HPV-vaccination in the Netherlands

The search for innovation system improvements for HPV-vaccination

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Preface

This is it, my graduation work after almost six years of study. It was a harsh road with many interesting sidesteps over the years, far away journeys and a minor in journalism. This minor turned out to be quite relevant for this thesis. HPV-vaccination is an innovation where media reports had a major impact. Both the media as the parties involved in HPV-vaccination can learn important lessons about the way a new vaccine is introduced in the Netherlands.

Despite a long lasting interest in vaccination in general and a previous study report on the market approval report of one of the HPV-vaccines, I did not foresee the extent and ferocity of this debate. An internship at one of the producers of the HPV-vaccination made this research even more interesting, it was a great help in finding information about HPV-vaccination and in gaining insight in the system behind HPV-vaccination in the Netherlands. In the search for a possible internship, the RIVM has been contacted as well, where a research centre or a pharmaceutical company was proposed as possible internship address. GSK, as provider of the HPV-vaccine to the RVP, was a logical partner for an internship and since GSK was interested in my research proposal, an internship was possible.

In this preface I specifically would like to thank Ellen Moors, my supervisor. Even though we – especially me at the start of this research- took some time before things were put on the road, her guidance and feedback helped me enormously. The same is the case for Lisette Schelbergen, my GSK supervisor, her knowledge on the HPV-vaccination in the Netherlands was of great help. Other people I would like to thank are other employees of GSK, which are too numerous to name, the people I have interviewed, which gave me new facts and insights on HPV-vaccination and my second reader which gave useful input on the theory I applied. And finally I would like to thank my friends and family for giving me support in performing this master thesis.

This research showed me that a big part of the success of a vaccine innovation lies in interests and distrust the societal debate is focused on, which seemed more important than facts and arguments in the discussion about the HPV-vaccination. I hope this research shines a light on the factors which hampered the success of HPV-vaccination. And that the HPV-vaccination will become the societal success the technology potentially possesses.

- *Everybody has interests*

- *Vertrouwen komt te voet en gaat te paard*

Dutch summary, Nederlandse samenvatting

Het Humaan Papillomavirus is een virus wat onder andere cellen in de baarmoederhals infecteert. Deze infecties gaan meestal ongemerkt voorbij, maar het virus kan aanwezig blijven en celafwijkingen veroorzaken. Bij sommige vrouwen ontwikkelen deze afwijkende cellen zich tot baarmoederhalskanker. In Nederland zijn er ongeveer 700 gevallen van baarmoederhalskanker per jaar en 200 á 250 doden, ondanks een screeningsprogramma wat al bestaat sinds 1976. In 2006 is er een eerste vaccin tegen HPV beschikbaar gekomen in Europa. Dit vaccin (Gardasil) beschermt tegen HPV type 16 en 18, die 70% van de baarmoederhalskankergevallen veroorzaken en beschermt ook tegen genitale wratten (HPV 6 & 11). In 2007 is er nog een vaccin beschikbaar gekomen, Cervarix, dat ook beschermt tegen HPV type 16 en 18. Na het beschikbaar komen van de vaccins in Europa, heeft de Nederlandse Minister van volksgezondheid een advies aangevraagd bij de Gezondheidsraad over HPV-vaccinatie in 2007. Dit advies is in maart 2008 gepubliceerd en adviseerde om HPV-vaccinatie toe te voegen aan het Rijksvaccinatieprogramma voor meisjes van 12 jaar en dat een inhaalcampagne voor meisjes van 13 tot 16 jaar zinvol was, als de prijs van het vaccin dat toeliet.
Maar slechts 52% van de 13 tot 16-jarige meisje die het vaccin in 2009 mocht halen heeft het vaccin genomen. Het RIVM, wat verantwoordelijk is voor het uitvoeren van vaccinaties in Nederland, heeft geprobeerd om de acceptatie van het vaccin te verbeteren in 2010, maar de vaccinatiegraad is niet toegenomen. Veel verschillende partijen en factoren hebben invloed gehad op de HPV-vaccinatie in Nederland en de partijen die HPV-vaccinatie mogelijk hebben gemaakt zijn er niet toe in staat gebleken om de ontwikkeling van het HPV-vaccin tot het gewenste maatschappelijk succes te maken. Dit probleem is onderzocht met innovatiesysteemtheorie, deze theorie focust zich op de actoren, instituties en netwerken achter een innovatie. Om de prestatie van dit systeem over tijd te bepalen, zijn functies van innovatiesystemen toegepast. Deze functies omvatten aspecten die het presteren van een innovatiesysteem bepalen, aspecten zoals kennisontwikkeling en diffusie, doelstellingen en verwachtingen opgezet door de overheid en industrie en de lobby voor en tegen een technologie. Naast de functies van innovatiesystemen wordt lock-in ook onderzocht. Lock-in is de inertie van actoren of van het systeem om zich aan een nieuw technologisch paradigma aan te passen vanwege voorgaande routines. Het innovatiesysteem en de dynamiek worden onderzocht met een kwalitatieve methode. Bronnen zijn wetenschappelijke artikelen, artikelen in de media, websites van gerelateerde partijen, interviews, bijeenkomsten en een stage bij GlaxoSmithKline. Om de dynamiek in kaart te brengen zijn gebeurtenissen gelinkt aan de functies op tijdslijnen weergegeven.
De resultaten laten zien dat de lage prestatie van HPV-vaccinatie (uitgedrukt in vaccinatiegraad) hoofdzakelijk gelinkt is aan een lage creatie van legitimiteit voor de HPV-vaccinatie, vooral tijdens de start van de vaccinatiecampagne in 2009. Kennisontwikkeling en diffusie begonnen laat en de begeleiding van de overheid was niet voldoende om de negatieve houding ten opzichte van de vaccinatie boven te komen. Een vergelijking met Engeland, waar HPV-vaccinatie succesvoller was, onderschrijft dit beeld. Een betere begeleiding heeft gezorgd voor een positievere publieke opinie in Engeland. De hoofdconclusie over het innovatiesysteem achter de HPV-vaccinatie is dat alle systeemelementen om HPV-vaccinatie in Nederland mogelijk te maken aanwezig zijn. Het RIVM is een centrale partij in het huidige systeem. Lock-in heeft niet plaatsgevonden op een specifieke technologie; HPV-vaccinatie is landelijk ingevoerd 2,5 jaar na introductie en verbeteringen in screening en vaccinatie worden onderzocht. Lock-in kan wel gezien worden bij de manier waarop het vaccin is aangeboden in het RVP, de vaccinatiecampagne is als te ouderwets beschouwd. Om de prestatie van de HPV-vaccinatie te verbeteren is een focus op acceptatie het belangrijkste. Hiervoor is een lange termijn beleid nodig, de vernieuwde campagne in 2010 liet zien dat een lage vaccinatiegraad niet gemakkelijk omhoog gaat. Verbeterde kennisdiffusie naar eindgebruikers en gezondheidsorganisaties door het RIVM is van belang. De activiteiten van de producten zijn zeer negatief bediscussieerd, een meer behoedzame benadering is wenselijk. Maar ook politici en media moeten bewust zijn van de consequenties van publieke uitlatingen over het vaccin. Een mogelijke systeemaanpassing is om het vaccin ook gratis via zorgverzekeringen aan te bieden.

English summary

The Human Papillomavirus is a virus which can infect cells in the cervix and other parts of the human body. Most of these infections pass unnoticed. But the virus can remain present and can cause cell abnormalities and in some women these cell abnormalities develop into cervical cancer. In the Netherlands there are around 700 cases of cervical cancer and 200-250 deaths per year despite a screening program which already exists since 1976. In 2006 a first vaccine against HPV gained market approval in Europe, this vaccine (Gardasil) protects against HPV type 16 and 18 which cause 70% of all cervical cancers and protects against genital warts (HPV 6 &11). In 2007 another vaccine became available, Cervarix, which protects against HPV type 16 and 18. When the vaccines were available in Europe, the Dutch Minister of Health requested the Health Council to develop an advice about the HPV-vaccination in 2007. This advice was given in March 2008. It stated that HPV-vaccination should be added to the National Immunization Program for 12 year old girls and a catch-up campaign for girls 13 to 16 years should be performed if the price of the vaccine would be low enough.

