases, the over-response of the immune system occurs as a result of the evasion of SARS-CoV -2 of the IFN system. This dysregulation of the immune system caused by the virus results in no activation of the adaptative immune component, usually responsible for solving the infection. Accordingly, in the severe cases of COVID-19, the B or T cells are frequently not activated and/or the antibody levels are very poor.[7]

Various studies that analyzed the transcriptomic responses of SARS-CoV-2 compared to SARS-CoV-1 and influenza viruses have shown the improved ability of the SARS-CoV-2 to evade the IFN system. Dr Gómez highlighted that is an evolutionary improvement of SARS-CoV-2 with respect to SARS-CoV-1. Dr Gómez explained that although many viruses have IFN evasion mechanisms, the redundancy of the innate immune system allows the activation of IFN by several convergent pathways. However, SARS-CoV-2 blocks several of these pathways so that IFN is activated late, causing the collapse of the immune system.[8] This late IFN signaling have a worse impact on the immune response than its absence.

The speakers discussed if the overactivation of genes related to TNF alpha and the same IFN 1 is an attempt from the host to desperately defend itself against the pathogen. In the opinion of Dr Gómez, the overexpression of the components of the innate immune response is a consequence of the late response and that is why despite being overactivated, they do not resolve the infection. In this line, Dr Salas added that two genomic studies in large cohorts have identified deleterious variants in the gene of IFN that cause deficient antiviral response and that many of these genes are related to auto-antibodies.[9,10] According to Dr Martinón-Torres these findings fit together like the pieces of a puzzle since the immunological response of the host fit both the described genetic predisposition and the functional response from transcriptomic studies.

The speakers also debated if the administration of IFN may be a solution and when it should be administrated. By November 2020, there were nearly a hundred clinical trials evaluating the use of different types of IFN for the treatment of COVID-19. However, most of the trials were failing because the administration of IFN was too late. According to Dr Gómez, in order to succeed, IFN should be given in the early phase which is unnoticed.

In addition, Dr Salas pointed out that the genomic studies, as the one previously mentioned that identify for first time patients with anti-IFN antibodies, could be helpful to determine the appropriate treatment. In the case of these patients, they should not receive, neither treatment with IFN nor convalescent plasma. Then patients should be screened to see if they are susceptible to failure of this type of therapy.[9]

Dr Martinón-Torres highlighted the need of personalized interventions for each patient. Although the disease appears with the same clinical symptoms, the host immune response against the virus and the mechanisms to counterattack the evasion of the virus can vary within each individual. In addition, the immune response of the host is influenced by several factors including genetics, age, and comorbidities. For example, an immune system in senescence might lose the plasticity to adapt and counterattack the evasion mechanisms of SARS-CoV-2.

The speakers commented that it is important to identify the immune cell type that acts as the driver of the immunopathology of the COVID-19 as a possible target for treatment. In this sense, Dr Gómez explained the identification of macrophage/monocyte cells of the innate immune system as key actors in the immunopathology of SARS-CoV-2.[11] Serum levels of sCD14 and sCD163, two soluble markers of monocyte activation, were significantly higher among COVID-19 patients. These markers were also correlated with other inflammatory markers in SARS-Cov-2 infection, as interleukin-6.[12] In addition, the clinical presentation of severe COVID-19 patients resembles viral-associated hemophagocytic syndrome, a clinical syndrome characterized by the accumulation of well-differentiated macrophages in several tissues.

Based on these facts, Dr Gómez suggested that the inhibition of granulocyte macrophage colony-stimulating factor (GM-CSF), a cytokine that stimulates monocytes to migrate into the site of infection, could avoid the pulmonary complications in SARS-Cov-2 infection.[13] Unlike inhibitors of other cytokines, the inhibitors of the GM-CSF can modulate the immune response in an early cascade level. Last 2020, 15 clinical trials were evaluating GM-CSF inhibitors in patients with COVID-19 with very promising results.[14]

The speakers also talked about the problem related to the diversion of several treatments as hydroxychloroquine or, ivermectin from diseases for which they were indicated, to be used in COVID-19 based on non-robust studies. And at the end, these treatments turned out to be not effective.

In the topic of clinical trials in COVID-19 patients, Dr Gómez highlighted the importance of selecting patients in the appropriate stage of the disease according to the type of treatment.[15] Some of the treatments tested with negative results failed partly due to the hasty design of the clinical trial, as is the case of tocilizumab that was tested in viral phase patients. During the viral phase, antiviral agents as remdesivir should be tested, whereas during the immunological phase, immunomodulators should be tested. However, to be able to differentiate the stages of the disease, there is an urgent need to identify suitable biomarkers.

The traditional treatment that has succeeded in the management of severe COVID-19 has been corticosteroids, as dexamethasone. Despite its medium and long-term side effects due to its unselective inhibition of immune response, they are cost-effective and affordable, especially compared to innovative selective inhibitors of the immune response.

The speakers questioned the use of antiviral agents in the COVID-19. In Dr Martinón-Torres´ opinion, the use of antiviral should be prophylactic, to prevent the infection and the entry of the virus in the cells. Once the patient is infected and the virus entered the host cells, the antiviral does not have effect anymore. In this line, it was pointed out that there are not effective antivirals against acute viral infection, except specific type of immunocompromised patient. Dr Gómez commented that until the people is vaccinated, the

management of COVID-19 patients should be based on the control of the host immune response by using corticosteroids or other immunomodulators.

In terms of COVID-19 vaccines, the speakers shared their vision. Dr Gómez was optimistic since a protective epitope for the vaccines that worked has been identified. Dr Salas thought that the solution to the COVID-19 pandemic is mostly vaccination. However, the vaccines may have limited efficacy and that the control of the transmission will be still a slow process since the progress of the vaccination depends on several factors beyond the administration as distribution, vaccine doses, and coverage. Therefore, he anticipated that at the beginning of 2022 population protection could be achieved. Dr Martinón-Torres was worried about the high expectations around the arrival of the vaccines because he thought that the social restricted measures would continue even with the vaccine until herd protection is achieved. Moreover, he highlighted that the design of this first generation of vaccines was generally more orientated to prevent the disease than the infection. Based on the preliminary results of that time, it was not discarded that vaccinated individuals could continue transmitting the virus. Another open question was the duration of vaccine protection. Considering the natural protection from other coronaviruses, it should last at least 1 y. Independently of antibody levels, the memory of the cellular component persists over time and protects the host against possible re-infections.[16] It has been demonstrated that the more severe the symptoms are the longest the protection last.

To conclude, Dr Martinón-Torres gave his opinion about the vaccines against COVID-19. He said that vaccines will be soon available, and he estimated that the doses for vaccination in Spain will be ready at the end of the first half of 2021. He opined that normalization will be reached in 2023. After discussing their visions, the speakers commented on the problem that will be the false expectations of the general population created by politicians around the rapid solution of the pandemic situation and its implications with the arrival of the vaccines.

Rethinking strategies from COVID-19 diagnosis to classical vaccines use

The talk of Dr Michael J. Mina (Harvard School of Public Health and Harvard Medical School, Boston, United States [US]) was about two major topics of interest: (i) the heterologous effect of vaccines and the immunological amnesia that is associated with measles, and (ii) new strategies to tackle the COVID-19 pandemic including the use of proper testing and the arrival of the new vaccines.

The session started discussing the heterologous effect of attenuated vaccines and the possibility of using other available vaccines to protect against COVID-19. The concept that a vaccine can stimulate an immune response that would protect against an unrelated pathogen has a complex underlying biology that is not yet fully understood. Several researcher groups have pursued this idea by working on the biological mechanisms behind this nonspecific response induced by some vaccine that could protect against other infections.[17,18] As an example, Dr Mina presented some unpublished results about the heterologous effect observed in a live-attenuated influenza vaccine in reducing secondary bacterial infections in mice. These results are inverse of what the influenza virus causes, which predispose patients to secondary bacterial infections. Moreover, the group of Dr. Netea in the Netherlands has shown many different effects suggesting, for example, that epigenetic reprogramming and other modifications of monocytes could exacerbate these cellular responses after the measles vaccine to protect against other infections.[18] However, according to Dr Mina, at the population level, data becomes a little less compelling because most of the available data are at high risk of population bias.

Regarding the particular case of the Bacillus Calmette-Guérin (BCG) vaccine and the research on its possible non-specific effects against COVID-19, Dr Mina indicated as an example, a very large study with the BCG vaccine in healthcare professionals to analyze the impact on the COVID-19 financed by Bill Gates.[19] This vaccine elicits a very strong T-cell response that for instance has been used as therapy for bladder cancer. A high dose of BCG vaccine is administered into the bladder and induces a very robust cellular response that causes the T cells to target the tumoral cells.[20] In Dr Mina´s opinion, this characteristic of the BCG vaccine has an evolutionary backing considering TB is a pathogen that has been co-existing with humans for a very long time and never destroyed and therefore is a permanent immunological stimulant. Thereby, the mechanism behind this may be related to the fact that BCG is an attenuated form of TB that keeps the host immune system alert.

During Dr Mina's research on this topic in relation to measles and its vaccine against other infectious diseases, it was discovered that measles infections are causing other infections, wiping out immune memory.[21] However, memory is preserved with the vaccine and other infectious diseases are reduced. By analyzing population dynamics, it was found out that the measles kinetics in the population almost fully explained all variations of mortality over decades and over many countries, before and after the measles vaccine. The introduction of the vaccine in these populations was associated with 50% reductions in mortality in children.[21] To understand the mechanism underlying this phenomenon, a study to profile the immune response in unvaccinated children in the US and in the Netherlands before and after measles was performed. The immune memory of those children was analyzed before and after the measles infection by profiling a large number of antibodies using VirScan.[22] After measles infection, many children had lost half or all of their immune memory compared to the control group that lost 5% to 10% of immune memory, considered as normal fluctuations.[22] This demonstrated that once the measles virus enters the body, the virus uses dendritic cells to gain access into the lymphatic system and then binds to memory cells using the cd150 or SLAM receptor and kills them. It then spreads throughout the body and kills immune memory. These same results were shown in monkey models. This strong evidence indicates that vaccinating children against measles, which is a virus that used to infect about 100% of children, reduces all-cause mortality due to the elimination of this effect of measles called immunological amnesia associated with measles infection.

In Dr Mina's opinion, much of the heterologous benefit of the measles vaccine, besides the elimination of measles and

prevention of immune amnesia, does not depend on the type of vaccine, attenuated or inactivated, but more on the immunological response induced. Since vaccines are designed to elicit immune responses that at least approach what a natural immune response looks like, technically, nonspecific immune responses like monocyte reprogramming and other approaches can be elicited by both vaccines. However, there are still a lot of questions that need to be answered to fully understand the mechanism underlying the heterologous effect of the vaccines.

Regarding the COVID-19 vaccines, Dr Mina indicated that the efficacy results of the early clinical trials of the first vaccines based on messenger ribonucleic acid (mRNA) needed to be put in context of how the immune system works. Although these results showed that vaccines elicit strong effects, they are based only on the spike protein and therefore they are specifically designed to elicit neutralizing antibody responses that will prevent the virus from binding cells. It is noteworthy that these vaccines stimulate an immense secretion of antibodies produced by plasmablasts which are temporary cells. Therefore, the persistence of this effect after 3 months is not clear yet clear at the time of this discussion, since the time schedule of the phase 3 trials of these vaccines matched the longevity of plasmablasts and their secreted antibodies.

Dr Mina was asked about his preferences on the vaccine candidates. He liked the concept of mRNA vaccines as a new generation of vaccine development. One of the advantages of this type of vaccine is that the vaccine production can be easily scaled up around the world, by having mRNA "printers". That is something that cannot be done with cell-based vaccines. Another advantage is in case the virus mutates, these vaccines are easy to adapt by adding new mutations or changing the mRNA sequence, instead of growing a new virus that needs to be attenuated or inactivated. However, Dr Mina was concerned about the development of COVID-19 vaccines in the world, since all the main candidates are clones based on the spike protein. Dr Mina explained that a pandemic virus has never been placed so quickly under a potential ecological pressure like the one that is going to be pushed through. He pointed out that it only takes one virus particle out of trillions of virus particles that grow every day around the world to find a way to escape the spike immunity induced by the vaccine. This highlights the importance of the development of different approaches like live-attenuated or inactivated vaccines or a multiprotein approach.

In the second part of the session, Dr Mina advocated for the importance of using the best testing in an epidemiological framework.[23] So far, testing is globally considered as medical tools what has been causing massive problems and significant delays in the management of the pandemic. In the US, all tests that are authorized have to go through a medical framework, meeting diagnostic criteria that may be not necessary for public health. In Dr Mina's opinion, a step back should be taken to look for the right tools to deal with an outbreak and, the perspective may have to be changed, first solving the pandemic so that the medical cases will resolve themselves.

Dr Mina compared the use of the benchmark standard clinical polymerase chain-reaction (PCR) test with a forensic investigation of a crime to explain that the detection of RNA (or DNA in the case of a crime scene) can remain positive long after the virus was cleared by the immune system (or the crime has been committed). The PCR test can be positive in a person with disease remission, who was infected 2 or 3 weeks ago by detecting remaining virus RNA preserved in double membrane vesicles. On the contrary, the antigenic tests, instead of detecting the presence of viral RNA, they detect the virus protein, which is associated with the presence of a viable virus.

Under these circumstances, Dr Mina analyzed what a public health tool needs to control the COVID-19 pandemic. The goal of public health tools should be to determine the transmissibility in infectious people by detecting alive viruses, not the presence of RNA, as the antigenic tests can do. This screening test does not need the highest sensibility of diagnostic tests as PCR test since a person becomes infectious when the viral load gets from millions to trillions of viral particles per milliliter. Another important aspect of these screening tests is the timing determined by the narrow transmissibility window of 2 to 5 d. To succeed in the identification of infectious people, tests need to be frequently repeated. Testing limited to symptomatic people do not help in the identification of infectious people, as they have already passed their transmission window. Unlike PCR tests, antigenic tests can be used for frequent testing, as they can be largely produced and easily performed at home. In Dr Mina´s opinion, the population needs to get involved to tackle such population event by testing themselves in a very frequent basis (e.g., twice a week) with a simple test. When the result of the test is positive, that person just stays home. With a participation of 40–50% of the population in the use of these screening tests, Dr Mina ensured that the R0 (reproductive index of the epidemic) may fall below 1, leading to an exponential decline of the cases instead of the exponential growth seen in the first and second wave. Rapid tests will allow people to monitor their condition and make individual decisions that have a positive impact on the collective response need to tackle the pandemic.

He stressed that a successful public health program to combat outbreaks only needs to ensure that for every 100 infected people, that they infect fewer than 100 additional people. Rather, he says that so far, testing policy has been driven by an idea that the test has to catch everyone to be useful, but this is false, it only needs to ensure that R stays below 1, and that means that 100 people infect less than 100 people, not that they infect 0 additional people.

