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MEETING REPORT

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TIPICO X: report of the 10th interactive infectious disease workshop on infectious diseases and vaccines

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ABSTRACT

TIPICO is an expert meeting and workshop that aims to provide the most recent evidence in the field of infectious diseases and vaccination. The 10th Interactive Infectious Disease TIPICO workshop took place in Santiago de Compostela, Spain, on November 21–22, 2019. Cutting-edge advances in vaccination against respiratory syncytial virus, *Streptococcus pneumoniae*, rotavirus, human papillomavirus, *Neisseria meningitidis*, influenza virus, and *Salmonella* Typhi were discussed. Furthermore, heterologous vaccine effects were updated, including the use of Bacillus Calmette-Guérin (BCG) vaccine as potential treatment for type 1 diabetes. Finally, the workshop also included presentations and discussion on emergent virus and zoonoses, vaccine resilience, building and sustaining confidence in vaccination, approaches to vaccine decision-making, pros and cons of compulsory vaccination, the latest advances in decoding infectious diseases by RNA gene signatures, and the application of big data approaches.

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Introduction

The 10th Interactive Infectious Disease TIPICO workshop took place in Santiago de Compostela, Spain, on November 21–22, 2019. Sixteen experts from different countries and more than 400 delegates came together in this 2-d academic experience chaired by Dr. Federico Martinón-Torres. The workshop addressed current and trending issues in the field of infectious diseases and vaccination through discussion, debates, and fora.

The sessions covered different areas from basic pathogenic mechanisms to epidemiology, prevention, and management of infections caused by respiratory syncytial virus (RSV), *Streptococcus pneumoniae*, rotavirus (RV), human papillomavirus (HPV), *Neisseria meningitidis*, influenza virus, and *Salmonella* Typhi. The present and future perspectives of vaccines, as well as policies and strategies for increasing vaccination uptake (e.g. vaccine resilience or approaches for vaccine decision-making) and the latest advances in personalized medicine through the application of genome-wide host response quantification and big data were also main topics addressed by TIPICO.

Keeping infectious diseases under control through vaccination

Progress against Respiratory Syncytial Virus

During his talk, Dr. Louis Bont (Wilhelmina's Children's Hospital University Medical Center Utrecht, the Netherlands, The Netherlands) summarized updates in the field of RSV vaccination. Globally, an estimated 33 million cases, 3 million hospitalizations and 120,000 deaths have been caused by RSV, and of the total deaths, more than 50% occur during the first 5 months of life.[1,2] Although several associated risk factors such as premature birth[3] and Down syndrome and other comorbidities[4] have been reported, the majority of hospitalized cases (73%) correspond to healthy babies born at term.[4] Importantly, RSV infection also affects older individuals, and

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is particularly relevant in high-risk adults.[5] In most cases, RSV causes upper respiratory infections and otitis, and although the infection is related to an increased risk of asthma,[6] for the time being, its causative role agent has only been confirmed in wheezing.[7] Currently, several types of vaccines targeting different populations (pregnant women, babies <6 months, babies >6 months and older people) are being developed, of which 21 are in the clinical phase (14 in phase 1, five in phase 2, and two in phase 3), including a nanoparticle-based RSV vaccine that is being tested in older adults (ClinicalTrials.gov Identifier: NCT02608502). According to a mathematical model for maternal vaccine-induced antibody dynamics of a maternal RSV vaccine (ResVax™) currently in phase 3 of clinical development, RSV vaccination during pregnancy may substantially decrease life-threatening RSV infections in infants.[8] Other alternatives, such as the use of recombinant human monoclonal antibodies for potential RSV prophylaxis including MEDI8897, with a highly potent extended half-life,[9,10] or the broadly neutralizing RSV monoclonal antibody RB1 derived from a human memory B-cell[11] are being tested. New vaccines include an attenuated RSV vaccine that has shown improved antibody responses in children,[12] a virus-vectored vaccine[13] and vaccines developed according to a structure-based design for virus F subunit stabilization. These latter preserve neutralization of sensitive epitopes and show potential improvements in efficacy, as well as a possible reduction of adverse effects compared to previous vaccines based on RSV F subunit.[14]

Is it possible to eliminate pneumococcus?

