MARBLE PROJECT – Institute for Public Health Genomics

Public Health Genomics: the Implementation of Vaccination Programs against Human Papilloma Virus (HPV)

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Executive Summary

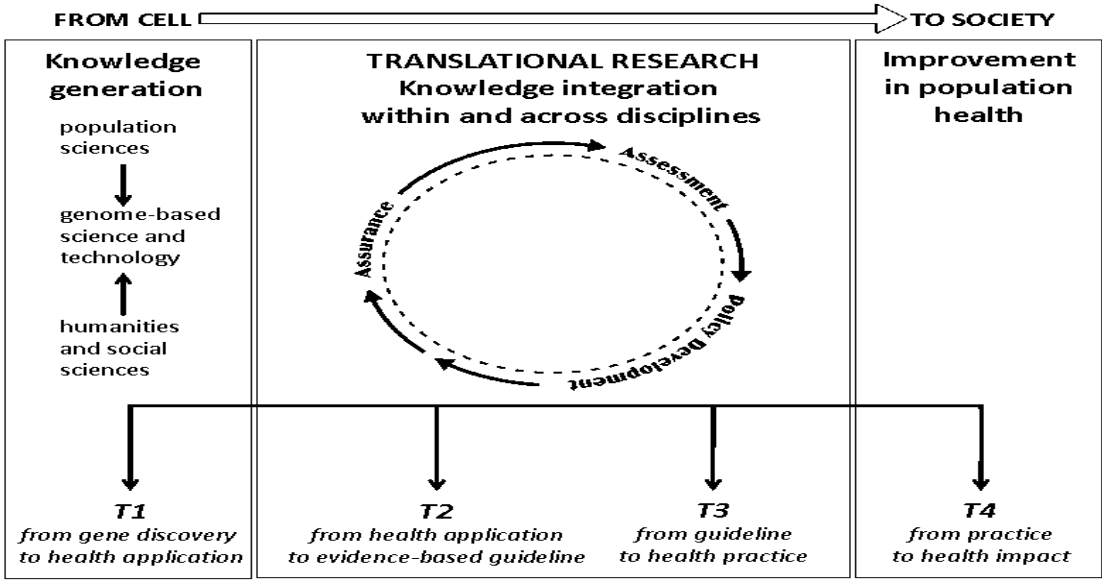
In the last two years, the implementation of Human Papilloma Virus (HPV) vaccination programs started in many countries around the globe. Years after a causal link between HPV and cervical cancer was proven, Public Health systems offer vaccines to young girls. The vast majority of countries opted for the vaccination of 12 year old girls and offered catch-up programs for girls between 13 and 16. The costs for the HPV vaccination differ with a median of 300 Euros for the vaccine. The coverage rate is lower than expected in most countries and substantial variations can be observed. Despite the financial burden in some countries like Poland, also cultural and gender specific issues need to be better reflected to ensure a higher coverage rate. From a biological and gender perspective more efforts are needed to assess the need for a vaccination of boys. A vaccination of boys may not be cost-effective based on the existing data but latest publications link HPV also to other cancer types like throat and penis. The discourse on the vaccination of boys should also address the disease burden related to genital warts which are often neglected. Within the study we observed a general weakness of Public Health systems to respond to upcoming and emerging genome-based knowledge in the field of HPV. Within the last ten years research groups have developed strategies which aim to accelerate and foster the process of translational research. The case of HPV demonstrates that these concepts have not been transposed into practice yet. Based on the weak uptake of new knowledge, substantial problems have also been observed in the communication strategy and the way parents, and in particular groups with specific needs are addressed. The HPV vaccination programs in many countries need further improvement and successful examples like the Australian school-based implementation concept need further exploration.

I. Introduction

Public Health Genomics (PHG) is an emerging translational multidisciplinary research field which builds on the expertise from various sciences and research networks, whose final aim is integrating the genome-based knowledge in a responsible and effective way into public health. Due to its multidisciplinary approach Public Health Genomics is ideal to stimulate the cooperation and collaboration amongst young scientists. It is also a field which works on the well-known bottlenecks of translational research.

The Public Health Genomics (PHG) MARBLE research project addresses the need for translational research in the field of health and life sciences. It is embedded in various research lines which focus on aspects of translational research. Translational research tries to enhance the up- and downstream of knowledge in a chain which links the basic sciences with the policy level. Maastricht University is hosting several international research projects and networks which address the field of translational research, amongst them the Public Health Genomics European Network (PHGEN). Public Health Genomics is often linked to genetic diseases with a high genetic penetrance, as Cystic Fibrosis and Sickle Cell Anaemia. The example of infectious diseases, and here in particular the case of Human Papilloma Virus (HPV), demonstrates that genome-based knowledge has to be considered adequately in all Public Health tasks. Many diseases and conditions however have a complex genetic basis involving interplay of a larger number of genes. Furthermore, epigenetic and environmental factors interact with them, and this overwhelming interplay can usually lead to an array of different outcomes. Therefore, proper translating of the state-of-the-art biomedical and public health knowledge into health practice is much needed.

Therefore, the topic of infectious diseases have been chosen by the team and the students in order to address the manifold issues which need to be considered as genome-based knowledge and technologies are introduced in the Netherlands and the rest of the world.



As we aim to enhance the effective and responsible translation of genome-based knowledge over the whole chain from cell to society, we encounter severe problems in the translation of basic science knowledge into practice and from practice into policy. To some extent the bottlenecks are due to different language sets in the different sciences and therefore, quite literally, more translational research is needed. Indeed, amongst the sciences we can assess inconsistent terminologies and also incomprehensive uses of abbreviations and sector-specific jargon. But we also see conceptual issues, for example weaknesses in the translation of relative risks (RR) into policies. The latter issues are probably more difficult to address but they are of utmost importance. If we describe the translational research as a pipeline, the conceptual frictions make the pipeline run dry as the next pump station cannot manage to facilitate the next level of translation.

The lack of translational research is also seen as a key barrier to the improvement of services and technologies. Many practitioners are unable to master the avalanche of emerging knowledge which affects their everyday activities. Thus, filters are needed to transform the scientific knowledge into operational knowledge. The Institute for Public Health Genomics (IPHG) at Maastricht University is one of a few institutions around the world which focus on the development of concepts for the translational

tasks ahead. Many more institutions are involved in sector-specific translational research activities.

II. The Example of HPV

The Human Papilloma Virus (HPV) infection is one of the most common sexually transmitted infections (STIs) worldwide. As it is transmitted through sexual contact with an infected partner, such virus affects mostly the genitals, but can also infect the mouth and the throat. Very rarely, a pregnant woman with genital HPV infection can pass the virus to her baby during delivery. In these cases, the child can develop a respiratory infection.

Epidemiological estimates suggest that the world prevalence of HPV infection is between nine and thirteen percent, which equates with about 630 million infected people. Because of its contagious nature approximately two thirds of all people who have sexual contact with an infected partner, male or female, will develop a HPV infection within three months.

There are nearly 200 different known types of HPV, but the majority is harmless and causes no symptoms in most people. Yet, 30 to 40 types may put a person at risk of developing cancer, and it is also possible to get more than one type of HPV.
Seventy percent of genital HPV infections are subclinical, and do not progress to disease, but regress spontaneously. Indeed, most infected people do not even realize that they are infected or that they are passing the virus on to a sex partner. A person can have HPV infection even if years have passed since he or she had sexual contact with an infected person.
The different types of viruses are identified by numbers and can be classified based on the severity of the disease they can cause. Low-risk HPV can cause genital warts, while high-risk HPV can lead to different kinds of cancers in women and men. The most frequent cancer triggered by HPV infection is cervical cancer, for with the HPV infection is the most important risk factor. Indeed, strong clinical, epidemiological and molecular biological evidence indicates that HPV is the central causal factor in at least 95% of invasive cervical cancers. It is the second most common cause of cancer deaths in women worldwide, and the fifth most frequently occurring cancer overall. Researchers estimate the global prevalence of clinically pre-malignant HPV infections at between 28 and 40 million. Moreover, cervical cancer affects every

year nearly 500,000 women worldwide and causes 270,000 deaths. Among them, 80 to 85% of cervical cancer deaths occur in the developing world, Africa, Central and South America and Asia, due to extremely limited availability of screening and treatment.

Such type of cancer develops in a minority of women with persistent pre-malignant cervical neoplasia, and it usually appears more than a decade after the initial HPV infection. This delay may be attributed partly to a need for cofactors that promote carcinogenesis, such as smoking. In immuno-compromised subjects infection tends to cause more severe and rapidly progressive cancer, reinforcing a growing body of evidence that the immune system plays a key role in controlling HPV disease.

There is no treatment for the virus itself, but there are treatments for the diseases that HPV can cause. Cervical cancer is most treatable when it is diagnosed and treated early. But women who get routine Pap tests and follow up as needed can identify problems before cancer develops.
Recently, two preventive vaccines have been developed: Gardasil by Merck and Cervarix by GSK.
Both are protective against infections by the two types of HPV (16 and 18) that are responsible for 70% of cervical cancer cases worldwide. In addition Gardasil also protects against HPV types 6 and 11, which cause about 90% of genital warts cases.
The two formulations currently available on the market have shown a nearly 100% efficacy in preventing development of cervical cancer due to infection by the HPV strains that they target.
Between 2007 and 2008 many European countries has approved and introduced such preventive vaccines in their national immunization programs.