Regarding the usefulness of antigenic tests in pre-symptomatic or asymptomatic people, Dr Mina explained the misunderstanding of the testing as a clinical tool that only works for symptomatic people. Public health tools, such as the antigenic test, detect if a person has enough virus load to spread, independently of the symptoms. And as it is known, an infected person without any clinical symptom will need a higher viral load to really be infectious because they do not cough or sneeze which may facilitate the transmission of the virus. Considering this, asymptomatic or pre-symptomatic individual will can be detected by using screening tests. The challenge in the authorization process of these screening tests is to recruit asymptomatic subjects at the peak of their infection to prove the efficacy of the tests. Moreover, these new screening tests should not be compared to the positivity of RNA detection but to the positivity of viral culture, regardless of the symptomatic status.

Dr Mina indicated that clear definitions must be created to explain the purpose of the different tests: medical tools for the diagnosis, surveillance tools for contact tracking and follow-up, entry screening tests before entering a specific location as a senior facility, and public health screening tests, which are massive screening to stop outbreaks. In the case of entry screening tests, they should be defined depending on the type of place the screening is for. For example, if it will be an entry screening for a nursing home, sensitivity should be the priority. Although PCR test are sensitive enough, they are not an option because it takes 48 hours to get the results. For example, a lamp-type rapid test should be used, like the one from the new company called DETECT, that is of the same quality as the PCR test, but it can be done in 30 minutes by thermal amplification. The sensitivity of antigen tests can be calibrating for entry screening, perhaps with less specificity. In that case, if a person is positive to an entry screening test, a confirmation PCR can be requested. False positives are not a problem as long as all the positives can be correctly identified by an accessible confirmatory test. Dr Mina compared this algorithm with the one HIV in hospitals, whereby 50% of the positive tests are false, but patients are informed after the confirmation test.

In any type of test, Dr Mina highlighted that speed is essential. For the detection of infectious people what is important is the time of getting the result, more than the time of being tested. If a person has a PCR 1 d, he will have to wait for 48 for the results, whereas, he could have a rapid antigen test a day later and no wait another 24 hours. If that person was positive, both tests would detect it, but with the quick one, he would know a day before.

Regarding antibody tests, Dr Mina believed that they are very useful. Initially, they seemed to be the ideal solution for tracking the pandemic, but they have been left out a bit because most of the time there has been a situation of crisis, and attempts have been made to control outbreaks in the community. Antibody tests are very important and they will allow understanding the immunological protection that a person may have[24] But for that, it will be also necessary to find protection correlation to determine what the level of antibodies represents in terms of the underlying cellular response.

Antibody tests will be also helpful in what Dr Mina called a global immunological observatory as a forecast system for viruses. Antibody tests can be used as epidemiological predictors. The group of Dr Mina has been working in a low-cost antibody test that with less than one microliter of blood from dried blood can simultaneously detect hundreds of thousands of different antibodies. These tests can be implemented as high-throughput screening systems and be used around the world. These complex antibody tests will help to understand how viruses move, even in asymptomatic individuals. If a person gets exposed to a virus, there will be an immune response detectable by these antibody tests. Therefore, they can be used for a global surveillance system to prevent the next pandemic but also in the COVID-19 pandemic, they can be useful as surveillance for SARS-CoV -2, like the PCR tests in wastewater.[25] With routinary blood samples during peacetime, they can be a very powerful surveillance tool to track whether there are new cases arising in the population.

To conclude the session, Dr Mina was asked about his prediction for the pandemic to be defeated. Dr Mina anticipated that closures and lockdown will be still happening since there has been an exponential increase in the number of cases, especially in the US. He also pointed out that those measures will not work, because they have to be unanimous, so in winter 2020 the number of cases will continue to rise, and cases will continue to be transmitted around the world. Dr Mina thought that the situation will not be under control until seasonality returns to be favorable, around late spring, and he encouraged the world to use the summer, when the transmission is lower, to take the pandemic under control. Dr Mina hoped that by fall 2021, a high percentage of the populations will be vaccinated, although not the whole globe and that all the proper control systems will be set up as the rapid antigenic test. As an example, Dr Mina mentioned Slovakia, where antigen testing has been used by a large part of the population on a weekly basis and the incidence has decreased considerably.[26] And finally, by January 2022 the pandemic will be controlled, by vaccination and by using these large-scale tests and by having regained people's trust in public health systems.

To summarize this session, all the strategies to tackle the COVID-19 pandemic were reviewed, from the use of existing vaccines and their potential heterologous effect, the caution regarding the efficacy and persistence of COVID-19 vaccines to the need of integrating quick and frequent testing as the antigenic tests as a central piece to control this pandemic.

A vaccine against COVID-19

Adolfo García-Sastre (Mount Sinai-NY University) and Andrew Pollard (University of Oxford) discussed with Dr Martinón-Torres the status in the development of vaccines against COVID-19 in November 2020 and what were the expectations of this first generation of vaccines. As a reminder for the readers, at the time of aTIPico series, there were no vaccines authorized for commercialization in the European Union.

The session started by asking the speakers when the vaccine will arrive. Dr Pollard pointed out that the time scales will be different depending on whether the question refers to the announcement of first results, the availability of the first doses, or the availability of a vaccine for the whole population around the world. The vaccines need to go through a whole process including the corresponding clinical trials, the assessment and authorization process and the production of enough doses. Dr Pollard was optimistic and stated that the first results for some of the vaccines would be available by the end of 2020 or early 2021, although there is still a lot to do from the regulatory perspective and preparation of supply of vaccine for distribution.

Dr García-Sastre also showed his optimism as the preliminary results of the vaccines in phase 3 clinical trials related to neutralizing antibodies in serum have shown very positive results, therefore it is likely that vaccines will work preventing the diseases without any significant adverse effects detected so far. In addition, the vaccines tested in animal models have shown good levels of protection under experimental challenges. Even so, all these data need to be evaluated by the

regulatory agencies in the coming months. Considering this, Dr García-Sastre estimated that by the beginning of 2021, there will be one or several approved vaccines. After that, it will start the distribution and the population vaccination. In this regard, Dr García-Sastre pointed out that all the vaccines closer to approval have two doses thus, several months will be required before enough population immunity can be developed to stop the impact of SARS-CoV-2. Thereby, Dr García-Sastre anticipated that by summer 2021, there will already be enough people vaccinated in several countries to stop the pandemic, although developing countries will still need help in the distribution and storage of the vaccine due to the required cold chain. In the end, there will be vaccines that solve the problems caused by the COVID-19, although they will not be able to eliminate the virus.

On the topic of the high expectations with the arrival of vaccines generated by different stakeholders, including politicians, Dr Pollard pointed out that the vaccines will be part of the solution, but they will not be the whole solution. The first limitation will be the supplying of the vaccines since it will not be possible to vaccinate the whole population at the same time. Moreover, once the population is vaccinated, there will be still transmission between certain unvaccinated groups either because they refused to vaccinate or due to health conditions. Another important aspect is the efficacy of the vaccines, as none of them have 100% protection, hence it is very likely that a percentage of the population will not be protected despite being vaccinated. Dr Pollard said better treatments will be necessary, especially for those people who are still at risk. And in the meantime, measures such as wearing masks and maintaining social distance, and close monitoring of the population will continue to be needed.

Dr García-Sastre gave his opinion about the target of the vaccines. First, neutralizing antibodies are generally an important component in the vaccine to be efficacious because they are one of the major effector molecules to prevent infection and/ or the invasion of the lower respiratory tract. The cellular immune response is also an important component, especially to guarantee a long-lasting immunity. The spike protein of SARS-CoV-2 is a large antigen with abundant cellular epitopes to induce cellular immunity. The first results available for the most advanced vaccines against COVID-19 relate to the humoral response a few weeks after vaccination and therefore it is still unknown the duration of the immunity.

Regarding the race of vaccine development, both speakers agreed that the development of different vaccine candidates at the same time is very positive, and the higher number of successful vaccines, the better. Dr Pollard added that most of the vaccines are focused on spike protein, thus if one of the candidates is successful, it is very likely that the others will succeed as well. In this line, Dr García-Sastre noted that the new technologies of COVID-19 vaccines as the mRNA approach, or less frequently used as adenovirus vector will be validated allowing in the future to use these same technologies in potential future pandemics.

Dr Pollard gave an insight of the status of the development of the Oxford vaccine developed in collaboration with Astra Zeneca. In November 2020, the Oxford vaccine was in phase 2/ 3 clinical trials with a participation of at least 24,000 people from several countries distributed around the world, including Brazil, South Africa, and the United Kingdom (UK) led by Oxford, with further studies led by Astra Zeneca in India, Japan, Russia, and the US. The clinical development of this vaccines is based on a large program that aims to cover different geographical regions from an ethnic perspective and different regulatory jurisdictions.[27,28]

Dr García-Sastre described the development of the vaccine candidate based on the Newcastle disease virus (NDV), on which he is working in collaboration with the groups of Dr Palese and Dr Krammer. In November 2020, this vaccine was about to start a phase 1 clinical trial. It is based on a vaccine vector based on NDV, an avian virus, that has been studied for several years. It has been evaluated in clinical settings for the treatment of tumors because of its oncolytic activity. The candidate vaccine against COVID-19 contains a highly stable form of spike protein what makes it very immunogenic. The main advantage of this vaccine is that its technology is the same as for the vaccine against influenza. Thereby, the same manufacturing procedures can be used to produce large amounts of doses to guarantee a wide supply around the world.[29]

Another important topic of discussion was the assurance that the vaccines against COVID-19 followed the same criteria and safety and efficacy protocols as any previously authorized vaccine. Dr Pollard explained although there is an urgency to develop a vaccine, there is the same regulatory scrutiny on the clinical trials and on the quality of vaccine manufacturing in the programs of the COVID-19 compared to normal times. There has not been any short-cut in the process. Similarly, the scale of the trials is also reassuring, as usually most vaccines in Europe are studied in a small population sample (3,000–5,000 people). The vaccine candidates against COVID-19 are tested in thousands of people in phase 3 clinical trials, having as an example the vaccine of Oxford-Astra Zeneca that will be tested in more than 50,000 individuals. The speed-up of the process goes through the reduction of the hurdles and waiting times between testing or getting funding because all the stakeholders, including regulatory agencies and international funders, are giving high priority to solving the COVID-19 pandemic.[30] Essentially, all the developments have moved extremely quickly through all these processes, but without cutting off any step and the safety has been done in the same way that in normal cases. Another aspect noteworthy is that for most of the vaccines, the duration of the trials is a bit shorter than normally would, but the number of people enrolled in these trials is an order of magnitude higher.

Regarding the safety and possible adverse events associated with these vaccines, Dr García-Sastre noted that the enhanced disease was one of the main initial concerns, based on experience with other vaccines. In rare cases, vaccination increase the risk of acquiring the disease. Although the cause of this adverse event is not clear, it is usually associated with the presence of non-neutralizing antibodies and another type of immunity that is detrimental in the case there is exposure to the actual virus.[31] In the case of the vaccine candidates against COVID-19, there is a good induction of neutralizing antibodies and no indication of Th2-mediated immunity. In addition, there have not been reports of individuals with natural immunity or already vaccinated that after reinfection have a more severe form of the

disease. Therefore, Dr García-Sastre opined that enhanced disease does not seem to be a major safety problem with these vaccines, although data needs to be checked and vaccines closely monitored. In addition, Dr García-Sastre pointed out that when a large number of people will be vaccinated, it is possible that some individuals will have a specific predisposition for developing adverse events. It is important to take this into account to be able to identify these adverse events and the people at risk. Dr García-Sastre concluded that although unfortunate adverse events might happen in a small group, the vaccine will be useful to save many lives by protecting against COVID-19.

In terms of the detection of infrequent and unexpected adverse events, Dr Pollard pointed out that it will be a challenge for the surveillance systems. For that, it is really important to have already established an integrated system that monitors who has been vaccinated and linked with electronic healthcare records. Although not all countries have this type of surveillance system in place, there are some European countries that have implemented them in the last decades, and they can be useful for detecting rare adverse events but also to assess whether they are caused by the vaccine.

Regarding the endpoints used to determine vaccine efficacy, both speakers agreed that clinical efficacy results are needed to draw conclusions. Dr Pollard indicated that there are encouraging data based on T cell and antibody responses from most of the vaccine developers and although they cannot be directly compared due to the different testing strategies, qualitatively, the same sort of response is being seen. However, in humans, it is not known yet the level of protection and neither if these endpoints are correlated with clinical efficacy. In this same line, Dr García-Sastre added that establishing good protection correlations in vaccines is really difficult and large studies are needed. For many vaccines, there are not correlates of protection. As an example, Dr García-Sastre cited the live-attenuated influenza vaccine used in children in several countries which is showing good efficacy results but without known correlates of protection.[32] Dr García-Sastre also highlighted that if a good correlate of immunity is found with these first vaccines against COVID-19, the following vaccines might be approved based not only on clinical efficacy but perhaps on reaching the correlates of immunity proved by the existing vaccines.

The speakers also gave their opinion on the acceptable threshold of efficacy. Dr Pollard commented on the 50% threshold indicated by World Health Organization (WHO), that it is not too low if half of the death or intensive care unit admissions or hospitalizations can be prevented.[33] In Dr Pollard's opinion, any level of efficacy is worthy if it allows preventing deaths. But the problem of low levels of efficacy is the difficulty to measure them and then larger studies or with longer duration are needed to measure low efficacy. Dr Pollard also highlighted the misunderstanding on media that if the vaccine will have low efficacy, then it is better to wait for the second generation of vaccines. In this sense, Dr Pollard pointed out that evidence from the first vaccines is needed in order to develop an improved second generation of vaccines.

Dr García-Sastre agreed with Dr Pollard that any useful vaccine is welcome. If the efficacy is low, the statistical relevance takes a long time and a lot of infection cases to demonstrate it. On the contrary, Dr García-Sastre was optimistic because if a vaccine could be approved at the end of 2020 means that the efficacy is good otherwise it would not have enough data for getting it approved. In addition, based on his experience, there are some viral infections that can be easily prevented by vaccination or at least the first vaccines have worked right away. The viruses that induce chronic diseases like HIV or herpes viruses are more difficult to prevent with vaccines, except for herpes zoster, or they are difficult to eliminate once they establish persistence. SARS-CoV-2 is not a persistent virus and therefore the neutralizing antibodies induced by vaccines can prevent the disease and at least some levels of infection, by protecting the low respiratory tract although they may not prevent complete infection as the protection of the superior respiratory tract is more difficult to achieve by systemic antibodies. It could also be expected that vaccinated individuals, if infected, will be less infectious and have fewer clinical symptoms.

In this sense, Dr Pollard commented that clinical trials should allow assessment of whether the vaccines will protect against disease but also against infection, although not all the studies will be able to measure direct transmission in the households or asymptomatic shedding of exposed individuals. He also highlighted that results in animal models are not easy to extrapolate to humans because of the difference in the immune system but also because of the number of different variables in the studies, including the use of different challenge doses of the virus.