Dr. Bradford Gessner (Pfizer Vaccines, USA) and Dr. Melvin Kohn (Merck Vaccines, USA) discussed the impact of pneumococcal polysaccharide vaccines (PPVs) and pneumococcal conjugate vaccines (PCVs) for pneumococcal disease prevention. The participants discussed the data supporting or not supporting the use of each vaccine technology in adult populations, recognizing that both Pfizer and Merck are developing next-generation PCVs for use in adult populations: PCV15 (15-valent pneumococcal conjugate vaccine; Merck & Co., Inc., Kenilworth, NJ, USA) and PCV20 (20-valent pneumococcal conjugate vaccine; Pfizer, Inc., Philadelphia, PA, USA). With respect to new PCVs, the participants discussed the importance of effectiveness evaluations, local pneumococcal epidemiology, and economic evaluations.

In his talk, Dr. Ron Dagan (Ben-Gurion University, Israel) focused on the efficacy of PCVs and the phenomenon of serotype replacement. Thus, non-vaccine serotype (NVT) replacement has been observed after PCV vaccination, which may be relevant for the disease and for vaccine effectiveness, making continuing surveillance necessary.[15] Furthermore, serotype replacement seems to be also influenced by age-related multimorbidity.[16,17] Despite replacement, the introduction of PCVs has greatly reduced the incidence of invasive pneumococcal disease[18] and has caused important changes in its clinical profile.[19] Additionally, the elimination of serotypes in vaccinated individuals has been shown to confer an indirect protective effect in other subjects, even when they are not vaccinated (herd immunity).[20,21] Regrettably, certain pneumococcal vaccine-associated negative outcomes have also been reported. Thus, vaccination has led to an increase in NVT-antibiotic resistance[22] and seems to perturb the nasopharyngeal flora leading to possible indirect undesirable effects. In this respect, pneumococcal vaccination has been seen to increase *Haemophilus influenzae* nasopharyngeal carriage in children.[23,24] An association of both this pathogen and *S. pneumoniae* with the presence of RSV has also been reported.[25,26] However, at present, and despite replacement and increasing antibiotic resistance, Dr. Dagan concluded that the overall impact of PCVs is impressive and beyond expectations and remarked that efforts to achieve total pathogen elimination must continue.

The success of vaccination against rotavirus

In this session, Dr. Daniel C. Payne (CDC Division of Viral Diseases Enteric Viruses Epidemiology, Atlanta, USA) summarized updates in the field of RV vaccination. RV infection is the most common cause of severe, acute diarrhea,[27] estimated to globally cause 215,000 deaths in children under 5 y of age in 2015.[27] More than 80% of these deaths continue to occur in South Asia and Sub-Saharan Africa,[28] although, as Dr. Payne remarked, the number of visits to the emergency services, as well as the number of hospitalizations caused by the virus, remain higher among unvaccinated individuals regardless of the country.[29] Additionally, most pediatric infections with RV are systemic.[30] RV vaccines mimic the protective first infection without causing the severe illness and may provide protection, not only against gastrointestinal effects but also against other extra-intestinal effects, such as seizures.[31–33] An abundance of evidence shows that RV vaccines work well in preventing severe infections. In clinical trials, both licensed vaccines (Rotarix™ [RV1, GSK Biologics, Rixensart, Belgium] and RotaTeq® [RV5, Merck and Co, Westpoint, Pennsylvania]) have proven efficacy in the prevention of severe infections in children during their first year of life in USA, Finland, South America, and some European countries.[34,35] These observations have been confirmed in real-world studies, with a great reduction in the number of hospitalizations due to severe infections even in low-income countries such as El Salvador,[36] Malawi,[37] and Kenya.[38] In post-licensing studies, RotaTeq® has successfully prevented serious RV infections during the first year of life with efficacy rates of 85–91%,[39–41] while Rotarix™ has shown more variable efficacy rates, probably due to the reduced sample population of the studies.[39,40] Overall, both vaccines have demonstrated similar public health impacts across populations regardless of the WHO mortality strata to which they belong.[42] In the case of milder RV infections, the evidence is more scarce and data suggest that the more severe the infection, the more effective the vaccine in preventing the disease.[43] Furthermore, in the postvaccine era, it is important to continue to monitor unvaccinated vulnerable populations, such as children, adults in assisted living facilities, and patients with complex medical needs.[44] Finally, recent data suggest that maternal anti-RV IgG antibodies that transferred via the placenta from mother to child before birth and developed as a result of a previous immunologic challenge, persist in the post-RV vaccine era.[45] These antibodies may protect neonates and unvaccinated infants during the period of immune system maturation and

possibly during this high-risk period for experiencing poor RV outcomes (Payne DC et al. In preparation).

