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New paths for sustainable solutions to tackle global and emerging infectious threats

A B S T R A C T

With the dramatic background of a newly emerged virus (SARS-CoV-2) spreading around the world, Coronavirus and other infectious health threats for the human and animal populations were illustrated and debated in excellent presentations at the IABS meeting 26–28 of February 2020. Historical evidence of pandemics and lessons learned from recent epidemics or epizootics caused by many pathogens (*e.g.,* Ebola, Zika, and African Swine Fever viruses) illustrated the overarching need for close international cooperation. New and old technologies in vaccine development and their use were presented, resulting in a call for greater interaction between the human and the veterinary fields in order to leverage the expertise and knowledge in both human and animal medicine. The One Health concept was also emphasized for eliminating the 59,000 fatal human rabies cases annually attributed to unvaccinated dogs. For preventable, infectious diseases commonly spreading in the poorer regions of the world, a new regulatory approach and governance structure was called for to give access to affordable vaccines. Vaccines were touted as one of the most successful health invention ever introduced; on a similar level to health improvements due to clean water.

1. Introduction

The International Alliance for Biological Standardization (IABS) celebrated its 65th anniversary with a festive ceremony at the magnificent Town Hall in Lyon, France, commemorating the founders of IABS and their vision for scientific advancement of biologicals. The reception was followed by a two-day conference on *New paths for sustainable solutions to tackle global and emerging infectious threats.* The presenters expressed appreciation of IABS's role in the past, present, and future battle against infectious diseases in the world and applauded the close cooperation with international organizations and stakeholders.

2. Tackling emerging infectious diseases

Stanley Plotkins opened the conference with an overview of the history and future of vaccination and was followed by excellent presentations from a broad range of experts (see list of presenters in the end of the report).

The development of vaccinology is an amazing scientific and biologic journey from the very earliest observation by Lady Mary Wortley Montagu who witnesses smallpox prevention by variolation in Turkey, over Edward Jenner's finding that milk maids were immune to smallpox and later introduction of vaccinia virus to immunize humans, and to Louis Pasteur who attenuated virus and bacteria in the laboratory and started vaccine production. Many new strategies for discovery and development of vaccines are employed in modern times, *e.g.,* viral deletion mutants, replicating vectors, DNA-plasmids, and the use of improved adjuvants. However, several deadly diseases are still not covered by vaccines, *e.g.,* HIV, where clinical trials fail because humans do not develop neutralizing antibodies except after long exposure to the virus or antigen. The impact of vaccination on human and animal health is hard to exaggerate and compares to the health improvements due to clean water.

The global impact of vaccines was exemplified by measles where 21 million deaths have been averted between 2000 and 2017, leaving an estimated 110.000 annual measles deaths [1]. However, outbreaks have recently increased to a situation where many countries have too low vaccination coverage to control the disease. Global vaccination currently covers 9 out of 10 children, which still leaves 19 million under-vaccinated children primarily in some African countries.

Maternal immunization may be a solution to neonatal mortality, *e.g.* from sepsis and respiratory syncytial virus infections, where immunity is transferred in-utero. Pertussis vaccination of mothers after an outbreak in the UK led to a dramatic drop in mortality in newborns [2]. It was emphasized that the normal background level of neonatal morbidity and mortality, abortion rates, and birth defects must be established before maternal vaccinination campaigns begin to ensure a fair assessment of vaccine safety.

Vaccine hesitancy is a growing concern, which is not new but increasingly expressed. It may be a function of the perception of reduced risk of disease outbreaks combined with observation of adverse events attributed to vaccination. Education about vaccines in medical schools is almost absent, which is unfortunate because patients and parents will ask their doctor's advice. In the area of social media, it is increasingly important to tell the factual stories about the benefit of vaccination.