The problem is that the vaccine is not successfully adopted. Only 52% of the 13 to 16 year old girls in the 2009 cohort took the vaccine. The RIVM, which is responsible for vaccination in the Netherlands, made efforts in 2010 to increase HPV-vaccination acceptance, but vaccination coverage did not increase. Many different actors and factors influenced the HPV-vaccination in the Netherlands and the actors which made HPV-vaccination possible were not able to make the invention of the HPV-vaccine into the desired societal success.

This problem is researched with innovation system theory, which focuses on the actors, institutions and networks behind an innovation. To determine the performance of this system over time, functions of innovation systems are used. These functions are linked to aspects determining the performance of an innovation system, aspects such as knowledge developed and diffusion, goals and expectations set by industry and government and the lobby for and against a technology are researched. Beside the functions of innovation systems lock-in is researched as well. Lock-in is the intertie of actors or the system to adapt to a new technological paradigm because of previous routines. The innovation system and its dynamics have been researched using a qualitative method. Information resources have been scientific articles, media articles, websites of related actors, interviews with key actors, meetings and an internship at GlaxoSmithKline. To get an overview of the dynamics over time, events related to the innovation system functions are put on a timeline.

The results showed that the low performance of HPV-vaccination (expressed in vaccination coverage) is mainly linked to a low creation of legitimacy for the HPV-vaccine, especially during the start of the vaccination campaign in 2009. Knowledge development and knowledge diffusion started late in the Netherlands and the guidance of the government was not sufficient to overcome a negative attitude. A comparison with England, where HPV-vaccination was successful, endorses this view, guidance of the government led to a more positive public opinion in England, making vaccination widely accepted. The main conclusion about the innovation system behind HPV-vaccination is that all system elements to make HPV-vaccination possible in the Netherlands are present, with the RIVM as a central actor in the current system. Lock-in did not occur on a specific technology; HPV-vaccination is offered nationwide within 2,5 year after introduction and possibilities of re-innovation of vaccination and screening practices are researched. Lock-in can been seen in the way the vaccine has been offered through the RVP, the vaccination campaign has been considered as too old fashioned.

To improve the performance of HPV-vaccination, increasing the acceptation is of most importance. A long term policy is necessary, since the 2010 campaign showed that a low vaccination coverage does not increase easily. Improved knowledge diffusion towards end-users and health organizations is of importance, the RIVM is most suitable for spreading knowledge. The activities of the pharmaceutical companies have been discussed very negatively, a cautious approach is desirable. But also politicians and media should be aware of their responsibilities, public statements have consequences. A possible system alteration is to provide the HPV-vaccine through the drug reimbursement system. If HPV-vaccination is offered in this way, vaccination coverage can increase.

List of definitions and abbreviations

CVZ	Healthcare Insurance Board, College voor zorgverzekeringen
GGD	Community Health Services, Gemeentelijke gezondheidsdienst
GSK	GlaxoSmithKline, pharmaceutical company
GVS	Medicine reimbursement system, Geneesmiddelen vergoedingssysteem
HPV	Human Papillomavirus
Minister(y) of Health	Minister(y) of Health, Welfare and Sports, Minister(ie) van Volksgezondheid, welzijn en sport
NVI	Dutch Vaccine Institute, Nederlands Vaccin Instituut
RIVM	National Institute of Health and Environment, Rijksinstituut voor volksgezondheid en milieu
RVP	National Immunization Program, Rijksvaccinatieprogramma
SP MSD	Sanofi Pasteur Merck Sharp & Dome, pharmaceutical company
VLP	Virus Like Particle

HPV-vaccination
The HPV- Vaccination is defined as the whole process of developing, producing, distributing, administering and guiding the HPV-vaccine from start to finish. So also aspects as informing the medical community and the end-users are part of the HPV-vaccination process, as well as research on vaccination uptake, side effects and efficacy.

Performance of HPV-vaccination
The performance of the vaccine implementation can be measured by researching vaccination coverage and societal acceptance. Data on the eventually desired effects of the vaccine, which is the decline of cervical cancer deaths, will not be available within the next couple of years. For the vaccine producers the performance of the vaccine can be measured by researching the sales and satisfaction by users and the medical community.

National Innovation System
The network of institutions in public and private sectors whose activities and interconnections initiate, import and diffuse new technologies (Freeman, 1987).

Technological Innovation System
A dynamic network of agents interacting in a specific economic/industrial area under a particular institutional infrastructure and involved in the generation, diffusion, and utilization of technology (Carlsson, 1991).

Actor
Actors are companies, government agencies, knowledge centrums, universities and other relevant institutions playing a role in developing and implementing a new innovation. Every actor has its own competences and role in the innovation system.

Institution
Institutions are formal and informal norms, rules, routines and values which guide the behavior of actors (Edquist, 1997).

Network
The links between actors, together with institutions, create a network.

Functions of innovation systems

The functions of innovation systems concern the activities that take place in an innovation system which can lead to technological change. These activities generate and diffuse innovations. A set of seven functions has been developed which can be applied to map key activities in innovation systems (Hekkert et al, 2007).

Lock-in

The inability of complete (social) systems to adapt to new technological paradigms (Smith, 1999). Edquist et al. (1998) address the same failure but do not distinguish so strictly between transition and lock-in failure. In this research lock-in is regarded in the broader sense.

Cervical cancer screening program / PAP Smear test

A Screening program performed since 1976 in the Netherlands, where women age 30 to 60 get a PAP smear test every 5 years at their general practitioner to check for cell abnormalities in the cervix.

HPV-DNA test

The HPV DNA test is a test where a cervical swap is taken (by a doctor or by a woman herself) which is examined on the presence of high risk HPV-DNA. HPV-DNA test outperforms PAP smear tests in detecting precancerous tissue in the cervix (Sankaranarayanan et al, 2009).

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1 Introduction

Vaccines are a specific type of medical products. Instead of treating a disease, vaccines prevent infectious diseases. The prevalence of numerous severe diseases has declined drastically after effective vaccines have been introduced. Currently, children in the Netherlands receive vaccinations for 12 types of diseases (RIVM, 2009). These vaccines are provided through the Dutch National Immunization Program (RVP). This vaccination program is generally considered as very successful, saving around 900 lives and 800.000 sickness periods each year (Rake et al, 2008). The National Institute for Public Health and Environment (RIVM) closely tracks the vaccination levels of all different vaccines. The vaccination rate of most childhood vaccines is higher than 95% and many infectious diseases are not or hardly prevalent in the Netherlands (RIVM, 2009). Efforts in developing new vaccines and adding them to the National Immunization Program are continuously ongoing (RIVM, 2009). One of the latest developments has been the addition of a human papillomavirus vaccine to the RVP.

In the 1980's it was discovered that the human papillomavirus is the cause of cervical cancer in women. Worldwide cervical cancer causes 290,000 deaths per year (Speck, 2006). In the Netherlands around 600 to 700 women are diagnosed with cervical cancer each year. And on average 222 fatal cases are reported annually (RIVM, 2009). Since the discovery that HPV is the leading cause of cervical cancer, efforts are put in developing a vaccine. Both GlaxoSmithKline and Sanofi Pasteur MSD have developed a vaccine, Cervarix and Gardasil respectively. Gardasil gained market approval in Europe in 2006, Cervarix in 2007. The Dutch Health Council (Gezondheidsraad) performed a research to advice whether one of these vaccines should be added to the National Immunization Program (RVP). The Health Council researches whether a vaccine meets criteria regarding necessity, efficacy, safety and costs to be added to the RVP. The health council research indicated this was the case and thus advised to add HPV-vaccination to the RVP and to perform a catch-up campaign (Gezondheidsraad, 2008). Following this advice the minister of Health decided that HPV-vaccination should be added to the RVP and a catch-up campaign should be executed for girls age 13 to 16 starting 2009. The Dutch Vaccine Institute (NVI) set up a tender, based on price and effectiveness, which has been won by Cervarix, making it the HPV-vaccine which would be implemented in the Dutch National Immunization Program (GSK Press release, 2008).

