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MEETING REPORT

TIPICO IX: report of the 9th interactive infectious disease workshop on infectious diseases and vaccines

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ABSTRACT

The Ninth Interactive Infectious Disease workshop TIPICO was held on November 22–23, 2018, in Santiago de Compostela, Spain. This 2-day academic experience addressed current and topical issues in the field of infectious diseases and vaccination. Summary findings of the meeting include: cervical cancer elimination will be possible in the future, thanks to the implementation of global vaccination action plans in combination with appropriate screening interventions. The introduction of appropriate immunization programs is key to maintain the success of current effective vaccines such as those against meningococcal disease or rotavirus infection. Additionally, reduced dose schedules might improve the efficiency of some vaccines (i.e., PCV13). New vaccines to improve current preventive alternatives are under development (e.g., against tuberculosis or influenza virus), while others to protect against infectious diseases with no current available vaccines (e.g., enterovirus, parechovirus and flaviviruses) need to be developed. Vaccinomics will be fundamental in this process, while infectomics will allow the application of precision medicine. Further research is also required to understand the impact of heterologous vaccine effects. Finally, vaccination requires education at all levels (individuals, community, healthcare professionals) to ensure its success by helping to overcome major barriers such as vaccine hesitancy and false contraindications.

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Introduction

The Ninth Interactive Infectious Disease workshop TIPICO was held on November 22–23, 2018, in Santiago de Compostela, Spain. This 2-day academic experience chaired by Dr. Federico Martinón-Torres brought together an international panel of 14 experts from different countries and 500 delegates, who addressed current and topical issues in the field of infectious diseases and vaccination through debates, discussion, and fora.

The sessions covered different aspects from basic pathogenic mechanisms to infectomics, systems biology, epidemiology, prevention, and management of the infections caused by enterovirus (EV), human parechovirus (HPeV), rotavirus (RV), human papillomavirus (HPV), influenza virus, flaviviruses, *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*. The present and future perspectives of vaccines, as well as barriers to vaccination (e.g., vaccine hesitancy), were also main topics addressed by TIPICO.

Next milestones to reach through vaccination

Cervical cancer elimination is within reach

During his presentation, Dr. Xavier Bosch (Catalan Institute of Oncology, Barcelona, Spain) provided an overview of the current global status and progress towards the elimination of cervical cancer. Bosch outlined that in May 2018, the Director-General of the World Health Organization (WHO)

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made a global call for action towards the elimination of this pathology as a public health problem;[1] its elimination threshold has been arbitrarily defined by experts as four cases per 100,000 women per year.[2] This initiative aims to ensure that, on one hand, all girls aged <15 years old are vaccinated against HPV and on the other, that every woman over 30 is HPV-screened and, if required, treated for precancerous lesions. To achieve these objectives, an integrated policy of "cervical cancer elimination" is required within the framework of general health services which, in addition, should be achievable for all countries within a sensible and encouraging time frame. There is currently a strong socioeconomic gap in the field, where sexual behaviors and herd effects are strongly driven by regional cultural trends, with unequal screening opportunities. Updated estimates indicate that, while 38% of 15–19-year-old females are vaccinated in high-income countries, this figure falls to 4% in low- and middle-income countries,[3,4] highlighting the need for special efforts in the latter. Moreover, evidence also demonstrates the need to include males in immunization programs. Despite some limitations, mathematical models allow predictions to be made on the effectiveness of already-implemented programs. Thus, Australia could be the first country to reach cervical cancer elimination by 2030.[5] Based on its model, several worldwide scenarios have been proposed. The optimal prediction from models, explained Dr. Bosch, considers broad-spectrum vaccination coverage of 80–100% globally, plus two lifetime screenings at 35 and 45 years old to reach a final total coverage of 70%. Finally, dose schedules will be critical in terms of efficiency and vaccine availability. In this regard, preliminary data from post-hoc phase 3 studies conducted in Costa Rica and from other research projects demonstrated single-dose protection for at least 7 years,[6] justifying current clinical trials investigating reduced dose schedules.

Can we currently beat meningococcal disease?