III. Gap I (From basic to clinical sciences)

1. INTRODUCTION

The following chapter will focus on the translational research leading from basic sciences to clinical applications in the context of HPV. These steps will be further explained throughout the pathogenesis of HPV infection and its progression to cervical cancer, the development of vaccines and their challenges, as well as the future prospects in HPV vaccine developments.

2. HISTORY OF HPV BASIC SCIENCES

1. The Human Papilloma virus

The HPV viral genome consists of approximately 8kb of circular double-stranded DNA and 8 open reading frames encoding early and late regions. There is also a third non-coding region called the 'long control region'. HPV strains can be divided into two groups based on the severity of the disease they cause: namely the low-risk strains leading to genital warts, warts appearing in the respiratory tract (Recurrent respiratory papillomatosis), warts occurring in and around the anal opening (Anal condylomata) and the naso-pharynx (Condylomata). With respect to women, types 6 and 11 are the most common HPV types leading to genital warts or very minor cell changes on the cervix. Regarding men, low risk HPV strains can cause genital condylomata, warts on the penis and scrotum, and in the urethra. The high-risk strains can lead to cancer: For women, type 16 and 18 are most dangerous as they can lead to cervical cancer. With regards to men, high risk strains can lead to cancer of the penis, which also suggests that further attention should be given to the prevention of HPV for men (see chapter 6). The following chapter will focus on cervical cancer.

2. Cervical carcinogenesis by HPV

The HPV enters the basal cells in the cervical epithelium through micro lesions. The early HPV genes E1, E2, E4, E5, E6 and E7 are expressed and the viral DNA replicates. The viral genome continues to replicate itself in the cells of the upper layers of the epithelium, where the late genes L1 and L2 and E4 are expressed. Then, L1 and L2 assembles in mature virions in the nucleus. The virions can then infect other cells. Productive viral replication is enhanced by low-grade squamous intraepithelial lesions (LGSIL), a disease characterized by the abnormal growth of squamous cells on the surface of the cervix. When the cells are very abnormal, and the cervix is highly affected, it is called high-grade squamous intraepithelial lesions (HGSIL). HGSIL progresses into moderate dysplasia and severe dysplasia of cervical intraepithelial neoplasia (CIN), and LGSIL progresses into mild dysplasia of CIN. The

latter is a disease characterized by precancerous changes in the epithelial cells lining the cervix.

3. VACCINE DEVELOPMENT AND ITS CHALLENGES

3.1 The progression towards finding a vaccine

German virologist Harald zur Hausen was the first to show that the papilloma virus is the most significant cause of cervical cancer. The year 1999 constituted a major step towards the development of a vaccine: In fact, VLPs (virus like particles) were generated through the expression of the HPV L1 and L2 proteins together. Virus-like-particles are 'a biological construct designed to look like a virus, but which are not infectious' because they do not contain any viral DNA. VLPs are self-assembled from the proteins that make up a virus outer coat. It was then discovered that VLP expression in mammalian cells leads to morphologically correct HPV proteins, which stimulate the production of neutralizing antibodies, thus inducing protection against the infection.

3.2 The HPV vaccines

There currently are two vaccines against HPV. Gardasil (by Merck & Co) is a quadrivalent vaccine made of VLPs consisting of proteins from HPV16, 18, 6, and 11, and it is produced in the yeast Saccharomyces cerevisae and uses a simple aluminum salt adjuvant. The Cervarix vaccine marketed by GlaxoSmithKline is a bivalent vaccine made of VLPs consisting of proteins from HPV 16 and 18. It is produced in L1 recombinant baculovirus-infected insect cells and uses ASo4 as adjuvant. Both vaccines are an example of the application of genome-based technology to a public health issue as they are produced by cheap and fast recombinant technology. In fact, both vaccines are based on VLPs, which can be produced because the genome codifying for the proteins which form the VLPs is known. Virus-like particles are formed in labs, by injecting recombinant DNA into producing cells such as yeast. These virus-like-particles have the same L1 capsid protein as the HPV virus itself, but the VLPs do not contain any genetic material of the virus, and thus are non-infectious. Moreover, vaccination with these VLPs induces an immune response, as the body makes antibodies that can recognize the HPV neutralizing it.

3.3. General requirements

Before testing vaccines in humans, they should always have been tested in animals. This is done in order to look for any unwanted or side effects. After the pre-clinical testing in animals, the vaccine can undergo clinical trials in humans, which are the only way to know whether a future vaccine is safe and effective. Trials are conducted in three sequential phases: Phase I, which often enrolls several dozen volunteers at low risk of getting infected, and which focuses on safety issues and looks at whether the vaccine is immunogenic; then Phase II consists of several hundred volunteers usually including some with a high infection risk, and gathering immunogenicity and safety data; and finally Phase III also called efficacy trials, involves several thousands of volunteers to statistically determine whether the vaccine works. Scientists need the approval from various regulatory bodies in the country where the vaccines are to be tested. Another thing to mention is that it is important to ensure a production line for tens of millions of doses, and that the vaccine produced at this scale will have the same effect in the clinic as the vaccine produced at a smaller scale earlier in the program. After phase III of the trials should be legally approved by the FDA in the United States, and by the EMA in Europe.

4. Clinical Trials

4.1 Phase III of Gardasil vaccine

Phase III of the FUTURE II trial of the Gardasil vaccine consisted of a randomized, double-blind trial recruiting 12 167 women between the ages 15 and 26 who were not pregnant, had no history of abnormal Papanicolaou smears, and reported no more than 4 lifetime sex partners. In a double blind trial, neither the researchers nor the individuals know who belong to the experimental group or the control group. The study participants received three doses of either HPV 16/18/11/6 vaccine or placebo. There were 90 study sites within 13 countries in total. The primary outcome was cervical intraepithelial neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV16 or HPV18. The follow-up time was 3 years. Vaccine efficacy for the prevention of the primary outcome was 98% for the study

participants. Further analysis showed that in young women who had not been previously infected with HPV16 or HPV18, those in the vaccine group had a significantly lower occurrence of high-grade cervical intraepithelial neoplasia related to HPV 16 or HPV18 than did those in the placebo group.

4.2 Phase III of Cervarix vaccine

With regards to Cervarix, the largest phase III trial to date was called HPV008 PATRICIA. The trial was randomized and double blind, and recruited a total of 18 664 women aged between 15 and 25 years from 14 countries across Europe, Latin and North America, and Asia-Pacific. This study assessed the efficacy of CERVARIX in the prevention of precancerous lesions and efficacy against 6 and 12 month persistent infection and high grade pre-cancerous lesions caused by HPV16 or HPV18 or other cancer-causing virus types. Study participants were randomized to receive either a Cervarix or a control hepatitis A vaccine. The results showed that Cervarix provided a high and statistically significant level of efficacy against pre-cancerous lesions associated with each of the HPV types included in the vaccine (HPV16 and HPV18). In addition, the data showed that the vaccine also provided type-specific protection against pre-cancerous lesions associated with cancer-causing HPV types other than HPV16 and HPV18, such as HPV31 and 45.

5. Future Prospects in Vaccine Developments

Challenges for a vaccine against more HPV types or for a therapeutic vaccine

The problem with prophylactic vaccines is that they cannot cure an infected person, and another problem with current vaccines is that they do not protect against all HPV types. Thus, even after vaccination, regular screening is required. One way to solve this would be to develop a highly multivalent vaccine comprising the VLPs of different HPV types. However, this will raise the costs and complicate the manufacture. Another low cost alternative would be to identify a conserved antigen. One possibility would be to use the minor capsid protein L2 which induces cross-reacting antibodies. The epitope from the L2 of a single HPV type may be able to

give protection against various types. Nevertheless, L2 is not as immunogenic as L1, as the antibody titers induced by L2 vaccination are much lower than for L1 vaccination. Another option would be to develop a therapeutic vaccine, which in contrast to a preventive vaccine, needs to include some antigenic determinants derived from the early HPV proteins such E2, E6, and E7 rather than late proteins. The aim of therapeutic vaccines is to activate and increase the number of cytotoxic T-cells. Cytotoxic T-cells are the most important defense against tumor cells and virus-infected cells. Numerous therapeutic vaccines are currently facing clinical trials. The Dutch biopharmaceutical company 'ISA Pharmaceuticals' in collaboration with the Dutch Leiden University Medical Center, recently published results from a clinical phase II study with the Synthetic Long Peptide-based therapeutic vaccine (HPV-SLP vaccine), to treat patients infected with human papilloma virus induced neoplasia, and the vaccines is now entering phase III trial. This holds promising results within therapeutic progresses.

