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Vaccination: Scientific and social perspectives

Summary report of a European Conference held on

22 October 2018 in Amsterdam

Disclaimer

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the European Academies Advisory Council (EASAC), the Federation of European Academies of Medicine (FEAM), the Netherlands National Institute for Public Health and the Environment (RIVM), the Royal Netherlands Academy of Arts and Sciences (KNAW) and their members.

All web references were accessed in December 2018.

Acknowledgments

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Overview

Vaccination is one of the greatest advances in medicine and it remains the major way to combat communicable diseases in humans and animals. Despite the contribution made by vaccines to people's health and well-being, vaccination programmes today face major challenges in the EU: declining coverage, supply shortages and growing vaccine hesitancy leading to refusal.

In recent years vaccination has also become a matter of controversy in which doctors, scientists and vaccine producers are under attack by ill-informed sceptics. This conference, which follows the recent Commentary on Vaccination in Europe by the European Academies Advisory Council (EASAC) and the Federation of European Academies of Medicine (FEAM), set out to identify the scientific issues relevant to future vaccine development and vaccine policy.

Moderators: Prof. George Griffin and Prof. Jos van der Meer

Programme

Welcome and introduction

The Moderator of the morning programme, **Prof. George Griffin, President of FEAM and Emeritus Professor of Infectious Diseases, St George's Hospital, University of London**, opened the meeting and introduced the first speaker.

A warm welcome was delivered by **Prof. Wim van Saarloos, President of the Royal Netherlands Academy of Arts and Sciences (KNAW).** Prof. van Saarloos said the symposium was timely, as evidenced by a number of journalists being present, reflecting the high level of interest in the topic from the general public as well as key stakeholders. He then explained the goals of each of the organisations jointly hosting the meeting: KNAW, EASAC, FEAM, the Netherlands National Institute for Public Health and the Environment (RIVM).

Vaccination has been considered one of the great success stories of science. Indeed, Steven Pinker's book *Enlightenment Now* provided a list of the hundreds of millions of lives saved through vaccination programmes. But the public discourse on side effects has moved on and been coloured, in part, by the accessibility of web-based information, of varying degrees of veracity.

Prof. Jos van der Meer, Immediate Past President of EASAC and Emeritus Professor of Medicine, Radboud UMC, introduced the EASAC-FEAM Commentary on Vaccination. The background to the Commentary goes back to an EU consultation earlier this year. Solitary voices will always have relatively little influence, but a collective voice based on a thorough

exploration of the issues could be very powerful. Hence the development of the joint commentary, today's meeting and a cross-sectoral policy workshop on the topic to be held by the FEAM European Biomedical Policy Forum in Brussels on 19 November 2018.

Box 1: Ten key recommendations as a result of the EASAC-FEAM collaboration to date

1. Investigate reasons for low and decreasing vaccine uptake at the level of EU Member States in order to develop tailor-made interventions. Make use of the WHO TIPS programme.
2. Develop and implement a European vaccination card and registry. Do not give normalisation of vaccine programmes (i.e. the choice of dose and timing) among different countries a high priority.
3. Recognise that not all vaccines in the vaccination programmes are of equal relevance for public health and individual protection. Make priorities within the programmes.
4. Recognise that not all vaccines are of optimal general quality in terms of efficacy and side effects (see recommendations 9 and 10).
5. To deal with the problem of vaccine rejection and hesitance, realise that the approach to vaccine hesitant, vaccine resistant and vaccine rejecting groups is different. With the help of social scientists, develop strategies to enhance vaccine uptake in vaccine hesitant and vaccine resistant individuals.
6. Develop a monitoring system for vaccine shortage and stimulate vaccine production by industry at the European level ensuring safety and quality of manufacturing.
7. Revisit the BCG vaccination programmes in childhood: the vaccine does not induce long-lasting protection against tuberculosis and there is a serious worldwide shortage of the vaccine.
8. Investigate and optimise vaccination schedules for those vaccines for which there is a shortage.
9. Develop a priority list of those vaccines that need improvement.
10. Develop a priority list of vaccines and adjuvants for which there is high need.

Prof. Jaap van Dissel, Director of the Centre for Infectious Diseases (CIB) gave a presentation entitled 'Not all vaccines are equal'. Immunity may follow natural infection or vaccination, which may be administered in different ways. Vaccines, like any medicine, can cause – usually mild – side effects and also, like other medicines, there is a range of efficacy. In terms of the dynamics of the risk-benefit ratio, public confidence can be impacted by reports of side effects or by outbreaks of the disease. Ideally, confidence sustains in the long term, leading in its purest form to eradication of the disease with the need for vaccination being eliminated. But

there is a strong cultural dimension to this process which can hinder speed of progress or even cause regression, often shaped, in part, by media coverage.