Cervical cancer elimination is possible with HPV vaccine

Dr. Laia Bruni (Catalan Institute of Oncology, Barcelona, Spain) provided an overview of the current global status and progress toward the elimination of cervical cancer. At present, 4.5% of all cancers worldwide (690,000 new cancer cases per year) are attributable to HPV.[46] Cervical cancer is caused by HPV types that belong to a few phylogenetically related "high-risk" species, HPV-16, 18, 31, 33, 35, 45, 52, 58 being the most frequent.[47] Indeed, types 16 and 18 are responsible for 71% of cervical cancer cases and 80% of anogenital and oropharyngeal cancer cases, respectively.[48] Most HPV infections are transient infections without clinical significance. However, persistent high-risk HPV infections may progress and eventually lead to precursor lesions and cervical cancer.[49] Current WHO recommendations aim to ensure that populations are vaccinated before exposure to HPV infection (main recommended age for vaccination: 9–14 y of age) and that women aged >30 y are screened for precancerous cervical lesions and, if required, treated.[50] Three adjuvanted noninfectious recombinant vaccines are available: Cervarix® (GSK),[51] Gardasil® (MSD),[52] and Gardasil® 9 (MSD).[53] Since their implementation in 2006, HPV vaccines have shown high safety profile, high efficacy, effectiveness, and impact, with strong herd effects and cross-protection against other types not included in the vaccines. The WHO has established a Draft Strategy for the elimination of cervical cancer as a public health problem based on three main pillars: HPV vaccination, screening, and treatment. To achieve global elimination in one century, every country must reach the following global targets by 2030: 90% coverage of HPV vaccination of girls (by 15 y of age); 70% coverage of cervical cancer screening (at least 70% of women screened twice in their lifetime with high-performance tests at ages of 35 and 45 y) and 90% treatment of precancerous lesions; management of 90% of invasive cancer cases.[50] Consequently, Dr. Bruni concluded that the efforts must be aligned and accelerated to achieve worldwide elimination.

Is meningococcal disease finally under control?

In this session, Dr. Andrew Pollard (Oxford Vaccines Group, University of Oxford, UK) provided a general overview on vaccine development against meningococcal disease and its impact on disease burden with special focus on the UK. The incidence of meningococcal disease presents great geographical, temporal, and age variability.[54,55] At present, despite vaccination not being available for some of the meningococcal capsular groups, the number of cases in Europe has decreased and the population's immunity remains high.[56] Although anyone can get meningococcal disease, rates of disease are highest in children younger than 1 y of age.[57] Among *Neisseria meningitidis* capsular groups, A, B, C, W, X, and Y have been the ones responsible for causing the most common invasive infections.[58] Between 2008 and 2012 a decrease in the number of cases caused by group B and C organisms was reported, largely due to the introduction of capsular group C (MenC) conjugate vaccines in a number of countries,[59] such as the UK.[60] Currently two subcapsular antigen-based vaccines against MenB are available: MenB-fHbp (Trumenba®) and 4CMenB [Bexsero®[61]]. Effectiveness has been shown for 4CMenB in preventing invasive disease and immunogenicity of both vaccines,[62,63] but several questions remain unanswered, such as those related to direct protection for MenB-fHbp, the duration of protection for both vaccines, the strains against which it would offer protection and those related to immunological memory, some of which have been estimated thanks to *in vitro* assays.[64,65] Specifically, the duration of protection is one of the major concerns. Although certain studies have shown antibody persistence after MenB-fHbp[62,66] and 4CMenB[67,68] vaccination, in the case of 4CMenB, the study of a particular outbreak affecting a university student community in the USA demonstrated no antibody persistence against the outbreak strain in around one-third of vaccinated individuals after 8 weeks of receiving the doses.[69] To ensure the success of vaccines, not only direct but also indirect effects are desirable, for which reason special attention should be paid to those age subgroups showing the highest carriage prevalence, such as adolescents and young adults.[70] To date, despite studies that have attempted to address the issue,[71–73] there is no conclusive evidence that either 4CMenB or MenB-fHbp may interrupt carriage, and indeed the balance is not in favor of an impact. As Dr. Pollard explained, the UK carefully assessed cost-effectiveness.[74] Implementation of 4CMenB in 2015 with a 2 + 1 schedule in infants has led to a 50% reduction in MenB cases in the vaccine-eligible cohort with an effectiveness of 82.9%.[75] Successful outcomes after vaccination have also been reported in other regions such as Canada.[76,77] In conclusion, vaccination has allowed control of meningococcal disease in countries such as the UK, but elimination of the disease has not yet occurred.[78] The real impact of vaccines will be thoroughly assessed in the next years.