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IV. Gap II (From clinical sciences to Public Health policies)

1. From clinical sciences to public health policies

Due to systemic problems, discoveries often do not make it into evidence-based applications. They get „lost in translation" (Khoury et.al.,2007). Communication is one of the main steps missing to achieve the implementation of discoveries into public health policies. Precisely, a bridge between researchers and policy makers should be established (Khoury et.al.,2007). However, questions often rise regarding who should rely on whom and whether there should be another body that enables this communication between the two parties. Although the main barriers to this communication have been recognized (Tunis et.al.,2010), little has been done. The obstacles are manifold from simple administrative and structural problems to issues with competition and the fact that working together is simply more time consuming and expensive. Such gaps might eventually lead to an uneven spread of discoveries into practice (Kerner, 2008) and to being unsuccessful at implementing effective interventions (Tunis et.al.,2010). „Communication" means a two-way partnership. As mentioned above, consequences can be serious if the researchers do not collaborate with policy-makers and do not produce context-free evidence. However, the collaboration of policy-makers is also needed. According to Kammen et.al. (2006) challeneges and questions raised by them are often not communicated to the researchers which can eventually lead to difficulties developing clear, evidence-based guidelines and recommendations. Moreover, money can be spent on the unsuitable technologies (Tunis et.al.,2010). In order to tackle these problems, workforce training would be needed as well as increased public health literacy and various information systems to provide a way to communicate for both sides (Khoury et.al, 2007). When analyzing an invention, collaboration is needed to see its full influence on society (legislation, acceptance, ethics), to back up its efficiency, safety and efficacy with evidence and to be able to apply it in different contexts. If these links are made between researchers and policy-makers, the discovery can be implemented efficiently.

2. Methodologies

In order to 'close' the existing knowledge-gap, methodologies are important tools to facilitate the process. The former are the most efficient and easy way to collect, translate and apply evidence and to enable communication between researchers and policy-makers. Three methodologies will be described, each applicable in different settings.

In order to review health issues of a population and to prioritize health problems, the best method to use is the Health Needs Assessment (HNA). This evaluation involves five steps to achieve its goal. As Cavanagh et.al. (2005) describe, firstly, the population, the goals and the resources have to be chosen and fixed. Secondly, based on data on health determinants, the health priorities have to be identified. Thirdly, the first priority has to be evaluated and in the next step an action plan needs to be brought up. Finally, in the last stage, an evaluation of the procedure should be done. The method's strenght is that it involves the community members who are not only partners but could be resources for the study. This teamwork and partnership enables improved communication with agencies, bodies (Cavanagh et.al., 2005). However, it also faces challenges, such as the difficulty of translation of knowledge both in language and among professions. Furthermore, the access to data and to achieve high committment levels among the population itself are problematic (Cavanagh et.al., 2005).

The Health Impact Assessment (HIA) is used when one wants to evaluate the extent and the importance of an intervention, furthermore the impact it would have on society if implemented. Similarly to the HNA, the procedure involves community members and decision-makers to inform them about the results. The latter is often difficult to carry out, since a selection has to be made on who to involve in the process. Moreover, data on social impact is often hard to access. Persisting the transparency while evaluating is troublesome. However, in order to help the policy-makers' jobs, the latter needs to be made possible (Parry et.al., 2005).

Probably the most comprehensive methodology to use is the Health Technology Assessment (HTA). This review basically determines the impact of an intervention with regards to its safety, efficacy, social, political, legal and ethical consequences (Tulchinsky&Varavikova, 2009). The assessment uses cost- benefit and cost-effectiveness studies, clinical outcomes and reviews the literature to determine the potential effects of the invention on society. The method is usually carried out country by country and thus makes the evaluation applicable in the context-in-question. The assessment is precise regarding the significance of the intervention,

however to access the data on each aspect and to keep the transparency up is often challenging (Tulchinsky&Varavikova, 2009).

As it becomes clear, the main problem all these methodologies face is the collection of high-quality data. Furthermore, to stay transparent and for the message of the assessment to reach the policy-makers and help their work. There is need from the decision-makers themselves to draw their attention to such evaluations and to give feedback. These methods are carried out by multidisciplinary teams (Tulchinsky&Varavikova, 2009) with experts from different fields, who can analyze and translate data and thus allow a connection between researchers and policy-makers.

Before discussing an intervention, it is very useful to conduct a HTA, since its a comprehensive approach looking at all its potential effects. However, this is often difficult, especially when the subject of such an assessment is very new. In order to demonstrate some of these difficulties, two HTA will be presented, conducted on – the earlier mentioned – vaccine against cervical cancer.

HTA on vaccines is rarely carried out, even thought there have been studies done, the full analysis is often not doable. As it is stated in an Italian study (La Torre, 2010): „Our work represents the first attempt, together with the Danish experience (DACEHTA, 2007), to apply the HTA to vaccines". Due to the fact that the Human Papilloma Virus vaccine is very new, studies are complex to perform because of the difficulty to access data. As an example of the usefulness of such assessment, this chapter will look at the HTA done on the vaccine against cervical cancer in Italy (La Torre, 2010) and in Denmark (DACEHTA, 2007). The former introduces the Cervarix vaccine, while the latter examines the Gardasil one. The Italian study shows in detail how the process has been established. First, they looked at the epidemiology of HPV and the current preventive strategies, which was followed by exploring the healthcare resources and the cost of illness with such an infection. Further on, the vaccine itself has been examined with regards to its safety, efficacy and efficiency. The evaluation was followed by the analysis of the social impact of the intervention, including ethics, law and attitudes towards the vaccine. The findings and the methods are then clearly stated. The latter is important to show that this study does not aim to influence opinions, but to help one make their decision. It is also mentioned in the discussion that the assessment could be a helpful tool for decision-makers. When studying the Danish HTA (DACEHTA, 2007), one gets a different impression. That is due to the fact that the report is more of a summary, a 'translated' version of the scientific report, done by an interdisciplinary group. This approach enables policy-makers to better understand the impact of the vaccine,

without having to know about the details of the assessment. This way it is easier for them to reach a decision compared to the Italian study, that is more adressed to professionals in the field. The Danish have done the HTA a little different to the Italians. They have tried to place the vaccine into scenarios and see how an implementation would be possible. Furthermore, few recommendations are given in the paper regarding this subject. The complexity was also tried to be reduced by simply grouping the advantages/disadvantages of the introduction of the vaccine into two paragraphs. Concerning the social impacts of the intervention, the study-in-question has gone more into detail regarding the assessment. This refers to the fact that actual group meetings with parents and young people have been oraganized to better understand the significance of the vaccine and the explanations for the fears, opinions.

As it shows, a HTA can be carried out in various ways, depending on its aim, the country and the interdisciplinary team itself. However, it is always based on the same steps and information. The three assessments mentioned in this chapter are essential tools for closing the know-do gap. They enable decision-makers to understand data better and thus, to be able to meet the five criteria for good public health policy (Birt et.al., 1997): firstly, that the policy is based on health needs, in which the HNA could help. Secondly, that policy should be evidence-based, in which case all the assessment could provide aid. Thirdly, the social-acceptance of the policy should be considered through either a HTA or a HIA. Furthermore, the decision should be politically credible and this factor could be analysed by the HTA. Finally, a good public health policy should enable democratic participation. If used together, these tools can contribute to not only the closure of the know-do gap, but also to more evidence-based decision-making.

3. Interim Conclusions

In the USA, the know-do gap has been recognized and action has been taken to fight it. Unfortunately, Europe seems to be one step behind which can simply be recognized even by trying to search for information on the topic. The tools mentioned in the previous paragraphs are a leap forward, but more could be done. Through the Center for Disease Control (CDC), networks have been set up in the USA. One of these is the so-called Genomic Applications in Practice and Prevention Network (GAPPnet) for stakeholders to work on four different domains which include: knowledge synthesis and dissemination, evidence-based guideline development, translation research and traslation programs. The system enables

communication and teamwork, not only through assessments. Regarding tools, the CDC has also developed the Evaluation of Genetic Applications in Practice and Prevention (EGAPP) that differentiates safe and efficient genetic tests. Such an evaluation is done based on different models and is interesting because genetic tests are quite new interventions. Consequently, a way to assess new discoveries is trying to be built up and could be useful for vaccines as well, such as the one against cervical cancer.

Policy-makers could also communicate their challenges to the researchers whom, after that can conduct specific studies. Clinical trials for these cases have been developed but are not used enough. Studies like this are called Pragmatic Clinical Trials (PCTs) and are established to answer questions posed by decision-maker through indicaters relevant to them (Tunis et.al., 2010). Furthermore, these trials can bring evidece-base into guidelines, recommendations in policy-making.

Despite all the networks and tools that could be used to tackle the know-do gap, few steps have been made so far. Moreover, while concentrating on buliding a bridge between reasearchers and policy-making, one should not forget about the community. The former could not only be a useful partner, but a resource as well in the procedure. A holistic approach and a combination of the various actions, tools should be set up.

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V. Implementation of HPV Programmes in the Netherlands and abroad

Positive health outcomes following the implementation of an innovation or a policy not only depends on the quality of the program, in this case the HPV vaccination program, but also on its implementation. As it is too early to notice some significant changes in health outcomes after the introduction of the HPV vaccine, this section will focus on coverage rates. The Dutch HPV vaccination program will be used as an example of how the implementation of specific programs can influence, negatively or positively, vaccination coverage rates.