In this session, Dr. Federico Martinón-Torres (Hospital Clínico Universitario de Santiago, Spain), Dr. Shamez Ladhani (Public Health England, United Kingdom), Dr. Rino Rappuoli (GlaxoSmithKline, Italy) and Dr. Jamie Findlow (Pfizer, United Kingdom) discussed the main advances in the vaccine prevention of meningococcal disease (MD) after presentation of some relevant data. In Europe, two quadrivalent conjugate meningococcal vaccines are available: MenACWY-TT (Nimenrix®) and MenACWY-CRM (Menveo®), which have been recently implemented in some countries given the increased incidence of MenW cases (due to a strain that originated in the United Kingdom [UK] and currently expanding even outside Europe[7,8]) and to lesser extent, of MenY cases. Additionally, two subcapsular antigen-based vaccines against MenB are licensed: MenB-fHbp (Trumenba®, indicated from 10 years of age and 4CMenB [Bexsero®], indicated from 2 months of age). Finally, two pentavalent alternatives are currently being developed, resulting from the combination of MenACWY-CRM and 4CMenB[9] and of MenB-fHbp and MenACWY-TT.[10] The UK represents a good example of the effectiveness and safety of some of these vaccines. As Dr. Ladhani explained, 4CMenB, implemented with a 2 + 1 schedule in infants, demonstrated 83% efficacy and a 50% reduction in MenB cases just 10 months after its introduction in 2015.[11] Three years later, similar trends have been observed (unpublished data) with a good safety profile. MenACWY was also introduced in 2015, targeting adolescents, who are the main carriers. Early data demonstrate that, even with low vaccine coverage (~36%), MenW cases have decreased and herd protection is now being observed (unpublished data). The experts then highlighted several important aspects of meningococcal vaccination. Dr. Rappuoli indicated that vaccination would be desirable for everyone. However, from a public health perspective, infants, followed by adolescents, should be prioritized as target populations. It is also important to stress the great potential of both MenB-fHbp and 4CMenB for providing cross-protection, for example against unrelated MenB strains, but also against different serogroups. The data from the UK suggest that the decrease in MenW cases in infants might be linked to this cross-protective effect of 4CMenB. Despite the general trend towards a decreased incidence of MD in Europe, the experts debated the recent increase in the number of MenW cases, and the urgent need for a preventive policy to help halt this epidemic, as well as any future increases. To that end, it is essential to ensure the continuity of programs that have already been shown to be effective. Furthermore, in Dr. Findlow's words, predicting and monitoring local, national and international meningococcal outbreaks, along with assessing their overall impact, would help design appropriate immunization policies. Finally, researchers discussed the recent implementation of MenACWY in the UK, whose main target is the adolescent population. Although adolescents are a challenging group in terms of compliance with vaccination schedules, Dr. Ladhani was hopeful that herd protection will occur rapidly once the teenagers targeted through the schools-based immunization program (with vaccine uptake of 80–90%) enter higher education, such as universities; additional results of the adolescent program will become available later this year.

To conclude, Dr. Martinón-Torres remarked that the tools to fight against MD are within reach. Consequently, selecting the appropriate vaccination programs, as well as the perfect time for their implementation and an appropriate surveillance system are critical to ensure the success of the strategy.

Pneumococcal vaccination: fewer doses needed for successful pneumonia prevention

Pneumonia is still a major cause of morbidity and mortality worldwide,[12,13] with *Streptococcus pneumonia* being the main causative agent, at least in cases reported outside the hospital setting (community-acquired pneumonia or CAP).[14] In TIPICO IX, two different sessions presented by Dr. Esther Redondo (International Vaccination Center of Madrid, Spain) and Dr. Shamez Ladhani (Public Health England, UK) provided updated information on pneumococcal vaccination with the 13-valent pneumococcal conjugate vaccine (PCV13) in Spain and the UK, respectively. Previous studies have demonstrated the effectiveness of this vaccine in preventing pneumonia in Europe and the USA,[15,16] even in adults aged >65