Prevention and control of animal infectious diseases are important for managing the risk of zoonotic disease, for animal health, and for maintaining global food security. The last 40 years, numerous zoonotic diseases have emerged, *e.g.* HIV, Lyme disease, bovine spongiform encelopathy (BSE), avian influenzas, Nipah virus, West Nile virus, Sudden Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Zika and latest the pandemic SARS-CoV-2 coronavirus. The factors that contribute to (re-)emergence of human and animal diseases are the rapidly expanding human population, intensive animal production, increased “backyard” animal holdings, close interspecies interaction facilitating pathogen transfer, climate change causing wider insect spread, globalized trade and travel.

In 2018, African swine fever spread in Asia with a highly virulent serotype causing almost 100% mortality in pigs. There was no vaccine available because the virus is a difficult pathogen, and colossal stamping out campaigns were initiated. The Chinese pork production, which covered half of the world's production, halved within 1–2 years and the meat price doubled.

Human rabies causes approximately 59,000 deaths worldwide per

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year and 98% of these cases are caused by canine rabies virus variant. Safe, killed rabies virus vaccines available for use in dogs helped eliminate canine rabies in the USA. International will to tackle the syndrome is currently missing and a serious call for action was expressed based on OIE and WHO global strategic framework.

Prevention and control of transboundary animal diseases that threaten food security and public health depends on the “One Health” principle and cooperation at an international level. This entails competent veterinary services, movement control of animals within a country and across borders, surveillance and vaccination programs, together with stamping out of diseases and controlled marketing of animal products.

3. New technologies and vaccine platforms

Approximately three million individuals die of vaccine-preventable diseases each year. Six of the top ten leading causes of death in low resource settings could potentially be prevented by vaccination [3]. Tuberculosis, which causes 1.5 million deaths annually, Malaria, which causes 435,000 deaths annually, and HIV are pathogens with considerable biological complexity. The antigen selection has been convoluted by the complex lifecycles of *Mycobacterium tuberculosis*, *Plasmodium* species, and Human Immunodeficiency Virus with each having the ability to establish chronic, asymptomatic infection and presumably escaping immune detection for at least part of the cycle. The challenges inherent to translation from the laboratory to clinical trials during the development of any vaccine include the complexity of the manufacturing process and analytical methods in the early phase, and the clinical assay optimization and running of large clinical trials in the later phases. Global international research cooperation is necessary to understand the immunopathogenesis and protection mechanisms while simultaneously testing vaccine candidates.

New engineering technologies have transformed the way we think of vaccines, making us able to use precise structure-based design, and manufacture faster from a gene synthesis platform. The emergent coronavirus was used to illustrate the potential for rapid vaccine development. The viral sequence selection was conducted in just three days, the production and proof of immunogenicity was completed in just 38 days, and clinical trials were expected to start in March 2020. This was possible because multiple groups work together and because a lot of preexisting work on coronavirus is available in the scientific community. For an unknown emerging virus, this progress was estimated to take years and therefore basic research was emphasized to play a huge role in preparedness for emerging epidemics.

Acceleration of development time and reduction of costs are paramount to future vaccinology for the global population. Structural biology is becoming more and more important *e.g.* in reverse vaccinology, engineered recombinant proteins, and Self-Amplifying mRNA (SAM) vaccines. Synthetic approaches to vaccine manufacturing have the potential to streamline development and enable rapid production of effective and safe vaccines. Pre-clinical proof of principle has been achieved for multiple SAM vaccines, which could radically simplify the way rationally-designed vaccine antigens are discovered, developed and manufactured [4].

The meeting called for setting up more collaboration between industry and academics to increase interactions and speed up the use of new scientific understanding. A successful vaccine development program contains five elements; worldwide surveillance alliances, traditional and rational vaccine development, global research and development capabilities, flexible manufacturing capacity, and competent regulatory authorities.