Closer to a universal flu vaccine

Over two sessions, Dr. Adolfo García-Sastre (Mount Sinai-NY University, USA) discussed the most recent advances toward the development of a universal influenza vaccine. Despite the available antiviral treatments and vaccines, until late 2017 the WHO estimated that seasonal influenza was associated with a total of 250,000 to 500,000 all-cause deaths annually.[79] The identification of key factors for virus replication and pathogenesis is key for developing new prophylactic and therapeutic candidates and may be successfully achieved by applying systems biology that provides an understanding of multidimensional interactions for personalized prevention and treatment.[80] Importantly, an effective "universal" influenza vaccine capable of conferring protection against both seasonal and newly-emerging pre-pandemic strains is required. One possible way to achieve broad protection is to develop hemagglutinin (HA) stem-based vaccines. Some of those strategies include the use of headless constructs[81-88] and repeated vaccination with influenza virus chimeric HA vaccines that induce protective antibodies against multiple subtypes of influenza virus. This second strategy has been effective in mice and ferrets, conferring protection against different influenza virus strains.[89–92] At present, sequential vaccination with an HA stem-

based vaccine is in clinical phase I, and it is expected to protect against H2, H9, and H18 subtypes.[93,94] In the second part of his talk, Dr. García-Sastre focused on a study of an alternative method for influenza vaccine development based on targeting the virus-coat glycoprotein neuraminidase.[95] In the study, the authors isolated three human monoclonal antibodies from an H3N2-infected donor that bound to several different influenza A and B virus neuraminidases. These antibodies were able to neutralize the virus and mediate effector functions, resulting in broadly protective *in vivo* and inhibited neuraminidase activity by directly binding to the active site. Structural and functional characterization of these antibodies will represent a step toward neuraminidase-based universal vaccines against influenza virus.

New alternatives for fighting typhoid fever

During his talk, Dr. Andrew Pollard (Oxford Vaccines Group, University of Oxford, UK) summarized the most recent advances in typhoid fever vaccination. Typhoid fever, caused by *Salmonella* Typhi, mainly affects low-resource areas with restricted access to improved sanitation facilities and clean drinking water.[96] Consequently, in Europe, it is a relatively rare disease mainly acquired during travel to countries outside the continent.[97] Children are greatly affected by typhoid fever and it is known that the highest incidence occurs in individuals from 5 to 15 y old.[98] At present, two effective vaccines are commercially available: Ty21a (oral) and Vi polysaccharide (parenteral; not indicated for children under 2 y old), but neither is used routinely.[99] To test pathogen-host and immunity interactions, as well as vaccine effectiveness, human challenge models with *Salmonella* Typhi have yielded promising outcomes. However, these models seem to underestimate the effectiveness of the vaccine compared to field studies.[100] Among the new alternatives, conjugate vaccines (TCVs) have demonstrated promising results in terms of efficacy and bacterial load reduction in human challenge models,[101] showing correlation between protection status and IgA and IgG1 levels.[102] Indeed, in 2017 the conjugate vaccine Typbar TCV® received prequalification by the WHO that recommended its use in children over the age of 6 months in all endemic areas.[103] The WHO specified that priority should be given to generating data that will further support typhoid vaccination policy and immunization programs. Consortiums such as TyVAC[104] may help to accelerate the introduction of new typhoid TCVs as part of an integrated approach. As Dr. Pollard pointed out, the implementation of the vaccine will have a major impact on controlling typhoid disease.