years old.[16] In Spain, an estimated 53% of cases of hospitalized pneumococcal pneumonia are caused by PCV13 serotypes,[17] highlighting the potential benefits of including the vaccine in the adult immunization program. As Dr. Redondo explained, this has led to vaccination policy changes at the regional level, with autonomous regions such as Madrid recommending PCV13 in adults from 60 years of age. In her opinion, to obtain successful outcomes, it is fundamental that programs are designed according to the epidemiological situation of the region/country. In England and Wales, PCV13 replaced the 7-valent pneumococcal vaccine (PCV7) in the infant immunization schedule in 2010, and was highly effective during the four first years of the program.[18] Despite an increase in invasive disease caused by non-vaccine serotypes, Dr. Ladhani explained that invasive pneumococcal disease is well controlled in the UK at present.[19] However, carriage of serotype 3 and 19A still remains, and disease due to these may not be eliminated with the current vaccine.[20] Because of the high herd protection offered by PCV13, the UK is currently considering a reduced priming schedule of PCV13 (1 + 1). Clinical trial data demonstrate that post-booster responses in infants primed with a single dose are equivalent or superior to those seen following the standard UK 2 + 1 schedule and, consequently, this reduced schedule might be an interesting option for countries with a mature PCV program and established herd immunity.[21] Furthermore, mathematical modeling supports only a small increase in cases across all age groups over the next decade, where the impact of non-invasive pneumococcal disease is likely to be equivalent to that of the invasive disease.

Rotavirus vaccines do work

During his presentation, Dr. Timo Vesikari (Tampere University, Finland) summarized the updates in the field of RV vaccination. Since 2006, two live-attenuated RV vaccines (Rotarix®, RotaTeq®) have been licensed,[22] which have already been introduced in 96 countries, according to the most recent data released in August 2018.[23] Implementation of the vaccine has been found to have a great global impact on mortality, preventing around 28,000 deaths in 2016.[24] Vesikari highlighted the successful introduction of immunization programs in Africa, where vaccination coverage has increased in recent years,[25] showing positive results in different countries such as Malawi.[26,27] However, its effectiveness on this continent, and in developing countries in general, is variable, probably due to several factors including malnutrition, passive transfer of maternal antibodies and co-infections, among others.[22] This might explain the discouraging results obtained in certain countries such as Pakistan.[28]

Both Rotarix™ and RotaTeq® have been found to confer protection against several RV genotypes other than those included in the vaccine, as evidenced by real-world data from Finland[29] and the USA[30]; see also.[31,32,33] In Dr. Vesikari's words, the effectiveness of the vaccine may depend mainly on dosing schedules instead of on genotype-specific protection. In Europe, RV vaccination programs have been successful in several countries, including Belgium, where vaccination coverage with Rotarix™ (RV1) is estimated at 90%[34] or the UK, with one of the highest vaccination coverage rates reported (Rotarix™, RV1).[35,36] Vesikari described the situation of Finland as an example of the optimal performance of an oral RV vaccine. Since the introduction of RotaTeq® (RV5) in 2009, the number of infection cases has significantly decreased, and vaccination coverage has reached 95%. However, certain residual disease remains, with a recent outbreak in 5 to 12-year-old non-vaccinated children and in the elderly not previously reported.[37] In conclusion, Dr. Vesikari highlighted that, despite the optimal results obtained worldwide, neither total elimination of RV circulation nor protection against emergent genotypes has been achieved, stressing the importance of continuing efforts at several levels.

New challenges and opportunities in infectious diseases

The growing importance of picornavirus

Two talks by Dr. Shamez Ladhani (Public Health England, UK) and Dr. Irene Rivero (Hospital Clínico Universitario de Santiago, Spain) focused on the growing importance of two picornaviruses: EV and HPeV. Both are a frequent cause of disease in children,[38] being responsible for some cases of meningitis and sepsis-like illness in infants.[39,40]As Ladhani explained, distinguishing between viral and bacterial meningitis is often difficult. Moreover, diseases caused by EV and HPeV are frequently associated with severe clinical presentations.[41,42]Although long-term sequelae are rare, they do occur, and are associated with severe neurological presentations,[43] making identification of individuals at risk and patient follow-up of utmost importance. Importantly, new outbreaks of different EV genotypes – EV D68[44–46] and EV 71[44,47,48] – have been reported worldwide in recent years, along with the emergence of some new HPeV serotypes.[49] Dr. Rivero commented on the present situation in the field of vaccination against these viruses, highlighting that no efficacious treatment options are available. Consequently, current efforts must be directed towards the development of effective vaccines. Furthermore, the use of new breakthrough approaches to identify diagnostic and prognostic markers, as well as putative genetic factors of susceptibility, will be useful for the management of diseases caused by picornaviruses.

