Vaccination in Europe

An EASAC and FEAM commentary on the EC Roadmap 'Strengthened cooperation against vaccine preventable diseases'

The European Commission (EC) Roadmap document 'Strengthened cooperation against vaccine preventable diseases' that was issued recently, aims to inform EU citizens and stakeholders about the ideas of the Commission regarding the current challenges of vaccination programmes (i.e. declining coverage, supply shortages and growing vaccination hesitancy[1]). The Commission invites stakeholders to give feedback and to participate effectively in the consultation activities. Since EASAC, the European Academies Science Advisory Council, and FEAM, the Federation of European Academies of Medicine, consider science-for-policy advice on vaccination to belong to their core activities, the two organisations are keen to take this opportunity to provide joint comments on the Roadmap document.

Vaccination is the major tool to combat and eliminate communicable diseases, as indicated in the Sustainable Development Goals (SDG 3.3)[2]. The Roadmap document deals with four related vaccine issues: 1. Vaccine coverage; 2. Vaccine hesitancy; 3. Vaccine availability; 4. New vaccine development.

Vaccine coverage

The document rightly views the recent outbreaks of measles in EU Member States as a major sign that there is a serious problem with the vaccination coverage in the EU, especially since measles is a serious, potentially lethal childhood infection and there is an effective vaccine against the disease. Furthermore, it is clear that low vaccine coverage may endanger the protection of children (as well as adolescents and adults) against other vaccine-preventable diseases with great public health significance (for example, poliomyelitis, diphtheria, rubella, pertussis, type B Haemophilus influenzae, pneumococcal and meningococcal infections).

It cannot be stressed enough that, despite the availability of excellent vaccines, vaccine coverage of children varies greatly within EU Member States. The reasons for these discrepant vaccine-uptake figures are not well established; they are clearly complex, heterogeneous and differ per Member State. This means that to improve poor vaccine uptake measures at the European level will need to be taken to identify specific problems related to individual countries. Thus, to be able to take adequate measures at the level of Member States, surveillance and research are needed into the local drivers behind the poor (and often falling) compliance with vaccination policies. For this purpose, the TIPS (Tailoring Immunization Programmes) instrument as designed by WHO should probably be used, because it offers the basis for a comprehensive, stepwise analysis of the problem, and also provides data that allow comparison between countries[3]. In that way tailored solutions to improve vaccine coverage can be designed and implemented[4].

The EC document aims to normalize the vaccination programmes in the various Member States. As these programmes regarding vaccine selection and vaccination schedule (including number of doses and timing) vary greatly for a variety of reasons (e.g. logistics within the public health infrastructure), it will

1 https://ec.europa.eu/info/law/better-regulation/initiatives/ares-2017-5925775_en

2 http://www.un.org/sustainabledevelopment/sustainable-development-goals/

3 http://www.euro.who.int/en/health-topics/communicable-diseases/poliomyelitis/publications/2013/guide-to-tailoring-immunization-programmes.

4 Dubé E, et al. The WHO Tailoring Immunization Programmes (TIP) approach: Review of implementation to date. Vaccine 2017; Dec 26. pii: S0264-410X(17)31752-8. doi: 10.1016

most probably be an enormous and futile effort to try and attain such normalisation across EU countries. Nonetheless, more might be done to share lessons on successes and failures from national variability in the operations of this European "natural laboratory". This could help answer such questions as why are certain Member States able to maintain high vaccine uptake, why do compulsory vaccination programmes work and, if so, what are the determinants of success? We encourage the Commission through the European Centre for Disease Prevention and Control (ECDC) to catalyse such sharing of lessons learned to inform national actions.

Much effort should be put into the implementation of an EU vaccination card and registry.

The health impact of vaccines

Vaccines are not equal either in efficacy with regard to their role in public health or in the health of the individual. Some vaccines play a critical role in the prevention of serious communicable diseases at the population level or are able to prevent a deadly disease in an individual. Examples of the former are diphtheria, poliomyelitis and measles vaccine; examples of the latter are tetanus and rabies vaccine. A number of vaccines belong to both categories (e.g. meningococcal vaccines). Other vaccines such as those against mumps, hepatitis A or chickenpox are less important for public health.