Vaccine composition differs, e.g.:

- inactivated
- toxoid
- live, attenuated vaccines
- subunit
- and conjugate vaccines.

Vaccines have developed significantly over time, from variolation before the time of Edward Jenner, to conjugated vaccines and those used in cancer; from 10,000 people with few data points to few people with 10,000 data points, as we move towards greater personalisation.

But why should we vaccinate? Reasons include:

- personal protection
- public health altruism and public protection
- personal altruism – e.g. when a pregnant woman is vaccinated, she also protects the unborn child
- enforcement by the law or an employer – e.g. if you are an airline pilot you need to be protected against yellow fever if you have to fly to Sao Paolo.

Risk of contagion needs to be taken into account, alongside range of efficacy. For example, measles and smallpox are very contagious, being carried by airborne means. Set alongside this is the level of social networking of at-risk individuals – teachers are more likely to become infected than an individual who works alone all day with little personal contact during their work. Spread of respiratory infection from children to parents and grandparents is well recognised.

Herd immunity is extremely important and is defined as immunity induced by vaccination which reaches a community level (often as high as 80%) which prevents transmission of infection. In certain areas where vaccination rates are low, for example the 'Bible Belt' in USA, herd immunity is not achieved.

Prof. van Dissel explained how the Dutch government attempts to reach herd immunity. This is done partly through working with a wide range of stakeholders, in particular the Health Council, at every stage from product authorisation to pharmacovigilance. Ultimately, the personal burden needs to be placed in the balance with the societal burden so that recommendations can be derived from an appropriately designed quantitative process.

Evaluation of the Dutch National Immunisation Programme is carried out in a number of ways e.g. disease and pathogen surveillance, with meningococcal disease as a case study, which

allows close analysis across the age range. Low uptake of the HPV vaccine, to protect against cervical cancer, is of particular concern. In 2017, there were 800 cases and 200 deaths from cervical carcinoma in the Netherlands. Understanding why HPV vaccine uptake is low is a pressing public health issue, and needs to include awareness of the benefits to be derived from vaccinating males in addition to females. It is also important to identify the health profile of immigrants, whose risk factors to infection may differ significantly according to background and where vaccination rates may be very low.

Dr. Piotr Kramarz, Deputy Chief Scientist of the European Centre for Disease Prevention and Control (ECDC), presented on 'Vaccine coverage in the EU', in particular what can be done to achieve better coverage. Dr. Kramarz explained that the ECDC mandate was to foster the exchange of best practices and experience with regard to vaccination programmes, in order to co-ordinate the collection, validation, analysis and dissemination of data at the European Community level, including on vaccination strategies.

In April 2018, the European Commission adopted a proposal for a Council Recommendation and a Communication on Strengthened Co-operation against Vaccine Preventable Diseases, with a focus on three pillars for action: 1) tackling vaccine hesitancy and improving vaccination coverage; 2) sustainable vaccination policies in the EU; 3) EU co-ordination and contribution to global health. This creates the momentum to stimulate debate and share ideas which can inform the work of policy-makers and the biomedical community in these areas.

Using measles as an example, the trend of vaccine uptake decreasing across the EU/EEA is apparent and yet also highly variable between countries, as seen from significant outbreaks in Bulgaria and France leading to more than 20,000 cases, and 15,000 cases, respectively. Moving to the issue of pneumococcal disease, we see that vaccine scheduling is important, including catch-up campaigns where appropriate. The VENICE project is helping the ECDC review policy issues and vaccination coverage data requiring specific attention e.g. poor HPV vaccination uptake by country. Moving on to another vaccine-preventable disease, influenza, Dr. Kramarz mentioned that, in some countries, uptake of seasonal influenza vaccine can be as low as 5% in target age groups.

The reasons behind this problem are many and often specific to disease, vaccine and community. For example, in some parts of the US, children can be exempted by a 'personal belief exemption', with some schools having up to 70% of children being exempted in this way. This fuels the vaccination paradox whereby wealthy societies may have coverage comparable with some of the world's poorest countries.

One of the main reasons for vaccine hesitancy and refusal is the insidious impact derived from a range of conspiracy theories. At the societal level, the fact that a divergence of opinions exists and seems to be growing can itself perpetuate levels of hesitancy or scepticism.

A particular problem is the knowledge and beliefs of healthcare professionals whose primary concern is often safety. This group can be targeted with specific education and training programmes.