Flavivirus mechanisms for human cell infection and immunocompetent animal models

In his talk, Dr. Adolfo García-Sastre (Mount Sinai-NY University, USA) explained the mechanisms used by flaviviruses to make humans their hosts, as well as the new approaches towards prevention of the diseases caused by them. Flaviviruses comprise more than 70 different viruses that, taxonomically, form a genus in the family *Flaviviridae*.[50] Some of their members include major causes of human disease, such as yellow fever virus (YFV), dengue virus (DENV) and Zika virus (ZIKV), among others.[51] The genomic structure of flaviviruses is simple, consisting of a single-stranded RNA with a large open reading frame that results in a single

polyprotein.[52] This polyprotein is cleaved into three structural proteins that are required for formation of the virion and seven nonstructural proteins, of which NS5 is key for virus replication.[53] Importantly, NS5 is also a potent and direct antagonist of IFN-I-dependent JAK-STAT signaling,[54] an immune mechanism that represents a powerful barrier to virus infection.[55] Surprisingly, as García-Sastre explained, YFV, DENV, and ZIKV evolved to antagonize the IFN-I pathway in different ways, all of them resulting in the interference of STAT2 activity (unpublished data). Based on this evidence, his group has focused on further understanding these mechanisms. The most recent data demonstrate that YFV, DENV and ZIKV NS5 proteins do not bind mouse STAT2, but do bind its human version.[56] This discovery led them to develop a humanized mouse model for ZIKV, based on replacing mouse STAT2 with human STAT2. Thus, humanized STAT2 mice might represent an immunocompetent mouse model not only for ZIKV, but also for flavivirus infection, and consequently, a first step for pre-clinical development of future vaccines.[57]

Infectomics

This session presented by Dr. Federico Martinón-Torres, Dr. José Gómez-Rial (Hospital Clínico Universitario de Santiago de Compostela, Spain) and Dr. Antonio Salas (University of Santiago de Compostela, Spain), aimed to provide an overview of how infectomics may help to solve infectious disease. The management and diagnosis of infectious disease has traditionally been done from a pathogen perspective. Considering that the same pathogen may trigger a variable spectrum of disease, the current view assumes that host-genetic factors may play a critical role in determining the outcome of infectious disease dynamics. According to the authors, promising results have already been obtained in, for example, genomics, first by way of genome-wide association studies (GWAS), where some genetic variants associated with host susceptibility to MD have been identified.[58,59] More recently, whole exome sequencing (WES) has allowed the identification of new susceptibility factors in empyema caused by *Streptococcus pneumoniae* in children[60] and in respiratory syncytial virus disease.[61] The speakers summarized the main results obtained in the emerging field of research in infectomics, understood as the study of infectomes (encoded by both host and microbial genomes, and a mirror of the interplay between pathogens and their hosts) by using systems biology and high-throughput 'omic' approaches.[62] It provides a global and integrative overview of the different 'omic' layers, including genomics, epigenomics, transcriptomics, proteomics, glycomics, and metabolomics. Reconstruction of global biochemical networks ('trans-omic' analysis)[63] requires the use of both multi-omic measurements and computational data integration (systems biology). Infectomics will contribute to precision medicine, a model that proposes the customization of healthcare, with medical decisions, treatments, practices, or products being tailored to the individual patient. In this sense, several studies have already demonstrated the existence of cell host transcriptomic signatures in different infectious diseases,[64–67] which might be considered as the patient's individual signatures, with great potential to be used for more personalized and precise treatment of the diseases. To conclude, the speakers highlighted that, although translation to patients is slow, these breakthrough approaches are slowly improving and being incorporated into routine diagnosis and prognostic methods.

Breakthrough approaches in vaccines

A universal influenza vaccine

Dr. García-Sastre (Mount Sinai-NY University, USA) discussed the most recent advances towards the development of a universal influenza vaccine. At present, most vaccines are designed to target hemagglutinin (HA), one of the main surface glycoproteins on influenza viral particles that mediate their fusion with the cell host membrane.[68] HA is comprised of globular head and stem (or stalk) regions, and the hypervariability shown by its amino acid sequences is largely responsible for epidemic and pandemic influenza outbreaks; these are the consequence of antigenic drift or shift, respectively,[68] forcing updated vaccines to be produced annually. Consequently, the development of an effective "universal" influenza vaccine capable of conferring protection against both seasonal and newly-emerging pre-pandemic strains is of utmost importance today. García-Sastre explained that a universal influenza vaccine should be multivalent and include antigens of both type A and type B viruses (including all virus A subtypes). One possible way to achieve broad protection against all influenza viruses is to develop new vaccines that induce protective antibodies against conserved regions of the HA, such as the HA stem region.[69] However, strategies to develop an HA stem-based universal influenza vaccine must overcome the HA-head immunodominance problem, that is, the ability of this region to elicit a stronger immune response. Some of those strategies include the use of headless constructs[70–77] 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. Based on these promising results, some vaccine candidates are currently being evaluated in clinical trials.