Despite the positive advice of the Health Council to implement Cervarix in the RVP and the free provision of the vaccine to the girls, it is not well adopted by the target population. HPV-vaccination coverage in the Netherlands is around 50%, while other vaccines are accepted by 95% of the indicated users (Giesbers a, b, 2011). It is interesting to investigate this problem. Why is HPV-vaccination adoption low by the target population and which system characteristics play a role? In the public media there has been a lot of attention on positive and negative aspects of HPV-vaccination (e.g. Zembla, 2008; Radar, 2009).

Several factors have been indicated to have a negative influence on the uptake of this new vaccine. Technological imperfection and a lack of societal acceptance have been discussed as factors explaining the low HPV-vaccination coverage in the Netherlands. A major technological disadvantage of the currently applied vaccine is that it only protects against two types of the human papillomavirus, not covering around 30% of the HPV-related cervical cancer. This still makes it necessary for women to take a PAP smear test, which tests for cell abnormalities related to cervical cancer (Tuma, 2009).

Other articles stated that the vaccine does not meet the criteria the Health Council has set up (Kok et al, 2008). A part of these authors also have performed a cost-benefit analysis stating that the costs outweigh the health gains of the vaccine, based on the Quality Adjusted Life Years (QALY's) the

vaccine could save (Kok et al, 2009). Research on vaccine uptake indicates that in people living in areas with a low socioeconomic status, voters for Religious Political Parties and several ethic groups have a low vaccine acceptance. Furthermore, it is suggested that information meetings with gynecologists might be beneficial to increase HPV-vaccine acceptance (Rondy et al, 2010).

The RIVM, which is responsible for the National Immunization Program (RVP) in the Netherlands, has put efforts in increasing the HPV-vaccination coverage, but with little success. Vaccination coverage in 2010 is around the same as in the catch-up campaign in 2009. The overall vaccination coverage in 2009 was 52,2% for the full series (Giesbers a, 2011) and in 2010 51,9% of the girls took the all 3 shots necessary to gain protection (Giesbers b, 2011). This shows that after the bad start of HPV-vaccination no improvement of the vaccination coverage has occurred in 2010 and that the vaccine is still badly accepted by the target population.

There are many different parties involved in the system behind the HPV-vaccination. All these actors play a different role at different times. GSK is the supplier of the vaccine to the RVP and is responsible for its efficacy, quality and safety. Sanofi Pasteur MSD plays a similar role and might be the supplier of the vaccine in the future. The EMA has given the HPV-vaccines European market approval. But market approval stands loose from funding decisions. This decision has been made by the Minister of Health, which has based this decision on the advice of the Health Council to add HPV-vaccination to the RVP. After a tender performed by the NVI, the RIVM has become the responsible actor for launching and monitoring the HPV-vaccination, just as for other vaccines. But the Municipal Health Offices (GGD) perform the vaccinations (Rijksoverheid, 2010). Because HPV-vaccines are a type of vaccine aimed at preventing cervical cancer also gynecologists, oncologists and related organizations have influenced the adoption of HPV-vaccination in the Netherlands.

1.1. Problem definition

From this introduction the following problem is defined. The low HPV-vaccination coverage and low societal acceptance indicate that the HPV-vaccination is not successful in the Netherlands. Other childhood vaccines in the RVP have proven to be successfully adopted, but the vaccination coverage for HPV-vaccination is still low. Many actors are involved and the vaccination is novel on several aspects (e.g. the age of the vaccinated girls and the type of disease), while the current vaccination system (the RVP) already exists for several decades. This makes it difficult to assess which actors should do what to improve the performance of the HPV-vaccination. The performance of the HPV-vaccination can be tested by evaluating whether goals regarding vaccination coverage, acceptance and eventually decline of HPV-related cervical cancers are reached.

1.2 Aim

The aim of this research is to indentify the barriers in the Innovation System behind the HPV-vaccination in the Netherlands. By identifying barriers and proposing policy implications to overcome these barriers the performance of the HPV-vaccination can be improved. The proposed research framework highlights key processes (system functions, actions) that influence the successful buildup of a new technology, such as HPV-vaccination, and give insight in how its surrounding system is created.

An innovation system approach is used because many different actors have been involved in the HPV-vaccination. Not one specific actor or factor can be determined causing the low performance of the HPV-vaccination; a system approach can give more insight in the low performance of HPV-vaccination. Innovation System theory does not regard innovation as a strictly linear process where technological improvements are put on the market. Instead, it is regarded as an iterative process, in which the whole network, its involved actors and institutions are researched. Making apparent which systems characteristics (both strengths as weaknesses) determine the performance of the HPV-vaccination (Edquist, 1997; Nelson & Winter, 1997). An analysis based on -functions of the-

innovation system makes it possible to map and measure the performance of the HPV-vaccination. A system approach is also useful because the HPV-vaccination has been added to the existing vaccination system –which cornerstone is the RVP-, providing defined actors involved in HPV-vaccination.

Accordingly the central question is as follows:
What is the performance of the HPV-vaccination innovation system in the Netherlands and how can this performance be improved?

In this central question 'the performance of the HPV-vaccination innovation system' is not regarded as the mere vaccination coverage, but also the performance of system aspects is taken into account, such as knowledge development, communication between system actors and guidance.

1.3 Demarcation and delineation
The research is delineated by mainly looking at the HPV-vaccination in the Netherlands. Other countries have made different choices on how to implement the HPV-vaccine. For example, in Finland the HPV-vaccine is not yet implemented in their vaccination program, because health authorities in Finland wanted more research data before starting a vaccination campaign (Syrjanen, 2010). A comparison with a European country where the HPV-vaccination is successful is made, giving an indication how system functions can be fulfilled to increase the HPV-vaccination performance. This helps to determine key functions related to the performance of HPV-vaccination and helps to develop policy implications.
During the research both previous and current developments concerning HPV-vaccination are mapped. Market approval of Cervarix took place in 2007 (EMA, 2007), but also before that date events have occurred regarding HPV-vaccination in the Netherlands. So data is mainly from the period 2007-2010, but relevant prior actions in the HPV-vaccination process are mapped as well.
In this research, the pharmacological development of the vaccine is not a focal point. This fundamental research is performed outside of the Netherlands and it is not a part of the Dutch innovation system. By focusing on the developments in the Netherlands and comparing these in European context it is possible to give an extensive overview on the Dutch Innovation System behind the HPV-vaccination. However, the most relevant international technological and clinical developments are mentioned.

1.4 Societal relevance
By mapping the innovation system behind the HPV-vaccination, the current HPV-vaccine and future vaccines can be introduced and adopted more successful. This can be done by reaching the eventual goal of this research; developing policy recommendations, which might help to increase vaccination coverage. This is a big societal benefit since higher vaccination coverage can prevent many disease cases. In the Netherlands cervical cancer is held accountable for 222 deaths annually (RIVM, 2009). Even though data on the long term still has to become available, the Health Council has indicated that the HPV-vaccination has a positive cost-benefit ratio and approximately 100 deaths can be prevented (Gezondheidsraad, 2008). But this decline can only be achieved if there is a high vaccination coverage, this is especially important to gain herd immunity and for reaching groups with a higher risk for cervical cancer.

The proposed research is beneficial for companies and government agencies involved in (HPV-) vaccination. Results might help them to respond more efficiently to technological or societal problems concerning vaccine development and implementation, specifically for the HPV-vaccination but also for other vaccines.

A third societal relevant aspect is that the innovation system behind vaccinations is changing. Vaccine research and production are shifting from a government based market to an industry based market

(DVG, 2007; VWS, 2010). The available HPV-vaccines are both developed by pharmaceutical companies. These changes can lead to different vaccination scenarios in the future. Vaccines still can be provided by the National Immunization Program, but perhaps more and more vaccine will be compensated by health insurance companies and performed by health care professionals (DVG, 2007). This process fits in a broader development where healthcare is privatized and more market forces play a role in the healthcare system. This research on the HPV-vaccination innovation system can give insight if alterations in the vaccination system are beneficial in the Netherlands.