Regarding the duration of the protection, Dr García-Sastre thought that it is too early to estimate it. In his opinion, stopping the infection and reducing the number of hospitalizations during the time that vaccines will be protective will be already a success. Whether the vaccines will be needed to be used again or not, there is not enough knowledge yet related to the molecular mechanisms that led to a long-lasting protection and this may be different depending on the virus. Dr Pollard added that the first evidence of the persistence of the immunity will be soon available because some vaccines as the Moderna candidate which has been tested since March 2020.[34] Perhaps, the duration of the antibodies or the T cell response can be established in the coming year, but it will not be clear if this translates to protection. Determining duration of protection is much more difficult as time is needed, and those vaccinated populations will be have to be exposed to the virus a year after vaccination to provide evidence that protection has been sustained. Although this key question cannot be answered yet, Dr Pollard cited a few lines of evidence that can give some indications. First, some of the vaccine technologies mentioned previously have shown persistent immune responses for more than a year. Second, coronaviruses infected children frequently but a strong immunity is not generated against these viruses because adults continue to have superior respiratory tract infections caused by the same viruses although they are usually not severe. Dr Pollard suggested that perhaps the first infection of SARS-CoV-2 can generate an immune response that prevents the individual from getting again a severe form of the disease. Although some cases of reinfection have been worrying because of their severity, they are rare and could be an exception. Therefore, perhaps, most infected people develop

sufficient immunity to protect them from severe disease. Those are just conjectures but solid evidence is needed to answer all these questions.

The speakers were asked about the evaluation and use of the vaccines in other populations as children or pregnant women. Dr García-Sastre pointed out that, although children do not have severe disease, there are some severe cases and deaths in children caused by COVID-19 that can be prevented and therefore vaccination will be positive. He also highlighted that it is not known yet the role of the children as transmission vectors as it is known for the influenza virus. Thereby, he opined that children should be vaccinated if the vaccine will be beneficial by reducing the risk of hospitalization or mortality in children but not as a strategy to protect high-risk groups. Dr Pollard agreed to some extent. The safety and efficacy of the vaccines need to be demonstrated first in adults. Children have not been included in the clinical trials because they are less affected by the virus. If the vaccines have a good safety profile and can control the transmission, certain subgroups of children at high risk should be vaccinated. But nowadays, the elderly and adults with certain health conditions should be the absolute priority. Regarding pregnant women, Dr Pollard opined it is a group at risk with some uncertainty, especially those pregnant women with other health conditions and at high risk. Establishing the safety of the vaccine for the mother and the fetus and then the infant is complicated because in the early clinical trials it is not usually acceptable to target pregnant women. The vaccine candidates against COVID-19 are still in relatively early phases. Dr Pollard thought that this is an area in which well-planned trials are necessary to determine the benefit of the vaccine in special population groups.

Dr Martinón-Torres explained the low vaccine acceptance in the Spanish population according to a survey carried out in Spain in October 2020[35] and with that asked the speakers what can be done to increase vaccine acceptance.

Dr Pollard believed that scientists have a great responsibility to communicate science about how vaccines are evaluated. According to Dr Pollard, this survey may be related to a period of uncertainty in which solutions are being tested and it is not known what will happen. He anticipated that society will accept and recognize these vaccines and start using them once the vaccines show positive results that will be reviewed and approved by regulatory bodies and endorsed by political authorities. To gain the trust of the population on the vaccines it is important to communicate properly and rigorously, and that public health systems and governments ensure that there is an understanding of what the behaviors of different populations are regarding health issues, and it is required to build that confidence. Dr Pollard cited the example of the UK where the point of view general practitioners is very important for building the confidence of the general public. It is an important communications exercise to explain what has been done, what is known, and what are the potential benefits of any vaccination program.

Dr García-Sastre considered the acceptance of vaccines one of the main concerns and a very complicated aspect. He agreed that scientists have the responsibility to tell the public how things work, but they are not enough to convince the public. Dr García-Sastre believed that it has to be a joint effort of multiple stakeholders including politicians, educators and healthcare workers. There has to be a consensus regarding how and what to transmit to the general population highlighting the importance of the vaccine and the individual benefit. It is complicated because there is no consensus among all sectors that influence the society, starting from the education in schools, to understand well the concepts of vaccines as children. Even so, Dr García-Sastre hoped that vaccine acceptance will not be a major problem in the case of the COVID-19 vaccines.

Dr Pollard showed his optimism because the animal data suggest that there will be protection and the same type of immune response has been seen in humans. Another reason for optimism is that there are many vaccine candidates in clinical trials. However, Dr Pollard pointed out that science is not about optimism but about establishing with certainty if the vaccine works or not. There will be enough results that will answer that question and, whatever the answer is, there will be a lot to do. If the vaccine is successful, it will be necessary to deploy it but if it failed, the reasons for that should be analyzed to develop the next generation of vaccines. Dr Pollard concluded by saying that it is good to be optimistic but, in this process, science needs to be done rigorously to build public confidence.

Other infectious diseases and their vaccines despite COVID-19: essential lessons

Does flu (and flu experts) matter anymore now we have COVID-19?

Prof. Dr Ab Osterhaus (Research Center for Emerging Infections and Zoonoses, Hannover, Germany) discussed with Dr Martinón-Torres the management of the pandemic and the development of vaccines in the context of influenza pandemics and the importance of being prepared for future pandemics.

SARS-CoV-2 was compared with other threatening coronaviruses such as Middle East Respiratory Syndrome-virus- coronavirus (MERS-CoV) and SARS-CoV-1. MERS-CoV infections are still ongoing, with more than 2000 cases all over the world, mainly in the Middle East and although new cases appear every day, it is not spreading so as fulminantely as SARS-CoV-2. SARS-CoV-1, discovered in 2003, caused a similar disease as COVID-19 with a higher proportion of severe cases and higher mortality rate (8–9%), but it did not become a pandemic because it could be contained early since it did not spread before or without the appearance of symptoms.[36] On the contrary, subjects infected with influenza are contagious, before the onset of the symptoms, and SARS-CoV-2 appears to do it even to a greater extent. Up to 3 d before having typical clinical symptoms, the SARS-CoV-2 may already be spreading which makes it very difficult to contain, especially if only the people with symptoms are isolated. Compared to the other coronavirus diseases, COVID-19 has a mild presentation in around 80% of the infected population, and the mortality is lower, however, as it spreads so widely throughout the world, the number of deaths will be much higher. Hence, Dr Osterhaus pointed out that unlike SARS-CoV-1, SARS-CoV-2 associated disease is normally less severe, but overall, it is dangerous enough to cause many deaths, mostly in people also belonging to the influenza risk groups,

including older adults and people with preexisting comorbidities. Regarding the pathogenesis, Dr Osterhaus mentioned the alteration of the coagulation system seen in patients infected with SARS-CoV-2 but also with influenza, meaning that the blood is more likely to clot, causing thromboembolism that may affect vital organs such as lungs, brain, or kidney. Another similarity to SARS-COV-1 and MERS-CoV, is the low incidence of SARS-CoV-2 associated disease in children younger than 10 y, in whom the virus does replicate well, but they usually do not develop severe disease and do not spread the virus as abundantly as adults. The reasons are still being discussed, with differences in social contact structure and the receptor distribution as possible causes that may explain this difference. However, the infection and virus spreading in children older than 10 y is more like those in adults, with the difference that severe symptoms are usually reported in the older adult population.

About the origin of SARS-CoV-2, besides the efforts to determine it, a possible link of the transmission chains is still missing. However, Dr Osterhaus assured that the origin of SARS-CoV-2 is most likely natural, and he believes that deliberately creating a virus as smart as SARS-CoV-2 from scratch in the laboratory is definitely beyond human capacity, although theoretically, laboratory escape after gain of function experiments cannot fully be ruled out at this stage. It is known that the virus originally comes from bats, but a possible other animal as link to humans is still unknown. In the case of SARS-CoV-1, small carnivore like civets, racoon dogs, were identified as the intermediate species, but in SARS-CoV-2 data about a possible intermediate host are lacking. Dr Osterhaus suggested as possible links of transmission to humans, by other animal species in direct contact with humans or used for human consumption. Even direct transmission from the bats or their excreta to humans with subsequent gradual adaptation to humans cannot be excluded. In wild caught pangolins, used for human consumption, a similar coronavirus was found, however these animals were dismissed as the intermediate link when the virus was phylogenetically studied. Be it as it may, further thorough investigation into the origin of SARS-CoV-2 is warranted.

Regarding the pandemic COVID-19, Dr Osterhaus gave his opinion about the management of the pandemic within European countries, specially comparing the strategy followed by some Asian-Oceanian countries like Singapore, Australia, New Zealand, or South Korea. The strategy in these last countries was based on implementing a complete lockdown for many weeks to eradicate the virus from the country and then gradually and in a very controlled manner lift the restrictions, with a very efficient capacity for border control, testing, tracing, and quarantine protocols. In European countries, the decisions rather seem to be taken based on hospital capacity and available number of intensive care unit beds, allowing the virus to circulate in a "controlled way," instead of eradicating it. The closing and subsequent limited opening of, e.g.,, hostelry and other business depending on the infection curve would eventually have a worse impact on the economy than a proper closure until the virus spreading is under control. Dr Osterhaus also compared the COVID-19 pandemic management with that of any infectious outbreaks in domestic animals such as foot-and-mouth disease, swine fever or chicken flu, in which veterinarians rigorously prevent every possible contact between infected and naïve animals for several weeks or months until the threatening virus has disappeared.

Another example of successful control of the pandemic is the one seen in China, where draconian measures were implemented very early to halt spreading of the virus. Despite the large population, low death rates and a rapidly recovering economy were observed. Taking China as reference, Dr Osterhaus considered that there is an inverse correlation between personal freedom on the one hand and successful containment of the pandemic on the other. The higher personal freedom as claimed in, e.g.,, European countries is apparently associated with higher mortality and economic damage. Even so, the European countries did not learn lessons after the first wave, when the free traveling to other European countries during summer holidays was responsible of the second wave in many countries in the fall 2020. Dr Osterhaus believes that if after summer holidays proper screening and quarantining measures had been taken upon returning, Europe would have been better prepared to face the subsequent waves during fall. Nevertheless, the current pandemic situation in Europe is apparently not only associated with the European culture and the freedom claimed by the European citizens, but also by divided opinions among scientific experts and advisors from different disciplines such as medical doctors, veterinarians, epidemiologists, virologists, and modelers, about how to handle the crisis.

Countries like Australia, New Zealand, South Korea with no totalitarian political systems should be considered a reference since the pandemic situation was better controlled and economy recovered better than in Europe. In Dr Osterhaus' opinion, the softer the measures were, the less success was achieved in the control of the SARS-CoV-2 transmission.

The position of the influenza in the COVID-19 pandemic was also discussed in this talk. Dr Osterhaus highlighted the importance of the protection against influenza because the circulation of both viruses can pose a greater risk especially for people in the risk groups. Cases of double infections with a high mortality rate have been described.[37] In this matter, it is also important to consider that the very rigorous measures taken to contain the SARS-CoV-2 in, e.g.,, Australia and other countries of the Southern Hemisphere coinciding with the expected flu season, resulted in nearly no cases of influenza or RSV.[38] A similar situation was observed in Hong Kong in 2003, with SARS-CoV-1, in which the typical biphasic peak in the curve of influenza infections completely disappeared in that year.[39] Dr Osterhaus indicated that influenza in the Northern Hemisphere may be expected to follow the same trend and therefore should not be a big problem as long as appropriate actions are taken against SARS-CoV-2.

Additionally, several studies have described interference between circulating respiratory viruses. An example of this viral interference was described in the French population during the pandemic influenza A (H1N1) 2009 virus where rhinovirus infections affected the spread of the pandemic virus and delayed the influenza pandemic in this region.[40] Despite the evidence of this type of viral interferences, its role in the current pandemic is difficult to assess.

Considering these aspects and the less rigorous measures taken so far in the European countries, Dr Osterhaus recommended influenza vaccination in high-risk groups. Children are also a relevant target group for influenza vaccination, since they also have an important role in the transmission of influenza virus. Epidemiological studies support it as the increased incidence of influenza in adults triggered by the interruption of influenza vaccination in Japanese children,[41] or the reduction of the influenza virus infections usually seen when children are on winter holidays and the subsequently increase when they are back to school in the Nordic countries.

In general, children at schools favor the spread of viruses in the population. However, in the case of SARS-CoV-2, children under 10 y of age do not seem to transmit it in the same way as those between 10 and 18 y old, who are more like adults in this regard. This is an important concern when questioning if schools should keep open, since it may favor the spread of the virus, but the closure of schools might cause other important problems.

About the development of vaccines against SARS-CoV-2, Dr Osterhaus showed his reservations on the general optimism about the availability of the first vaccines for the world. The mRNA vaccine as developed by Pfizer has shown positive results in terms of efficacy in a large cohort of 20,000 individuals. However, the distribution system of the vaccine, which must be kept between −80°C and −60°C, represents an important challenge especially in areas where the cold-chain is hard to maintain. Furthermore the novelty of using a mRNA approach from which so far limited data have been gathered, especially in terms of immunity longevity and breadth of immunity, which are still open questions.[42]

Concerns of Dr Osterhaus, based on his own experience, were mainly related to the safety of the vaccines not only after the exposure to the vaccine but possibly also after later exposure to the virus. As an example, dengue vaccine was associated with a late detected safety issue. This vaccine initially protected against dengue virus, but later it was possibly associated with a higher risk of severe dengue symptoms than in non-vaccinated individuals after the natural infection with one of the subtypes of the virus.[43] With this example, Dr Osterhaus pondered over the use of the whole spike protein or the receptor binding domain (RBD) as the antigens of choice by most developers of the SARS-CoV-2 vaccines. This in contrast to a whole inactivated virus approach, which has been associated with adverse reactions upon exposure to the virus in animal models for SARS-CoV-1. Another example with important safety issues after re-exposition to the pathogen, was the classic measles vaccine which also showed cases of children in a worse situation after being vaccinated with whole inactivated measles. Also, the rare cases of narcolepsy after vaccination with a certain adjuvanted pandemic vaccine against Mexican influenza in young children highlights the possibility of very infrequent adverse events which are normally not detected in these relatively limited trials.[44] Although the COVID-19 vaccine candidates developed by Pfizer, Moderna and others have been tested in large cohorts, these might also not be large enough to detect less frequent adverse events that happen in a sample of 1 or 5 million people.

Beyond his concerns, Dr Osterhaus was very optimistic about the rapid development of candidate vaccines and also showed great optimism regarding the hundreds of varied initiatives that are currently running, of which around 65 are being tested in clinical trials. He believes that before summer 2021, there will be vaccines available to largely start vaccinating the general population. Additionally, the candidate vaccines are thoroughly assessed by strict regulatory agencies as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), who are watching over the safety of the vaccines.