Heterologous vaccine effects: growing evidence

Heterologous effects of Bacillus Calmette-Guérin vaccine and type 1 diabetes

During her presentation, Dr. Denise L. Faustman (Massachusetts General Hospital, USA) summarized the updates related to the heterologous effects of Bacillus Calmette-Guérin (BCG) vaccine, that has been shown not only to confer long-term protection against tuberculosis[105] but also to have significant off-target effects. Thus, there is evidence that BCG may protect against lung cancer and against type 2 diabetes in high-risk populations,[106] prevent mortality in low-weight infants,[107] decrease hospitalization rates due to unrelated-tuberculosis respiratory infections and sepsis,[108] protect adults from Mycobacterium tuberculosis infections,[109] prevent the progression of multiple sclerosis,[110] confer neuroprotection against Parkinson's disease,[111] and decrease the incidence of Alzheimer's disease.[112] Importantly, BCG could also exhibit protective effects against type 1 diabetes (T1D) through immune, metabolic, and DNA-related mechanisms.[113,114] Co-administration of TNF with the vaccine would protect pancreatic insulin-producing cells by selective death of autoreactive T cells and by stimulating the proliferation of protective regulatory T cells (immune mechanisms).[115] Additionally, BCG vaccine has been seen via an epigenetic mechanism to reset six central T-regulatory genes for genetic reprogramming of immune tolerance (DNA-related mechanisms).[116] Metabolically, BCG vaccination in established and long-term type 1 diabetics improves glucose metabolism by systemically switching from oxidative phosphorylation to aerobic glycolysis (a high glucose consumption state).[117,118] Although a phase I double-blind clinical trial did not achieve successful results at 20 weeks after two BCG vaccinations (probably due to the long-term follow-up required for the vaccine to exert its effects on the immune system),[113] follow-up of patients showed statistically significant lowering of blood sugars at year 3 that persisted for a total of 8 y. Larger and repeat Phase II double-blind trials are underway to characterize these promising trial observations in established diabetic cohorts.[117]

Rotavirus vaccine and type 1 diabetes prevention

In his talk, Dr. Daniel Payne (CDC Division of Viral Diseases Enteric Viruses Epidemiology, Atlanta, USA) explained the most recent findings on the association of RV vaccination with the decreased incidence of T1D in children.[119] This association had been previously suggested in 2000[120] and led the authors to hypothesize that RV vaccination might decrease the incidence of the disease over time. Thus, an interrupted time-series analysis was performed in Australian children by comparing the 8 y before with the 8 y after the introduction of routine oral RV vaccination for all infants aged 6 weeks and older. Results demonstrated that, in children aged 0 to 4 y, the number of incident cases of T1D decreased by 15% after the introduction of the vaccine, while no changes were observed in children aged 5 to 9 y and 10 to 14 y during the entire 16-year study period.[119,121] These results confirmed previous studies performed in animals, in which RV infection was shown to trigger pancreatic cell apoptosis in mice, and RV peptides displayed molecular mimicry with T-cell epitopes in pancreatic β-cell autoantigens.[122] Although the relationship between RV infection and the decrease in T1D may be influenced by genetic and environmental factors, among others, the confirmation of this finding would be the first example of a method of prevention of the disease conferred by a heterologous effect of the vaccine. These promising outcomes are in line with those recently reported in an American cohort.[123] To conclude, Dr. Payne explained that childhood vaccination against RV might be useful in other scenarios as well, as it has been associated with a 20% reduction in the risk of seizures that

require hospitalization or emergency care in the year after administration specially in children under 2 y.[124] The reduction in that population has been reported to be greater than 40% compared to unvaccinated children.[32,125]

Novelties in virology

Dr. Albert Osterhaus (Research Center Emerging Infections and Zoonoses, Hannover, Germany) discussed the most recent advances in the field of zoonoses. The frequency of new human and animal viruses has increased in our changing and globalizing society due to a complex mix of predisposing factors while the emergence of more advanced surveillance techniques has been of great help in the discovery of previously undiscovered viral pathogens. Zoonoses have been at the origin of the major outbreaks of human diseases occurring throughout history, more recently including human immunodeficiency virus (HIV), Ebola, influenza A (H5N1, H1N1), Zika, and Chikungunya, among many others.[126] Unexpectedly, in some cases, zoonoses have been reported to increase after disease control or eradication. This is, for example, the case for smallpox eradication, after which poxvirus infections in humans caused by related poxviruses originating from animals, such as cowpox and monkeypox viruses, increased after disease eradication, with important and more severe consequences for humans.[127,128] Consequently, the ability of some viruses to cross species barriers is an important issue to be considered. A good example for this is viruses from the Morbillivirus genus belonging to the Paramyxoviridae family that includes measles virus. These viruses have been responsible for infections in different mammals, crossing species barriers, and raising questions on whether after its eradication, measles vaccination should continue forever. The study of morbilliviruses, such as rinderpest, canine distemper, and cetacean morbilliviruses, but also viruses closely related to rinderpest virus that has been eradicated recently, may provide important lessons for future measles eradication.[129] Moreover, the study of measles infections has recently yielded striking data. For example, it is known that the virus induces long-term immunosuppression that increases overall childhood infectious disease mortality,[130] consistent with data obtained in macaques that attribute its immunosuppressive effects to depletion of memory B and T lymphocytes.[131] This hypothesis was further confirmed recently by studying measles infection in a subpopulation of children in the so-called bible belt in The Netherlands.[132] Other new viruses are also worth exploring, such as parvoviruses, responsible for a wide spectrum of disease in both animals and humans,[133] non-polio Enterovirus associated with acute flaccid paralysis[134] or astroviruses, of which new members have been associated with undiagnosed cases of gastroenteritis.[135] Viruses associated with pneumonia are especially important, since they are a greater worldwide cause of childhood mortality than malaria, tuberculosis, HIV, Zika virus, and Ebola virus combined.[136] Pneumonia is caused by viruses in 61% of cases, and by RSV in one-third of cases, so they must be an important focus of our attention.[136] These also include the newly discovered human metapneumovirus that causes similar clinical symptoms in children to those caused by human respiratory syncytial virus infection,[137] the new coronaviruses SARS-CoV and MERS-CoV, responsible for causing acute respiratory distress syndrome (ARDS),[138–142] or the influenza A viruses, responsible for four major pandemics in the last century.[143] Among the influenza A viruses, the H5N1 subtype caused a public health emergency in recent years, following outbreaks of bird flu in Asia and its subsequent expansion to other regions,[144] while the H7N7 subtype, generally of lower pathogenicity, has been associated with the development of conjunctivitis.[145] As Dr. Osterhaus remarked, because of the epidemic and pandemic risk associated with certain zoonotic infections, international collaboration, and coordination is urgently needed; initiatives such as the Zoonosis Anticipation and Preparedness Initiative (ZAPI) project[146] and the Coalition for Epidemic Preparedness and Innovations (CEPI)[147] are key initiatives to prevent and counteract zoonotic infections that pose major public health and pandemic risks.