1. The Dutch HPV vaccination program

In 2002, the incidence of cervical cancer in the Netherlands was quite high compared to other European countries (7.3/ 100,000) (Globocan, 2002). The main prevention method was then an organised national screening program: women aged 30 to 60 were invited for a cytological examination once every 5 years. In 2009, it was complemented by an HPV vaccination program in order to decrease the incidence of cervical cancer significantly. As in every other country, the implementation of the vaccination program did not have any impact on screening programs and this is the reason why they will not be discussed in this section. The target group of the vaccination program was 12 years old girls but a catch-up program was also implemented for girls born between January 1st 1993 and

December 31st 1997 (13 to 16 years old girls). The vaccination of the target group began on the 29th of March 2010, while the catch-up program was already implemented in spring 2009. It is worth noticing that the vaccine is only reimbursed for the target group (12 years old) and other women who might consider the vaccination, such as women part of the catch-up program, have to pay the full price of the vaccine. The Community Health Services sends invitation and information letters to the families of the 12 years old girls and of the girls in the catch-up program, for the first two doses of the HPV vaccine. The CIB, centre for infectious disease control, also provided some toolkits on the internet (with posters, magazines, or fact and data sheets) designed for health professionals interested in some more information on patient communication (RIVM, 2010).

The initial aim of the national program was to cover 70% of the target group. Even though positive results were observed at the beginning of the program, HPV vaccine uptake levels fell quickly and by the end of the year 2009, only 45 % of the catch-up group was vaccinated with considerable regional differences ranging from 31 to 61% (RIVM, 2010). There were also significant differences between particular cultural, social, or religious groups (See table below). Girls with parents born in the Netherlands, from a higher Socio-economic Status or living close to the vaccination centres were more vaccinated than others. At the municipality level, the use of incentives, anti-HPV action or simply the media had a negative impact on coverage rates. Finally it was noticed that in municipalities where more than 15% of citizens voted for the Christen Union at the last elections, vaccination coverage rates were particularly low (Rondy et al., 2009).

Nationality		Distance house–centre		SES	
Dutch	Moroccan	0 km	10 km	High	Low
51.8%	24%	47.7%	52.6%	53.1%	46.9%

MUNICIPALITY LEVEL							
Vote for Christen Union		Use of Incentives		Anti-HPV action		Use of Media	
0-5%	>15%	Yes	No	Yes	No	Yes (4 sources)	No
52.1%	26.6%	44.5%	50.4%	48.9%	51.5%	48.1%	61.3%

HPV vaccination coverage rates in the Netherlands, 2009 (Source: Rondy et al., 2009)

These data show that many factors can contribute to parents' opinion about the HPV vaccine but they also suggest that the Dutch government was not able to handle upcoming challenges and perhaps to address some specific groups in a

different, more appropriate manner. What alternative programs could be considered in order to reverse this negative trend?

2. Factors influencing coverage rates

This section will discuss some factors which could have influenced Dutch parents' decisions to vaccinate their children and how they were handled in various countries. The United Kingdom and Australia were chosen as example of countries with effective vaccination programs. In the UK, cervical cancer incidence rate in 2002 was slightly higher than in the Netherlands (8.3/100 000) (Globocan, 2002). Their vaccination program was launched in 2008 and focused on 12 to 13 years old girls with a catch-up program for 15 to 18 years. After a year, the coverage rate for the third dose of the vaccine was 70% in the country and up to 80.1% in England (Department of Health, 2010). The incidence of cervical cancer in 2002 in Australia was even higher than in the UK (10 / 100 000) (Globocan, 2002). A year after the implementation of the vaccination program in 2006, the uptake of the 3rd dose of vaccine was approximately 75 to 80% (Shefer et al., 2008). The Australian program targeted 12 to 13 years old girls and 12 to 18 years old girls as a catch-up program. The United States and Poland represent countries with less successful programs and lower coverage rates. The US had an initial incidence rate of 7.7 / 100 000 in 2002 (Globocan, 2002). Following the implementation of the vaccination program, 17.9% of the target group (11 to 12 years old girls and a catch-up program for 13 to 26 years old) received the third dose of the vaccine with state differences ranging from 8% in Idaho to 34.2% in South Dakota (CDC, 2010). Although cervical cancer incidence in Poland was the highest of the four countries (18.4 / 100 000, Globocan, 2002), no vaccination program has been implemented. Furthermore, age recommendations can be quite confusing as the Polish Society of Gynaecology recommends the vaccination for 11 to 12 years old girls while the Polish Association for HPV Prevention recommends it for 13 to 26 years old girls and for 9 to 15 years old boys. This might be an explanation for the lack of data on coverage rates in Poland. This section will discuss some major factors influencing HPV vaccine uptake levels by comparing the various situations in the UK, Australia, the US and Poland.

2.1 Costs and reimbursement

One of the most obvious factors influencing parental decision to vaccinate their child is the cost of the vaccination itself. The HPV vaccine is very expensive, especially compared to other vaccines, and its price varies between countries (279€ in the US,

312€ in Australia, 345€ in the UK, 354€ in the Netherlands and 399€ in Poland). Even thought the vaccine costs more in Australia and in the UK than in the US, coverage rates are still higher in the two former countries. This is perhaps partly due to the full reimbursement of the HPV vaccine for all eligible people. In the United States, on the opposite, insurance companies can decide whether to reimburse the HPV vaccine or not. In addition, programs such as the "Vaccines for Children program" can cover parts or the total cost of the vaccine for people without health insurances (VFC, 2010). Finally, in Poland, all girls or women who are interested in the HPV vaccine have to pay the full price on their own. In the Netherlands, the price of the HPV vaccine is not a problem per se, as it is reimbursed for 12 years old girls. However, other eligible women, such as women part of the catch-up program, have to pay the full price of the vaccine; and in order to increase total coverage rate, reimbursement for all eligible people should have been considered.

2.2 Information and education campaigns

In our society, the media influences greatly citizens' choices and decisions and this is also true for HPV vaccination. Due to doubts of health professionals or scientists, there were a lot of negative messages about vaccination; and the information provided by the media often confused Dutch citizens. For instance the "Nederlandse Vereniging Kritisch Prikken" (the Dutch Association Against Vaccination) published an article with the title: "Girls, caution: vaccination against cervical cancer for 12 years old girls is a health-experiment" (NVKP, 2010). Furthermore, the use of incentives decreased the credibility of the vaccine as an effective prevention method. In order for the vaccine to be accepted as safe and efficient by the public, the media needs to inform citizens about HPV, cervical cancer, the prophylactic vaccines but also to respond to anti-vaccine groups and to reassure people about misleading and incorrect information and about fears of stigmatisation or certain ideas such as unsafe sexual behaviours. In the UK, information and guidance was provided in various languages in order to reach as many people as possible, and letters were sent to teachers, parents and health professionals. Advertisements were launched via television, the written press and the radio, to promote the routine vaccination program and to remind the girls to get the three doses of vaccine. The particularity of the Australian education campaign was that they provided specific information various groups. For instance, they had specific communications for religious groups where they focused more on cervical cancer rather than on sexually transmitted diseases and HPV. Furthermore, they responded

to some “HPV Vaccine Alerts” or other types of campaigns from anti-vaccine groups which claimed that “Anyone with a HPV infection (and they are common), who is given the vaccine risks immune system shutdown or autoimmune disease” and that the vaccine could cause “HPV infection, cervical cancer, birth defects, miscarriages and infertility” (Watson et al., 2009). The Australian government provided some question and answer sheets discussing each of the points and arguments of the anti-vaccine groups and discussed the influence and the power of the media on citizens. In the United States, the media could have had a bad influence on HPV vaccination. In addition to the promotional campaign launched in 2007 by the CDC, manufacturers had the right to produce “direct-to-consumers advertisement” as for every other medicinal product. It has been proven that DTCA can have a negative impact on citizens, and this might have been a reason for low coverage rates.

2.3 Type of vaccination programs

Finally, the type of vaccination program can greatly influence the final vaccination coverage rate. The UK and the Australian governments both decided to implement school-based vaccination programs. The HPV vaccines are thus provided at schools, by doctors or nurses and this helps to get through to girls with a lower socioeconomic status. Furthermore, such a program enables governments to reach religious groups: when two Australian Christian schools refused to provide the vaccine, the government had to change its policy and requested the schools to provide information to girls about the vaccine and about the possibility to get vaccinated at local clinics. In the US, the HPV vaccine is recommended at routine general practitioners’ visits and it is provided by primary medical care centres. In Virginia, although schools do not provide the vaccine, vaccination is mandatory for school enrolment (National conference of state legislatures, 2010). As the vaccine is not part of the national immunization program, the case of Poland cannot really be discussed. Since 2009, the HPV vaccine became part of the recommended vaccines, and it is now the role of general practitioners to inform patients about the possibility to get vaccinated. Many of the issues the Dutch government is facing could be resolved by implementing a school-based vaccination program such as in the UK or in Australia, as the alternative implemented in the US and in Poland are clearly not effective. First of all it would resolve the problem of the distance between homes and vaccination centres. Second of all, it could have an effect on the negative opinions of some people due to the influence of anti-vaccine groups as vaccines provided in schools are usually seen as accepted, effective and safe. And finally, it

would enable the Dutch government to reach more girls, from various backgrounds (cultural, social or religious) as school attendance at this age is quite high in the Netherlands, and in Europe in general.