Dr Osterhaus also gave his preferences on the vaccine candidates, choosing the use of the spike protein or more specifically the RBD as the most potent specific antigen inducing virus neutralizing antibody. Among vectored vaccines, he considered the use of adeno- or poxvirus (e.g. MVA based) approaches partly based on his own experience. It would be preferable to opt to these more classical strategies, as it was done for the Ebola outbreak, even if the development takes longer.[45] Dr Osterhaus believed that a negative experience with SARS-CoV-2 vaccines, if it would happen, could have a negative impact on other vaccination programs, including the one for children and it might ignite anti-vaccine movements. Nevertheless, he considered the use of innovative vaccines such as the mRNA vaccines interesting approaches and that all possibilities must be explored not to be biased, but without skipping any step of the authorization regulatory processes.

Comparing SARS-CoV-2 and influenza virus and their vaccines, the latest is very difficult to manage because influenza A and B viruses have even greater variability than SARS-CoV-2. Although SARS-CoV-2 will eventually escape immunity, the adaptation of the vaccine will be relatively easy because changes in the sequence of SARS-CoV-2, including the epitopes of the spike and the RBD, will be rapidly identified. However, on the other hand the development of virus vaccines has been a big challenge in the last decades with no vaccines available for most viral infections in humans. Examples of these challenges are RSV and HIV vaccine that despite the many years of research, there have not been developed yet.

Another important topic discussed during this session was the possibility of future pandemics and how to be prepared. Virology experts have been warning for decades about the increased risk of pandemics.[46] Dr Osterhaus stated that is necessary to be better prepared for possible pandemics of the coming decades. With that, the lack of sufficient medical supplies and hospital as well as intensive care facilities seen at the beginning of the COVID-19 pandemic could probably have been avoided.

Dr Osterhaus stated that there is a permanent threat from animal viruses that can cross the species barrier and infect and adapt to humans as it happened with corona- and influenza viruses. He also speculated that the next pandemic could be caused by yet another influenza A or coronavirus. A preparedness plan for pandemics should include the development of several measures including the stockpiling of medicinal products and supplies, besides the development of broadly acting vaccines, antivirals, and antibodies. The latter, Dr Osterhaus noted, can be used as a preventive measure in

individuals at high risk such as healthcare professionals but these can also be used early in the virus infection, especially when no vaccines or antivirals are yet available.

In this regard, Dr Osterhaus explained his contribution in the Zoonotic Anticipation and Preparedness Initiative (ZAPI), a European project that started in 2015 to create antibodies and vaccines against coronaviruses, especially MERS-CoV. Monoclonal and humanized antibodies and vaccines against MERS in camels were developed with positive results.[47] A large repository of monoclonal antibodies was also generated in transgenic mice, some with cross-reaction between MERS and SARS-CoV-1 or 2. One of these antibodies showed cross-reaction with SARS-CoV-2 with a high neutralization titer and is in production to be used in clinical settings.[48] In addition, Dr Osterhaus is collaborating with several research groups around Europe and several groups from India to develop an influenza vaccine that will cover a whole range of influenza viruses.

To conclude, Dr Osterhaus hoped that after the experience with the COVID-19, the warning of the high risk of pandemics by experts around the globe, will be taken seriously. To face them, it is important to invest, as an insurance policy, in the development of wide-activity or even universal vaccines and antiviral agents and antibodies against whole groups or families of viruses.[49]

Can RSV teach us something about COVID-19?

In this session Dr Octavio Ramilo (Nationwide Children's Hospital and the Ohio State University College of Medicine, Columbus, US) summarized the progress made in the field of RSV vaccination and how it can relate to and help current research on SARS-CoV-2.

RSV infections are associated with substantial disease burden around the world, and especially among young children, causing 33 new million episodes of acute lower respiratory tract infection in children <5 y of age, and approximately 120 000 deaths annually.[50,51] RSV infection is also particularly relevant in high-risk adults.[52] Innate immunity plays an essential part in shaping early responses, providing an early, non-programmed first line of defense against RSV infection. Infants display an immature immune system that often lacks immunologic memory and, for that reason, the relevance of innate immunity is critical in this population.[53]

Of all cytokines and chemokines released during RSV infection, IFNs are one of the best characterized because of their intracellular antiviral properties. Furthermore, IFNs initiate the adaptative immune response, amplifying the signals required for other cells to eliminate the virus. An adequate IFN response to initial viral infection is associated with good control of disease progression and usually prevents hospitalization. There are three types of IFNs: type-I IFNs, (IFN-α/β) have direct antiviral effects; type-II IFN (IFN-γ), produced predominantly early on by natural killer (NK), NK T-cells (NKT), and type I innate lymphoid cells (ILCs); and type-III IFN (IFN-λ) or mucosal IFNs, structurally and functionally similar to type-I IFNs, but they bind to a different receptor and control the infection locally, rather than systemically.[53]

It is not surprising that viruses have developed mechanisms to restrict IFN production such as the non-structural RSV proteins (NS1/NS2) that inhibit the production of IFN-α/β.[54]

Initial studies in healthy infants under 6 months of age revealed that IFN and inflammation genes were under-expressed compared with older infants.[53] This, together with the incomplete, weaning response of maternal antibodies, makes infants in early life especially susceptible to respiratory viral infections. Furthermore, infants do not develop immunologic memory toward the invading pathogen, making them susceptible to yearly reinfections. From 6 months of age onwards, IFN can, in itself, protect infants against invading pathogens but also facilitate antibody production by B-cells from the adaptative immune system.

After more than 6 decades of research, there are still no licensed RSV vaccines. This is in part due to the young age of the target population as it is not easy to carry out clinical studies in young children, but also due to a lack of adequate resources. Progress has been made in recent years, with a renaissance in passive and active immunization strategies moving through the drug discovery pipeline.[55] The goal is to identify an intranasally administered vaccine that provides active immunization that imitates natural infection without leading to enhanced RSV disease.[55,56] The aim is to balance attenuation with immunogenicity, to avoid IFN inhibition while achieving a better immune response than that obtained from natural infection.

SARS-CoV-2 presents 16 NS proteins, and it is therefore extremely successful at blocking IFN production. This is done at 3 different levels: SARS-CoV-2 inhibits RNA splicing, preventing the production of mature mRNA; it prevents mRNA from producing IFN proteins; and it blocks IFN transfer to the cell's surface.

Some studies have shown that adult patients with inborn defects in type-I INF or that present preexisting autoantibodies against type-I INF, are more likely to suffer life-threatening COVID-19[10].

As previously mentioned, type-III IFN (IFN-λ) is present in the respiratory mucosa and, together with interferon-induced protein-10 (IP-10) biomarker, is associated with immune protection against viral infections. In pediatric patients, the presence of either of them in the respiratory mucosa correlates with milder forms of RSV infection. However, their correlation with SARS-CoV-2 severity is yet to be demonstrated, as there is data that shows that infants with SARS-CoV-2 present extremely high viral loads. Furthermore, IFN-λ may not always have a protective function against viral infections and its long-term effects on lung physiology continue to be overlooked. Mice models indicate that chronic exposure to IFN-λ causes changes in the lung epithelial tissue that makes mice more vulnerable to lethal bacterial superinfections.[57] The potential role of early IFN therapy to improve or potentiate immune response against SARS-CoV-2 and prevent the inflammatory cytokine cascade is being evaluated in clinical studies.

Research into preventive strategies for RSV infection in infants demonstrated that IFN response against RSV is not mature until 6 months of age and it correlates with the ability of infants to produce a robust antibody response. This has led

to redefine the vaccination strategy to begin at 6 months of age and not earlier. In younger children passive immunization with monoclonal antibodies or maternal antibodies is the preferred strategy.[58,59]

The fusion (F) protein is a structural glycoprotein in the surface membrane of RSV virus. It initiates viral penetration by integrating cellular and viral membranes, later causing infected cells to fuse. RSV F protein has 2 conformations, pre-fusion (pre-F) and post-fusion (post-F). Pre-F is the functional form, it is metastable and unpredictably folds into its post-F conformation, whereas post-F is exceedingly stable and cannot revert to its active pre-F form.[58] Potent neutralization sensitive epitopes are mostly present in pre-F form and, therefore, pre-F is the best target for research and development of monoclonal antibodies and anti-RSV vaccines.

The RSV vaccine is the first vaccine developed based on the crystallographic structure of the target protein. This prior work on RSV vaccines informed the strategies for the development of vaccines against the coronavirus that cause the Middle East respiratory syndrome (MERS-CoV) and, later, SARS-CoV-2.[60]

Comprehensive knowledge of IFN expression responses and how it relates with antibody responses can help understand the required mechanisms of action of vaccines and, in the future, it can facilitate the development of tailored vaccination strategies.

On day 1 after intramuscular flu vaccine administration or on day 7 if administered intranasally, a peak of IFN-stimulated genes (ISGs) expression can be observed. When the vaccine is administered intranasally this IFN peak is higher in younger children that had not been as exposed to the virus as older children.

A yet unpublished study on pediatric vaccination showed that in a small cohort of 2-month-old children that received the normal vaccines in the regular immunization schedule (Pneumococcal, Haemophilus, Diphtheria, etc.) a transient peak in IFN expression, followed by increased number of plasmablasts and then antibodies were observed. Therefore, at 2 months of age there are already signs of immune system maturation with IFNs modulating the response to conjugated vaccines. This means that during gestation and within the first 2 months of life different stimuli regulate the children's immune system maturation and development.

All this evidence reiterates the relevance of understanding IFN response to RSV infection to comprehend the role of IFNs regulating responses to SARS-CoV-2.

Safety is a fundamental goal for vaccines that are administered to otherwise healthy people, and there is a risk that SARS-CoV-2 infection could be made more severe by prior vaccine immunization.[60] This vaccine-associated enhanced respiratory disease (VAERD) has occurred before, when children were immunized with formalin-inactivated alum-precipitated whole RSV vaccine in the 1960s. Combined efforts of many research groups over the last 30 y have resulted in a better understanding of this adverse reaction. The studies completed by several groups, mostly using in animal models, have provided immunological parameters that help evaluate the probable safety or possible risks of a new vaccine.[61] Immunizing with limiting doses of RSV antigen, especially if they are conformationally inaccurate such as incorrect F-protein presentation, can cause enhanced respiratory disease (ERD) by inducing a high ratio of binding antibody to neutralizing antibody that results in immune complex deposition and complement activation. Another phenomenon that has been observed in mouse models is an allergic inflammation resulting from immunization with whole-inactivated virus vaccines followed by RSV infection. Reactions that increase the production of cytokines result in increased mucus production, eosinophil recruitment, airway hyperresponsiveness, and attenuated cytolytic T cell activity, collectively known as T_H2 immune responses. Information on ways to reduce the risk of vaccine-enhanced syndromes obtained from this previous work on RSV should be considered during SARS-CoV-2 vaccine development. It will be important to use conformationally correct antigens to avoid induction of non-neutralizing antibodies and T_H2 immune responses. Furthermore, it will also be important to measure the induction of neutralizing antibodies in early clinical trials to prove the potential for vaccine efficacy.[60]

Another syndrome previously associated with vaccine-enhanced disease is antibody-dependent enhancement (ADE). Although SARS-CoV-2 cellular tropism has not been completely defined, it is a respiratory virus, and consistent with other betacoronavirus that cause Middle East respiratory syndrome (MERS-CoV) and SARS (SARS-CoV-1), and it is yet unknown whether cross-reacting antibodies could induce ADE. However, infection of respiratory epithelium results in a very different pathogenesis and the T cell activity is clearly T_H1.

On the other hand, patients who have experienced betacoronavirus infections generate antibodies and virus-reactive memory B cells (MBCs) against the S2 subunit of the betacoronavirus S protein, which is the same for all betacoronavirus including SARS-CoV-2.[62] It is also possible that patients that have been infected with SARS-CoV-2 develop original antigenic sin, or antigenic imprinting, similarly to what happens after influenza virus infection, where the body's immune system preferentially utilizes immunological memory based on a previous infection when a second slightly different version of that virus is encountered.

Despite the pathophysiological similarities between RSV and SARS-CoV-2, it is worth highlighting several striking differences in the reactions to both infections observed in the pediatric population: viral load is a key factor in the severity of RSV symptoms in children while it doesn't seem to be a crucial factor in COVID-19 disease; the younger the child, the more severe RSV presentation is, whereas infants have proven to develop mild to none COVID-19 symptoms; finally, teenagers are more likely to suffer severe SARS-CoV-2 infection while they hardly ever suffer from RSV.

Dr Ramilo explained how patient categorization is essential for designing treatment and vaccination strategies. There must be an in-depth analysis of each patient´s features and symptoms to enable this categorization into simplified groups that will allow for a tailored management. In order to achieve this, readily available technology must be used to further research pediatric diseases.

This accurate categorization is vital for the appropriate management of respiratory diseases. The most appropriate management of COVID-19 patients of different ages, with different comorbidities, that present with different levels of

disease severity, etc. is still unknown. So far, we know that remdesivir is appropriate in moderate cases but not for those with extremely severe disease; we also know that steroids are useful at the beginning of the disease; and that monoclonal antibodies could present both therapeutic and preventive treatment options.

Dr Ramilo stated that he is very optimistic in terms of the future of RSV immunization. Better understanding of RSV protein's structure and conformation, identification of potential viral targets, and the immune system's responses to RSV infection have been essential to the development of new strategies for RSV immune prophylaxis. Further research into RSV vaccines is required because even though their safety has been confirmed, an increase in efficacy is still required. On the other hand, maternal immunization has become a promising alternative to protect infants < 6 months, the most vulnerable group.[59] There is also heightened interest in monoclonal antibodies with prolonged half-life and greater potency that with a single dose may reduce RSV-associated lower respiratory tract infections and hospitalization by 70% and 80%, respectively. This could represent a more effective option than current strategies for prevention of RSV infections.[63]

Regarding SARS-CoV-2 immunization, Dr Ramilo was also optimistic as both mRNA vaccines and adenovirus vector vaccines were available for adults from the end of 2020. However, he reiterated the importance of including infants, children, and adolescents in the development of preventive and therapeutic strategies to reduce the impact of COVID-19. This will not only solve challenges related to COVID-19, but can also help design efficient strategies to address pediatric needs posed by future pandemics.[64]

In summary, RSV and SARS-CoV-2 present similarities but also some differences in the immune response they elicit. The insight accrued throughout the last 3 decades on RSV infection can help understand SARS-CoV-2 and joint research on both viruses can facilitate the development of vaccines against them.

HPV vaccination and COVID-19 vaccination: lessons to be considered

In this session, Prof. Xavi Bosch (Institut Català d'Oncologia) discussed the HPV and its vaccines, which marked a before and after in cancer prevention and the lessons learned about the rapid implementation of the vaccine and the proper communication to the health-care professionals and general population.