In every country there is an advisory committee on immunisation (NITAG) and the ECDC works to establish a platform for collaboration of these bodies so that they can share their experiences. ECDC is also finalising technical guidance on Immunisation Information Systems (IIS) based not only on a literature review, but combined with interviews with experts from across the world. This will be published in November 2018.

Finally, the IMI-funded ADVANCE project is now at a late stage and aims to describe a prototype of a framework for rapid, integrated risk-benefit assessment of vaccines based on real world and real time data.

Overall then, ECDC suggests that:

- implementing/improving electronic monitoring of immunisation systems would be helpful to support performance evaluation of programmes
- access barriers to vaccines be reduced (financial, structural and legal) as much as possible to increase vaccination coverage where needed
- vaccination status of healthcare workers be more of a focus (particularly influenza vaccination)
- healthcare professionals, especially in primary care, need to be empowered to be effective advocates for vaccination.

Prof. Ron Fouchier, Professor of Virology, Erasmus MC, spoke on 'How to improve the flu vaccine', beginning with what influenza is clinically and how it is far from being just a serious cold. There are three types of influenza, A, B and C, but as C is mild, vaccination programmes target types A and B. Antibodies after vaccination are directed against hemagglutinin, but the problem is that there are at least 16 varieties of hemagglutinin and those can change through mutation and gene reassortment.

There have been 4 major pandemics of flu over the last century, the worst being in 1918, which caused over 50 million deaths. The most recent was Mexican flu in 2009, which caused <200,000 deaths, a significantly lower figure, partly because of prevailing levels of population immunity. Annually now there are around 0.5 billion cases of influenza, with the elderly population and immunosuppressed most at risk of severe disease and death.

The current flu vaccine is largely effective, but varies greatly. There is a 70%-90% effectiveness in healthy adults, but with antigenic drift changing the profile of the virus this efficacy can vary and be difficult to sustain. Moreover, lower effectiveness is reached in target populations with poor immunity. The Cochrane Review of the effectiveness of the flu vaccine casts doubt on its levels of efficacy, but experts have identified several problems with the review. Effectiveness should be based on laboratory-confirmed influenza virus infections only. Moreover, if conclusions are drawn from years where there is little flu this can misrepresent the longer-term cost-benefit ratio. Likewise, in years where there is an antigenic mismatch, extrapolation for the longer term is undermined.

The search for a pan-influenza vaccine is currently a 'holy grail' of vaccine research. In the meantime, short-term benefits are sought from e.g. use of adjuvants, increased antigen dosing and switching from trivalent to quadrivalent vaccines. However, the benefits so far seem to be limited. Antigenic cartography is helping to predict future influenza mutations leading to epidemics, allowing earlier vaccine updates and – hopefully – fewer mismatches of the vaccine. Other influenza protein targets, such as neuraminidase, should be pursued.

The long-term target is a universal vaccine that would offer protection against all strains of influenza. It is anticipated that such a vaccine should target conserved influenza virus antigens, with antibodies targeting epitopes of HA (e.g. the stem domain), NA and M2, and T-cell responses targeting the internal virus proteins M1, NP and the polymerases. The use of live virus vaccines, including vectored ones and strong adjuvants, is currently being explored to achieve these goals.

Prof. Mihai Netea, Professor of Experimental Medicine, Radboud UMC, presented on 'BCG vaccines and innate immune programming'. BCG remains the only licensed vaccine against TB. Innate immunity is an effective but non-specific part of the human immune system yet, until now, it was believed to provide no immune memory. Adaptive immunity is slower (requiring 10-14 days), provides specific activation against particular antigens microorganism and builds immunological memory.

When BCG was introduced to Sweden in 1932, it was observed that mortality in children in their first year of life decreased from 11% to 4% and was not TB-specific. This raised the possibility that, in addition to specific anti TB effects, BCG may provide non-specific immune protection, maybe through the innate immune system. Memory can be defined as the ability of a system to store and recall immune information on previously encountered antigens. Consequently, innate immunity is devoid of memory or the response to infection in general is non-specific.

In a study from 2012, 20 healthy young adults had BCG vaccination and the immune and biochemical effects of such vaccination were longitudinally evaluated. It was discovered that epigenetic reprogramming was induced, with histones significantly modified, and chromatin became more loosely packaged. Subsequently this was observed during a trial in 2018 where volunteers were given yellow fever vaccine. It was observed that those given BCG had much less yellow fever vaccine virus in their system, i.e. an adaptive immune response had taken place, stimulating monocytes to produce interleukin 1 and 6, mediated by epigenetic mechanisms.