3. Interim Conclusions and recommendations

The specificity of the Dutch HPV vaccination program was the implementation of the catch-up program before the target group program. This could have been used as a great advantage, as it was possible to evaluate the catch-up program and then improve it for the second group. It could have been used as a Health Impact Assessment tool, such as the ones used in Italy and Denmark and described in the previous section. However, probably due to a lack of communication between researchers and policy-makers, the program was not modified. In the UK, regular meetings were organised, in which regional best practices were exchanged on ways to resolve upcoming issues and challenges. Implemented vaccination programs need to be flexible enough to adapt them when necessary and meetings such as the ones in the UK could be organised in the Netherlands in order to reduce regional coverage rates differences. Furthermore, a school-based program with full reimbursement of the vaccine for all eligible citizens should be considered. In addition, the education and information campaign should be revised in order to deal with anti-vaccine groups and to avoid the spread of fear and concerns about the HPV vaccine. This sort of program could also be implemented by countries which do not have an HPV vaccination program yet, like Poland, or countries facing difficulties in improving their coverage rates, like the United States.

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VI. Gender Issues

1. Introduction

Human Papilloma Virus (HPV) affects both men and women. However, the diseases that can result from an infection with HPV are different in men compared to those in women. Due to the high burden of the HPV-related cervical cancer in women, HPV vaccination programmes have been implemented for young females in many countries. Even though the vaccine Gardasil has been approved for use in young men and would have several benefits for both genders, there are still no campaigns supporting the vaccination of both sexes.

From one point of view, women are advantaged by having – often free - access to the vaccine, while men do not. They are protected against infection from HPV type 16 and 18, and with the vaccine Gardasil additionally from HPV types 6 and 11.

But it can be argued as well, that addressing only women counteracts the often disadvantaged status of women. It is well known that infectious diseases are the disease of the poor part of the population. When taking into consideration the fact that 70% of the poor are female, it becomes clear that it is women being the higher risk group (Hartigan, Price &Tolhurst, 2002).

Especially those with early sexual activity, a high number of deliveries, and with changing sexual partners are at high risk of HPV infection (Hartigan, Price &Tolhurst, 2002). In addition, women have to deal with higher obstacles in their access to health care. This is the major reason why many women are not attending regular screenings as part of their health check-ups (Hull &Caplan, 2009).

On the other hand, the vaccination of only women is often seen as stigmatizing them. While it is both sexes that can be infected with HPV and both sexes that can transmit HPV, the vaccination of only females creates the idea that it is merely the disease of women. Following this notion, women could be blamed to be the offender that spreads the disease.

This chapter will examine different gender aspects by looking at the vaccination of only women. First, the stigmatization of women is described. Second, it will present several arguments why men should be vaccinated. The aim is to contribute to the discussion of including young men in the vaccination programmes. This shall be achieved by analysing several aspects of such an implementation, such as costs and the willingness of men to use the vaccine.

2. Stigmatization of women regarding HPV and vaccination

The current vaccination programmes, which address only women within a certain age group, promote the stigmatization of women in several ways. Women experience health disadvantages in all stages of disease progression. The discrimination of females can be found in the prevention of diseases. However, women are often at a higher risk of becoming infected. Also, other factors lead to an unfavourable position of women when it comes to detection and treatment outcomes (Hartigan, Price &Tolhurst, 2002).

Certain norms of gender behaviour within society counteract with the public prevention strategies. As sexual activity of women often remains an unspoken topic, obviously, preventing women to infect with sexually transmitted diseases through vaccination is not a hot topic. Furthermore, religious arguments were brought up especially by the Catholic Church implicating that HPV vaccination would promote

promiscuous behaviour of women. Sexually transmitted diseases such as HPV are commonly associated with a promiscuous sexual behaviour and sometimes imply a 'dirty' image of the infected patient (Hull &Caplan, 2009). However, previous Hepatitis vaccinations did not result in any changes of sexual behaviour (Hull &Caplan, 2009). Certainly, the late onset of clinical trials with men led to the feminization of the HPV vaccine. As a result, the assumption that HPV merely is the disease of women was fostered.

It is assumed that women rejected the vaccine due to the fear of acquiring a promiscuous image. In the US, denying the existence of HPV among youngsters has led to low coverage rates of the vaccine (Hull &Caplan, 2009). Many people are still not aware of the link between HPV infection and cervical cancer.

With regards to infection, it is the expectations on women and their destined role in community which puts them at higher risk of disease. For instance, being the passive part during sexual activity is the accepted role of women in many societies. This role increases their risk of infection, by impeding them to show initiative to demand the use of preservatives. In addition, biological factors, such as higher susceptibility of the female body, contribute to the increased risk of infection. The greater surface of the female vulva results in a higher risk of HIV infection in comparison to the smaller penile surface of men.

Several obstacles complicate the detection of HIV. The main role plays the disadvantaged position of women in access to health services. In families with culturally men-orientated background, where wives do not have the control of financial resources, it is not their choice whether to spend money on health services. One obstacle to vaccination is that some societies deny noticing that women do have sex before marriage. Hull & Caplan stated in 2009 that testing for HPV entails the stigmatization of women of Indian or Pakistani origin because it is associated with promiscuous behaviour (Hull &Caplan, 2009). Furthermore, they identified within their study the fear of Muslim women to loose their virginity through HPV testing. Among Nigerian women, it has been observed that the detection of cervical cancer resulted in an enormously high stress for the patient. The degree of stress was higher than in the case of diseases other than HPV-related cancer. Determining for the stress was the sexual background of the disease. Taking into account the stress of HPV detection, it is assumed that Nigerian women, and as well other women, avoid testing for HPV because of fear (Hull &Caplan, 2009).

However, even the detection of a HPV infection through pap smears and the detection of genital warts or carcinoma lesions, does not necessarily lead to treatment of the disease. First, the access to treatment might be hampered by

lacking resources. Second, Hull & Caplan presumed that physicians might treat patients differently when thinking that the patient is responsible for the disease through his/her behaviour, in the case of HPV; his/her sexual activity (Hull &Caplan, 2009). This could lead to a lower quality of care and treatment by the physician.

Biological and social factors interact and create the individual susceptibility to HPV. In addition, the social factors predict the stage detection and treatment, and thus the outcome of a HPV infection. Created social factors are the main reason for, and are part of, the gender inequity. The debates on HPV vaccination focus only on women, even if men are infected as well. Astonishing in the debates about protective measures used by only one sex is the double standard concerning sexual promiscuity. The recent debates on male circumcision as a protective measure for HIV infection (male circumcision is said to have 30 - 50% preventive influence on male HIV infection) were not triggered by the argument that this intervention would promote promiscuous sexual activity (Carpenter & Casper, 2009). This example shows that men and women are not treated in an equal way when discussing their behaviour. Especially, the existing double standard among men and women is striking when valuing their sexual activity.

3. Arguments for men to receive HPV vaccination

Many arguments in the literature have been brought up which advocate the inclusion of men in the current HPV vaccination programmes. These arguments are of biological, moral and social nature.

Biological arguments focus on the direct benefits on the male body. The vaccine Gardasil has evidently proved to prevent the infection with HPV strains, which generate genital warts and some cancers. The lifetime prevalence of genital warts in men was stated to be 5.6% in the US (Hull & Caplan, 2009). More recently, the prevalence was estimated to be 0.13-5.01 per 1000 men (Hibbitss & Cuschieri, 2010). Furthermore, Giuliano argued in 2007 that men would suffer longer from genital warts than women, resulting as well in heightened treatment costs (Giuliano, 2007). While the vaccine plays obviously an important role in avoiding the transmission of genital warts, the picture of preventing cancer is different. First, only some of the classified cancers, such as anal, penile and throat cancer could be prevented. Second, not all of the named cancer types are solely caused by an HPV infection. Nevertheless, the vaccine could prevent a high percentage of these cancer types; 77.5% of penile cancers, 18% of head and neck cancers, and 90% of anal cancers (Carpenter & Casper, 2009; Giuliano, 2007). Cancers of the penis count for <

0.5% of the total male cancers. This cancer type has several non-related independent causes. Whereas Hibbitss & Cuschieri state, HPV causes less then half of these cases (Hibbitss & Cuschieri, 2010), Giuliano claims HPV type 16 to be responsible for 77.5 % (Giuliano, 2007). The main risk factor for head and neck cancer is not a HPV infection but smoking and alcohol consumption. Evidence for a correlation of HPV (type 16) and head and neck cancer was found in 18% of cases. Additionally, the high risk types of HIV play an important role in the development of anal cancer. The incidence of anal cancer is 0.8 per 100 000 men in the US and 90% of the cases are correlated with a HPV infection (Hibbitss & Cuschieri, 2010). Beside genital warts and certain cancers, HPV infection with type 6 and 12 can cause recurrent respiratory papillomatosis or condylomata of the throat and other warts (Ferris et al., 2009). Often disregarded is the impact of HPV on the male fertility. It has been stated that an infection would reduce sperm motility and could even lead to infertility (P. Verdonk, personal communication, March 2, 2010). Moreover, vaccination of males is the only way to address the high prevalence of HPV in homosexual men, which do not benefit from female immunity.