Firstly, the expansion of the HPV vaccine indications and recommendations were described. In 2006, the initial indication was for female adolescents prior to sexual initiation, focusing on a single cancer, single gender, and single cohort, partially due to the vaccine price of that time. Since then, till 2020, these indications have increased. The indication of initial multiple cohorts from 9 to 15 y old and extensions until 16, 18 and 26 ye old have been proposed and applied in several countries, especially since the number of necessary doses and prices went down. Later, the vaccination was extended to women of intermediate ages, especially those who rely on screening as the main prevention strategy. In the US, the vaccination authorization for adult women is up to 45 y old, while in Europe and Canada, there is not superior limit of age, ranging from 9 y old upwards. Next, it was learned that these vaccines prevented tumors in men, and there are already 35 countries that vaccinate men in the same age groups as the female vaccination program. HPV vaccination have been also studied with positive results in vulnerable groups, such as those who are HIV positive, or those who are immunosuppressed because of transplant or other type of immunosuppression or those with lesions associated with papilloma. As it mentioned before, this expansion of indications has happened in the context of reduction of vaccine costs, doses needed and rise of options with the arrival of new vaccines. Recently, it was confirmed through several meta-analyses that vaccinating women who had been treated for cervical intraepithelial neoplasia grade 2+ (CIN 2+) or for a papilloma-associated lesion reduced the risk of recurrence after conization. The pediatric indication, still under evaluation, would be favored the great coverage of pediatric vaccines and is supported by the fact that these vaccines confer long-term protection based on all the indications available to date.

Hence, HPV vaccines have a favorable safety profile and offer protection to all population groups investigated.[65,66] The cost-effectiveness tends to be loosened with the increase of the age, because of the reduction of the risk of exposure to infection, despite the constant risk of progression of infections. However, over time, the introduction of the vaccine in women of intermediate ages may be cost-effective due to the changes of cost assumptions. Finally, evidence of the HPV vaccines preventing against invasive cervical cancer (ICC) is likely to predict prevention of all HPV-related cancers.

The speakers emphasized the significant changes in the paradigm with respect to the messages that were previously highly concentrated on the vaccination of prepubertal girls and that now have practically been extended to universal vaccination, highlighting the role of men. In this line, Dr Bosch noted that in countries with good cervical cancer screening programs as the US and some Northern European countries, the incidence of oropharyngeal tumors in the male population exceeds the incidence of ICC for already 10 ys. These countries are facing the beginning of an epidemic of oropharyngeal tumors in men and, hence, they are considering the importance of including children in the HPV vaccination programs.

Despite HPV vaccines were initially authorized based on surrogated efficacy endpoints, results from phase I and III clinical trials have met very consistently showing that vaccines prevent not only HPV infections and persistent infections but also all known preneoplastic lesions in the cervix, vulva, vagina, and anus and ultimately the development of cancer. Although no preneoplastic lesions have been identified in oropharyngeal tumors, the strong associations with genital lesions, allow anticipating that the same results will be reproduced in the lesions of the oral cavity in the ongoing clinical trials.

Additionally, genital warts have been very helpful in the HPV research as they are a reason for a medical visit and consequently, they are well registered. In addition, the natural history of genital warts has a very short interval between infection and the appearance of the lesion, and the natural protection lasts short. Therefore, genital warts were the first indicators of the high efficacy of the HPV vaccines in the prevention of these lesions and hence of the rest of the lesions associated with HPV.

As one of the most remarkable points of this talk, Dr Bosh presented the results of an updated systematic analysis and meta-analysis related to the herd protection induced by the HPV vaccine in multicohort vaccination programs.[67] This analysis included a total of 65 publications from 14 countries with consistent data between 2014 and 2018, that represent the follow-up of 60 million individuals during 8 y after vaccination. The impact of the vaccination was evaluated in populations before and after participating in a vaccination program with coverages from 60% to 80% of the population.

Dr Bosch commented the changes in anogenital wart diagnosis during 8 y after the introduction of girls-only HPV vaccination in countries using the quadrivalent vaccine. Populations with high vaccination intensity (countries with multi-cohort vaccination and/or vaccination coverage ≥50%) were compared to those with low vaccination intensity (countries with single-cohort vaccination and/or vaccination coverage <50%). In the group of girls of 15 to 19 y that belonged to populations with high vaccination intensity, the incidence of genital warts practically disappeared in the 5-y interval, whereas in the same group of girls from populations with low vaccination intensity, the reduction of genital warts was less important and slower. This change was repeated in all age groups except for women older than 29 y. Identical results were observed in boys and men, who were not vaccinated. In the populations with high vaccination intensity, there was a herd protection effect in boys and men until 29 y old. The effect was not observed in the populations with low vaccination intensity. These results showed that the herd protection induced by vaccination of only half of the population, women, was directly linked to vaccination intensity. In light of these results, Dr Bosch recommended to those countries that are considering the introduction of an HPV vaccination program to consider including as many cohorts as possible.

Another important milestone in the evaluation of the HPV vaccines is related to its efficacy and effectiveness in preventing ICC. A recent Swedish study of a population of near 1.7 million girls and women between the ages of 10 and 30, recruited from the beginning of the HPV vaccination program in Sweden (2006) until 2017, assessed the association between HPV vaccination and the risk of ICC.[68] During the follow-up, the cumulative incidence of ICC was 47 cases per 100,000 persons among vaccinated women (19 cases of diagnosed ICC) and 94 cases per 100,000 persons among non-vaccinated women (538 cases). The incidence rate ratio for the total cohort between vaccinated and unvaccinated women was 0.37, which estimated an overall protection for this population of 63% against ICC. It is noteworthy that despite Sweden having a highly developed screening program, the incidence of ICC is still registered, and that the HPV vaccination reduced this incidence. The incidence rate ratio for girls who received the vaccination before the age of 17 was 0.12 which means an estimated protection of 88%. It is also important to consider that the onset of active sexual life could happen between 14 and 15 y of age, therefore, in the group of girls who received the vaccination before the age of 17, there may be a proportion of girls already infected, on whom the protective HPV type specific effect is very limited. For vaccinated women between the ages of 17 and 30, there is still an estimated 53% protection. Dr Bosch highlighted that these results will be improved as more cohorts of girls will be vaccinated and group protection effects will be fully operational. In addition, this analysis was limited to girls who received the vaccines against types 16 and 18, thus the use the 9-type vaccine will have an even more important impact on infections and preneoplastic lesions. Therefore, this study confirms that the generalized broad spectrum HPV vaccine has the potential to prevent ICC with an efficacy above 90%.

However, the cancer community has not yet fully processed that ICC is the sequelae of infectious and particularly sexually transmitted disease and consequently it can be preventable by vaccination. Therefore, the prevention of ICC could be improved, and this would be the case of young women (around 25–30 y old) who decided not to get vaccinated at younger ages (i.e., before 15 y of age) and who, in light of the positive results choose to be vaccinated.

The third point of discussion that has implications in prevention regards the importance of the control of transmission of the infectious agent, something that national healthcare systems and general populations around the world have recently learned from the COVID-19. In the case of HPV infection and the prevention of ICC, the diagnosis and management algorithms until nowadays have been exclusively focused on the identification and classification of morphological lesions into four stages (CIN I–III and ICC) and their options for surgical treatment. However, since these lesions are initiated following HPV infections and that the mode of transmission is by sexual contacts, there are multiple actions that could be taken to control the HPV transmission and ultimately reduce the incidence of ICC such as sexual education and potentially by generalized vaccination including the HPV carriers.

In order to improve the strategy in cervical cancer prevention, Dr Bosch pointed out two essential characteristics of HPV and its vaccine to be considered. The first one is that humans are the only reservoir for this virus since it is not transmitted through animals or vectors. That fact simplifies the entire intervention only focusing on humans and no on other animal species. The second key point is that there are already screening programs for women that are routinely identifying female carriers of the HPV by using well-developed and validated HPV testing. Conventionally, the objective of the screening has been the identification of positive HPV subjects to individually prevent the progression to CIN-3 by increasing the frequency of visits, diagnostic tests, and ultimately surgeries. This process does not fully contemplate the infectious origin of this cervical cancer. However, besides the control and treatment, if needed, of positive HPV women, several actions can be done to interrupt the transmission. According to Dr Bosch, the strategies for the control of other sexually transmitted diseases should be taken as reference including contact tracking and sexual education. Although modifying the sexual behavior trends of certain populations is difficult, in the case of HPV infection, there is the option of targeting the education and sexual hygiene in women identified as positive in screening programs who may not be aware that they are a source of contagion. Another strategy in the control of HPV transmission could be the vaccination of social reservoirs of HPV[69,70] as

for example sex workers, which are a source of infection dissemination in the community. Another target population to receive the vaccine as an intervention for the control of HPV transmission may be the positive HPV women identified in screening programs. This scenario is currently under investigation to evaluate whether vaccination of these women could reduce transmission to their sexual partners and thus boost the herd protection. In this same line, there is a proposal, HPV-Faster, to vaccinate all women at screening ages and which will increase the vaccinated fraction and rescue those who were not vaccinated at younger ages.[71] The HPV vaccination of negative HPV women would not only help in the control of the transmission but also would dramatically reduce the need to continue screening, which could be simplified to once or twice for the rest of their lives. In this scenario, the cost of vaccination programs would be offset by the savings in screening ones. Finally, the arrival of an antiviral treatment capable of interrupting the progression of the disease in infected women would act on two fronts; it would protect the positive HPV women to ensure the prevention of progression to CIN3 and it would reduce the viral load in these women by limiting transmission to the population.

The last topic of the session was regarding the controversy around the safety of the vaccines and in particular around the HPV vaccine. About this topic, Dr Bosch commented on the phenomenon of temporal and random associations when a vaccination program is introduced in an entire cohort. This argument is typically presented when a healthy individual receives a vaccine and afterward suffers an undesirable health effect. A cause–effect relationship could automatically be generated and identifying the vaccine as the cause. This line of common reasoning ignores many other factors that are in operation at the same time interval including the largely ignored genetic load responsible for the temporally coincident side effect. In this situation, there is no responsiveness capacity to explain that the seemingly causal relationship between a health problem and the vaccination could be nothing more than an coincidental time-association. This phenomenon clearly explains the consideration that all pathologies other than the one targeted in the vaccination program will appear with the same frequency and intensity with which they were appearing before vaccination, and therefore this type of associations will inevitably continue to occur. Another worrying situation is the vaccine hesitancy among health-care professionals, especially pediatricians who are a reliable and impactful source of information on vaccination in children. Dr Bosch discussed the results of a survey carried out in 2016 and 2017 among pediatricians in Spain regarding vaccination.[72] When pediatricians were asked to choose which vaccines from the recommended vaccination program they would administer to their own children, acceptance of vaccination was very high for most diseases, except for HPV and chickenpox. A total of 15% of pediatricians expressed doubts, refused to vaccinate, or preferred to postpone the HPV vaccination. These types of results require the maximum attention of the health community since the greatest determinant of whether a child will get vaccinated is the recommendation of their pediatrician. This responsibility cannot be ignored because it is strictly selective for two vaccines, of which one of them, HPV, is guaranteed to be a cancer vaccine.

Another source of (dis)information with high impact on vaccination acceptance is social media as it is shown in an analysis of traffic information on internet with messages in favor, against or skeptics regarding vaccination. From a global pool of around three billion Facebook entries in a given period, 100 million active messages were identified on the topic of vaccination.[73] In this case, anti-vaccine messages corresponded to 4 million individuals on 317 clusters whereas pro-vaccination messages to 7 million but from fewer clusters (124). The largest group was the "undecided individuals" that represented 74 million individuals on 885 clusters with the highest growth of new out-links. When the time trends were analyzed, the anti-vaccine groups were much more active and recommended many more other readings and additional pages. This analysis predicted that anti-vaccine views will dominate the scene in a decade.

Dr Bosch pointed out that in 2019, before the COVID-19 pandemic, WHO identified vaccine hesitancy among the 10 priority threats to global health for the coming years.[74] Climate change and environmental pollution, non-communicable diseases, global influenza pandemic, that will inevitably come, were the first three priorities and at number 8 there was vaccine hesitancy, ahead of dengue and HIV. This recognition shows the importance of this problem, that at the time of the aTIPiCO meeting was also starting to be reflected with the possible new arrival of vaccines against COVID-19. Dr Bosch commented that this threat needed to be addressed by analyzing the drivers that lead healthy and rational individuals to reject this preventive option and to try to change these attitudes.

In this same line, the speakers commented on the responsibility that each social agent has in communicating about vaccines. The responsibility of health-care professionals and experts with media exposure cannot be compared to the one of the general population. In Dr Bosch's opinion, health education training and the reiteration of messages by using the best available communication channels must be put operational. For that, it is necessary to invest in social and professional communication resources professionally and financially. Regarding the results of the COVID-19 surveys performed in autumn 2020 with a quarter of the population that would have not been vaccinated regardless of the vaccine,[75] Dr Bosch thought that the problem lied in a general mistrust of the authorities without discriminating between healthcare, political or any other authorities. The insecurity and hesitancy in the political decisions for the management of the COVID-19 pandemic, for which there was no preparation, has been extended to the topic of vaccines. In addition, Dr Bosch commented that the survey carried out in France in the midst of the pandemic identified 28% of individuals who expressed not wanting to be vaccinated against COVID-19. When the political profile of those individuals was analyzed by asking who they voted for in the last presidential elections, the results indicated that they were in favor to extreme political wings or were abstentionists. Somehow this reflects a generic distrust of everything that the system and authority represent. Dr Bosch thought that the political authorities should be aware of this phenomenon, and they should use the necessary resources to communicate with the population in order to improve understanding of vaccine information and the benefits of vaccination.

Dr Bosch concluded his talk with some optimistic results related to the HPV vaccine in Spain. Before the COVID-19 pandemic, the coverage of this vaccines was around 70–75%. In his opinion, improving the coverage is possible once the pandemic will be over and surely the skeptics about vaccination will end up getting vaccinated.

Measles and pertussis, the lessons in front of your eyes

Dr James D. Cherry (The David Geffen School of Medicine at UCLA, Los Angeles, US) discussed with Dr Martinón-Torres about measles and pertussis and their vaccines and the lessons that can be learned from these two contagious diseases to tackle the COVID-19 pandemic.

Dr Cherry started his talk explaining his concerns about the rush in the development of vaccines and possible abnormal responses. However, the methods used for the mRNA vaccines negate this concern. At the MRC, Common Cold Research Unit, in Salisbury, England Dr Cherry and an associate developed a chicken trachea organ culture system to study viruses and mycoplasma. He first worked with infectious bronchitis virus (IBV) of chickens, a chicken coronavirus. Previous to his time in Salisbury, while working in Madison, Wisconsin in 1963 he first became aware of IBV. In Madison, there was a company that made animal vaccines including vaccines for IBV. In one of the early whole virus killed vaccines, the chickens became sensitized, so that on subsequent exposure to IBV they developed more severe disease than if they had not been vaccinated.

Subsequently, while working in Saint Louis, MO he noted a similar event related to a killed measles vaccine. In this case, the formalin inactivation modified the fusion protein so that an aberrant cellular immune response occurred. These vaccinated children at a later date when they had lost their serum antibody and were exposed to measles, atypical measles occurred. This was a severe illness. This is a lesson to take into account especially in vaccines based on inactivated viruses. Since the two mRNA COVID-19 vaccines do not contain whole virus, this is not a present concern.