Vaccine resilience

Measles cases have dramatically increased in the last 2 y in the WHO European region despite high vaccine coverage by measles-containing-vaccine first-dose (MCV1) and measles-containing-vaccine second-dose (MCV2).[148] Importantly, in countries where the highest number of cases have been reported (most of them middle-income countries), immunization coverage rates established by the WHO are not met.[148] In this session, Robb Butler (UNICEF, New York, USA) explained in detail the importance of vaccine resilience to build and sustain confidence in and demand for vaccination. Vaccine hesitancy is an important issue undermining protection from vaccine-preventable diseases. It is a complex phenomenon influenced by multiple social, economic, cultural, political, and religious factors, whose main determinants are complacency, confidence, and convenience, that may be observed at multiple levels.[149] On the other hand, as a preventive intervention, immunization is one of the best strategies in the healthcare field, helping to hamper medical impoverishment in populations with fewer immunization resources.[150] Regrettably, several barriers are still encountered at multiple levels, including the lack of knowledge of both the value of immunization and service, attitudes of rejection or fear of immunization, complicated logistical preparation and low priority, occupational and social financing costs, convenience and communication with the health center, and an ineffective post-vaccination service in patient follow-up.[151] Resilience is an attribute of the community.[152,153] Promoting program and community resilience generates the greatest health impact & economic return. Thus, resilient communities minimize the disruption caused by vaccine safety concerns, politicization, and misinformation on vaccination uptake.[154] They display a resilient demand for vaccination, where resilience is intrinsic to the community allowing it to adapt and react positively to safety events and vaccine misinformation.[152] According to Dr. Butler, this is important since the fear of vaccination in terms of safety can spread rapidly within communities and promote the generation of anti-vaccine movements. The emergence of these movements leads to a reduction in vaccine coverage and a subsequent significant increase in the incidence

of vaccine-preventable diseases. The impact of the lack of vaccination not only affects a specific community but also compromises the population's health at a global level, especially that of neighboring countries.[155] Importantly, interventions to create a resilient policy should focus on schools. These interventions offer unique opportunities to reach target groups with nuanced health information and to promote positive behavior change for children and caregivers.[156] Furthermore, school-based interventions provide an opportunity to create understanding of vaccination at an early age, foster life-long acceptance and stimulate critical thinking regarding information and misinformation about vaccination with an impact, not only in children but also in their caregivers.[157] In conclusion, every immunization program should ultimately strive toward building resilient demand.