1.5 Scientific relevance

Many applications of functions of innovation system research focus on technologies where an innovation system still has to emerge, so the technology still has to be optimized and to be adopted by the potential users (Negro, 2007; examples from Bergek, 2005). The HPV-vaccination differs in several aspects from these previous applications of the functions of innovation systems approach. Since it takes a long time before a medicine is approved, it is not possible to make quick alterations on the current technological aspects of the HPV-vaccines. This makes technological change difficult. Another difference is the diffusion rate of vaccines. As mentioned before, vaccination coverage is around 95% in the Netherlands. Also new vaccines have reached high vaccination coverage immediately after their introduction, such as the Meningococcal C vaccination which started in 2002 (RIVM, 2009). For other innovations such a rapid diffusion rate is uncommon. And because the HPV-vaccine is added to the RVP, the government can be seen as an intermediate between companies and end-users, giving governmental agencies a major role in the innovation system. All these aspects of the HPV-vaccination make it a new/another type of innovation system to test the function of innovation system approach on its general applicability.

When a vaccination is added to the National Immunization Program it usually stays the same for a long period of time. Perhaps technological and system improvements do not occur sufficiently. This research might give insight in the link between innovation systems and lock-in. By researching if aspects of the innovation system are influenced by lock-in, the role of lock-in on the innovation process can become apparent. The reason that lock-in is researched with regard to HPV-vaccination is that HPV-vaccination is introduced in a system (the RVP) which already exists for several decades. This increases the chance that actors are institutionalized and do not successfully adapt to the new aspects regarding HPV-vaccination. The concept of lock-in is further explained in the theory section.

The research is also scientifically relevant because the results give insight in the way the HPV-vaccination system is organized. Thus clarifying which organizations should receive scientific findings to successfully apply new research results. An example is that this research might point out there is an improper link between new knowledge creation and the provision of this information to related health organizations. So the research can improve knowledge diffusion of scientific research.

Al these aspects make the introduction of the HPV-vaccination and its implementation in the National Immunization Program a scientifically relevant case for innovation research. By applying theory regarding innovation systems on a specific type of medical product, new insights can be created on how innovative performance can be improved.

In chapter 2, the innovation theory behind this research is given. Following this introduction and the theory, the main and sub research questions are proposed in chapter 3. The method to answer these research questions is given in chapter 4. Chapter 5 gives some short information about the technological and clinical aspects concerning HPV and HPV-vaccination. Chapter 6 & 7 give the results of the innovation system analysis and dynamic analysis, describing and analyzing all system aspects. Chapter 8 gives an international comparison of the Dutch situation with other European countries and a more detailed comparison with England. In chapter 9 the research questions are answered based on the results and in chapter 10 the research design and outcomes are discussed.

2 Theory

The HPV-vaccination coverage is low in the Netherlands and efforts to in increase the acceptance of the vaccination have shown limited success. In order to grasp this problem, related innovation theory is discussed in this chapter. By applying this theoretical framework, the innovation system surrounding the HPV-vaccination in the Netherlands can be mapped and analyzed. This gives insight in the factors responsible for low vaccination coverage and can help to develop policy to overcome these hampering factors.

Big efforts in the field of innovation research are made by Joseph Schumpeter. In his work innovation is seen as a linear process where a new product is placed on the market. Schumpeter saw innovations as 'Neue Kombinationen', often derived from existing elements (Schumpeter, 1934). But gradually new insights indicated that developing new products and placing them on the market is not a sufficient way of looking at innovation. Instead innovation should be seen as an iterative process with feed forward and feed backward loops (Tidd, 2005). An example of such as system can be seen in figure 1.

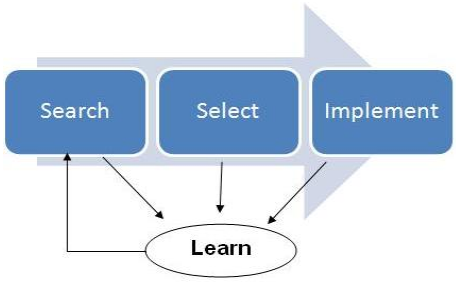

Figure 1: Innovation process model (Tidd, 2005)

A major part of the scientific developments in searching and selecting an HPV-vaccine has been performed outside the Netherlands. These international developments however, influenced the HPV-vaccination in the Netherlands. The latest phase of the innovation process is the implementation phase (see figure 1) and this is the phase where the trigger idea is translated into something new which is launched in an internal or external market, for HPV-vaccination this market is mainly the Dutch RVP. Attention is required on acquiring the proper knowledge resources, executing the projects under the right conditions, launching the innovation and managing the process and eventually sustaining the invention. The original innovation idea can be revisited in this phase and re-innovation is possible. In all these phases learning is beneficial for enterprises to build their knowledge base and improve the ways in which the process is managed (Tidd, 2005).

Two main points can be detected as the start of the implementation phase of HPV-vaccination in the Netherlands. Market approval for both Cervarix and Gardasil can be seen as a starting point, since this made the use of the technology possible. A bigger event is the addition of Cervarix to the RVP, which made widespread adoption possible. But also before the market approval of the HPV-vaccines efforts have been made to make HPV-vaccination successful in the Netherlands.

2.1 Innovation System theory

The main theory behind this research is the theory of innovation systems. This theory is applied because a system can be defined behind the HPV-vaccination and the performance of this system is sub optimal. By researching a whole innovation system and its involved actors it can become apparent how an innovation can become successful (Edquist, 1997; Nelson & Winter, 1997).

Innovation systems can be viewed from several perspectives. There are national, technological and sectoral innovation systems.

Freeman (1987) describes a national innovation system as *"The network of institutions in public and private sectors whose activities and interconnections initiate, import and diffuse new technologies."* Carlsson (1991) defines a technological innovation system as *'A dynamic network of agents interacting in a specific economic/industrial area under a particular institutional infrastructure and involved in the generation, diffusion, and utilization of technology'.*
The HPV-vaccination is a specific type of technology, Dutch regulations and actors can be defined in the development and implementation of the HPV-vaccination. So both a national focus and a technological focus are possible frameworks in researching the HPV-vaccination innovation system. Because the research focus is on the Netherlands, the aim is on the Dutch National Innovation System of HPV-vaccination.

An example of a National Innovation System regarding a technology is given in figure 2. An innovation system consists out of three different elements: actors, networks and institutions (Carlsson et al, 2002). The innovation system behind the HPV-vaccination still has to be mapped, and does not correspond to figure 2. For example, the industrial system does not have a direct link to the end-users, since governmental agencies involved in the RVP are intermediating actors. By researching the actors, networks and institutions a new model can be developed, mapping the HPV-vaccination system in the Netherlands. This model is developed during an innovation system analysis.

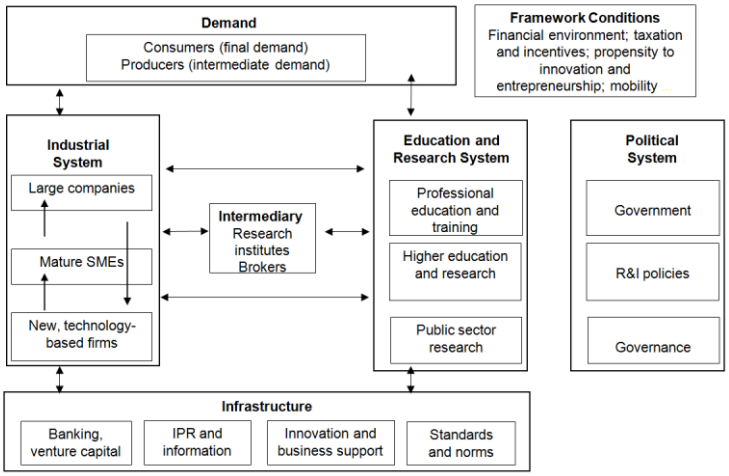

Figure 2: Innovation System model (Kuhlmann & Arnold, 2001)

Actors
Actors are companies, government agencies, knowledge centers, universities and other relevant institutions playing a role in developing and implementing a new innovation. Every actor has its own competences and role in the innovation system (Hekkert et al, 2004). Involved actors in the HPV-vaccination field vary from the RIVM, NVI, GSK, Sanofi Pasteur MSD, GGD, oncological and gynecological organizations to the EMA, Health Council and more.