When Dr Cherry was asked about the life-long immunity following measles, he talked about the first evidence just at the beginning of Pasteur's germ theory studies. When Peter Panum, a Danish medical student traveled to Faroe Islands in 1864 he noted that those who had had measles in 1781, 65 y before, they were still protected. Dr Cherry also commented about the life-long immunity induced by live measles vaccines. The original vaccine Edmonston B of 1963 was strong and generated frequent reactions that led to the development of the current further attenuated vaccines. In the original study of the Edmonston B vaccine, the curve of antibody levels over time was similar to the one of natural infection, so probably this vaccine would have induced life-long immunity. However, the same curve following further attenuated vaccines was different. The level of antibodies waned considerably over time and after 10 y, the level of antibodies was low. In this line, several studies showed that around 5% of people, despite being vaccinated, will get secondary measles if they are exposed to the measles virus.

Regarding the measles vaccine failure, Dr Cherry explained the difference between primary and secondary failure. In primary failure, there is not virus recognition whereas in the secondary failure, there is virus recognition, but the immune response is only based on Ig G, without IgM and the illness tends to be less severe. The secondary vaccine failure was firstly described by Dr Cherry and associates in 1972.[76] Later, a study of Centers for Disease Control and Prevention (CDC) shown that in vaccinated people the level of antibodies waned, with the cutoff of failure in 120 international units (IU)/mL. Below this concentration, people could get secondary measles, in a less severe form. In this context, measles can be categorized into three types of cases. First, people who have not been vaccinated and they have the most severe form of disease and may need hospitalization. Second, people who have been vaccinated with one dose will be either a primary or secondary failure with less likely need to be hospitalized. The third category is of people receiving two doses of measles vaccine with secondary failure and unlikely to be hospitalized.

In the cases of secondary vaccine failure, the disease is less severe, and the contagious rate is lower than measles infection. In a study of 20 cases of secondary failure, only 3 of those transmitted to other people who had very close contact. In Dr Cherry's opinion, secondary vaccine failure should not be an important problem, however, as time goes up as the population is protected by herd immunity, if measles is introduced, eventually the number of secondary measles will increase.

Dr Cherry reminded us about outbreaks in recent years. In some European countries, like Romania, there are hot spots. In France among other European countries, there was a general upswing of cases with a significant number of deaths. In the US, there is also a high number because of several hot spots. A few years ago, there was also an outbreak in Disneyland with a large number of cases, that could have been a lot more except for the incredibly good work of the public health workers. Quarantine and the closure of schools helped in the control of the measles outbreak. Similar measures work for measles and COVID-19, with the difference that measles is far more contagious. Dr Cherry highlighted that new cases of measles appear when the immunization coverage goes below 95% and therefore the herd immunity is lost.

Related to the mortality associated to measles, Dr Cherry pointed out that malnutrition and especially vitamin A deficiency are important risk factors. In countries with malnutrition and vitamin A deficiency as the Democratic Republic of the Congo (DRC), measles mortality rates are higher. In Europe and the US, measles mortality rates are normally associated with primary measles pneumonia. In Europe, the rate is around 1 death per 1,000 measles cases whereas, in the US the rate is 1: 500.

The last topic about measles was about the phenomenon called "post measles immune amnesia" observed after measles infection, discussed previously during Dr Mina's talk. His findings of the decrease in the number of deaths associated with other diseases than measles in vaccinated populations led to the concept that measles produces immune amnesia.[21] Thereby, people who have measles infection lose the immunity memory and are more susceptible to bacterial and virus

diseases. This phenomenon was also described in some studies in the DRC.[77] In children who had had measles later at around age 5 in a two-week period they were more likely to have the signs of virus diseases as cough, fever or diarrhea than in children who had been vaccinated against measles. The immune amnesia of measles also affected the immune memory induced by diphtheria-tetanus-pertussis (DTP) vaccine measured by the tetanus antibody level. In children vaccinated with the three doses of DTP (at 6, 10 and 14 weeks of age) who had measles, the tetanus antibody levels were lower at 4 y compared to those who received the measles vaccine. After 4 y, some of the children that had measles were susceptible to tetanus, when the antibody level after tetanus immunization usually lasts 20 y. In addition, some studies showed that people who have had measles were more likely to be admitted to the hospital for a different infectious disease than those who did not have measles.

The second part of this session was focused on pertussis and its vaccines. In the last years, there have been an increase in the number of cases of pertussis all around the world. In 2012, in the US, 48,277 cases of pertussis were reported being the highest number and rate since 1955.[78] According to Dr Cherry, the main reason for this is the increase of the knowledge about the disease and vaccines and therefore of awareness of the disease.[79] The second reason is the improvement in diagnosis by using PCR tests and serology to identify cases rather than conventional culture.

Dr Cherry pointed out some aspects of importance to consider about pertussis. First, *Bordetella pertussis* has been circulating in the same way as it was in the pre-vaccine era, although the incidence of reported pertussis is 20 times less than it was before the vaccine. Unlike natural infection, patients with vaccine failure do not die.

In terms of pertussis vaccines, Dr Cherry explained that whole-cell vaccines, which contained lipid A (endotoxin), were very reactogenic causing fever and swelling at the injection site. It was also observed that the vaccine provoked first seizures in children who later would have seizure disorders. However, they were not responsible for any neurological disease.[80]Several studies demonstrated that there is not an relationship between pertussis vaccine sudden infant death syndrome (SIDS).[81,82] In fact, children who were vaccinated had less SIDS compared to unvaccinated children for unclear reasons.

Acellular and whole-cell vaccines induce a different type of cellular immune response according to baboon models. The whole-cell vaccines induce a Th1 and Th17 cellular immune response whereas, acellular vaccines induce a Th2 response, and it gives a lower protection.

Regarding the components in acellular vaccines, they can contain a maximum of five antigens: fimbria 2 and 3, pertactin, PT and filamentous hemagglutinin (FHA) whereas whole vaccines contain more than 3,000 antigens. In two studies of acellular vaccines, Dr Cherry found out that the antigen balance, without an excess of PT is really important for the efficacy of the vaccine. FHA is a less important component despite its abundance in the vaccines whereas, fimbria and pertactin are the most important antigens responsible of 70% of vaccine protection.

The one-component vaccine containing PT used in Denmark for a long time confers protection, but not as much as the five-component vaccine. In general, vaccine failure and vaccine diseases associated with the one-component vaccine are less severe. The same way, with the vaccine with two-component (PT, FHA), vaccine failure was observed since only antibodies to the two components were generated. In Dr Cherry's opinion, there are still several important proteins (autotransporters) that the current components of the acellular vaccines do not have. Thus, vaccinated people are still susceptible to new infections although the disease is usually mild.

Dr Cherry mentioned his research in collaboration with Rachel Fernandez about a whole-cell vaccine with modified lipid A. However, there has not been enough economic interest for further development. Although currently, there are not new vaccines, Dr Cherry stated that the current vaccines are fine, and a good level of protection can be achieved if they are used properly. In this line, Dr Cherry commented that the protection of the booster dose Tdap (diphtheria-tetanus- acellular pertussis) vaccine in adolescents only lasts for 3 y. Therefore, some researchers suggested removing the adolescent dose of the DTaP vaccine from the vaccination program and only use it when there is an outbreak. This approach was studied in a school by Dr Cherry with positive results. Even so, most countries will not consider this approach. Adult people who were initially primed by natural pertussis or a whole-cell vaccine, a booster dose of an acellular vaccine increases the protection for 10 y, whereas if people were primed by an acellular vaccine, the booster dose only confers protection for 3 y. Considering this fact, to protect properly the population, young adults should be vaccinated every 3 y and older adults every 10 y. However, Dr Cherry did not believe that this vaccination strategy will be ever implemented.

Dr Cherry was asked about the reason for patients infected with pertussis to cough. However, it is still unknown. *B. pertussis* contains approximately 3,000 proteins that play a role in the infectious process by inhibiting the host response or decrease phagocytosis. On the contrary, there are two proteins that play a prominent role in the disease. One of them is PT, responsible for causing leukocytosis with lymphocytosis that leads to pulmonary hypertension. This is an irreversible condition that causes infants death. However, there are some studies that show that blood transfusion in time, before any organ failure or systemic shock, can prevent a systemic crisis. The other protein is responsible for the cough, called cough-toxin, but it has not been yet identified. Although Dr Cherry had some theories about this unknown toxin, he thought it would be necessary to investigate original samples from patients with whooping cough to discover this toxin.

At the end of the session, Dr Cherry gave his opinion about the COVID-19 pandemic situation in light of the knowledge and information available in November 2020. The social distancing measures are working, and the population must keep following them; wearing masks is also important. Dr Cherry concluded that vaccines are the solution but appropriate steps for their development should be followed as it has been done with other vaccines over the years.

To summarize Dr Cherry's discussion, measles, and pertussis despite being more contagious pathogens than SARS-CoV -2, have been contained and vaccines have been used for over 50 y. In the case of measles vaccines, they can be even better than expected, because they present post measles immune amnesia. It is also important to keep the vaccination of the population with the existing effective and safe vaccines against disease as measles and pertussis. Finally, continued research is the solution to answer the unknown questions of diseases like pertussis or COVID-19.

Tuberculosis vaccine and beyond. From MTBVAC to COVID-19 protection

Dr Carlos Martín (Universidad de Zaragoza, Spain) provided an overview of the current status of TB vaccines, with a special focus on the MTBVAC vaccine developed by his research group. Additionally, Dr Martín discussed the possibility of other alternative administration routes of the vaccines and the possible use of TB vaccines for the protection against severe COVID-19.

Firstly, Dr Martín commented on the effect of the current pandemic in the TB, which seems to have been relegated. The last annual report of WHO, previous to the COVID-19, showed that the same number of cases were maintained, with a 1.2 million deaths per year, reaching 1.4 million deaths if HIV-positive patients were added in 2019.[83] These figures are repeated annually despite having an effective treatment. Compared to the millions of deaths of COVID-19 in the last year, the annual numbers of TB deaths are lower, but they occur year by year. Although the TB bacillus strategy is slower, it also affects people with weaker immune systems.

For TB patients, the pandemic has been a disaster because, with the lock-down in Africa and other developing countries, where many people live together in the same household, the TB bacillus transmission increases, and treatment does not reach all people. The WHO has issued an alert that the number of cases has increased what will be seen in next year's report. According to Dr Martín, it is a very worrying situation, not only from the increase of TB cases, with close contact, but also in terms of the clinical trials conducted in South Africa that have been paralyzed for months, due to the COVID-19 pandemic.

In terms of the current state of vaccine development in the field of TB, considering that nothing new has appeared since the 100 y old BCG vaccine, Dr Martín pointed out that last year was very positive in terms of the efficacy of new vaccines. The M72/AS01$_E$ candidate vaccine (GlaxoSmithKline) contains a recombinant fusion protein derived from two *Mycobacterium tuberculosis* antigens (Mtb32A and Mtb39A), combined with the AS01E adjuvant system, currently used in herpes zoster vaccines in the US.[84] Among adults previously infected with *M. tuberculosis*, vaccination with M72/AS01$_E$ provided protection against progression to pulmonary TB disease compared to non-vaccinated participants.[84] These encouraging results have brought some optimism in the field of TB vaccine development after the absence of efficacy of the vaccine Vaccinia Ankara virus expressing antigen 85A (MVA85A), clinically tested in 2013.[85] The promising results of BCG revaccination in adolescents showed possible prevention of *M. tuberculosis* infection.[86] Other TB vaccine candidates in different phases of clinical trials include subunits vaccines that used human or simian adenoviruses as vectors with diversities similar to those of SARS-CoV -2, subunits of mycobacteria with different adjuvants, inactivated whole-cell mycobacteria vaccines and recombinant BCG vaccines.[87] Dr Martín is working on the development of MTBVAC vaccine, which is a live attenuated vaccine, based on a human clinical strain.[88,89]

Regarding the advantages that MTBVAC could have over BCG and other vaccine candidates, Dr Martín mentioned that vaccines based on a single protein with an adjuvant or on a single gene, that codes for that protein in a virus, can be fast developed, as we have seen with COVID-19, however, until now, in the absence of protection correlation, the protection can turn out to be not very significant. When the disease is unknown, the use of a whole attenuated pathogen with all the antigens may be beneficial, despite being the slowest approach in the vaccine development due to the need of bacillus isolation, attenuation process and comparison with the gold standard which is BCG in TB vaccines. The development of MTBVAC started 20 y ago and have encountered several obstacles. The MTBVAC attenuation is based on two genetic deletions, encoding two major virulence factors that result in a more attenuated vaccine than BCG. It took between 7 and 8 y of research in animal models to prove whether these live-attenuated strains produced an immunity in animal models that protected against TB. Compared to BCG vaccine, isolated from TB pathogen in cattle, MTBVAC produced two antigens, ESAT-6 and CFP-10, that group most of the protection epitopes in animal models such as macaque and guinea pig.[90] Another major challenge in the development of MTBVAC was finding an industrial partner to escalate the production of the vaccine and be able to start the clinical program. Dr Martín highlighted the importance of the role of biopharmaceutical companies from the beginning of the vaccine development. Since 208, Biofabri, a Spanish biopharmaceutical company joined forces with the group of Dr Martín in the development and production of MTBVAC. So far, the phase 1 clinical trials in adults[91] and newborns[92] of MTBVAC have shown that the vaccine is safe, with immunity results trend positive based on the number of participants, tested in Western countries. From 2015, MTBVAC has shown to be totally safe and with greater immunity than BCG in 3-d newborns in South Africa. MTBVAC is currently in phase 2 clinical trials using BCG as reference comparator to elucidate the efficacy dose, in volunteer adults infected and not infected with TB (NCT02933281) and neonates (NCT03536117) in South Africa, however, the pandemic has delayed the vaccination with the highest dose (10^6) and therefore the completion of the studies. Soon, it will start the clinical efficacy trials. The development of MTBVAC will take more than 20 y due to the complexity of working with live-attenuated strains. On the contrary, an acceleration of the usual process for the development of new vaccines has been seen for SARS-CoV-2.