4. Pandemics and vaccine field efficacy

Reactive vaccination strategies to contain global and emerging infectious threats has been implemented in many epidemics, *e.g.,* mass vaccination of all individuals, cluster vaccination of schools or workplaces, and ring vaccination of either geographical or in-contact rings around the outbreak. The number of averted cases per 1000 doses of vaccine is much larger with ring vaccination than other strategies. In recent Ebola outbreaks, ring vaccinations reduced the risk with 75% for those in the ring even with just 50% vaccination coverage due to the difficulties with identifying the contacts and contacts-of-contacts [5].

Mathematical modelling based on the specific pathogen parameters can be used to design trials, evaluate spread of the virus, and decide on optimal control strategies. As the IABS meeting took place just when the COVID-19 spread from Asia to Europe and the Middle-East, a real-time modelling and outbreak response was performed for the audience, providing a simulation based on estimated key parameters like incubation period, R_0, asymptomatic spreading, and case-fatality ratios, estimating the predicted outcome of a pandemic. The modelling can also be used to evaluate early control policies, *e.g.,* travel restrictions, contact tracing, and school closures.

Preparedness aims to flatten the curve of a pandemic and especially social distance and protection equipment may work in the early phase to slow down spreading. Early antiviral medication was also discussed as a tool to control the impact of epidemics. Influenza vaccines are strain specific due to the fast antigenic drift in the virus strains, so they soon become obsolete and stockpiling of large amounts of vaccine is not useful.

A historical overview showed that zoonoses caused human pandemics for thousands of years, exemplified with influenza, measles, smallpox, and coronavirus. After a first pandemic, which often rolls over a territory in several waves, they may become epidemic or endemic human diseases. For example, the epidemic “Spanish Flu” of 1918 became a seasonal influenza type after approximately five years, and we know of four coronaviruses that exist as common colds, which may have been pandemics once.

During the outbreak of Zika virus in 2017, a vaccine was produced and tested very fast but still came too late because the outbreak had burned through the population before it was available. The manufacturer is now trying to license the vaccine based on serology to protect pregnant women and babies.

5. Successful One Health networks build on trust, complementarity, and mutual benefits

The round tables discussions explored how to effectively transfer knowledge from the veterinary to the human field and vice versa. During centuries most vaccine technologies have been first developed and used in animals before moving into humans. Mass production of veterinary vaccines at low price for farm animals gives hope for affordable human vaccines. Cross-fertilization between the two fields requires an extra effort in projects but could be facilitated if funding organizations would stress the desire for vet/human representation in each funded project. Many priority vaccines share research, technology, or pathogen family with similar veterinary projects although some physiological parameters and the benefit-risk models are different. This is demonstrated by the narrower range of technologies used in human vaccinology, such as very few types of adjuvant.

Animal models could be much better explored to predict human efficacy, and there is a need to look for a broad input from veterinary science. Before human challenge models are developed, animal challenge models may have existed for decades. Some cooperation initiatives are taken, *e.g.,* the MERS animal model in camels was set up by a human company. On the other hand, it can be frustrating to have to rely on animal models and potentially end up with wrong doses or irrelevant immune responses, so the final answer is always in the target population requiring the further development of human challenge models. The decrease in companies that have both a human and a veterinary vaccine department is an obstacle to fast cooperation.

Global collaborations and data sharing are critical for rapid

development and in-depth knowledge of key viral families and platform vaccine technologies can accelerate product development for new diseases. Ideally promising vaccine or therapeutic candidates are available at the beginning of an epidemic to facilitate evaluation of their efficacy in the field. The WHO works on standardization of human vaccines, including for zoonotic diseases, while the OIE builds technical standards for animal diseases and vaccines, *e.g.* bovine tuberculosis, and promotes awareness and capacity building globally.

The Zoonoses Anticipation and Preparedness Initiative (ZAPI) is a public-private partnership project funded through the Innovative Medicines Initiative (IMI). It aims to enable swift responses to major new infectious disease threats and deliver effective vaccines and therapeutic antibodies against (re-)emerging zoonotic diseases within a few months after first clinical cases, *i.e.,* providing a One Health « standardized tool » to address disease outbreaks in animals and humans. The methodology comprise fast GMP production for several targets by identifying immunogenic subunit domains that are then coupled on protein scaffolds.