Networks
The links between actors create a network. These links are important in spreading knowledge. Since the HPV-vaccine is not developed in the Netherlands, technological knowledge necessary for production is of less importance compared to knowledge transfer regarding the vaccine's safety, efficacy, acceptance and knowledge on efficient distribution and application of the technology. Examples of networks concerning HPV-vaccination are the distribution network and the network of advice and decision makers.

Institutions
Institutions are formal and informal norms, rules, routines and values which guide the behavior of actors. These institutions give actors information on how a market is shaped, make cooperation

possible and create incentives (Edquist, 1997). Institutions should be adapted to new technologies to make diffusion possible (Bergek et al, 2005). An example of a major institution regarding HPV-vaccination is the National Immunization Program.

2.2 Functions of Innovation Systems

In order to unravel the performance of the innovation system, it is not sufficient to map the innovation system (including its actors, networks and institutions) surrounding the HPV-vaccination in the Netherlands. An innovation system analysis only gives a static view of the situation. In order to measure the performance of the innovation system over time, a more dynamic analysis is necessary. The framework which is used to analyze the dynamics of the HPV-vaccination is functions of innovation systems. According to Simona Negro: *"…the major goal of using the concept of System Functions is to understand processes of technological change and innovation. By analyzing the various System Functions, virtuous and vicious cycles can be identified which enlarge our understanding of the dynamics of a system. By using the process method, the order and sequence of relevant processes is taken into account (Negro, 2007)."* So with this approach there is not only a focus on the structure of technological development but also on the system behind the emergence of the new technology. The functions of innovation systems focus on a number of processes that are highly important for well performing innovation systems, these processes can be analyzed by mapping and discussing events and activities (Hekkert et al, 2007). The functions help to map the development of a technology in interaction with the system in which the technology is embedded. The method can be characterized as a process analysis or historic event analysis (Bergek et al, 2005; Hekkert et al, 2007; Negro, 2007).

The following functions have been distinguished:

Function 1. Entrepreneurial activities	Function 2. Knowledge Development
Function 3. Knowledge Diffusion through networks	Function 4. Guidance of the Search
Function 5. Market Formation	Function 6. Resource Mobilization

Function 7: Creation of legitimacy/counteract resistance to change (Hekkert et al, 2007)

In order to give some understanding on the different functions, the functions will be discussed shortly in the paragraphs below. All these functions influence the dependent variable which is the 'performance of HPV-vaccination', which is given first. How the functions are measured is explained in the method section.

Performance of HPV-vaccination in the Netherlands

The performance of the HPV-vaccination can be viewed in several ways and concerns the development, implementation and diffusion of the technology. The main way is by measuring vaccination coverage and societal acceptance of HPV-vaccination. Data on the eventually desired effects of the vaccine, which is the decline of cervical cancer (deaths), will not be available within the next couple of years, so only estimates can be used.

Function 1: Entrepreneurial Activities

The role of the entrepreneur is to turn the potential of new knowledge, networks, and markets into concrete actions to generate new business opportunities (Hekkert et al, 2007). The available HPV-vaccines started with university research and have been further developed by pharmaceutical companies, operating on an international scale. Research regarding HPV-vaccination is taking place in the Netherlands, but not on developing a new preventive vaccine. Entrepreneurial activities to alter the surrounding system might take place in the Netherlands. Perhaps re-innovation is performed in the Netherlands by making alterations in the implementation process (e.g. by shifting from mass-vaccination to a more individual approach), which can be considered as an architectural innovation (Tidd, 2005). Such a development can be seen as an entrepreneurial activity besides the vaccines themselves.

Function 2. Knowledge Development
With the creation of knowledge, more can be learned about making the innovation process successful. Learning can be done both by searching (scientific research) and by doing (performing the vaccination) (Hekkert et al, 2007). Knowledge development, concerning the creation of the vaccine, mainly has taken place on an international scale. But knowledge development regarding the vaccine efficacy, side-effects, cost-effectiveness and acceptance is performed in the Netherlands.

Function 3. Knowledge Diffusion through networks
Knowledge diffusion spreads the outcomes of research to all involved actors to make sure knowledge to make innovation more successful reaches related actors. This is considered as learning by interacting (Hekkert et al, 2007). By providing information to all relevant actors, they can be prepared for the medical, organizational and societal effects of the vaccine. Intermediary actors like the RIVM and the Dutch Vaccines Group can play such a role. The RIVM is responsible for the vaccines in the RVP and monitors the vaccination coverage of the HPV-vaccination and prevalence of the human papillomavirus in vaccinated and unvaccinated girls (RIVM, 2009).

Function 4. Guidance of the Search
Since resources are almost always limited, it is important that, when various technological options exist, specific foci are chosen for further investments (Hekkert et al, 2007). Both government and companies have made decisions and set targets to make the HPV-vaccination available, with these limited resources. Still there has been much discussion about the necessity of HPV-vaccination, despite the guidance efforts of pharmaceutical companies and the government.

Function 5. Market Formation
For a new technology it is difficult to compete with embedded technologies (Hekkert et al, 2007). This also is the case for HPV-vaccination. Market formation is necessary for HPV-vaccination to find its place among other technologies, since multiple technologies to prevent cervical cancer exist. Market formation is also necessary to create competition between the available vaccines and to create a proper way of offering the vaccine to vaccination population. Since two companies (GSK and Sanofi Pasteur MSD) have developed a vaccine and there might be new HPV-vaccines in the future, a proper market formation can assure that competition based on price and benefits occurs, decreasing health costs for the Dutch government and make incentives for future innovation.

Function 6. Resource Mobilization
Commodities, financial and human capital are necessary as a basic input to all activities within the innovation system (Hekkert et al, 2007). Resource mobilization mainly has taken place by adding the HPV-vaccine to the National Immunization Program. This assures the producer of a longstanding return of its investments and makes re-innovation more attractive. Since people capable of performing HPV-vaccination and commodities to produce the vaccine seem sufficiently available, it is not expected that there is a potential lack of resources other than capital.

Function 7. Creation of legitimacy/counteract resistance to change
In order to develop, a new technology has to become part of an incumbent regime, or it even has to overthrow it (Hekkert et al, 2009). Creation of legitimacy/counteract resistance is the process of convincing parties with vested interests, the government and end-users (12 year old girls) of the usefulness of the HPV-vaccine. Lobby to convince the government has been performed by pharmaceutical companies and medical actors. And the government has put effort in informing end-users, which has not resulted in high vaccination coverage yet. Counteracting resistance to change is necessary to convince people focused on PAP smear tests of the usefulness of the vaccine. Anti-vaccination groups which have opposed against the HPV-vaccination, play a role in this function as well. It is important to correctly and fully inform end-users and make sure vaccination is properly legitimized.

Lock-in

Additionally, the concept of lock-in (Arthur, 1989; Smith, 1999; Edquist et al, 1998; Klein Woolthuis, 2005) is taken into account in determining the performance of HPV-vaccination. Lock-in is the inability of complete (social) systems to adapt to new technological paradigms (Smith, 1999). Edquist et al. (1998) address the same failure but do not distinguish so strictly between transition and lock-in failure. A transition failure is the inability of firms to adapt to new technological developments (Klein Woolthuis, 2005). In this research lock-in is regarded in the broader sense; lock-in can occur when past routines of actors or from the system as a whole have negative influence on the success of a new technology. In the field of vaccination, lock-in can become a problem when vaccine development and system improvements stop after a vaccination is implemented in a vaccination program. This effect is observed with the polio-vaccine in the US, where a suboptimal technology became leading due to past routines (Blume, 2005).