Another point of discussion was the use of alternative administration routes in the vaccination against respiratory infection disease as TB and COVID-19 to seek a target to avoid infection or to avoid clinical disease. Dr Martín

explained the importance of the route of administration, being especially relevant the mucosal route in the respiratory infections and results in macaques had shown promising results conferring both trained[93] and adaptive[94] immunity after pulmonary vaccination with MTBVAC. For instance, BCG was able to produce an important mucosal immunity when the first doses were orally used. Nowadays, BCG is administered intradermally, but it only protects against the invasive forms but not the respiratory form of the disease, partially due to the lack of essential virulent antigens. Even so, exploring alternative routes especially for respiratory diseases is important. Recently, the eradication of TB infection was reported for the first time in an animal model by administering BCG intravenously in a 1000 times the clinical dose.[95] With this striking result, Dr Martín highlighted the importance of choosing a viable administration route, as it is known that mass vaccination by intravenous route is practically impossible, and a nontoxic dose to be clinically valid. The group of Dr Martín is studying the effects of using MTBVAC via the respiratory route in animal models as mice and macaques to protect against the respiratory form of the TB. Instead of using the usual bronchoscope to administer intratracheally the exact dose in macaques, the study of Dr Martín is based on the use of nebulizers suitable for clinical use.[96] Even, if the inhalation route will show better protection results than intradermal route, it will have to be submitted to the whole regulatory process and it will take another 10–20 y. Therefore, for now, the main goal is the authorization of the use of intradermal MTBVAC as a vaccine with great possibilities of protecting against the respiratory form of the TB and save millions of lives as soon as possible, while new alternative and potentially more effective routes are under research.

The last topic of the session was the indirect protection or the heterologous effect of some non-specific vaccines, as BCG, against the COVID-19, commented also in previous sessions. Dr Martín described the nonspecific protection of BCG against unrelated pathogens as *Staphylococcus* or *Candida albicans* in SCID mice but also in vaccinated volunteers.[97] In addition, BCG, which is worldwide given to newborns with a coverage of 80–90%, in developing countries, not only protects against severe forms of TB but it has also demonstrated to have an important role in the reduction of infant mortality independent of its effect on TB.[83,97] This trained nonspecific immunity induced by BCG has demonstrated to give protection against experimental infections with several viral pathogens, including yellow fever virus in humans.[98,99] With MTBVAC, the group of Dr Martín in collaboration with the groups of Dr Netea and Dr Yuste, has seen that this live-attenuated vaccine induces trained immunity and confers protection against experimental lethal pneumonia.[100] In the time of COVID-19 pandemic, as it was previously mentioned, BCG is very much in vogue with more than 20 registered clinical trials in health-care workers and elderly to study the possible protection of BCG against COVID-19, despite the lack of proof of concepts in animal models. In this context, the WHO does not recommend BCG vaccination for the protection against of COVID-19, preventing the diversion of local supplies of BCG vaccines needed to immunized newborns in countries or settings with a high incidence of TB.[101]

Several trials of BCG against COVID-19 started at the beginning of the pandemic including a large international trial in health-care workers in Australia and Europe (Netherlands, Spain, and United Kingdom).[19] At the time of aTIPICO, data related to the BCG protection against COVID-19 was not published yet. It is noteworthy that in the elderly, the BCG vaccination has demonstrated to give stronger protection against respiratory tract infections, of probable viral origin such as influenza.[102]

On the proof of concept in animal models, Dr Martín's group is currently studying the changes in the immune response in a macaque model vaccinated with intradermal BCG and by other routes, and with MTBVAC and subsequently infected with SARS-CoV-2. The main problem of the macaque model is that after infection with SARS-COV-2, the animals, regardless of whether they are vaccinated or do not heal a week after the infection, so it is a good model to study cellular immunity but not the COVID-19 disease (unpublished data). According to Dr Martín, it is important to know if MTBVAC immunity is the same as BCG in macaque model, in order to later have the capacity to produce the vaccine. If the different undergoing studies in humans will show that BCG vaccine protects against COVID-19, MTBVAC is expected to protect too, and therefore protection studies against the severity of COVID-19 would be initiated.

Looking at the meeting points that may exist between TB and COVID-19 and the mechanism of BCG to induce trained immunity by epigenetic reprogramming of monocytes itself, the speakers hypothesized that BCG may have a more specific effect against COVID-19, where the dysregulation of monocytes/macrophages plays a fundamental role in the subsequent cytochemical, and pathogenic storm seen in the severe cases of COVID-19. On Dr Martín's opinion, the BCG or MTBVAC vaccines will produce a regulated immune response against SARS-CoV-2, avoiding the hyperstimulation of all cytokines (interferon gamma, TNF alpha, IL2), whereas a specific vaccine against SARS-CoV-2 containing the spike protein or inactivated virus will produce antibodies that can protect against infection. Therefore, in the clinical trials of BCG against COVID-19, it is important to assess the reduction of severe cases of COVID-19 caused by the cytokine storm, instead of the prevention of viral replication. In contrast, the aim of vaccination in the TB is to generate a controlled immune response based on the activation of monocytes to generate memory that recognizes the TB bacillus, but without an overreaction of the immune system responsible of the development of the TB disease.

So, the regulation of the immune response observed with BCG and other live-attenuated TB vaccines may be relevant in the control of COVID-19 once it is scientifically supported and until the s the key for both diseases, and it might help in the control of the pandemic once the evidence.

Bacterial infections and COVID-19: friends, foes, or we just do not know?

In this session, Dr Shamez Ladhani (Public Health England, UK) talked about important bacterial diseases as meningococcal and pneumococcal, which were concerns before the

COVID-19 pandemic, and their immunization programs. Also, the impact that the COVID-19 pandemic and the consequent lock-down had on children was discussed.

In the UK, the first concern with the arrival of COVID-19 in January 2020 and subsequent lock-down by middle March 2020, was the national falling of the immunization of children. Up to a quarter of infants had delayed immunization, and even if they were at low risk of vaccine-preventable infections during the lock-down, they would remain susceptible when they came out of lock-down. During the month after the lock-down, immunization uptake was reduced, but after that period, there was a quick recovery of the uptake, and it was possible to maintain a high level of protection from the pneumococcal and meningococcal diseases in infants and young children. And a couple of months later, other age groups were also protected. Another major concern was pneumococcal disease, because in previous pandemics secondary pneumococcal disease disease, especially pneumonia, following viral infections was observed. In the case of influenza, for example, secondary pneumococcal pneumonia was associated with very high mortality rate, and very little about the risk of secondary bacterial infections following SARS-CoV-2 infection was known during the current pandemic.

Dr Ladhani commented on the epidemiological data from the UK showing that, as soon as lock-down began, the number of cases of pneumococcal disease dropped sharply in all age groups. From July 2019 to June 2020, there was a 30% reduction in cases compared to the previous year, with the vast majority of reductions occurring during lock-down (March–June 2020).[103] The reduction was the same in all age groups including older adults who had the highest risk of both COVID-19 and pneumococcal disease.

Possible co-infections were studied in the UK by linking the cases of SARS-CoV-2 with those of pneumococcal disease. From February to June 2020 there were around 40 co-infections within 48 hours of each other. Surprisingly, there were more cases of people who came to the hospital with pneumococcal disease and then contracted COVID-19 secondarily, which is the opposite of what usually happens in a pandemic. Most of these co-infections affected very old people, with a mean age of 80 y old and there were no cases in children (<16 y). These results lighten the concerns about pneumococcal disease playing an important role in co-infection cases.

Dr Ladhani was asked about the 1 + 1 infant vaccination program against pneumococcal disease which was implemented in the UK just before the COVID-19 pandemic. Under this circumstance, it was difficult to collect and interpret surveillance data needed for the rest of the world to support the change in strategy. In the UK, it took 2 y for all the stakeholders to accept the change from a 2 + 1 pneumococcal conjugate vaccine (PCV) schedule (doses at 2, 4 and 12 months of age) to a 1 + 1 schedule (3 and 12 months). The reason that supported that change of strategy included data showing the herd protection offered by the program is superior to direct protection from vaccination in infants.[104] Hence, if there is good population protection, even infants under 1 y of age are well protected. Although the effect of the first year of the program was difficult to interpret because of the low number of cases of pneumococcal disease, especially in younger children after lock-down, Dr Ladhani expected that in the coming years, enough data could be accumulated that would show the positive results of the program.

In terms of meningococcal disease, Dr Ladhani pointed out that a year there are only 500–600 cases per year before the pandemic in England. In the UK, since 2015, two vaccination programs against meningococcal disease were implemented, which help reduce annual number of cases even further.[105] An infant vaccine program against meningococcal capsular group B *Neisseria meningitidis* (MenB) and an adolescent program against groups A, C, W, and Y meningococci (MenACWY). Following national lock-down after March 2020 till October 2020, there were fewer than 50 cases, across all age groups in England. The greatest reduction was in group B meningococcal, which was responsible for the majority of the cases, while diseases caused by other serogroups were extremely rare.

This reduction in meningococcal disease was genuine because patients with suspected meningococcal disease continued to have blood cultures done and meningococcal PCR testing, although positivity rates dropped significantly during lockdown. It was, however, possible, that some meningococcal cases and deaths might have been missed because patients did not seek medical care in a timely manner during lockdown.

Continuing with meningococcal disease, Dr Ladhani explained the emergency program of ACWY vaccine that started in 2015 because of a rapid increase in group W meningococcal disease caused by a highly virulent strain belonging to clonal complex 11 (MenW:cc11).[106] Over a period of 3 y, all adolescents, between the ages of 13 and 18 y, were vaccinated. This was the first program to target a specific age-group of meningococcal carriers to induce herd immunity, since adolescents have a low disease incidence but the highest meningococcal nasopharyngeal carriage rates. After 3 y of program, cases due to serogroups W, Y, and C declined as a result of the population protection offered by the program. In addition, meningococcal group W cases were also reduced in infants and young children. After almost 5 y, the reduction in cases were increased every year as more cohorts received the vaccine. Data also showed that in addition to the herd immunity effect of the ACWY vaccine, there were additional reductions in group W meningococcal in disease in children eligible for 4CMenB vaccine.[107] Broader protection, including against group W meningococcal disease, could be expected from 4CMenB since this is a broad-spectrum vaccine based on meningococcal surface protein antigen that are not restricted to serogroup B meningococci alone, but across all meningococci. Nevertheless, the protection provided by the meningococcal ACWY conjugate vaccine was nearly 100% because it is a conjugated and highly immunogenic vaccine.

Dr Ladhani also explained the experience of the UK with the 4CMenB program and its impact on the serogroup B cases. This program was implemented in 2015 and at that time there were very few cases in infants (around 100). The challenge of this program was that 650,000 infants needed to be vaccinated for 100 cases and only 65% of the children would be protected because this vaccine does not protect against all meningococcal serogroup B strains. To be a cost-effective program, one of the

three infant doses was removed, with implementation of a schedule of 2 + 1 doses instead of the licensed 3 + 1 schedule. This strategy was based on data that showed that two doses were already immunogenic, and the booster dose could provide longer-lasting immunity. This strategy was hopeful since any vaccine would be better than no vaccination, considering the 3 + 1 schedule was not affordable. It was also a great opportunity to show that the 2 + 1 program works with very positive results.[108] In addition, the group of Dr Martinón-Torres also published results that show that 2 + 1 and 3 + 1 schedules are very similar in terms of immunogenicity and persistence.[109,110] Dr Ladhani hoped that 5-y data from the UK will support other countries implementing similar affordable schedules.

Dr Ladhani was asked if the same pattern observed for meningococcal and pneumococcal disease during the COVID-19 pandemic was observed with any other infectious disease. The lack of physical contact has reduced many infections, as has been seen with influenza and RSV in countries like Australia. As an unexpected anecdote, Dr Ladhani explained an increase in cases and outbreaks of bacterial gastrointestinal infections, like listeria and salmonellosis which public health investigations suggested were occurring because people are cooking more at home when they were not used to cooking and therefore did not cook their food properly. Additionally, the food sources have changed because of the restrictions and many products are coming from sources and countries that were not permitted before, resulting in more contaminated food reaching households during lockdown.

Following on the topic of the impact of COVID-19 on other infectious diseases, Dr Ladhani highlighted that isolation and maintaining social distance with less physical contact are limiting the natural boosting of infections. Thus, the longer social distance is maintained, the bigger will be the susceptible population afterward. Dr Ladhani was concerned that this increase in susceptible populations will compensate for the reduction in cases of meningococcal and pneumococcal, as well as many viral infections, once the lock-down and other restricted measures are over. He warned that health systems have to be prepared and take care of those susceptible cohorts, particularly ensuring that all eligible children are appropriately immunized for their age.

The role of children in the transmission chain of SARS-CoV -2 was also an important topic during this session. In the first few months of the pandemic, there was very little attention paid to children. Many early articles showed that children represented only 1% of the cases and were not major contributors to the disease hospitalizations or deaths. However, in Dr Ladhani's opinion, it was really important to monitor and understand COVID-19 in children. With the data collected in Public Health England, the low incidence of hospitalized children with COVID-19 was confirmed as was the low number of fatal cases, most of them being older children with neurodisabilities.[111] Surveillance was also initiated within weeks of identification of the pediatric multisystem inflammatory syndrome (PMIS), similar to Kawasaki disease, in children and adolescents that was temporarily related to COVID-19. In the UK, around 400 children developed the condition with data showing similar findings as in other countries. PIMS, also known as multisystem inflammatory syndrome in children (MIS-C) is a rare outcome of COVID-19 that is strongly associated with SARS-CoV-2 and appears between 2 and 4 weeks after SARS-CoV-2 infection. These cohorts will continue to be monitored for 12–24 months after their illness because this is the most severe outcome in children and the long-term outcomes are still unknown.

Another important point of discussion in the role of children in the COVID-19 pandemic was the role of schools in infection and transmission of SARS-CoV-2. In the UK, after the first lock-down, schools did not open completely and, only some year groups were allowed for in-person education in primary schools. There was hesitancy about the use of molecular testing of oral/nasal swabs as it may underestimate SARS-CoV-2 infection due to issues with test sensitivity and test timing. A study of the exposure to SARS-CoV-2 in children from 4 to 11 y old after the reopening of schools in the UK in June 2020 by using serology tests showed that being in school was not associated with a high risk of infection in staff or students.[112] The majority of children were infected at home usually from their parents, who in many cases were healthcare workers. Dr Ladhani highlighted that this study was carried out in summertime, and it was a different situation than in winter when schools reopened fully for in-person teaching.

Dr Ladhani differentiated three concepts about the COVID-19 pandemic which are infection, disease and transmission. He also pointed that children can not be considered as a single group, because pre-school, primary school, and secondary school children behave differently in terms of their risks and outcomes. In Dr Ladhani's opinion, the idea that children do not get infected is misconceived. All the studies carried out in schools have shown that the seroprevalence in primary and secondary school children is similar to the school staff and the local community. When children are exposed to the virus, they most likely get infected as the same level as adults. The difference is that they do not get as sick as adults and are therefore less likely to get tested than adults. When infected, however, children develop a robust immune response against SARS-Cov -2, possibly even better than adults. Therefore, children are not behaving that differently from adults. Perhaps, at the beginning of the pandemic the children were more protected and less exposed to the virus and therefore, which may explain the lower antibody positivity rates in children compared to adults in the earlier reports, but not anymore.