Hull & Caplan claim male vaccination with moral reasoning. Their main point is that one has to take the responsibility for ones behaviour. Therefore, men are responsible for transmitting HPV to a sexual partner and thus should prevent this by using the vaccine. Their own immunity would help decrease numbers of cervical cancers and thus the burden of women. As it is not only women's behaviour putting them to be at risk, it is also that of their husbands: married women that did not have sex before marriage can be infected by their husbands, e.g. when they had sex with prostitutes before marriage (Hull & Caplan, 2009).

Many more arguments originate from the fundamental principles of society. Because women are predominantly infected through men, it is their role to protect this transmission. Following example shows that male gender plays the crucial role; Giulinao described a study which found out that "male promiscuity was associated with a 6.9-fold increased risk of cervical cancer in the female partners" (Giuliano, 2007). Moving away from the responsibility for the sexual partner, responsibility of society goes further. In principle, every member of society has to take care of the society in whole. In that sense, a male vaccination would help oneself get concerned regarding the health of one's daughters, sisters, and in general all women. Furthermore, vaccination of both sexes would increase the acceptance of the vaccine. This would help to achieve higher coverage rates of the vaccination. Only through a greater acceptance, it will be feasible to achieve herd immunity. In addition, addressing both sexes in the vaccination programmes would help to see

HPV as a common disease. Thus the stigmatization of women with regards to HPV would be stopped. A fact that is often neglected is that genital warts can be vertically transmitted from mother to baby. The baby may suffer from recurrent respiratory papillomatosis, which can lead to death in 1-2% of the cases. Besides, the disease can promote a pathogenesis of head and neck (Hull & Caplan, 2009).
Finally, there are no risks when vaccinating men. The clinical trials have shown that the vaccine has barely any side-effects. The reported side effects such as bronchospasm, gastroenteritis, headache, hypertension, local pain at the place of injection, or impaired joint movement at the injected limb, were reported in both - trial and control – groups (Rambout, Hopkins, Hutton & Fergusson, 2007). It has been concluded and reported that the HPV vaccine is well tolerated and effective. The vaccine implicates low risk and, as laid out above, has several benefits for men, women and society. Therefore, current vaccination programmes which focus only on women should be reconsidered.

4. Potential implementation of vaccinations for both sexes

For the implementation of both gender vaccination programmes, the main determinants to consider are efficacy and costs of the intervention. Moreover, it should be considered how it would be possible to convince boys to receive the vaccine.
At first, the costs for the vaccine seem to be high. A 3-dose series of the vaccine Gardasil costs on average 300€. However, HPV vaccination would prevent genial warts and thus resulting treatment cost. The costs of diseases following a HPV infection, excluding cancerous lesions, were $418 million in the US (€280 million), and 60% of this sum was used for the treatment of genital warts (Hibbitss & Cuschieri, 2010). The total cost resulting from a HPV infection were $2.8 billion among US men and women, aged 15-24 (Giuliano, 2007). Finally, Hibbitss & Cuschieri report that the result of a US cost effective assessment of HPV vaccination programmes, including boys, was $ 90 870 per QALY. This amount is below $ 100 000, which is the threshold in the US for a successful intervention (Hibbitss & Cuschieri, 2010). For a continuation, experts suppose that it is advantageous to vaccinate everybody, because thereby herd immunity would be achieved. Only herd immunity would mean that the disease would eventually be eradicated. For example in Asia, the vaccination of solely risk groups against hepatitis did not achieve the prevention of the disease (Hull & Caplan, 2009). As well, the experiences with preventing Rubella through female vaccination lead to the reappearance of the

disease in men. Moreover, a study in the UK concluded female vaccination would not be cost-effective if the effective period of the vaccine is short-term – about 10 years (Hibbitss & Cuschieri, 2010). Considering that more people use the vaccine, the price of one series is likely to decrease.

For the potential implementation of both gender campaigns, it is important to consider the willingness of men to get vaccinated. The study by Ferris et all, published in 2009, examined this issue "[HPV] vaccine acceptance by men" (Ferris et al., 2009). The results indicated 33% of the participants would use the vaccine, 27% do not want to receive vaccination, and 40% were undecided. The analysis showed that greater general education, high-risk behaviours, and knowledge about HPV, increased the choice of vaccination. Other beneficial determinants while making the decision where recommendations by the doctor (56%), vaccination implies no cost for the receiver (51.4%), and whether there was evidence-based information reporting the efficacy of the vaccine for men (50.7%). The study showed the importance of the factors general education and being informed. The focus in future campaigns should be set on educating the determined vaccine receivers in order to increase their willingness to use the vaccine.

5. Interim Conclusion

Is it effective to include boys into the HPV vaccination programmes? Regarding the transmission of genital warts, one could argue the incidence would decrease because of female vaccination. However, at this point in time, the coverage rates of female-focused programmes remain too low. The resulting diseases of HPV, such as HPV-related cervical cancer, could dynamically be eradicated through the vaccination of both sexes. Furthermore, boys would be protected from infection and following diseases like genital warts and some cancers.

Future campaigns have to be designed more carefully. Societal norms have to be factored in when designing one-gender campaigns. The design should take into account double standards, which are still present, especially regarding sexuality. Therefore, it is important to educate men and women about HPV and its resulting diseases. Furthermore, more information on sexually transmitted diseases and available screening should be provided, in order to normalise these diseases. The proposed change has to start at the level of policy making. In general, all European and national health policies should consider, and if necessary address, gender issues.

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VII. Legal Aspects of HPV and Public Health Genomics

The field of infectious diseases has been subject to international regulations and agreements for a long time. Several international and European institutions address regulatory aspects related to infectious diseases and Public Health. While many people are aware of the International Health Regulations (IHR) (WHO, 2005), other regulations addressing global trade and travel are less frequently taken into consideration. The legal rationale behind the norms is quite simple as law serves as a tool to prevent the spread of infectious agents. Legal norms therefore address the factors which influence the transmission of infectious agents on a global, European, national and regional level. The situation is way different for sexually transmissible diseases as the concept behind the specific regulations for infectious diseases does not work in this case.

Law is used in modern society to perform certain tasks; with Llewellyn (Llewellyn, 1930) and Kelsen (Kelsen,1960) we can say that law steers the behavior of

individuals in society as it sets normative benchmarks. Law therefore defines behavioral expectations and defines modes of cooperation within and beyond societies. While different legal systems can face the same conflicts like different societies as they interact, legal norms in the context of infectious diseases have developed in a relatively harmonious way. Following a precautionary approach law take preventive measures which are addressing either all member of one society, members of different societies (such as all EU citizens) or even the global population.

The case of Human Papilloma Virus has shown that infectious diseases can induce the development of cancer in humans. Like with other infectious agents the mode of transmission and the potential negative effects on society allow policymakers to take rather strict and paternalistic measure. So far no specific norms have been created for this new sort of sexually transmissible infectious diseases. In other cases such as HIV /AIDS, legal systems have reacted by applying norms of the criminal law to the voluntary or negligent transmission of the infectious agent to stimulate preventive behavior in society (Lowbury&Kinghorn, 2006). While such use of criminal law has turned out to be unsuccessful it is also questionable whether a person can be prosecuted due to the transmission of HPV if it subsequently leads to cervical cancer. From a strict legal approach the jurisdiction which has been developed in the field of HIV might be applied to HPV as well if a proof of a causal link between the infection and the subsequent development of cancer is possible. In reality this option can be ruled out and law can only be used as a preventive measure.

Thus, law can be used to promote health goals and to achieve a reduction in the burden of disease caused by cervical cancer. Legal instruments are in place to assist media and information campaigns and to empower citizens. Law is also the tool to include HPV vaccinations into the national immunization programs as demonstrated in Chapter XX of this report. In many countries only 12 year old girls are vaccinated; while this may follow a cost-effectiveness rationale it also obstructs the equal access to healthcare of other girls and boys who are generally excluded from the vaccination. Within the new fundamental rights development in Europe, the equal access to health services is a basic condition for the execution of personal freedom in Europe (Smith, 2005). This does not imply that all Member States of the European Union have to offer the same health services, and therefore the same programs for HPV vaccination (EU,2006). Member States can develop their own strategies and they are also empowered to reflect on national, regional and local cultural values in

the context of HPV. Still, if there is a substantial evidence base for the extension of program to boys and other groups of girls, the enforcement of fundamental rights can force governments to re-consider their programs. Governments may also face legal pressure to modify their programs if deficits in the implementation are observed or if other programs prove to be more successful. For the Netherlands this might lead to an introduction of a school based program and to improved communication tools. In many Member States of the European Union, Health Technology Assessment (HTA) is a prerequisite for the introduction of new technologies and approaches in the Public Health system(Banta, 2003). While law is supportive if HTA serves a better, more evidence based and equitable distribution of resources, it may also overrule decisions based on HTA reports. The missing vaccination for boys can serve as an example that law does not follow the cost-effectiveness approach even if it is endorsed by health technology assessment reports (HTA). Such a report and the policy decision based on it cannot be seen as a solid argument for the infringement of fundamentals rights of young girls and boys.
So far, law has been used in a reticent way to facilitate the implementation of HPV vaccination programs in Europe. With the changing evidence base this might change in the future. The application of criminal law rules is unsuitable in the case of HPV. The traditional regulations for infectious diseases are not applicable either in the case of sexually transmissible diseases. So far, the sole role of law is the enforcement and alignment of fundamental rights in the context of HPV.