The next generation of tuberculosis vaccines

During his presentation, Dr. Carlos Martín (University of Zaragoza, Spain) summarized the main advances in the field of tuberculosis (TB) vaccination. At present, tuberculosis one of the top 10 causes of death worldwide, and the leading cause from a single infectious agent (above human immunodeficiency virus).[78] Notably, only 5–10% of infected people develop the disease, and those infected individuals have a 79% lower risk of progressive TB after reinfection than uninfected ones.[79] The Bacille Calmette-Guérin vaccine (BCG) is the only TB vaccine currently available, with 89% coverage at birth worldwide.[80] Nevertheless, despite providing strong protection against disseminated forms of the disease, BCG does not protect against respiratory forms of TB.[81] In August 2018, the WHO published the preferred product characteristics for new vaccines. Thus, these should preferentially target, on the one hand, adolescents and adults, since they constitute the main reservoir and transmitters of the disease, and on the other, neonates and infants, in which

new live-attenuated vaccines should replace BCG.[80,82] Clinical trials of several vaccine candidates have been unsuccessful over the years.[83] Recently, the results obtained in a phase 2b trial have shed new light on the field, showing that the M72/AS01E vaccine is able to provide 54.0% protection for latent TB-infected (LTBI) adults against active pulmonary TB disease, without evident safety concerns.[84]At present, 12 ongoing clinical trials are evaluating new candidates.[80] Dr. Martín focused on MTVBAC, a new live-attenuated vaccine that contains mutations in two genes responsible for the pathogen virulence; *phoP* and *fadD26*.[85] This vaccine has shown promising results in both animal models[86–89] and clinical trials. Thus, the initial findings of a phase 1a study conducted in healthy adults in Switzerland have already been published,[90] and results from a phase 1b dose-escalation safety and immunogenicity study to compare MTBVAC to BCG in newborns in a TB-endemic region of South Africa are expected for 2019 (ClinicalTrials.gov NCT: 02729571). Furthermore, a phase 2a MTBVAC study in adults with and without LTBI in South Africa (ClinicalTrials.gov NCT02933281) and a phase 2a dose-defining safety and immunogenicity study of MTBVAC in South African Neonates (ClinicalTrials.gov NCT03536117) are currently underway. In the future, efficacy studies for BCG replacement at birth and for boosters with MTVBAC in previously BCG-vaccinated adolescents/adults will be required to demonstrate better protection against pulmonary TB than the one offered by BCG.

Assessing the heterologous effects of vaccines

During his presentation, Dr. Adam Finn (Bristol University, UK) discussed the heterologous effects of vaccines, also known as non-specific effects (NSE) or "off target effects", defined as effects of a vaccine beyond their intended target pathogen or disease. Heterologous effects can be subsequently classified into downstream effects and "lateral" effects. The former occurs when, by preventing the target infection (directly or indirectly), other infections which can otherwise follow the target infection are also prevented (e.g., measles and influenza vaccines both preventing bacterial respiratory infections and deaths). The latter include those effects reported when vaccines alter host susceptibility to off-target infections, such as BCG for example, which in addition to conferring protection against TB, may induce trained immunity and nonspecific protection from infections[91] such as sepsis and respiratory infections in animals and infants.[92] The new NSE paradigm may broaden our understanding of vaccines, although the importance and implications of such effects remain controversial (reviewed by Pollard et al.[93]). The more general concept that early life immunization with live vaccines may have beneficial effects on mortality in low-income settings, and that immunization with non-live vaccines may have disbeneficial effects, especially in females, may prove to be an oversimplification. For example, young children immunized with non-live-adjuvanted monovalent H1N1 influenza vaccine had enhanced responses to an unrelated H3N2 seasonal vaccine a year later.[94] The example provided by the RTS, S/AS01 vaccine against malaria, which demonstrated promising results in a recent clinical trial, is also intriguing.[95]Although efficacious, the vaccine was unexpectedly associated with meningitis and cerebral malaria safety signals that, curiously, were only apparent in the older infant age group in the study, in whom a non-live rabies vaccine was used as a comparator/control. This raises the hypothesis that lateral beneficial NSE of the rabies vaccine could be responsible.[96]A systematic review of the literature reveals several other pieces of evidence that both uphold the notion of rabies antigen-induced protection against unrelated infections and mortality in several animal species, and at least one possible biological mechanism.[97–101] Dr. Finn concluded that further studies are required to support the biological plausibility of this hypothesis in animals and humans, leading, perhaps, to a large placebo-controlled randomized clinical trial (RCT) of the rabies vaccine in children in a high mortality setting that includes meningitis, malaria, and other infections, with mortality as the primary endpoint.