In terms of disease, children are less likely to become symptomatic than adults and the majority do not develop severe disease or die from their infection. A small proportion, however, will go on to develop PIMS-TS, but this too has good outcomes. The role of children in transmission of SARS-CoV -2, however, is really difficult to estimate. In the UK, since the beginning of the 2020/21 academic year (September 2020), every academic year from 3 y of age until university registered a weekly increase in cases at different rates, depending on the age group. Compared to primary school children, the rate of infection in secondary schools was double and 5–10 times higher in university students.[113] This increase was associated with in time with the reopening of all educational settings, but the trends in infection closely followed trends in adults infection rates in the community. Additionally, there was very

limited evidence of transmission occurring in schools. Instead, the whole process of the opening of schools, including parents go to work, bringing children to schools, using public transport, going to the playground after school, all these actions increased the number of contacts between children themselves and between children and adults, which likely contributed to the increase in childhood cases observed after schools reopened fully in September 2020. The increase in cases among school-aged children, however, has remained very low and does not justify school closure, which is associated with significantly more indirect harms to the children in terms of their education, physical, mental, and emotional health, as well as access to social services and school immunizations.

Regarding the impact of the school closure or the lock-down in children, Dr Ladhani stated that at the beginning of the pandemic, with the recommendations to stay at home, in the UK, there were twice as many deaths of children dying because they did not access healthcare than because of COVID-19. With this example, Dr Ladhani pointed out that different rules may be necessary for the children, as keeping children at home could be more harmful than the same COVID-19. At this line, Dr Ladhani and Dr Martinón-Torres agreed that COVID-19 is having a negative impact on children's health, for example by reducing routine vaccination, but also by diverting attention from other severe infectious diseases in children. Dr Ladhani commented on the impact of the closure of school-based immunization programs in the UK for several months. As an example, in the ACWY immunization program, vaccine uptake in primary care was below 40% compared to 80–90% uptake with school-based programs. If such school-based immunization programs do not continue at the highest level as they did, population protection will be jeopardized. This is an additional detrimental effect of closing schools.

At the end of the session, Dr Ladhani and Dr Martinón-Torres discussed about the COVID-19 and the arrival of vaccines. Dr Ladhani considered that the first vaccines should have been available by the end of 2020. They also talked about vaccination against COVID-19 in children. Dr Martinón-Torres thought that children vaccination is not the priority. Until there are sufficient doses for wide distribution, the priority should be essential workers and the population at risk. Therefore, infants and young children should not be included in the first phase of vaccination, just like they were not included in the initial clinical trials. However, the burden that COVID-19 causes in children should also be considered in the vaccination plan to prevent the few severe cases there might be. Dr Ladhani agreed that children must always be protected from any possibility of contracting severe COVID-19.[114]Some of the risk factors for severe COVID-19 in hospitalized adults which have been recently published, including Down syndrome and hemoglobinopathies may be directly applicable to children.[115] Such children may be protected by vaccination; it is therefore necessary to identify and offer vaccination for such children. Thereby, Dr. Ladhani stated that vaccines should be available for children, even if its just for a small group of high-risk children.

To conclude, Dr Ladhani estimated that in winter 2020 the health-care systems would be overloaded by COVID-19 cases and from other respiratory diseases and, consequently, vulnerable population as elderly and risk people would suffer disproportionately either direct or indirectly from COVID-19. However, he believed that by spring 2021 there would be an immunization program that would continue to accumulate protection, the weather would be better, there would be more outdoor activities and less transmission and more knowledge of the virus. Hence, Dr Ladhani hoped that winter 2021 would be a normal winter.

To summarize this session, cases of meningococcal and pneumococcal disease have decreased during the first year of the COVID-19 pandemic because of several factors, including the lock-down and other restriction measures. However, it is necessary to maintain surveillance of these diseases as well as the immunization programs to guarantee herd immunity and long-term protection. Regarding the COVID-19 pandemic in children, the impact of some restricted measures such as school closures should be exhaustively reconsidered as they will have a higher negative impact than COVID-19. In addition, it is important to identify and vaccinate the few children that are at risk of severe COVID-19.

COVID-19 and infectious diseases – a paleoanthropological perspective. Do we get sick of the same causes as we did half a million years ago? (special session)

In this special session, Dr María Martinón-Torres (CENIEH, National Research Center on Human Evolution, Spain) provided a paleoanthropological perspective of infectious diseases and other types of pathologies faced by humans throughout their evolution, as a good reflection of the weaknesses but also the strengths of an individual and their group.

The first point of discussion during this session was whether infection diseases are a sign of current times or not. She pointed out that the pandemics are not new, but the way of coping it is typical of this time. Epidemics and pandemics have accompanied the human species since its inception. No sign of infectious diseases could be identified in another previous species of modern humans. In the fossil record, the first evidence of infectious diseases is dated from around 50,000 y ago. At that time, the *Homo sapiens* had a sufficient demographic density to be able to leave Africa and spread all over the globe. This is a fundamental premise for the transmission of the infection. In addition, around 10,000 y ago, the lifestyle of humans changed from nomads to a sedentary species that including practices of the Neolithic age such as livestock raising and animal domestication. These activities had put humans in a very close contact with animals, which is another fundamental element of infectious diseases. Close coexistence with animals enables mutations in pathogens that were only affecting animals to happen and be able to become human pathogens and some of them even exclusive to humans. Dr María Martinón-Torres pointed out that pathogens accompanied humans for years and that is sort of the price to pay for being such successful and numerous species, with such a high population density in the animal kingdom.

Regarding the diagnosis of diseases from the fossil record, Dr María Martinón-Torres explained that it is a complicated task. In the context of paleopathology, there is an important limitation, because only the diseases and conditions that had left a mark or alteration on the bone can be detected, since only bones and teeth

do fossilize whereas organs and soft tissues disappear, missing an important part of the medical history of the individual. Dr María Martinón-Torres cited the example of what is believed to be the oldest evidence of an infectious disease in the fossil record. It is a particular and highly controversial case of a cranium found in Turkey approximately half a million years old. In the internal side of the cranium, a series of coalescing granulations were found which may be an indicator of leptomeningitis tuberculosa.[116] Fortunately, nowadays innovative techniques can be applied in paleontology which were not usual in this field and are opening up diagnostic possibilities. For example, with molecular biology techniques, sequences of pathogens like TB or typhoid fever were analyzed to reconstruct their phylogenetic tree. As an example, Dr María Martinón-Torres indicated that the ability of *Salmonella typhi* or *Shigella* from infecting humans occurred around 50,000 to 80,000 y ago, when population density reached a critical level to allow the pathogen to spread. The possibilities are expanding because in the field of paleo-proteomics, these pathogens can be identified, and their evolutionary history can be reconstructed to also define vulnerabilities and all species that have been exposed to this pathogenicity calendar.

To answer the question of whether the human species gets sick from the same kind of diseases as thousands of years ago, Dr María Martinón-Torres commented that there are some causes that are the same, but others have changed. Although diseases may be associated with vulnerability, many times they are a sign of strength in terms of how humans have faced the disease. Currently, cardiovascular, and cerebrovascular diseases are the main causes of mortality and morbidity in the world population, causing millions of deaths a year. According to Dr Martinón-Torres, these diseases can actually be interpreted in an evolutionary way, since they are conditions that are related to a conflict or mismatch between our anatomy or physiology and new lifestyles we are not optimized for. Practically no differences are found when comparing the anatomy of modern humans with the one of the *H. sapiens* of 200,000 y ago, who had anatomy optimal to live outdoors, with daily activities that demanded a lot physically, like hunting, or gathering. The current human anatomy is similar, but the lifestyle has drastically changed, and humans have not coevolved with it. Therefore, many of these pathologies such as obesity, diabetes, hypertension, are related to this imbalance between the anatomy well-adapted for physical activities and the current lifestyle. These diseases are the difference between then and now whereas traumatic events can be considered common to the past and nowadays. In the fossil record, there are many fractures and signs of scaring, healing, and survival. At the present time, traumatic events happen although in a different format, because one of the main causes of death due to non-disease in these times is car accidents. Therefore, traumatic events have been a common cause of death in humans throughout history.

In relation to the traumatic accidents, Dr María Martinón-Torres commented on a possible evolutionary interpretation for the constant presence of violent deaths in human history. In difficult times, individuals tend to be alert and defend themselves and this is connected to fear, which is an evolutionary adaptation. Dr María Martinón-Torres commented on the classic question if humans are more violent than other animals. In the context of the animal kingdom, humans are more violent than the average mammal animals, but within the group of primates, humans are not more violent. In the animal kingdom, up to 40% of violent deaths among mammals occur among members of the same species. Some interesting studies analyzed this pattern of violence in human populations and highlighted that violence is greater in social groups because it is precisely within the proximity that conflicts arise. Dr María Martinón-Torres noted that this is the price to pay for being a social species. Dr María Martinón-Torres added that some studies of degrees of violence in humans throughout history showed that violence depends a lot on the context, the situation, and the culture. Humans do not have a violent nature and thus violence can be controlled and modulated through education and culture.

Regarding other diseases such as cancer or neurodegenerative diseases, that are usually more linked to the current world, Dr María Martinón-Torres commented that they are interesting pathologies from the evolutionary point of view. However, they are very difficult to find in the fossil record because they have probably never happened since they are diseases associated with advanced ages. In a way, humans are paying the price for their longevity, which is nearly 30 y greater than that of other primates. This longevity increases the probability that these diseases will develop for which time was not enough in the past. Dr María Martinón-Torres also explained, following the Darwinian theory, that natural selection has not eliminated these diseases, because they mostly occur in the post-reproductive period. Natural selection is focused on the perpetuation of the species, not on the health or well-being of the species. It is interesting to understand why this type of thing happens, since the human species is considered highly adapted to the world and with a high capacity to control what happens to it.

Dr María Martinón-Torres was asked about the evidence of respiratory diseases. As it was mentioned previously, the evidence is very limited because the organs and soft tissues do not reach the fossil record. With the application of the novel techniques, it will be possible to extract pathogens from the fossil record and study their natural selection and evolution alongside humans, in a constant struggle for improvement. Even so, some estimates can be made regarding respiratory diseases such as studying the thorax and its change in shape and capacity in different human species. Neandertals were very similar to modern humans, but their thorax had a more flared shape than that of *H. sapiens*, which could have influenced the position of their diaphragm and increase the lung capacity up to 20% more. Perhaps this reflects higher metabolic or respiratory needs although it is still unclear. Another way of approaching respiratory problems that may have existed in *H. sapiens* thousands of years ago is related to certain circumstances as the paleo-pollution that could favor respiratory diseases, not necessarily infectious. This approach considers behaviors that may not have been benign, such as sitting around the fire, because the incomplete combustion of wood generates toxic and irritating chemicals that, if accumulated in significant quantities, can produce acute respiratory conditions and even premature mortality, especially in groups living in caves. In addition, in the sediments and ashes of prehistorical bonfires has been identified traces of copper or zinc, which are also toxic metals to the respiratory tract. However, Dr María

Martinón-Torres explained that curiously there is a mutation in modern humans that helps metabolize these toxins, which was apparently absent in Neanderthals. It is another way of studying the vulnerability or susceptibility of ancestral hominids to respiratory diseases.

Dr María Martinón-Torres also commented on the recent finding of a Neanderthal gene increasing the susceptibility to severe forms of COVID-19.[117] She highlighted that diseases are multifactorial, hence trying to link a specific and isolated mutation with a greater propensity to suffer from a severe form of a disease, like COVID-19 is risky. In addition, the effect of this specific mutation has not even been identified. Dr María Martinón-Torres opined that it is easily resorted to blaming the Neanderthals of inheritance in the modern human suggesting a greater propensity to diseases such as diabetes, lupus, Crohn's disease, or even the most aggressive variety of HPV. However, she suggested reversing the reading since today it is known that thanks to hybridization with Neanderthals, humans have probably inherited genes related to the immune system or keratin production, which may have been beneficial for the skin and hair of the ancient humans leaving Africa to go to Europe, a cold and inhospitable region. It is important to be cautious with the interpretation of associations which are not necessary a causal relationship, especially in disease about which so little is known. Dr María Martinón-Torres concluded that it is important the good interpretation of the results and escaping from these sensational headlines, especially in a field that still has to be developed to a greater extent.

The speaker also discussed the ability of humans to heal themselves and the resilience capacity. In this sense, she explained that there is an inherent instinct to survive in any living being, in that there is no difference from ancestral humans. However, the human species has the overwhelming ability to fight against disease and death and has a remarkable awareness of diseases, so much so that the humans live knowing that they are going to die and dedicate an enormous number of resources and time daily to defend against disease. This capacity is more than purely palliative or curative that can be observed in some animals that are also cured by using certain plants. In human life, the fight against the disease is so important that it has become institutionalized. Dr María Martinón-Torres found it curious as the disease is an individual experience, but *H. sapiens*, as something exclusive to the species, has included a third party, which is the doctor. There is no evidence in the fossil record that doctors existed before, and this is clear from the absence of traces of any proactive rather than palliative treatment. Apart from the isolated case of a possible amputation in a Neanderthal individual, examples of intervention were not observed until *H. sapiens*.

In this line, both speakers talked about the remarkable role of vaccines in the survival of the species and their impact in evolutionary terms. The "paleontologists of the future" will see that the calendar of pathogenicity was intervened by humans, who had the ability to change the history of what was happening to them. Dr María Martinón-Torres considered that vaccines and prevention may be the pinnacle of *Homo sapiens*' capabilities because the capacity for abstraction is unique to understand how a pathogen works and prevent its infection. With vaccines, humans are capable of reproducing how a pathogen works and how to combat it. Dr María Martinón-Torres opined that this ability to project into something that has not yet happened is the smartest and most "*sapiens*" strategy.

Finally, when Dr Martinón-Torres was asked if all the answers are in The Sierra de Atapuerca, in Burgos (Spain) she replied that most of them are and compared Atapuerca with book that generously tells many details of the ways of living and suffering of ancient humans.[118]

Conclusions

After the aTIPiCO 2020 edition, several conclusions can be drawn around the COVID-19 pandemic and other important infectious diseases. To tackle the current pandemic situation, research is essential to understand the pathogen, the disease and what are the best options to manage COVID-19. Using the best testing, rapidly and frequently, should be central in the control of the transmission. Vaccination is part of the solution although there are still unknown aspects regarding clinical efficacy, long-term safety, infection protection and duration of the immunity that need to be addressed. The use of other available vaccines as BCG vaccine against TB could be proven to be of use against COVID-19 due to its capability to generate a strong nonspecific immune response.

Despite COVID-19, it is necessary to keep the surveillance of other infectious diseases and their immunization programs, in those vaccine-preventable diseases, to guarantee individual protection and herd immunity. Despite the low incidence of influenza and pneumococcal disease during 2020, probably due to lockdown and social distance measures, these diseases need to be monitored closely and managed via vaccination to prevent major health problems associated with coinfection. In the case of measles and pertussis, more contagious diseases than COVID-19, they are a good example of disease control by using vaccines. In particular, measles vaccine is even better than expected, preventing the immunological amnesia associated with natural infection. The HPV vaccine, the first vaccine to prevent cancer, has had a firm evidence trajectory that supports its benefits and increases acceptance.

Finally, awareness of future pandemics is essential in order to be prepared through the development of broad-activity vaccines and medicinal products.

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