For those vaccines that play a critical role in public health, a high vaccine uptake is necessary to maintain adequate herd immunity to prevent endemic transmission of the infectious agent. It is clear that efforts to raise vaccination uptake should be primarily aimed at those vaccines with the greatest health impact but there must be expert consultation on the need for vaccines in specific countries and in potential epidemic situations (e.g. meningococcal disease).

Quality of vaccines

An important issue that is not dealt with in the Roadmap is the difference in general quality of different vaccines in terms of efficacy and side effects. Many childhood vaccines that are currently in use are highly protective with few side effects. However, a good example of a vaccine that yields a relatively low and variable protective effect is influenza vaccine. The consequence of this is that many health-care workers are sceptical about its use and are not actively promoting vaccination with the seasonal flu vaccine. In fact, the general quality of this vaccine, the weak evidence of its benefits, and the controversies among health-care officials seem to harm the discussion on vaccination in general. Rather than trying to increase the current vaccination coverage, research into a universal and highly protective influenza vaccine must have the highest priority (see below) and there are several promising candidate vaccines being developed.

Another problem has recently emerged. It is now evident that live-attenuated poliovirus vaccine (Sabin vaccine) can cause paralytic polio syndrome, and routine use of this vaccine is contraindicated[5]. Furthermore, it is anticipated that the culture of highly pathogenic wild-type poliovirus for Salk parenteral inactivated vaccine will be superseded with avirulent virus.

5 McCarthy KA et al. The risk of type 2 oral polio vaccine use in post-cessation outbreak response. BMC Med. 2017 Oct 4;15(1):175. doi: 10.1186/s12916-017-0937-y

Vaccine rejection and hesitancy

The declining uptake of vaccination in young children in Europe and elsewhere in the world is in part due to the growing numbers of individuals who choose not to have themselves or their children vaccinated. The reasons for making that choice vary. In that respect, the three categories proposed by Hagood and Mintzer Herlihy are very useful[6]. They distinguish between:

1. *Vaccine rejecters (VRj)*; these people are "unyieldingly entrenched in their refusal to consider vaccine information" and often think in terms of conspiracy.
2. *Vaccine resistant (VR)*; these people reject vaccination but are willing to consider information. They are less inclined to belief in conspiracies.
3. *Vaccine hesitant (VH)* tend to have anxiety about vaccination but are not committed to vaccine refusal.

The approach to these different categories is different. It is clear that efforts for improved vaccine uptake should primarily be directed towards the VR and to VH. For optimal communication approaches, the input of social scientists is essential. An excellent analysis of the problem has been given by Smith; this paper also discusses approaches to enhance vaccine uptake[7].

Vaccine availability

As indicated in the document, there are vaccine shortages in a number of Member States mainly concerning the vaccine against tuberculosis (BCG), acellular pertussis vaccine and inactivated polio vaccine (Salk vaccine). With regard to BCG, we would recommend the reconsideration of the vaccination policy in EU Member States. BCG vaccine is not very potent in its capacity to induce (long-lasting) protection against tuberculosis. Rather the vaccine induces an enhanced state of the innate immune response (trained immunity)[8]. In some European countries (e.g. the Netherlands), BCG has never been used for routine childhood vaccination but nevertheless has been able to control tuberculosis effectively. In some regions in the UK, BCG vaccination is recommended for neonates in the first month of life in view of the perceived risk of contracting tuberculosis.

Multinational efforts should be undertaken to enhance the production of BCG (as it is also an important drug for the treatment of superficial bladder cancer). Measures to enhance production should also be undertaken to increase the availability of other vaccines for which scarcity exists (such as those mentioned above, and at the global level also yellow fever vaccine). In the meantime, it should be investigated whether those vaccines for which there is a scarcity, when given at a low dose, intracutaneously, are equally immunogenic as when given as a full dose intramuscularly[9].

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6 Hagood EA, Mintzer Herlihy S. Addressing heterogeneous parental concerns about vaccination with a multiple-source model: a parent and educator perspective. Hum Vaccin Immunother. 2013 Aug;9(8):1790-4. doi: 10.4161/hv.24888. Epub 2013 May 31.

7 Smith TC. Vaccine Rejection and Hesitancy: A Review and Call to Action. Open Forum Infect Dis. 2017 Jul 18;4(3):ofx146. doi: 10.1093/ofid/ofx146. eCollection 2017 Summer.