Vaccinomics

Thanks to the control of infections through the implementation of hygiene measures, the use of antibiotics and the introduction of vaccines, a remarkable improvement in health and an increase in life expectancy have occurred in the last century. Dr. Rino Rappuoli (GlaxoSmithKline, Italy) focused his talk on vaccinomics, defined as "the integration of immunogenetics and immunogenomics with systems biology and immune profiling" and based on the "omics" technologies and on bioinformatics for the development of next-generation vaccines.[102] Rappuoli reviewed the milestones in the history of vaccine development, from classical vaccinology in the 1930s[103] to reverse vaccinology in 2010, a new approach based on the ability to access the genomes of microorganisms, first made possible in 1995, when Craig Venter published the genome of the first free-living organism (revised in[104]). The first pathogen addressed by the reverse vaccinology approach was Meningococcus B (MenB). Since then, sequencing of the B cell repertoire, the high throughput discovery of protective human antibodies and the increasing structural characterization of protective antigens and epitopes have provided the molecular and mechanistic understanding to drive the discovery of novel vaccines that were previously impossible. This is known as the reverse vaccinology 2.0 era.[105] In addition, other next-generation technologies for the development of new vaccines are currently available, including structural biology, synthetic biology and the development of adjuvants. To conclude his talk, Dr. Rappuoli emphasized the need for a rational application of the new technologies used for vaccine development. Thus, vaccines should focus on new targets, such as the elderly and developing countries,[106] where life expectancy is reduced and infections are a major cause of death. New vaccines should also target emerging infections, and might be useful in the field of immunotherapeutics, to prevent diseases such as cancer or neurodegenerative diseases. In Rappuoli's opinion, we are not prepared for the challenge posed by the new technologies, as evidenced by the unsuccessful initiatives towards the global implementation of vaccines over recent decades. As a result, new policies are required to take full advantage of them.

The practice of vaccination: hesitancy and false contraindications

Vaccine hesitancy

Despite the high vaccination coverage rates registered in the European region according to the WHO, vaccine hesitancy remains an important issue that is undermining individual and community protection from vaccine-preventable diseases. In this session, Robb Butler (UNICEF, New York, USA) went into detail about this phenomenon, its causes, and the actions that must be taken to respond to it, an objective also addressed by a WHO SAGE working group (*Strategic Advisory Group of Experts on Immunization*) created in 2012.[107] Vaccine hesitancy occurs on the continuum between high vaccine demand and complete vaccine refusal. It is a complex phenomenon, influenced by multiple social, economic, cultural, political and religious factors. According to the SAGE working group,[108] the three main determinants of vaccine hesitancy are complacency, confidence, and convenience. Complacency may exist at individual, community, healthcare center, and political level when perceived risks of vaccine-preventable diseases are low, and vaccination is not considered a worthwhile investment. Confidence is defined as trust in the effectiveness and safety of vaccines and in the administration system that delivers them. Finally, convenience encompasses the factors that may affect vaccine uptake, such as geographical accessibility and affordability among others. Given this complexity, and in order to provide tools and methods to design targeted strategies, the Guide to Tailoring Immunization Programmes (TIP) was created.[109] As Butler also explained, to fully understand hesitancy, it is important to know that individual decisions are often based on emotions, where risk perception is critical. Individual risk perception is based on probability and severity; individuals perceive risk according to how likely they believe it is that a specific type of event will take place (probability), and how concerned they are with the consequences of such an event (severity).[110,111] To facilitate risk perception, the human being has developed 'mental shortcuts', also known as heuristics, that may sometimes lead to biased judgments and decisions.[110,111] All these factors must be considered when designing strategies to combat vaccine hesitancy. Strategies should always correct misinformation[112–114] and deliver messages in the most culturally appropriate way. In this regard, it is important to consider how different framing of the same fact can lead to different risk-perception and behavior.[115] Thus, emphasizing the positive rather than the negative aspects of vaccines increases preference and support for them.[116–118] He also noted the power of narratives versus scientific evidence and data. Furthermore, since our perceptions and behaviors are influenced by (often unconscious) triggers that create certain emotions, it is advisable to utilize those that create positive associations and avoid the negative ones. To conclude, Butler stressed the importance of the education sector in anchoring future resilient communities, by reaching the parents of tomorrow with vaccination education in school settings. He concluded by stating that every immunization program should ultimately strive towards building resilient demand – where the community's functional capacity is able to positively cope with significant anti-vaccination rhetoric and guard its members against media amplification and social copying/contagion associated with vaccine safety fear-mongering, myths, and politicization of vaccination, where it surfaces.

