Vaccines: why and how do we need to improve vaccine coverage?

Group n° 03

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1. Introduction

1.1 Why do we need to improve vaccine coverage?

Vaccination is unarguably the single most important public health achievement ¹. The introduction of Vaccines by Edward Jenner in 1796 for small pox led to a major breakthrough in the control and prevention of many infectious diseases including but not limited to measles, mumps, rubella, and most importantly, the eradication of smallpox from the face of the world ². Despite the major successes achieved, potentially preventable infectious diseases still pose a major public health burden to both the developed and developing world. This is evident from studies in the developed world which reported a total of 88,956 health-adjusted life years (HALYs) (729 per 100,000 population) and 74,297 (83.5%) years of life lost (YLL) were due to infectious diseases amongst which vaccines preventable bugs such as Hepatitis B virus (HBV), Streptococcus pneumonia, human papillomavirus infection (HPV), influenza were listed among the top 10 microbes ³. This is even worse for the developing world ⁴.

Over the last 2 centuries, tremendous efforts have been made towards up-scaling safe vaccine production, mass immunization to achieve herd immunity and thus reduce outbreaks of potentially deadly diseases such as meningitis. However there has been some major setback preventing full-scale vaccination of every community. Thus, studying such barriers along with their associated factors may go a long way to provide health systems, policy makers and other health stakeholders with key solutions to enhance vaccination programs and thus promote global health.

1.2 Mechanisms of action of vaccines

Although much insight as to what comprises the immune system and how it functions has been discovered, the complexity of the immune system has not been fully understood to scientist. The immune system comprises of two major distinct components: the innate and adaptive immune systems. Vaccines are known to mediate their effect by modulating the adaptive immune system either via up-regulation of the humoral immune response by stimulating Th2 cells resulting in antibody production after recognition of a ‘foreign’ antigen (Th2-response) ⁵. These antibodies help clear the foreign antigen (pathogen) via one of the following mechanisms; neutralization, enhance phagocytic-opsonisation or by stimulation of the other arm of the adaptive immune system known as cell-mediated immune system. Also upon stimulation of the humoral immune system the foreign antigen is also committed to memory via specialized memory B cells which results in a rapid recognition and stronger immune response if the subject gets exposed to the same antigen (ie pathogen) in the future ⁵.

The Cell-mediated immune system also known as (Th1-response) destroys intracellular foreign antigen resulting in acute inflammation most of the time. These two arms are usually in a steady state balance. In the case of the BCG vaccine, improvement of Th1-response is needed.

The goal of vaccination is to trigger an immune response in individuals without causing the acute symptoms of the disease. This is achieved by introduction the foreign antigen to individuals at concentrations that is just enough to trigger antibody production and memory-B cells (humoral immune response) without stimulating the cellular immune system. Vaccines can be classified as either live-attenuated vaccines (e.g. measles/mumps/Rubella vaccine), which involves the introduction of a weakened form of the pathogen or as subunits which comprises of parts of the pathogen carrying one of specific antigens conjugates (e.g. Meningococcus), carbohydrates (pneumococcus vaccine) or the inactivated toxin (e.g. tetanus toxoid) produced by the microorganism known as a toxoid. Most vaccines also contain adjuvant which are to enhance the immune recognition and reaction to the vaccine e.g. aluminium phosphate adjuvant ⁶. Even with this knowledge, the vast majority of vaccines have been developed empirically, with little or no understanding of the immunological mechanisms by which they induce protective immunity. It is therefore paramount to foster new research in the vaccine field to better understand how they confer immunity to individuals. This may also provide an insight for the development of vaccines for pathogens that constantly mutate, for instance the HIV virus.

1.3 Future trends

Advancement in science and technology has actually expanded the traditional scope of vaccines from prevention of communicable diseases to prevention and possible treatment of some non-communicable diseases such as in oncology and neurobiology. This new progress in vaccine development has been successful this far thanks to discovery of both human and microbial genome sequencing, proteomics, molecular biology ⁶.