8 Benn CS, Netea MG, Selin LK, Aaby P. A small jab - a big effect: nonspecific immunomodulation by vaccines. Trends Immunol. 2013 Sep;34(9):431-9. doi: 10.1016/j.it.2013.04.004. Epub 2013 May 14.

9 Yousaf F, et al. Systematic review of the efficacy and safety of intradermal versus intramuscular hepatitis B vaccination in end-stage renal disease population unresponsive to primary vaccination series. Ren Fail. 2015 Aug;37(7):1080-8. Epub 2015 Aug 10. Review.

In the Roadmap it is rightly stated that EU level arrangements for effective maintained procurement are needed.

New vaccine development

The Roadmap document states that there are challenges related to research and development for new and existing vaccines. Here the document is rather vague. Improvement of existing vaccines that are suboptimal and the development of vaccines protecting against infections for which no vaccines exist are urgently needed.

Regarding the first category, solutions may be sought in designing vaccines with greater antigenicity, vaccines containing better adjuvants, or both. As mentioned above, current influenza vaccines are not optimal. First of all the prevalent seasonal influenza virus may not be represented in the vaccine that is made available in a particular year. The choice of influenza strains is agreed annually on the basis of epidemic influenza trends and is based on a scientific 'best- bet'. But even if the vaccine contains the right virus, egg-grown virus may differ from the natural virus in its glycosylation sites, leading to antibodies that do not optimally neutralise the natural epidemic influenza virus[10]. In addition, the immunogenicity of the vaccine in elderly patients is poor when they are impaired in their daily activities and this poses a problem for a major group of people who get these vaccines[11]. Finally, when given to young children, there is uncertainty whether the vaccine may enhance the susceptibility to other infections[12]. Thus, one hundred years after the 1918 flu pandemic, the development of a new influenza vaccine that induces broadly neutralising antibodies, and with improved adjuvanticity, is a major priority. It should be noted that there is currently no priority list of vaccines that need to be developed or improved. The aim should be to develop vaccines with a high health impact. Vaccines against bacteria to which a serious antimicrobial resistance problem emerges should be high on the list. EASAC and FEAM would be prepared to develop such a list that would aid the priority setting at the level of the EU research agenda. Given that the EU also has global responsibilities, vaccine innovation for global threats should be part of this agenda.

At the same time, the Commission should stimulate and encourage pan-European public private partnerships in vaccine discovery and development.

10 Zost SJ, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci U S A. 2017 Nov 21;114(47):12578-12583. doi: 10.1073

11 Remarque EJ, et al. Functional disability and antibody response to influenza vaccine in elderly patients in a Dutch nursing home. BMJ. 1996 Apr 20;312(7037):1015.

12 Cowling BJ, et al. Increased Risk of Noninfluenza Respiratory Virus Infections Associated With Receipt of Inactivated Influenza Vaccine. Clin Infect Dis 2012;54:1778–83

Recommendations

Based on the points discussed above, we would like to make the following recommendations:

1. Investigate the 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. Recognize that not all vaccines in the vaccination programmes are of equal relevance for public health and individual protection. Make priorities within the programmes.
4. Recognize 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 for which there is high need.

It should be noted that the present commentary from EASAC and FEAM represents an initial response on some of the important issues that have been raised by the European Commission. We recognise the responsibility of our academies to continue helping to lead discussion, collect evidence, address challenges and resolve uncertainties. Later this year we will be considering options for a new Vaccines project by our academies, bringing together experts from across Europe and from a range of disciplines. We welcome the opportunity to explore further with the European Commission our mutual interests and priorities.

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FEAM – the Federation of European Academies of Medicine

FEAM's mission is to promote cooperation between national Academies of Medicine and Medical Sections of Academies of Sciences in Europe; to provide them with a platform to formulate their collective voice on matters concerning human and animal medicine, biomedical research, education, and health with a European dimension; and to extend to the European authorities the advisory role that they exercise in their own countries on those matters.

EASAC - the European Academies' Science Advisory Council

EASAC is formed by the national science academies of the EU Member States, Norway and Switzerland, to enable them to collaborate with each other in providing independent science advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.

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