False contraindications

Dr. Martinón-Torres (Hospital Clínico Universitario de Santiago, Spain) discussed false contraindications and their influence on vaccination. False contraindications are common in routine clinical practice,[119,120] and partly explain the low vaccination coverage registered in some countries and the missed opportunities for immunization. Importantly, median missed opportunities are estimated at 32% by the WHO,[121,122] representing interesting targets for focusing efforts to improve vaccine uptake. As Martinón-Torres explained, education is critical to avoid missed opportunities and to fight against false contraindications. In this regard, he stressed the role played by healthcare professionals (HCPs), whose proactive recommendation is fundamental. This recommendation must be made based on a deep knowledge of the topic, providing evidence that helps to support it. Different initiatives have been promoted in an attempt to improve these aspects. These include the ESPID Wiser Immuniser online course, developed by the European Society for Paediatric Infectious Diseases (ESPID) and aimed at any HCP involved with vaccination, or the training and educational material developed by WHO-Europe with the intervention of the WHO collaborating center in Vaccine Safety of Santiago de Compostela, Spain.[123] All of them have been endorsed by the WHO ETAGE (European Technical Advisory Group of Experts on Immunization) expert group.[124] To conclude, Dr. Martinón-Torres stressed that a combined global effort (communities, individuals, HCPs, healthcare authorities) can help to improve the perception of vaccines, and to eliminate doubts and false myths.

Conclusions

Vaccination is key to preventing and managing infectious diseases. Although several vaccines have demonstrated their effectiveness, such as RV, HPV, PCV13, BCG, influenza, and meningococcal vaccines, there is still a need for better candidates that help to prevent new emerging serotypes/strains, and for vaccines against EV, HPeV and flaviviruses which, to date, have no preventive alternative. The development of new vaccines will be possible thanks to next-generation technologies and vaccinomics. The emergence of infectomics will ostensibly allow precision medicine that will positively impact on vaccination outcomes. The design and implementation of appropriate immunization strategies is also crucial for success, and requires awareness of the importance of vaccination at all levels, which can only be met through education. In this sense, education is also critical to combat vaccine hesitancy and false contraindications, two important issues that undermine protection from vaccine-preventable diseases.

Disclosure of potential conflicts of interest

FM-T has received honoraria and/or research grants from Astra Zeneca, GSK group of companies, Janssen, Merck Sharp & Dohme, Pfizer, and Sanofi Pasteur, and trials fees paid to his institution from Ablynx, Astra Zeneca, the GSK group of companies, Janssen, MedImmune, Merck Sharp & Dohme, Novartis, Novavax, Pfizer, Regeneron and Sanofi Pasteur. IRC has received research grants and honoraria as an advisor and speaker, and for attending conferences and practical courses from GlaxoSmithKline, Sanofi-Pasteur, Merck Sharp & Dohme, Novartis, and Pfizer. JGR has received honoraria as an advisor and speaker from GlaxoSmithKline, Merck Sharp & Dohme, and Pfizer. AG-S has received a research grant from GSK to explore universal influenza virus vaccines, and he is the inventor of several patents owned by the Icahn School of Medicine at Mount Sinai in the field of influenza vaccines. CM is co-inventor in three patent applications on 'Tuberculosis vaccines'' filled by the University of Zaragoza. RR is a full-time employee of GSK group of companies. The rest of the authors declare no conflicts of interest.

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