1.4 Major barriers to vaccination

Existing and new vaccines continue to exert their immunological power by boosting the immunity of individuals. The emergence of new strains of some pathogens and also new organisms which are capable of causing infection by evading the immune system may render previous vaccines powerless. This has also been a major setback to the development of vaccines for pathogens that constantly change their surface particles such as HIV and reasons why a new flu vaccine needs to be developed almost every season. Vaccine utilization has

virtually reached most parts of the world especially low-income countries thanks to international organizations and private funders such as the World Health Organization (WHO), United Nations Children's Fund (UNICEF), Bill and Melinda Gates Foundation via GAVI just to name a few. These organizations have been the major source of funding and the success of Expanded Programme on Immunization (EPI) launched since 1974.

Vaccine production until today is carried out by only a few pharmaceutical firms. Many firms consider vaccination production not be profitable, results in financial losses in addition to very strict ethical and governmental regulations involved in the production of a new vaccine. This is one potential factor that may lead to shortage in quantity of vaccines. This was evident in 2004 with the shortage of the flu vaccine in the United States partly due to limited number of production firms, unwillingness of some firms such as King Pharmaceuticals to produce the vaccine due to high cost of setting up its plant ⁷. This is true for many other childhood vaccines. Also the successes of vaccines which have made most infectious diseases no longer a threat has also resulted in reduced funding to research and vaccine development companies. Governments from the developing countries are still very much dependent on foreign aid to get vaccines to their communities. Also, even when vaccines are provided at almost free-of-charge to some developing countries, there still exist some inequalities in its distribution throughout the territories. Factors which favour inequalities include but not limited to: poor accessibility to rural areas either due to poor transport network, lack of infrastructure and equipment to preserve the vaccines, shortage of health workers and volunteers to aid in administering the vaccines and some sociocultural practices ⁸. Most of these factors either lead to a delay in month-specific vaccination or a complete miss of the vaccine. It has been shown that delays in administering vaccines at stipulated age for more than 4 months increases the risk of preventable death due to communicable diseases by almost 18% ⁹.

1.5 Immunization rate around the world

Whereas it is estimated that immunization averts 2 to 3 million deaths per year in the world, an additional 1.5 million lives may be saved annually given the vaccination coverage can be improved ¹⁰. 1 out of 5 children worldwide is missing routine immunization and further efforts to abolish “vaccination gap” is needed. The global vaccination coverage has stalled at 86 % over the past years without any significant changes ¹¹. As an example of diphtheria-tetanus-pertussis (DTP3) vaccine, 130 countries had reached at least 90% coverage. Nevertheless, 19.5 million infants are estimated to miss out on DTP3 vaccine. Even in

Europe, vaccination gap exists (Figure 1). In this report, we focused on the vaccination gap in Europe, the raise of anti-vaccination movement, and how the movement was propagated and recent measles outbreak in Europe as a consequence. We will also explore possible solutions from best practices to improve immunisation coverage in developed countries.

Figure 1. Vaccination Gap in European region and its neighbourhood.

The share of children at age of 12 to 23 months old vaccinated against Diphtheria, Tetanus and Pertussis (DTP3) in 2015 in the Europe and surrounding countries (adapted and modified from Vanderslott and Roser. 2018). There is an important vaccine gap worldwide. The great majority of the countries have 99% of vaccine coverage (Belgium 99 %) except for Ukraine 23 %, Romania 89 %, Bosnia Herzegovina 82%, Syria 42 %, and Iraq 58 %.

2. Methods

Search strategy and data sources

We searched electronic databases including PubMed, EMBASE and MEDLINE from inception to 1 April 2018 using MESH and Key Terms including vaccine*, immunisation*, outbreaks*, coverage*, compulsory vaccination*, voluntary vaccination*, vaccination policies* to identify pertinent information on outbreak, vaccination coverage and policies. We hand-searched the reference lists from reviews to find additional information. We also referred web of science, WHO website, government guidelines, web available news sources written to non-scientific public in journals.

3. Results

3.1 The rise of anti-vaccination movements in the post-truth era

Andrew Wakefield, an English ex-doctor who made fraudulent publication, later retracted, described an association between the onset of autism after vaccination against measles, mumps and rubella (MMR) ¹². No such association was later confirmed in a population-based study ¹³⁻¹⁵. Furthermore, some vaccines contained Thiomersal, an organomercury compound as antifungal agent and Thiomersal was suspected to cause autism in infantile brains ¹⁶. Although the scientific evidence was not clear in relation to autism, Thiomersal has been not used for US and European vaccines since 1999. Because of lack of exposure to the dangers of

non-vaccinated populations and lack of medical education regarding vaccines, parents are not aware of the benefits of vaccination and tend to overemphasize possible benign reactions to vaccination such as local swelling. Nations have yet to determine centralized policies to fight anti-vaccination movements and ensure the improvement of vaccination coverage.