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VIII. Ethical and Normative Aspects

1. Background

In the range of philosophical aspects of Public Health, ethics has an outstanding position dealing with the pivotal questions what is morally right or wrong to do if an action (or its omission) has an impact on others.

As a special challenge for Public Health Ethics, one can see the implementation of genomic knowledge into the goals and approaches of Public Health – e.g. is the genomics screening for disease X morally permissible or even obligatory?

According to the progresses in genomics and its potential to care for the health of all, one can discuss its challenges from an explicit Public Health Ethics perspective – this is especially true after the horrible experiences made with eugenics in the last century. Now we have the chance to discuss the issues we will encounter with implementing genomics into public health goals prospectively.

Ethical principles are useful tools for public health ethics. To find guidance for ethical evaluation, one can use a concise set of broad ethical principles. This can consist of the following generalised norms that reflect the public health enterprise to maintain and promote population health – whilst still acknowledging "side constraints" (Robert Nozick) that remind practitioners that populations consist of valuable individuals. These principles are: health maximisation, respect for human dignity, social justice, efficiency and proportionality.

These principles can be considered an "ethical toolbox" for public health (genomics) practitioners and scientists and benchmarks for *ethically* good and right public health (genomics) research and practice. It is the role of public health practitioners and researchers to balance these principles in their daily work and/or specify them to more concrete moral rules and judgments within particular contexts. The principles are named and their normative content is (roughly) explained below.

2. Ethical Principles as Moral Benchmarks

Health Maximisation. This principle is for public health (genomics) what "beneficence" is for medical practice. Both enterprises – public health and medicine – try to generate good health. Whereas "beneficence" is traditionally the principle of personal ethics to describe a moral duty of the physician or the genetic counsellor to his/her patient; "health maximisation" is a variant of the principle "social utility" for social ethics. The net-benefit of "health maximisation" is to be sought in the whole of the population that is under consideration. Some people in public health believe that "social utility" is at the heart of public health and many public health practitioners came into public health to facilitate maximum health gain within the target population.

Respect for Human Dignity. If only "health maximisation" was focused as a moral norm to abide by public health genomic practice and research, this might have devastating consequences. It would then be allowed to use individuals (or whole groups) for other than their own ends and even sacrifice them if only this provided a greater net-benefit, i.e. maximised health. Although in extreme cases it might be ethically permissible to restrict individual liberty, "respect for human dignity" reminds us of our duty not to sacrifice or exploit individuals and to respect their free wills, their self-determination.

Social Justice. "Social Justice" is another side constraint to "health maximisation". It does not only matter to enhance the net-benefit; it also matters how the benefits and burdens are distributed. At the core of public health research there are questions of health inequalities. Until now, it is not *a priori* clear what inequalities are justified and which are morally unacceptable. Social justice is the norm that tries to keep public health from discrimination, stigmatisation and exclusion. It promotes fair treatment for those who have less chances for health and less chances to lead a full and flourishing life – regardless of whether supporting this population means that the overall net-benefit rises (or not).

Efficiency. When goods are distributed – raising the net-benefit and bringing health to all, or supporting the most disadvantaged – "efficiency" becomes an essential principle that needs to be included in the concise set of principles for public health ethics. Although it seems only to support social utility or social justice through guidance to spend resources responsibly, it has to be a principle at the forefront of public health practice – particularly in prevention.

The resources of public health systems are limited. Thus, the efficient use and distribution of scarce resources is a moral duty, which results in greater benefit to more people, including disadvantaged individuals and groups. The principle "efficiency" is thus demanded by the public health discipline, for example through the use of evidence-based public health measures and the implementation of cost-benefit-analysis. It should be included in the concise set of ethical principles in order to permanently reassure public health practitioners and researchers that to be efficient and not wasteful is also a moral duty.

Proportionality: The fifth ethical principle demands that when weighing and balancing individual freedoms (stemming from dignity) against the social good (in this case "health maximisation"), this should be achieved proportionally. In the words of Childress et al. (2002) it is "essential to show that the probable public health benefits outweigh the infringed general moral considerations [...]. All of the positive features and benefits must be balanced against the negative features and effects."

3. Conclusions

The mentioned norms build a framework for ethical assessment and consultation for decision-making when implementing genome-based knowledge to Public Health. These norms should contribute to making justifiable decisions in policy development. The criteria presented constitute benchmarks that have to be considered for good and right Public Health Genomics – in fact, Public Health in general – research, practice and policy making. E.g. they can help finding criteria if a certain screening programme should be implemented or not (yes, it should be implemented if it is efficient and maximises health, however, should not be implemented if it infringes individual dignity and social justice by using force or discriminating citizens; or at least the weighing process should be proportionally in outcome: slight violations of some of the benchmarks are acceptable if – and only if – this is balanced out by a maximal health gain that cannot be differently achieved).

These mentioned norms and ways to handle them – specification and balancing – can be taught to students of Public Health Genomics to give them tools making ethically justified decisions in their future as Public Health (Genomics) professionals.

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IX. Patient and Lay People Involvement

During the past several decades, advances in Public Health, increase of welfare and strengthening position of non-governmental organisations on the international arena, led to changes in stakeholders' position in Public Health Policy process. Before moving on with discussion of the stakeholders' involvement in Public Health Genomics some basic definitions used in the text will be given, and then list of the stakeholders in public health in general will be identified. After that frame-reflective policy approach in connection to stakeholders' participation in Public Health policy process is going to be discussed. Finally some conclusions will be drawn and some suggestions for future development of situation will be made.

According to C.-E. A. Winslow, Public Health is the science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals. Thus Public Health Policy-making can be defined as scope of policy actions targeted on achievement of goals of Public Health. As in any Public Policy field, the policy-making process is not independent, but is influenced by several groups of stakeholders. The changed definition of stakeholders provided by Freeman is going to be used here: «A stakeholder in an organization is (by definition) any group or individual who can affect or is affected by the achievement of the organization's objectives». A stakeholder in policy process is any group or individual

who can affect or is affected by the decision-making and policy implementation process. Usually in Public Health the following stakeholder groups are identified:

- Government – combines all stakeholders legally responsible for policy-making in the field;
- Provider – unites stakeholders involved in provision of healthcare services to population as well as national and international NGOs representing point of view of medical professionals;
- Patient – this group involves not only actual patients: the ones receiving public health and medical services, but also NGOs acting in the field and representing point of view of lay people;
- Insurer – this group involves public and private companies providing insurance services for population;
- Pharmaceutical industry – unites representatives of companies, public or private, which produce equipment and substances used in medical service provision.

It is important to note that role of organisations representing interests of stakeholders and unions play increasingly higher role in the field of Public Health Policy making than individual stakeholders. Thus in this work attention will be focused on the participation of NGOs representing different stakeholder groups in policy-making process.

Until relatively recently the power of decision-making in the field of public Health was concentrated in the hands of medical professionals. Lay people were considered to be less knowledgeable in the field and thus did not participate in debates. Joanne Shaw in her article Reformation for our times is comparing traditional paternalistic relationships of patients and doctors with religious situation in Medieval Europe. “Although church going was an essential part of everyday life, lay people could not participate in services in any meaningful way”.

Nowadays scientists and policy-makers do believe that the shift towards empowering patients and NGOs is “unstoppable”. However a lot depends on the health care system established in the country. Scientists define 2 major types of

Health Care systems: Rhine model (used for example in the Netherlands, Italy and Germany) and Anglo-American model (used in USA and UK). While Anglo-American model focuses on introduction of free-market capitalism and subordination of the state bureaucracy to the economy, Rhine's model is distinguished by the high value of debates and consultations among stakeholders in order to reach collectively stated objectives. Thus it can be stated that in countries with Rhine Health care system level of patients and patient groups involvement in Policy making in health care is relatively higher than in countries with Anglo-American systems.

However difference in established health care systems is not the only point to consider while speaking about increasing patient involvement in health care provision. It is common knowledge that patients now became more aware about different trends in health care provision, which was aided by access to Internet.

Now let us turn to the way patients' positions on different issues can influence Public Policy making. Recently the so called "framing approach" to policy making became increasingly popular. The idea of thinking in terms of frames appeared in the field of public policy in 1970s and 1980s. It was used to provide a «discourse» of the public policy analysis. Frames are believed to be different ways of formulating, structuring and viewing the problems by different stakeholders. Frames are tools to construct the boundary around the reality that is viewed similarly by a group of actors or a community.

Frame was defined by Marvin Minsky in 1978 as «a particular way of representing knowledge», later W. Gamson introduced the term «packaging», which defines a special type of framing – «the process by which a central organizing idea, a frame, is embodied in a policy position that is then expressed through such condensing symbols as metaphors and slogans».

One of the major works on the topic of reframing in public policy is *Reframing* by Schon and Rein, published in 1993. The idea of rationality was stated there. According to their vision rationality is not the prerogative of the state and experts to decide about what is rational, but government together with «lay» people, who may have different perspective, «frame».