But there are other ways lock-in can occur, besides technological lock-in. As a result of systemic failures, actors or the system can become locked in their current way of working. This can happen because of weak ties which are unable of bridging structural holes, lack of complementary cooperative relationships or lack of technological and organizational capabilities within firms (Klein Woolthuis, 2005). This is in line with the view that lock-in is seen as the inertia of an actor or system to respond adequately to new developments, because the actor or system is focused on previous routines (David, 1985). In order to overcome lock-in it is important to consider the interconnectedness of a technology with its social and economic environment. The causes of lock-in should be eliminated both at firm and system level, because both the individual actors as the whole system can be affected by lock-in (Klein Woolthuis, 2005).

Even though lock-in events can be linked to different functions (e.g. when guidance is 'locked-in' on funding only existing technologies), there is chosen to discuss lock-in events separately and linking it directly to the performance of the HPV-vaccination. This is done because lock-in is regarded as a result and not as a cause of systemic failure, in line with Klein Woolthuis (2005). The effect of lock-in is discussed in relation to the dependent variable 'performance of HPV-vaccination'.

After the innovation system and dynamic analysis is performed, an overview is given of the factors which have positively and negatively influenced the seven system functions, these factors are derived from the dynamic analysis and the interviews which will be performed with key actors. The functions of innovation systems subsequently have influenced the performance of the HPV-vaccination in the Netherlands. This extra step is performed to show the most important events in the dynamics in the innovation system behind HPV-vaccination.

2.3 Motors of innovation systems

To make conclusions about the dynamics of the innovation system behind HPV-vaccination in the Netherlands, the concept 'motors of innovation' system is used. The assumption of motors of innovation is that forms of cumulative causation may occur in the dynamics of a technological innovation system (Suurs, 2009). In different phases of the innovation process, functions can create feedback loops, promoting the innovation. The outcomes of this research are compared with functional patterns which have already been developed in research from Eveleens et al. (2010). These patterns discuss the feedback of functions per phase of the innovation system. The different phases which are described are pre-development, development, take-off and acceleration (Eveleens et al, 2010). The take-of phase of HPV-vaccination started in 2008, when it was decided to add HPV-vaccination to the RVP. The outcomes of the dynamic analysis will indicate the relations between the different functions of innovation systems in the HPV-vaccination innovation system.

Now all relevant innovation theories have been discussed a theoretical framework is presented of the relations between the theoretical concepts (see figure 3). This framework shows all theoretical concepts and the relations between these concepts. The innovation system analysis will show the structure of the innovation system behind HPV-vaccination and the functions of innovation systems give insight in the dynamics of the HPV-vaccination innovation system.

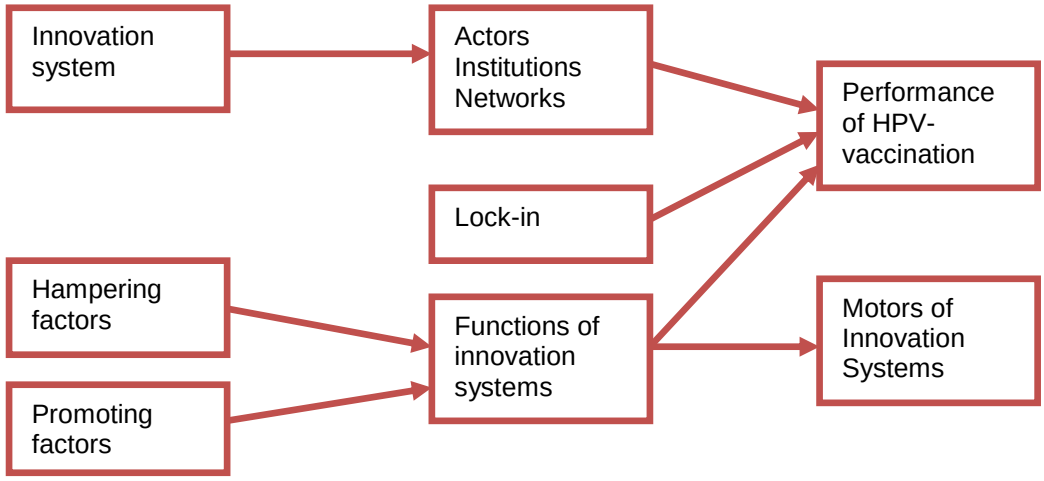

Figure 3: Theoretical framework, explaining the link between innovation system concepts, factors, functions of innovation systems, lock-in, performance of HPV-vaccination and motors of Innovation Systems (derived from Schuttelaar, 2007)

In this framework the innovation system analysis, the dynamic analysis and lock-in are linked to the performance of HPV-vaccination. The functions of innovation systems are related to motors of innovation systems as well. The lines between the theoretical concepts give an indication of the relations between the theoretical concepts, but some concepts are interrelated in other ways as well. For example, the information gained from researching the actors, institutions and networks will be used as input for determining the hampering and promoting factors in the dynamic analysis. And policy recommendation will be developed based on the innovation system analysis, the dynamic analysis, their link to the performance of HPV-vaccination and motors of innovation systems.

The theoretical framework in figure 3 shows how to the sub research questions and main research question will be researched. In the next chapter the main and sub research questions are proposed. These research questions are derived from the problem definition supported with the theoretical concepts discussed in this chapter.

3 Research questions

The aim of this research is to find the factors which have led to the low vaccination coverage using innovation system theory. This theory, combined with the research aim, leads to the following main research question:

- *Which functions in the HPV-vaccination innovation system determine the performance of the HPV-vaccination in the Netherlands?*

These functions are defined as events or set of events which influence the performance of the HPV-vaccination. This proposed relation is based on innovation system literature.

Sub questions:

- *Which actors, institutions and networks can be defined regarding HPV-vaccination in the Netherlands?*

- *What is the influence of lock-in on the HPV-vaccination in the Netherlands?*

- *Which functions explain the differences in the performance of the HPV-vaccination innovation system in England compared to the Netherlands?*

- *How can the performance of the innovation system behind HPV- vaccination in the Netherlands be improved?*

The first sub question is used to map the static part of the innovation system, giving a full overview of the related actors, the networks and the institutions playing a role in the HPV-vaccination. Roles of actors can be diverse, e.g. on performing the vaccination, guiding the vaccination in the National Immunization Program and diffusing information.

The answer to the second sub question indicates whether lock-in is a problem for HPV-vaccination and what its role is in the performance of HPV-vaccination. If lock-in did occur, this could have an effect on the performance of HPV-vaccination besides the events related to the functions of innovation systems.

The third sub question is focused on England. By performing a small analysis of the HPV-vaccination in England, a comparison between the English innovation system and the Dutch innovation system can be made. This helps to gain insight in the most important functions influencing the performance of HPV-vaccination.

The last sub question has to be answered in order to provide useful policy recommendations. It can point out which system failures have occurred, which system alterations are desirable and how similar innovation processes can be performed more successful in the future.

4 Method

In order to answer the research question and its related sub questions, data has to be gathered on the HPV-vaccine innovation system and its dynamics. Different types of data collection are used to get a full overview of the complete innovation system behind the HPV-vaccination in the Netherlands.

4.1 Research design

The research design is a case study of the HPV-vaccination system in the Netherlands, where qualitative data is gathered to answer the research questions. This method is chosen because the innovation system theory used for this research is well suited for qualitative research and because information about HPV-vaccination in the Netherlands mainly will be gathered from literature references describing a specific case. Innovation system research is very useful for its heuristic value and giving insight in the innovation process (Hekkert et al, 2007).

HPV-vaccination cannot easily be compared with other vaccine innovation processes in the Netherlands due to differences in technology and end users; therefore no comparison is made with other vaccine introductions in the Netherlands. A short comparison with HPV-vaccination in England is made, although the majority of the research is focused on HPV-vaccination in the Netherlands.

The research is explorative. Factors explaining the performance of HPV-vaccination have not been clearly defined on beforehand, so no hypotheses have been developed. The outcomes of this research helps to define the factors influencing the performance of HPV-vaccination, but conclusions have to be drawn cautiously, since research outcomes should be further tested (e.g. by performing the research in other countries) to confirm the proposed linkages.