3.2 Drop off of vaccine coverage and outbreaks in Europe

The death toll of vaccine preventive diseases (VPD) has been rising wherever immunisation coverage has dropped. For instance, Measles is spreading across Europe, notably in France, Germany, Italy, Poland, Romania, Switzerland and Ukraine ¹⁷, leading to more than 14,000 measles cases, causing 34 deaths from January 2016 to June 2017 ¹⁸. Although it is recommended that at least 90-95% of the population should be vaccinated against measles for herd immunity, many developed countries still struggle to achieve that. One of the reasons why the vaccination coverage has waned in some regions is unvaccinated individuals affected by the anti-vaccine movement. A serious outcome of anti-vaccine movement was remarkable in Ukraine. In 2013, one third of Ukrainian parents were against vaccinations and only 1 out of 2 children are fully immunized against polio, measles, rubella ¹⁹. Notably, 3-dose polio vaccine coverage declined from 91% in 2008 to 15 % by 2015. This acute drop-off of vaccine coverage was caused by a death of a young boy following a measles and rubella vaccination. Although his death was not directly related to vaccination, incorrect media reporting caused a mistrust of vaccination among Ukrainian citizens, ending up with an extremely powerful anti-vaccine movement. In 2015, Ukraine is faced polio outbreak of 2 unvaccinated children paralyzed by a highly divergent cVDPV1 ²⁰. Although Ukrainian law requires parents to provide a certificate of immunization before their children start school and the vaccines are free throughout the state healthcare system, the vaccination coverage remained low and outbreak of measles, rubella and mumps has been observed in 2010 ¹⁹. For instance, measles outbreak continues up to now estimating to affect more than 3000 people and to take 5 lives of children and adults in 2017 in Ukraine ¹¹. Such disaster was caused by multiple reasons such as public mistrust against vaccinations, poor vaccine supply and corruption in the health system ¹⁹. In Italy, recent outbreaks of VPD because of vaccine hesitancy have led to a decree: mandatory vaccinations should be made in order for a child to enter kindergarten (See 3.5.1).

3.3 Vox populi: personal opinions and social networks

An anti-vaccination movement is understood as the political *alter ego* of vaccine hesitancy in an individual, which ranges from refusal of vaccination to unanswered questions about vaccines. In order to try to better define the anti-vaccination attitudes, Martin and Petrie ²¹ validated a Vaccination Attitude Examination self-reported scale (VAX). They found four factors representing vaccine hesitancy: mistrust of vaccine benefit, worries about unforeseen future effects, concerns about commercial profiteering and preference for natural immunity. Anti-vaccination movements spreading vaccine hesitancy get in the way of optimizing the immunization rate of a given population: this is particularly the case of measles, whose rate must be over 90% in a population to prevent an outbreak ²². Anti-vaccination has been powered by notable politicians and influential celebrities in the last few years in the developed world. In the post-truth era, scientific arguments can be won over during political debates by using arguments appealing to the feelings of the electorate. This is replicated in social media: Evrony and Caplan ²³ looked into the communication strategy of a well-known website present on social media, “A Voice for a Choice”: the website states that aluminium present in 60% of human vaccines works as a neurotoxin to infants receiving it through vaccination. As this website, countless others as well as Facebook, MySpace ²⁴, feeds are driven by people sharing alleged experiences of vaccinate children being diagnosed with autism, alleged secondary effects of vaccination ²⁵. While people on Twitter mainly share positive opinions on the efficacy of vaccination ²⁶, negative opinions may generally have more significant impact on the decision not to receive vaccination ²⁷.

3.4 Shortage of vaccine

80 % of vaccine worldwide today is produced by five big pharmaceutical industries: Sanofi Pasteur, GlaxoSmithKline, Merck, Pfizer and Novartis ²⁸. Since the vaccine had become so cheap (60 cents for each vaccine in 2008), very few companies continued production and consequently world stocks of vaccines were nearly zero ²⁹. Some countries where the vaccine coverage is sufficiently high are almost running out of vaccine stocks. For instance, Romania experienced shortage of MMR vaccine and Romanian government took emergency measures. This should be at least partially responsible for the worst outbreak of measles that led to more than 17 deaths and at least 4,800 cases in 2016-2017 in this country ^{30,31}.