Overall, BCG vaccination leads to non-specific protection against unrelated infections; leads to the induction of trained immunity in monocytes; trained immunity induces long-term reprogramming of both circulating monocytes and myeloid cell progenitors in bone marrow, observed in mice and humans; and is responsible for induction of innate immunity-dependent early clearance.

A key note of conclusion, therefore, is that vaccines lead to adaptations in innate as well as adaptive immunity and this knowledge, in turn, may lead to the development of more effective vaccines.

Ms. Katrine Bach Habersaat, Vaccine Preventable Diseases and Immunization (VPI), WHO, addressed the question of 'The tailoring immunisation programme (TIP)', explaining the diversity of the WHO Region for Europe, covering 53 member states and a population of around 900 million.

The trend in measles, where the goal remains elimination, is of concern to WHO Europe. 2016 saw an all-time low of only around 5,000 cases in the region, but 2018 has seen a large increase, to around 40,000 cases.

So, it is important to understand the reasons behind people's choices on vaccinations. Currently there are significant limitations of:

- data
- evidence
- political prioritisation / investment
- and, therefore, limited capacity to tackle the problem.

So, the organisation has set up its Tailoring Immunisation Programmes (TIP). This approach is informed by behavioural science and theory, and takes a stepwise approach to identify the most effective interventions, which will then lead to implementation, evaluation, adjustment and scale-up.

Using a case study of the Charedi ultra-orthodox Jewish community in north London, where low vaccination rates had been identified, Ms. Bach Habersaart explained how this form of community resistance had been interrogated as part of the project. Trust of information sources was suspected, together with religious concerns and an assumption that this community was receiving very limited education on the topic.

But dialogue revealed that convenience was, in fact, the biggest influencing factor on their decisions: this group often has large families, so transport was a barrier, as was the size of waiting rooms and no private area for breastfeeding. In fact, these issues have been seen to be barriers to vaccination in a range of other community settings too.

Therefore, the solution was to adapt service provision to remove some of these barriers e.g. by hiring a Charedi nurse who was sensitive to their needs and wishes. This package of changes has led to an uptake in vaccination but has also strengthened community relations, which is important for the sustainability of these changes going forward.

Thus, simple practical issues may be of major importance in ensuring vaccine coverage.

Prof. Tara Smith, Professor of Epidemiology, Kent State University, spoke on 'Dealing with vaccine hesitancy and rejection', highlighting many of the prevailing myths e.g.:

- vaccines are toxic; vaccines are for depopulation / money for big pharma
- too many / too soon; vaccines overwhelm the immune system
- natural immunity is better; big pharma wants you to be sick
- shedding (the fear of vaccinated people shedding and spreading germs)
- vaccines didn't do anything; VPDs decreased because of hygiene.

Self-appointed entities such as the National Vaccination Information Centre in the US are continuing to promote such, or similar, beliefs and President Trump has also promoted on Twitter the notion that vaccinations can lead to autism.

Biases against the facts in vaccines can derive from a number of sources, including one's sense of identity ('I like natural not manufactured / chemical things going in to me'.) So, education alone will not sway everybody – trust and shared values with the person who is communicating on the issue can be just as influential.

One way to change views would be if more people communicated about the experience of them and their families after vaccination i.e. where nothing bad happens. Some of those who do not allow their children to be vaccinated may be vehemently in denial of the evidence, but others may just be 'on the fence' and actually want to be persuaded by a more positive narrative, to feel reassured about the extent of the risks to their children.

At government level, several countries are introducing mandatory vaccinations or are providing material encouragement to citizens to participate in vaccination programmes, such as Australia's 'No jab, no play' policy meaning that only vaccinated children can attend play centres and have their medicines reimbursed.

Prof. Piek Vossen, Professor of Computational Lexicology, Faculty of Humanities, VU University, spoke about 'Vaccine discussion on the internet'. He advised that it is more helpful to see where we live not as an information society but a communication society. The knowledge which is available on the internet is one thing, how it gets communicated is another – and is in many ways more powerful.

To illustrate this, Prof. Vossen presented an anti-vaccination 'news' story claiming that nobody in the US has died from measles since 2013, but 108 people have died in the same period 'from measles vaccines'. Only those checking the sources of the story would find that the authorities cited made no such claim, but have been quoted or referenced out of context to imply an entirely different meaning.

It is also important not to confuse online posts with debate. With differing views being posted there is no alignment around the discourse, as prior views are not taken into account during the response except to contradict.

However, Prof. Vossen is currently involved in developing new automated ways of scanning the dispersed medium of the internet to dispassionately analyse and seek evidence for

propositions around a specific topic such as vaccinations. This will create a hub for evidence and will also help to separate claims being made which lack supporting evidence.