A successful network requires a clear vision that all partners can align to and a team where all members can learn from each other, *i.e.,* a true partnership with partners on the same level and no dominating powerful player. Three factors are paramount: trust, complementarity, and mutual benefit. It takes time to build up the trust to ensure sharing of knowledge. Complementarity means that people who are not too alike and who challenge each other must be brought together, for example by mixing academics, industry, and biotech people and having a manager to direct the team. In mutual benefit, the synergies must be used but without duplicating efforts. In international development projects it is essential to involve the countries/people that are the key stakeholders. Bridging the veterinary and human side in projects could be very beneficial but it requires the extra step to acknowledge the usefulness of differences.

Many networks are on pre-competitive research while delivery of concrete products require a cooperation under confidentiality or agreements. It is necessary to develop an environment where options can be shared and compared, *e.g.,* candidate vaccines, before deciding which one to go forward with. Many networks arise in areas where normal industry development has failed. Networking among regulators, both for technical topics and best practices, must not be forgotten.

6. Governance of sustainable vaccination in all regions

In many areas of the world, vaccines are not available due to costs and distribution obstacles. The vaccine industry outside the EU and US is developing rapidly, *e.g.*, in India and China, which may contribute to reduce the time of license and cost of production down from 12 to 15 years and 1 billion $ for a licensed product, including manufacture in less expensive facilities. Several public, private, or philanthropic institutions are trying to improve the situation. For example, the European Vaccine Initiative (EVI) develops vaccines for poverty or neglected diseases like Malaria, Zika, Nipah, and Leishmaniasis that are not developed by industry. The approach is based on cooperation because few institutions can do the entire development pathway comprising screening, optimization, adjuvants, delivery, analytical services, GLP, GMP, animal models, and clinical trials. Gavi, the vaccine alliance, funds immunization programs and vaccines for the poorest countries and correlates the amount of funding with the income of the country so the help is phased out when the country's economy improves.

A new governance model was called for to accelerate global health innovation and impact, where private and public partners are aligned in a manner that proactively defines roles and responsibilities, specifies key data needed for future policy decisions, secures procurement and implementation, and shares risks in a reasonable manner. The overarching challenges for the private industry are the limited return on investment for many vaccines against poverty diseases, the opportunity cost, *i.e.,* money taken from other development projects, inconsistent resourcing due to shifting global attention or disease prevalence, and scientific complexity of many “remaining” pathogens, *e.g.,* HIV, which continues to be a disaster in the human population. There are examples of private industry companies that despite lack of commercial opportunity decided to support the development of an Ebola vaccine.

Health economics demonstrate an underuse of vaccines, partly due to the low understanding of the total value for money by vaccination when not only health parameters counts but also the economic benefits in society. Vaccination is among the most important public health innovations of all time and saves 6 million lives each year, including those of 2.5 million children [6]. However, in Europe less than 0.5% of the Gross Domestic Product (GDP) is devoted to prevention and less than 0.5% of health expenditure (or 0.05% of GDP) is devoted to vaccination [7]. The growing awareness of socio-economic benefits of vaccination demonstrates benefits achieved in education [8], productivity [9], poverty reduction [10], fiscal [11], and macroeconomic impact; the latter demonstrated in the ongoing COVID-19 pandemic. A better appreciation of the full socio-economic benefits of vaccination, in which return on investment from investing public funds in healthcare is about 300%, should lead to greater spending, innovation, and access.

Regulators must deal differently with emergency situations that require a lot of flexibility. Some mechanisms exist already in regulatory legislation and acceptance, but a coordinated understanding and end-to-end process is missing. Expert communities, such as the IABS, were suggested to be available for discussion with regulators on emerging or complex diseases that have failed to get an industrial vaccine licensed.