4.2 Data gathering & analysis

Innovation System Analysis

The first step needed to answer the main and the first sub question is aimed at mapping the HPV-vaccination innovation system. This is done with an extensive literature research on the HPV-vaccination in the Netherlands. References have been gathered from scientific research, media reports, governmental publications, websites of involved actors and email contact with related actors. Also knowledge from GSK is used to map the full system, this includes contact with GSK employees involved with HPV-vaccination and written resources such as dossiers with media report and scientific articles, tender information and information to doctors. Actor information and references mentioned in articles are used to find and map other actors and events related to HPV-vaccination in the Netherlands. This snowball method used for data collection helps to find all actors, institutions and networks which are involved in HPV-vaccination in the Netherlands.

Dynamic analysis

In the next paragraphs the indicators for the functions of innovation systems, indicators for lock-in and indicators for performance of HPV-vaccination are discussed. The proposed indicators are used to measure the innovation system functioning over time. For the dynamic analysis based on the functions of innovation systems all events related to a function are discussed and if possible counted and put on a timeline.

Functions of innovation systems

The indicators used for the functions of innovation systems are derived from existing research as much as possible. This is done to assure that the functions are measured according to innovation theory standards. Due to differences in the HPV-vaccination innovation system and previous applications of functions of innovation systems several alterations to function indicators have been

made. These alternations have been discussed with Simona Negro, who has extensive experience with applying functions of innovation systems.

- Entrepreneurial activities are measured by the number of available vaccines in the Netherlands and by discussing the activities of the producers in the Netherlands regarding HPV-vaccination research and production. Since few entrepreneurial activities took place, no quantitative overview has been developed.
- Knowledge development is measured by counting the number of scientific articles per year worldwide and in the Netherlands. Each article is labeled as a positive event and put on a timeline. The most important knowledge developments are described as well.
- Knowledge diffusion is measured by looking at the number of meetings where HPV-vaccination was a major subject, both in the Netherlands as in Europe. These meetings are labeled as positive events and are shown on a timeline.
- Guidance of the search is measured by scanning media articles and policy documents for goals or expectations about HPV-vaccination or an expressed lack of goals or expectations. Events are labeled as positive or negative and put on a timeline. The most important developments regarding the guidance of the search are discussed as well.
- Market formation is measured by discussing the creation of the market of HPV-vaccination in the Netherlands. Three different aspects are of influence on the market formation of HPV-vaccination: the influence of other technologies which can prevent cervical cancer, the competition between available vaccines and the market toward the users of the vaccines. All developments related to these three aspects are discussed, but no timeline is presented.
- Resource mobilization is measured by looking at funding decisions of the government. A decision not to fund HPV-vaccination is labeled as negative and a decision for funding is labeled as positive and these events are presented on a timeline.
- Creation of legitimacy is measured by mapping positive and negative statements regarding HPV-vaccination of interest groups over time and by performing a media analysis which shows the number of positive and negative articles about HPV-vaccination over time. Since there are differences in interest groups (statements of health organizations are different from questions of member of parliament), these statements are depicted separately.

Besides events related to the seven functions, external factors are discussed as well. External factors are regarded as factors which are not part of the innovation system behind HPV-vaccination, but have influenced the performance of HPV-vaccination. An example of an external factor is the influence of the oil price on sustainable energies.

Lock-in

Lock-in is taken into account as a separate concept, influencing various aspects of the system and thus the general performance of HPV-vaccination. It is measured by comparing choices made regarding the introduction of HPV-vaccine to previous routines of actors or the system and assessing the results of these choices. During the interviews with key actors additional information on lock-in has become apparent.

Performance of HPV-vaccination

Detailed information of HPV-vaccination in 2009 and 2010 per municipality is available to determine the performance of HPV-vaccination expressed in vaccination coverage. Information on the effects of the HPV-vaccination on the decline of cervical cancer in the Netherlands is discussed, based on scientific literature. Research on acceptance of HPV-vaccination is included in measuring the performance of HPV-vaccination.

The following overview shows the indicators for the functions of innovation systems, lock-in and performance of HPV-vaccination.

Indicators (are measured over time)	Value
Function 1: Entrepreneurial Activities	
Licensed vaccines, clinical trials in the Netherlands	(no value)
Function 2. Knowledge Development	
Patent development regarding HPV-vaccination (international based)	(no value)
Research regarding HPV-vaccination worldwide	+1
Research regarding HPV-vaccination in the Netherlands	+1
Function 3. Knowledge Diffusion through networks	
Number of conferences and workshops regarding HPV-vaccination in the Netherlands	+1
Intermediary organization in the Netherlands	(no value)
Function 4. Guidance of the Search	
Goals or expectations expressed by industry and government	+1
Expressed lack of goals or expectations by industry and government	-1
Function 5. Market Formation	
Events related to formation of the market between different technologies, available vaccines and the formation of the market to end users.	(no value)
Function 6. Resource Mobilization	
Decision on funding HPV-vaccination	+1
Decision not to fund HPV-vaccination	-1
Function 7. Creation of legitimacy/counteract resistance to change	
Statement of interest groups in favor of HPV-vaccination	+1
Statement of interest groups against HPV-vaccination	-1
Positive media coverage about HPV-vaccination	+1
Negative media coverage about HPV-vaccination	-1
Lock-in	
Observed inertia of actor to adequately deal with new aspects of the HPV-vaccination because of routines	(no value)
Performance of HPV-vaccination	
Vaccination coverage, societal acceptance	(no value)

(Derived from Hekkert et al, 2007; Negro, 2007 and personal research)

Data analysis

The collected data will be mainly analyzed by a qualitative discussion of the results. The value of the data collected on the innovation system, functions of innovation systems and lock-in has to be determined in relation to the performance of HPV-vaccination. Functions might describe a positive development, but perhaps this development is not sufficient to create a well functioning system. According to Bergek et al. (2005) the evaluation of the system functioning can be done in two ways. It can be done by relating the collected data to the phase the system is in. This is done in this research by applying motors of innovation systems. The other way is by making a comparison with another technology specific innovation system. This is done by comparing HPV-vaccination in the Netherlands to HPV-vaccination in England.

After the innovation system is mapped and its dynamics have been researched according to the function indicators, semi-structured interviews have been performed. This research step is taken because interviews are a better source compared to literature research to gain in-depth information on how actors have coped with the HPV-vaccination. Interviews help to unravel underlying assumptions and motives behind the choices made regarding HPV-vaccination in the Netherlands. During the interviews, the results of the innovation system analysis and the dynamic analysis are discussed with key actors in the HPV-vaccination field. The interviews helped to fill gaps in the data collection, make clear which actors and events have the most influence on the performance of the HPV-vaccination innovation system and gives information on possible policy implications to improve the performance of the HPV-vaccination innovation system.
The interviews all have been performed face to face and have been recorded. Interview transcripts have been send to the interviewees, so alterations could be made and the interview transcripts could be approved. A list of the people which are interviewed can be found in appendix I.
The subjects discussed during the interviews are: the role and responsibility of the actor, the innovation system which has been developed after the innovation system analysis, the seven system functions, the influence of lock-in, the barriers and opportunities for HPV-vaccination in the Netherlands and a comparison of HPV-vaccination in the Netherlands to other countries. An extensive list of the interview questions can be found in Appendix J.

The complete research is performed during an internship at GSK, the producer of Cervarix. This internship improves the data collection, but also has a risk of bias. In the discussion chapter of this research this possible effect is further discussed. The period in which the data is collected is from November 2010 to 31 March 2011. Events and information which became apparent after this date are not taken into account, this means that vaccination coverage information about the campaign in 2010 and 2011 is incomplete because definitive data will become available later.

4.3 Research Quality

In order to assure the research quality different types of validity have to be met. This to make sure the research truly measures which is intended to be measured (Yin, 2003). These types of validity include construct validity, internal validity and external validity. Besides validity, reliability is also a criterion to assure valid research outcomes.