3.5 How to encourage vaccination

We looked for articles discussing about potential solutions to improve vaccine coverage. One of the most effective ways to improve vaccination coverage is to improve immunization rates

of the children whose parents are against vaccination ³². Today, there are several countries that apply compulsory laws to vaccinate children and/or a variety of incentives and penalties ³³. We looked for vaccination policies in several countries in Europe and worldwide to determine which strategies are pertinent to raise awareness for immunization.

3.5.1 Vaccination policies in European countries

There is a much variation in vaccination policies in EU (Figure 2). The Venice project survey reported that about a half of EU countries had no mandatory vaccination and the rest had at least 1 mandatory vaccination in 2017 ³⁴, **but the vaccination policies in EU countries have been rapidly changing since a few years after outbreaks of VPD.** After measles outbreak in Europe, at least 6 countries have adopted clear and strong vaccination policies (Italy, Germany, France, Romania, Poland and Cyprus) since 2017-2018. In Italy, vaccination against 10 diseases have become compulsory (Italian law 119/2017) to enter school ³⁵ and unvaccinated children can still enrol in school but their parents will be fined (€500-€7,500) from 2017 ^{36,37}. In France, vaccinations against 11 diseases are compulsory before 2 years of all the children born after January 1 2018 ³⁸. Those who haven't received all these vaccination will be refused admission to nurseries and schools in France ³⁹. In Germany, vaccination remains "voluntary" but a new legislation was introduced in June 2017 that parents can be fined as much as €2,500 for failing to vaccinate their children. The German parliament has made a decision that kindergartens report parents who don't vaccinate their children ⁴⁰. In Poland, failure to bring children for mandatory vaccinations against 11 diseases can lead to fines to the parents ⁴¹. In Romania, the senate voted in October 2017 for a new law for vaccine mandate and the parents who refuse to vaccinate their children could be fined up to 10,000 RON (2,200 €) ⁴². In Cyprus, mandatory vaccination against 11 diseases started from January 2018 ⁴³. It has to be noted that in Ukraine, certificate of vaccination is required for school entry of children, but some parents buy fake certificates from medical doctors ²⁹ and further regulation may be necessary. In Portugal, vaccinations against 2 diseases are compulsory (diphtheria, tetanus) ⁴⁴. In Belgium, only Polio vaccination is compulsory by law, but children in French-speaking nursery schools must receive additional mandatory vaccinations for 7 diseases (diphtheria, tetanus, whooping cough, type b Haemophilus influenza, measles, mumps and rubella) and additional vaccinations are also highly recommended ⁴⁵. On the other hand, the vaccination is not a legal requirement in some countries such as UK, (mandatory only for healthcare workers), Spain, Sweden, Switzerland, Austria, Denmark, Estonia, Finland, Iceland, Ireland, Lithuania, Luxemburg, Netherland,

Norway, and Russia ³³. Most of these countries have sufficiently high vaccine coverage although vaccinations are highly recommended but considered as “voluntary”. A study suggest that there is not yet significant positive correlation between compulsory law and vaccine coverage between 2007 and 2013 ³³. However, **preliminary data in Italy suggest significant efficiency of vaccination compulsory policy showing that more than 30 % of unvaccinated children born 2011-15 have now been vaccinated** ^{37,46}. In contrary, pilot schemes in the Veneto (5 million people) region in Italy suggested that **health education itself was not able to raise voluntary vaccine uptake when vaccination compulsory policy was suspended** ⁴⁷. These studies suggest that a strong vaccination policy is efficacious, at least, in a short time period.

Country	Polio	Diphtheria	Tetanus	Haemophilus influenzae B	hepatitis B	pertussis (whooping cough)	PCV (pneumococcal disease)	meningitis C	measles	mumps	rubella	BCG Tuberculos	HPV	Varicella	Nb of Mandatory immunisation
Austria															0
Belgium															1
Bulgaria															11
Croatia															10
Cyprus															11
Czech Republic															9
Denmark															0
Estonia															0
Finland															0
France															11
Germany															0
Hungary															11
Ireland															0
Italy															10
Lithuania															0
Luxembourg															0
Netherlands															0
Poland															11
Portugal															0
Spain															0
Sweden															0
United Kingdom															0
Switzerland															0
Iceland															0
Norway															0
Russia															0

Mandatory
 Recommended
 Mandatory to start school

Figure 2 A table of European countries' recommended or mandatory vaccination information. Mandatory vaccinations are shown in red. Vaccinations necessary for school entry are shown in yellow. Recommended vaccinations are shown in light green. The last colon shows the number of the diseases for which the children need to be vaccinated. Some countries were omitted, as no English information was available. EU countries are shown in blue and neighbour countries are shown in Black.