Research and development in rich areas of the world does not mean more access in poor areas after a while, i.e. the *trickle-down* model does not work. The current economic model creates the lack of availability of medicines to poor children due to the lack of income for the private industry manufacturers. Outbreaks are opportunities for philanthropic and public investments to create new governance systems with better decisions and not based on return of investment. However, when vaccines are developed in common with public bodies but licensed by a private company, the public institutions often lose influence on the final pricing, production facilities, and distribution areas. Medicines and vaccines are typically ordinary goods existing by the rules of the financial market; however, a new governance model should provide a new special status to tackle this topic particularly in poorer regions, because you cannot both maximize profit in medicines and have affordable medicines for all.

7. Conclusion and recommendations

Vaccination is complex and complicated, but its value to humanity and animal health makes it one of the most important medical discoveries ever. Many new strategies for discovery and development of vaccines are employed in recent time, but several deadly diseases are still not covered. Education about vaccines in medical schools is almost absent, which may hamper doctors’ advice. In the era of social media, it is increasingly important to tell the factual stories about vaccination.

Maternal immunization may be a solution to neonatal mortality, where immunity can be transferred in-utero, but the normal background level of neonatal morbidity must be established before vaccine trials start.

Many priority human vaccines share research, technology, or pathogen family with similar veterinary projects although some physiological parameters and the benefit-risk models are different. The last 40 years, numerous zoonotic diseases have emerged, *e.g.* HIV, Lyme disease, bovine spongiform encelopathy (BSE), avian influenzas, Nipah virus, West Nile virus, Sudden Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Zika, and the pandemic SARS-CoV-2 coronavirus. Animal models could be much better explored to predict human vaccine efficacy, and there is a need to look for a broad input from veterinary science. Prevention and control of transboundary animal diseases that threaten food security and public health

depends on the “One Health” principle and cooperation at an international level. Benefits within reach like tackling the many human fatalities from canine rabies is currently missing an international will, and a serious call for action was expressed.

Acceleration of development time and reduction of costs are paramount to future vaccinology for the global population. Global collaborations and data sharing are critical for fast progress, and in-depth knowledge of key viral families and platform vaccine technologies can accelerate product development for new diseases. Abundant preexisting research on coronavirus speeds up the development towards control and vaccination for COVID-19, and robust basic research is instrumental for adequate preparedness.

The meeting called for setting up more collaboration between industry, academics and other stakeholders to increase the use of new scientific understanding. Three factors are paramount in creating successful networks: trust, complementarity, and mutual benefit.

Mathematical modelling based on the specific pathogen parameters can be used to design trials, evaluate spread of the virus, and decide on and monitor control strategies in epidemics. Regulators and health authorities must deal differently with emergency situations that require a lot of flexibility. The growing awareness of socio-economic benefits of vaccination, besides the direct health improvement, demonstrates benefits achieved in education, productivity, poverty reduction, fiscal, and macroeconomic impact.

A new governance model was called for to accelerate global health innovation and impact, where private and public partners are aligned in a manner that proactively defines roles and responsibilities, specifies key data needed for future policy decisions, secures procurement and implementation, and shares risks in a reasonable manner. Particularly to improve the availability in poorer regions, medicines must be governed better because it is not possible at the same time to maximize profit in medicines and have affordable medicines for all.

Declaration of competing interest

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Speakers:
Stanley Plotkins (University of Pennsylvania).
Kathryn Edwards (Vanderbilt University)
James A. Roth (Iowa State University).
Penny Heaton (Bill & Melinda Gates Medical Research Institute).
Andrew J. Pollard (Oxford University).
Margaret Ackerman (Dartmouth College).
Barney Graham (NIAID).
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Sangheeta Sagar (Sanofi).
Ira Longini (University of Florida).
John Edmunds (London School of Tropical Hygiene & Medicine).
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