In the works of Baldwin and Kohler it is possible to find the common hypothesis that there were several different frames in healthcare in Europe in general and in child healthcare in particular. They argue that because of the shift of frames the priorities in the national policy-making were changing over time. For example in the book *Disease and democracy* by Baldwin provides vision of different approaches to treatment of people with AIDS. The author states that in the beginning HIV positive people were seen by the policy-makers as trouble-makers, representatives of the marginal parts of society that were potentially dangerous for the common wealth. Thus often sick people were forced to receive treatment and the process of treatment could be violating their rights. However, the more the illness spread the more liberal approaches started to be used by policy-makers. More attention started to be paid to the prevention of the illness and making people responsible not only for their own health, but also for the state of health of others. Nowadays, according to Lennart Kohler healthcare is in the stage when preliminary concern is search for new knowledge and reassertion of such principles that were used in the past, as prevention, protection and promotion together with high level of consultation with the general public.

Another good example of how framing theory can be used in policy-making in the field of Healthcare is presented in the PhD thesis of Margriet Moret-Hartman, Problem Structuring in Health Technology Assessment: An argumentative approach to increase its usefulness, 2008. She presents the result of the analysis of policy decisions in the Netherlands concerning the drug mebeverine, which was used to treat irritable bowel syndrome (IBS), however by the clinical trails was proven not effective. Moret-Hartman argues, that the decision was not thoroughly thought through and thus after some time had to be reconsidered. This happened because only one side of the problem was taken in consideration: for the authorities the evidences on the positive effects produced by this drug were not persuasive. However patients believed the drug to be effective, despite the possibility of placebo-effect. Thus as for the policy-makers the biological mechanisms of drug effect were of importance – for a lot of patients it had a positive effect due to other

reasons. When this was communicated to the policy-makers by the researchers the policy measures were reconsidered.

As it was shown above, position of the stakeholders is becoming more and more important for policy-making in all the fields. Patients can influence policy-making in several ways: protest actions, joining the communities that lead dialogue with authorities, direct communication. But the aimed result is the same: patients are trying to explain their frame of the problem to the policy. On the other hand for the policy-makers it is important to be open for perceiving this frame and act accordingly.

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X. Aspects of Global Public Health Genomics

1. *Global Health disparities*

In the last fifty years, the disparity in income per capita between the 20 richest and 20 poorest nations more than doubled. In the last three decades, the inequality within countries has also increased, making the gap between those at the top and those at the bottom of the economic pyramid even more pronounced.

Poor health status is the direct result of the reduced economic growth. Indeed, the impact of such growing inequity on the essential right to health was pointed out in 1990 by the estimate that only 5% of the world's resources for health research were being applied to the health problems of low- and middle-income countries, where 93% of the world's preventable deaths occurred. Later, the term "10/90 gap" was

coined to capture this major imbalance between the magnitude of the problem and the resources devoted to address it.

Up to now, such disparity in health did not show signs of major improvements. Indeed, in the most recent World Health Statistics report, the WHO estimated a four times higher neonatal mortality rate in developing countries compared to developed countries and a 20 years difference in life expectancy at birth.

However, poor health status not only is the result of reduced economic growth; in turn it inhibits as well economic improvements, resulting in a vicious circle that is difficult to escape.

2. Role of science in Global Health

On the other hand, improved health also participates to greater economic development, and the resulting increase in wealth contributes to a further improvement in health. This interaction produces a virtuous circle. Thus, investing in health is an effective strategy to boost economic development.

Over the last 100 years, innovations in Science & Technology have resulted in improved health, quality of life, and a rise in life expectancy worldwide. Indeed in the 2001 Human Development Report, the UNDP endorsed Science & Technology as the largest contributor towards reduced mortality rates and improved life expectancy during the late 20th century.

Moreover, in 2004, the then UN Secretary General Kofi Annan himself drew attention to the importance of science in improving global health, essential if the world is to face and tackle its main development challenges.

3. The potential of Genomics

Since the completion of the Human Genome Project in 2003, genomics is considered to be one of the emerging fields in science. It is the comprehensive examination of an organism's complete set of genes and their interactions with the environment. Genomics and genome-related biotechnologies are rapidly growing sciences, constantly generating a vast amount of new information.

The role of such knowledge in global health was highlighted in 2002 by the WHO report "Genomics and World Health". In the report, the WHO suggested that genome-based solutions have the capacity to meet the needs and tackle health problems of developing countries. Also, the application of knowledge gained from the characterization of the genomes of organisms holds enormous promises for the

development of new health care innovations over the coming decades. Indeed, genomic has the potential to improve global health by elucidating basic mechanisms of diseases, susceptibility and resistance, thus guiding the development of future health interventions. Such advances can also influence the prevention, diagnosis and treatments of some of the major diseases, including malaria tuberculosis and HIV.

4. The Genomic divide

In the 2002 report, the WHO also recognized that, as resources devoted to health research in developing countries are limited, there is an urgent need to focus attention on the most promising technologies, such as genomics.

Yet the benefits of modern medicine have still not reached millions of people around the world. Indeed, since the beginning of the genomics era, it has been evident that researchers in many countries will not be fully participating in such research, mainly because of their limited resources and scientific capacity, combined with the urgency of other health priorities.

This growing "genomic divide", if unchecked, could lead to even greater disparities in health. As wealthier countries become healthier, their health concerns will take even more precedence over those of poor countries, and the spread of infectious diseases, and the rise in chronic illnesses will continue to degrade health in the latter. Thus, to prevent widening of the already large gap in global health, and to share the benefits of this technology worldwide, developed and developing countries alike should participate and invest in the genomic research.

5. Genomics applications in resource-limited settings

By now, there are already several examples of successful application of genomics to health problems of less-developed countries.

For instance, using genome-related biotechnologies infectious diseases can be diagnosed more rapidly and less expensively than using existing techniques. Also, pathogen sequencing boosts the development of genetically engineered vaccines, which are cheaper, safer and more effective than those currently available, thus holding new promises in the fight against diseases like HIV, malaria and tuberculosis. Alike, recombinant therapeutic proteins, such as erythropoietin for the treatment of anemia, alpha interferon for the treatment of infections and insulin for diabetes

type I, are cheapest and fastest to produce. Furthermore, as minor genetic variations between people can influence their responsiveness to certain drugs, such as for HIV, tailoring treatment to the specific characteristics of individuals or communities can improve health and cost effectiveness.

Other potential applications of genomics are bioremediation, where genetically modified bacteria are used to reduce environmental pollution and clean up contaminated air, soil and water; or the creation of nutritionally enhanced crops such as beta carotene- and iron-enriched rice, or potatoes rich in all essential aminoacids.

The ultimate power of genomics in resource-limited countries is evident in the field of molecular epidemiology, where genetic information of the host or infectious agent is evaluated with clinical and epidemiological data to develop and implement proper interventions. As an example, molecular characterization of a polymorphic marker is used to monitor bacterial and viral infections. That enables the analysis of transmission patterns, helping identify variations among strains, and facilitates the evaluation of the global distribution, transmissibility and virulence of different infectious agents.

Lastly, genome-based tools allow a refined case definition and thus have tremendous potential for decision-making support and targeted public health interventions in countries with high burdens of disease and limited technological resources.

6. Interim Conclusion

As the development gap between industrialized and developing countries continues to grow, genomics and related technologies could help reducing such divide. Indeed, biotechnologies, especially molecular diagnostics, can be made affordable for the developing world and contribute to the prevention of diseases and the promotion of health. Nonetheless, although several less-developed countries have started to strengthen their biotechnology sector, others still continue to stay behind, with potentially devastating consequences for their development and health. Thus, in order to harness the benefits of genomics for progress, a more concerted effort should be made to include in the genomic research countries with limited scientific resources, and scientists should expand their collective efforts to serve the needs of the poorer.

XI. Summary and Conclusion

The biological causation pathway from HPV to genital warts and different types of cancer is becoming increasingly common knowledge in Public Health among professionals as well as lay persons. The development of vaccines and the use of recombinant methods is a routine procedure in the pharmaceutical industry. In the last years many countries have implemented programs which specifically address HPV or include HPV vaccination into the national immunisation programs. The current HPV vaccination programs in many European countries are not working sufficiently and need further adjustments. The improvement of coverage rates requires better and more targeted education and the provision of more financial resources. Special target groups need to be identified and their concerns need to be addressed both in the design of the program and the communication structure. The lagging adaptation of gender concepts is another major weakness of many current programs. This implies further considerations whether to or not to vaccine boys as well. A better use of knowledge from gender research can be seen as a key to better health outcomes in the HPV domain. From a general perspective, the example of HPV once again underlines that Public Health systems struggle to take up emerging genome-based knowledge in a timely and systematic manner. Various tools such as Health Needs Assessment (HNA), Health Impact Assessment (HIA) and Health Technology Assessment (HTA) exist to guide the improvement of translational research. Still, Public Health systems need to increase their commitment to translational research in order to cope with the avalanche of innovations in the life sciences. It has taken far too many years to implement HPV vaccination in Europe. Public Health systems need to increase their efforts to make HPV vaccination more effective and to protect citizens better.

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