Vaccine decision-making: public health *vs*. regulatory approach

In this talk, Dr. Bradford Gessner (the University of Maryland and Pfizer Vaccines, USA) explored the role of both public health and regulatory approaches in vaccine decision-making. He began by stating that regulatory approaches have guided vaccine decision-making, not only for licensing but also for public health decisions. Importantly, this focus on regulatory frameworks may undermine the understanding of public health science supporting vaccine use. For example, many models used by Vaccine Technical Committees (VTCs) focus on etiologically and diagnostically confirmed outcomes (e.g. RV confirmed gastroenteritis *vs*. the ability of vaccines to prevent all-cause gastroenteritis). Traditionally, vaccine efficacy/effectiveness has been used for etiologically confirmed diseases and has been applied to estimate how they can be prevented. However, as Dr. Gessner indicated, this is a regulatory approach designed for specificity at the expense of sensitivity. Public health-based outcomes, by emphasizing sensitivity, provide a more accurate assessment of the total preventable disease burden and thus, are more informative for funders instead. PCVs constitute a good example. It is known that reliance on etiologically or diagnostically confirmed outcomes will underestimate vaccine-preventable disease burden for numerous reasons.[158–160] For the pediatric use of pneumococcal vaccines, VTCs accept this approach in part, because there is no test for etiologic confirmation of the most common severe outcomes, specifically NBPP. Nevertheless, even the use of all-cause outcomes likely underestimates the true PCV preventable disease burden. In contrast to pediatric PCV use, when assessing adult PCV use, VTCs consistently rely on etiologically and radiologically confirmed outcomes for several reasons. Firstly, there is a serotype-specific urinary antigen detection test validated for identification of adult NBPP, even if sensitivity for this outcome is limited and poorly recognized by clinicians. Secondly, the inability of epidemiologists to accept that no definitive outcome exists and finally, a lack of awareness of how large an underestimation occurs in estimates of vaccine-preventable disease incidence when relying on etiologically confirmed outcomes. According to Dr. Gessner, it is important to bear in mind that regulatory and public health approaches have different and complementary roles, and that confusing these roles will undermine accurate assessment of vaccine performance and public health value. Specifically, public health value will be underestimated by an inappropriate focus on etiologically confirmed outcomes; by failure to include all important outcome measures (such as long-term declines in quality of life, exacerbations of chronic diseases, and long-term declines in mortality); by the lack of incorporation of indirect effects for all relevant age groups; and by the focus on regulatory rather than public health endpoints. In conclusion, underestimation of public health value leads to inefficient allocation of resources, a bias away from prevention measures such as vaccines, and increased disease and death from otherwise preventable diseases.

Is mandatory vaccination a solution?

In this session, Dr. Francisco Giménez (Balmis Vaccine Institute, Almería, Spain) and Dr. Francisco Álvarez (Committee on Vaccines [CAV-AEP], Spain) discussed the pros and cons of mandatory vaccination. As Dr. Giménez explained, mandatory vaccination is not a unitary concept, and coercive childhood immunization policies are complex context-specific instruments.[161] However, under certain epidemiological circumstances and in certain diseases it may be beneficial. Thus, positive outcomes have been observed after compulsory vaccination policy implementation in some countries, such as France, which has excellent vaccination coverage for mandatory vaccinations in early childhood;[162] Italy, where a national law extending the number of compulsory vaccines from four to 10 in July 2017 increased vaccine coverage for all vaccines;[163] the USA, where immunization mandates generally led to increased short-term and long-term vaccine uptake;[164] or Australia, where the "No Jab, No Pay" policy that withholds certain state payments for parents with children who are not fully immunized, obtained widespread support among the population.[165] However, these new regulations are not sufficient to achieve and maintain infectious disease elimination, as has been observed with the resurgence of measles in the recent years,[166] and vaccine hesitancy remains a key issue to be solved. Thus, countries such as Spain keep high vaccination coverage rates despite no compulsory policies being implemented, probably due to the ease of access to the National Health System and free provision of vaccines. Furthermore, according to the Action plan on Science in Society related issues in Epidemics and Total pandemics (ASSET) report, mandatory vaccinations on immunization did not appear to be relevant in determining childhood immunization rates in the EU/EEA countries, and constitute a possible short term but never a long-term solution.[167] Remarkably, making vaccination compulsory for children could result in "irreparable damage," by turning the decision on whether to vaccinate into a rights issue and impoverishing the parent-healthcare provider relationship.[168] In Dr. Álvarez's opinion, to overcome vaccine hesitancy and improve vaccination coverage, we require not mandatory vaccination but rather a long-term approach involving the education of children and adolescents on the basics of immunization and critical thinking.[169] This may be accomplished via different communication channels, in which health-care providers are key sources of vaccine-preventable diseases.[170] The ease of

access to vaccines, fighting against anti-vaccine movements, together with strategies that complement key regional health policies, such as The European Vaccine Action Plan 2015–2020 set by the WHO, may help to achieve immunization objectives and control preventable diseases with vaccination.[171]