Concluding remarks

Prof. George Griffin wrapped up the meeting by discussing 'The way ahead'.

Vaccines play a crucial role in medicine in preventing infection and saving lives. In addition, great advances in vaccination protecting against cancer attributable to viral infection have been made and have reached implementation. For example, HPV has been shown to be a cause of female cervical cancer and vaccination against the virus has been shown to be highly effective in reducing overall cancer incidence. Vaccination affects an individual throughout the whole life course and is not just an infant (or parental) health issue. Vaccination in pregnancy is being regarded as an important way to prevent neonatal infection. In addition, vaccination against herpes zoster infection and influenza in old age is seen as an important advance.

The symposium had also addressed service delivery issues, particularly the childhood programme. In the UK, for example, accelerating the childhood triple vaccine programme from a 4-month wait for a booster to 1 month, has made a great difference in effective uptake. There are other practical ways to promote vaccines by making their delivery more user-friendly.

The issue of sustainability of vaccine programmes is critical and this needs to be underpinned by ongoing research so that we have continuous improvement. In the same way, new vaccines can create helpful knock-on effects too, to develop ever more effective interventions, especially in serious epidemic diseases such as Ebola virus infection.

Polio is also an important area, in which the manufacture of the vaccine involves the use of live virus, which carries a risk in terms of accidental release during manufacture. Thus, the culture of 'safe' polio virus strains, which can be inactivated by formularisation and used for parental vaccination, is an important area currently being considered and evaluated.

In terms of health behaviours, reluctance is completely understandable, but refusal is highly dangerous, preventing the herd community benefits which society needs. So, education and persuasion, especially for healthcare professionals, has to be clear and also firm in its recommendations.

So, in conclusion, the event had successfully met its objectives of gathering together key scientific and social perspectives on the topic of vaccinations. It had also delivered very strong and clear messages about the challenges faced and some of the steps that can be taken in this hugely important area of health and social policy.

Partners and organisers

European Academies Advisory Council (EASAC) brings together the National Academies of Science of the EU Member States, Norway and Switzerland to provide independent science-based advice on important challenges for Europe.

Federation of European Academies of Medicine (FEAM) is the European umbrella group of 19 national Academies representing thousands among the best biomedical scientists across Europe and disciplines with the mission to provide independent, evidence-based biomedical and health policy advice.

The Netherlands National Institute for Public Health and the Environment (RIVM) performs tasks to promote public health and a safe living environment by conducting research and collecting knowledge worldwide.

The Royal Netherlands Academy of Arts and Sciences (KNAW) is an organisation dedicated to the advancement of science and literature in the Netherlands.

Appendix: Conference programme

Vaccination
Scientific and social perspectives

Date: Monday 22 October 2018, 10.00 a.m. – 5.00 p.m.
Venue: De Nieuwe Liefde, De Costakade 102, 1053 WP Amsterdam
Moderators: George Griffin and Jos van der Meer

Programme

9.30 a.m.	*Coffee*
10.00 a.m.	**Welcome** *Prof. Wim van Saarloos* – President of the Royal Netherlands Academy of Arts and Sciences
10.05 a.m.	**The EASAC-FEAM statement** *Prof. Jos van der Meer* – Immediate Past President of EASAC and emeritus Professor of Medicine, Radboud UMC
10.30 a.m.	**Vaccine coverage in the EU** *Dr Piotr Kramarz,* – Deputy Chief Scientist of European Centre for Disease Prevention and Control (ECDC)
11.05 a.m.	**The tailoring immunisation programme** *Dr Katrine Bach Habersaat* – Vaccine Preventable Diseases and Immunization (VPI), WHO
11.40 a.m.	**Not all vaccines are equal** *Prof. Jaap van Dissel* – Director of Centre for Infectious Diseases (CIB)
12.15 p.m.	**The effects of vaccines on innate immunity** *Prof. Mihai Netea* – Professor of Experimental Medicine, Radboud UMC
12.50 p.m.	*Lunch*
2.00 p.m.	**How to improve the flu vaccine** *Prof. Ron Fouchier* – Professor of Virology, Erasmus MC
2.35 p.m.	**Dealing with vaccine hesitancy and rejection** *Prof. Tara Smith* – Professor of Epidemiology, Kent State University
3.15 p.m.	*Tea*
3.40 p.m.	**Vaccine discussion on the internet** *Prof. Piek Vossen* – Professor of Computational Lexicology, Faculty of Humanities, VU University
4.15 p.m.	**The way ahead** *Prof. George Griffin* – President of FEAM and Professor of Infectious Diseases, St George's Hospital, University of London
5.00 p.m.	*Closure and drinks*