Information was retrieved from web site of the government of each country published between 2015 and 2018^{33,37,38,48-51}.

3.5.2 Vaccination policies in other countries

In US, conscientious objection is allowed to justify that the parents do not agree for vaccination of their children. Nevertheless, certificates of vaccination are required to enter schools in some of the states and the vaccination policies are different in each state ⁵². In Canada, vaccination is not compulsory due to Canadian constitution ⁵³. Australia does not apply a compulsory law for vaccinations but vaccinations are mandatory for school entry of children. Japan applies compulsory vaccination policy against 13 diseases ⁵⁴. The share of children at age of 12 to 23 months old vaccinated against DTP3 in 2015 are 95 % for US, 91 % for Canada and 93 % for Australia and 96 % for Japan ²⁹.

3.5.3 Remove socio-economical barrier

Routine vaccinations are basically given to children for free of charge in European countries. Nevertheless, vaccine coverage was lowest in deprived, urban areas with mobile population as reported in a study in UK ⁵⁵. Thus it is presumed that associating incentives with routine vaccinations might attract attention. For instance, Australia offers incentives for vaccinating children on time and such incentives could be paid as tax rebates, insurance rates or direct payment. This plan is called “No Jab No Pay” and conscientious objector exemption is not accepted ³².

3.6 Educating parents with IT technology and eDigital tool

Smartphone applications can also be useful to ensure a pertinent immunization rate. Smartphone user penetration has been continuously growing and now accounts for 67.3 % of whole population in Europe in 2018 ⁵⁶. There is already one free smartphone app named ReadyVax from Emory University, USA. ReadyVax provides parents with up-to-date evidence-based information ⁵⁷. It has to be noted that patient-reminder recall should efficiently prevent parents from forgetting routine vaccines of their children and further increment of IT technologies should be one of the most promising solutions.

4. Discussion and conclusion

4.1 The need for European unified policies on vaccines

The first step to improve immunization coverage all over Europe is to define a unified policy on vaccines. For instance, the number and sorts of mandatory vaccines are different within Europe. Collaboration is needed to define public health endpoints for all countries in Europe.

4.2 How to improve vaccine coverage

In this work, we analysed multiple obstacles to a proper immunization rate. Vaccine coverage can be improved with simple solutions, but European countries must overcome recent challenges such as anti-vaccination movements and social insecurity together.

After analysing best practices, we found several measures to be pertinent in order to improve vaccine coverage. First, following the example of Italy ³⁵, **other countries in Europe must render vaccination mandatory for school entry and family allowances**. The family physician should take a lead role in the process of vaccination of children as well as the information of parents. Second, following the example of Germany, **parents who do not vaccinate their children on schedule should be fined**. Third, following the example of Australia, **parents who vaccinate their children on schedule, should receive financial support, such as tax reduction and incentives**. Fourth, investing in education and abolishing socio-economic barriers will lead to more aware and **educated parents**, who will vaccinate their children therefore improving coverage. Fifth, **stable and sustainable vaccine supply needs** to be further established. The governments need to acknowledge the value of vaccine industries and ensure the long-term financing of vaccination programmes to foster sustainable supply ⁵⁸.

4.3 Future challenges for vaccination in the post-truth era

The post-truth era has been challenging countries in their aim to obtain good immunization rates because personal opinions are now considered facts. National tools of pertinent information on vaccines should be offered to educate the public, such as mobile applications⁵⁷ and website who are proven to be effective ways to communicate useful information. Website and blogs promoting vaccine hesitancy should be overlooked, and the public should be informed when looking at “fake news”. Also, our medical practitioners should be educated to answer common vaccine questions so as to not raise vaccine hesitancy. In the next decade, the world will face new challenges regarding vaccinations; governments should be aware that funding for research, ensuring education and fight poverty are the best weapons to overcome these challenges.

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