Decoding infectious diseases

Gene signatures

In this session, Dr. Myrsini Kaforou (Faculty of Medicine Imperial College London, UK) discussed genome-wide host response quantification as an approach to characterize and manage infectious diseases. Infection by a pathogen triggers an immune response in the host characterized by specific gene patterns in immune system cells that can be measured in blood. Blood gene expression "signatures," quantifiable by either microarrays or RNA sequencing (RNA-Seq)[172] have been shown to have great diagnostic potential for infectious and inflammatory diseases.[173] For example, the identification of 51-transcript signatures was able to distinguish tuberculosis from other diseases in South African and Malawian children.[174] Additionally, a 2-gene signature can discriminate bacterial from viral infections, as has been evidenced in a cohort of febrile children from Spain, the UK, the Netherlands and the USA.[175] By discovering the diagnostic signature in the patients with "gold-standard" bacterial and viral infections, and applying it to patients in whom the causative pathogen remains unknown, the signatures can elucidate the cause of infection and guide antibiotic use.[175,176] However, moving from a dichotomous classification (bacterial *vs.* viral) in patient management to multi-class classifications that reflect better the clinical approach in patient management remains a challenge. Translation of the signatures for use as tests in a clinical setting also requires rigorous cross-platform and cross-cohort validation studies. Some studies have already proven the reliability of this approach,[177,178] and certain host microarrays have successfully translated into fast, highly accurate, and relatively inexpensive *in vitro* assays easily implemented in routine clinical practice.[179] According to Dr. Kaforou, although translation to patients is slow, RNA signatures are emerging as a promising tool for future personalized medicine.

Big data

In this session, Xabier Bello (GENVIP, Hospital Clínico de Santiago de Compostela, Spain) explained how big data may be useful in the field of personalized medicine. Big data has been crucial for recent important achievements, for example, producing the first picture of a black hole.[180] In the field of medicine, the application of big data for personalized medicine was demonstrated in a study in which an integrative personal omics profile that combined genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual was enough to interpret healthy and diseased states.[181] Although initially highly expensive, costs associated with big data have progressively decreased,[182] but complex and sophisticated methodologies, including artificial intelligence (AI) tools, are still required for their analysis and interpretation. Some of these tools have shown success in the field of medicine: cancerous skin lesions have been classified by the use of deep neuronal networking,[183] epileptic seizures can be efficiently predicted using deep learning,[184] and a host RNA signature has helped to discriminate bacterial *versus* viral infection in febrile children.[175] Despite its advantages, AI tools and in particular machine learning need to overcome important barriers, including errors derived from the analysis of large amount of data or the possible bias in the training phase leading to subsequent misinterpretation of results. Additionally, machine learning may raise troubling ethical issues that need to be properly addressed. Consequently, the engagement of relevant stakeholders is mandatory for the future successful implementation of machine learning systems in health care[185]

Conclusions

Vaccination is one of the most effective public health interventions for the management of infectious diseases, and several vaccines have demonstrated efficacy in preventing infections caused by HPV, influenza virus, *Streptococcus pneumoniae*, RV, *Salmonella* Typhi, and *Neisseria meningitides*. However, despite these successful outcomes, continuing efforts are necessary if total elimination is to be achieved. Importantly, strategies such as BCG and RV vaccination might represent interesting alternatives for managing pathologies not related to those for which they were initially developed, thanks to heterologous vaccine effects. Specifically, promising results have been obtained in the field of type 1 diabetes. Vaccination will also have to face new emerging zoonotic pathogens and we must continue to counteract vaccine hesitancy by working on vaccine resilience and following both public health and regulatory strategies in vaccine decision-making. Although compulsory vaccination may be an alternative in certain contexts, the education of children and adolescents on the basics of immunization and critical thinking should be the focus in order to achieve improved vaccine coverage and to fight against vaccine hesitancy. Finally, advances in cutting-edge methodologies such as genome-wide host response quantification and big data will make personalized medicine possible in the future.

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Disclosure of potential conflicts of interest

Adolfo García-Sastre is the inventor of patents on universal influenza virus vaccines owned by the Icahn School of Medicine at Mount Sinai. FM-T has received honoraria from GSK, Pfizer, Sanofi Pasteur, MSD, Seqirus, and Janssen for taking part in advisory boards and expert meetings, and for acting as speaker in congresses outside the scope of the submitted work. FM-T has also acted as principal investigator in RCTs of the above-mentioned companies, and Ablynx, Regeneron, Roche, Abbott, Novavax, and MedImmune, with honoraria paid to his institution. The remaining authors declare no conflicts of interest.

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