Construct validity

Yin (2003) defines construct validity as establishing correct operational measures for the concepts being studied. Construct validity is focused on the data collection. All relevant data should have been acquired because the research is on a well demarcated subject: the HPV-vaccination innovation system in the Netherlands. When resources only refer to information which is already appllied in this research, it is expected that all events are accounted for. By discussing the information with key actors it can be confirmed that the innovation system and its dynamics are fully mapped. And by mapping the concepts which are studied according to the proposed indicators, it can be assured that the concepts are correctly operationalized.

Internal validity

Yin (2003) states that internal validity is establishing a causal relationship, whereby certain conditions are shown to lead to other conditions. Internal validity can be assured by critically testing the linkages in the function of innovation system model. By using existing innovation theory, empirical data to test the linkages and interview outcomes an innovation model should arise where there are causal relations between the innovation functions and the dependent variable. Applying motors of innovation systems improves the internal validity through looking at the cumulative causation of the functions of innovation systems.

External validity
External validity establishes the domain to which a study's finding can be generalized (Yin, 2003). The external validity of this study is improved by making a short comparison with HPV-vaccination in England. This comparison shows that the proposed research can also be applied to HPV-vaccination in other countries.

Reliability
Reliability can be achieved by demonstrating that the operations of a study can be repeated with the same results (Yin, 2003). The function indicators make it possible to repeat this research. The reliability of the data can be assured by gathering references from academic sources and to assure reliable data from actors it is important to have actual contact with the actor and not only gather information from media articles and websites about the actor. Reliable information on lobby activities and guidance of the search can best be gathered from involved actors themselves and not from third partner websites or news articles. Also the interviews assure that data and its interpretation are correct. To assure the interviewees stand behind their comments, they have been asked for a confirmation of their statements. By using both literature references and interviews, different types of data collection are used. This is a form of triangulation, which increases the confidence of the results.

Now all research steps theories have been discussed a scheme is given (see figure 4). This scheme shows all different steps which are taken in order to perform this innovation system research on the HPV-vaccination in the Netherlands.

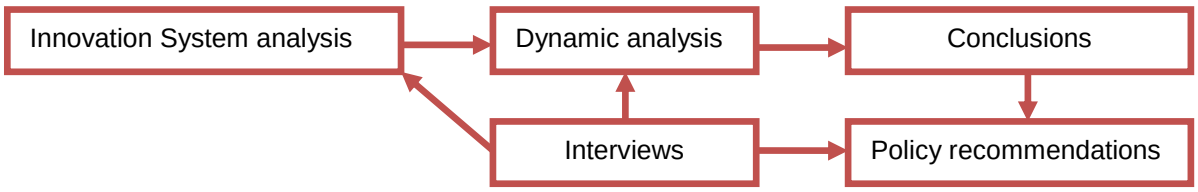

Figure 4: Research steps (Derived from Schuttelaar, 2007)

The next chapter will give concise information about HPV and HPV-vaccines. Then the result section of this research is given, in which the innovation system is described and analyzed.

5 HPV and HPV-vaccine state of knowledge

In this paragraph the essential characteristics of HPV(-vaccines) are given. This is done to give some insight in the technology which is researched. More extensive information can be found in external references.

Table 1 Papillomavirus proteins

Designation	Location in infected keratinocytes	Function of protein
E1	Nucleus, basal cells	DNA helicase
E2	Nucleus, basal cells	Transcription factor
E4	Cytoplasm, spinous layer	Structural within infected cells
E5	Transmembrane, spinous layer	Cofactor for EGF receptor, regulates MHC class I expression, oncogenic
E6	Nucleus, basal, and spinous	P53 degradation, telomerase inhibitor, oncogenic
E7	Nucleus, basal, and spinous	Pocket protein binding, E2F release, oncogenic
L1	Nucleus, mature squames	Major capsid protein
L2	Nucleus, mature squames	Minor capsid protein

Figure 5: HPV genes (Frazer et al, 2011)

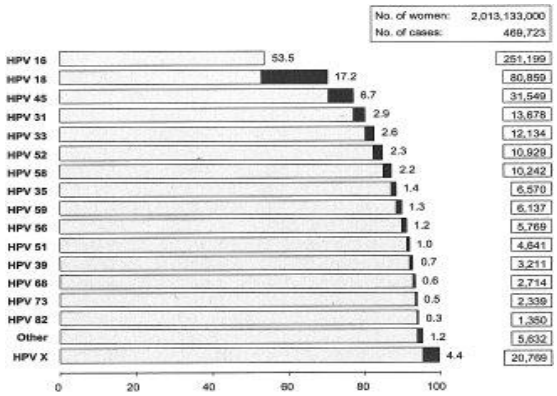

Figure 6: HPV DNA types (Munoz et al , 2004)

Human Papillomaviruses can be found in 99,7% of all cervical cancer cases, proving that HPV infections are a necessary prerequisite for cervical cancer (Walboomers et al, 1999). HPV-16 and HPV-18 are the most oncogenic types, causing over 70% of all cervical cancer cases worldwide (see figure 6). It is expected that HPV is oncogenic because of the E6 and E7 genes of the 8 genes of the virus (see figure 5). Another reason HPV is dangerous is that most infections only trigger a minor immune response, partially because the virus does not cause cell death or a strong inflammation reaction (Frazer et al, 2011). In a small part of the population HPV-infections can slumber for years.

The two available HPV-vaccines work prophylactic, which means that the vaccine only works if a woman is not already infected with the HPV type she is vaccinated against (Frazer et al, 2010). If a woman is infected with a type of HPV in the vaccine, the vaccination does not work, but neither does harm. Even though the Virus Like Particles in the vaccines are based on HPV type 16 and 18, the vaccines gives cross protection in various extents to HPV type 31, 33, 45 and 51, Cervarix giving the highest cross protection (Harper, 2010). For the knowledge on duration of protection see figure 7. However, research shows that even with no measurable antibody count HPV-vaccines still give protection (Frazer, 2011).

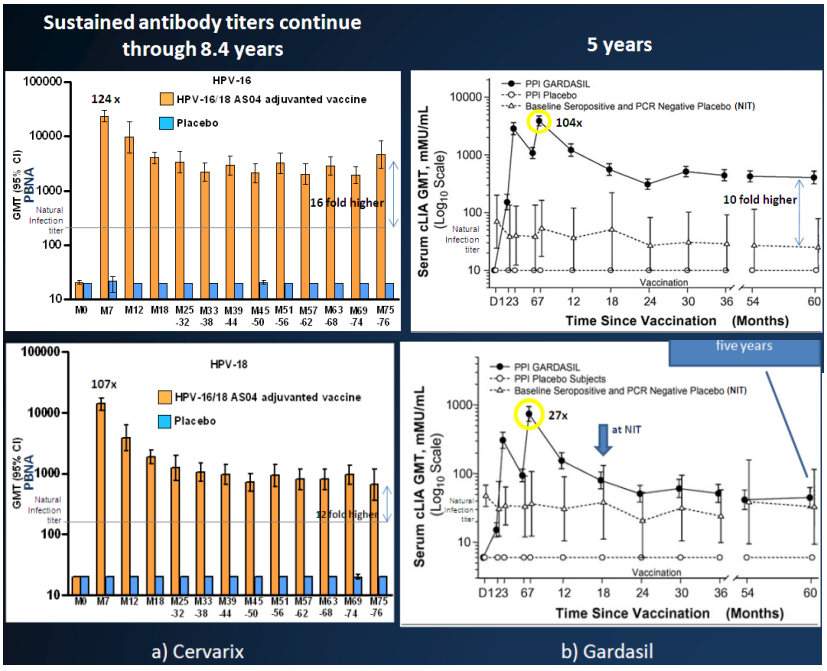

Figure 7: Antibody titer against HPV 16 & 18 (Harper, 2010)

Even though there has been a fierce public discussion on the safety of HPV-vaccines no deaths have been causally linked to the vaccines (VAERS, 2011). Side effects are usually mild and transient (van der Maas, 2009).

But still many critical questions regarding the HPV-vaccines remain: Will the vaccine ultimately prevent not only cervical lesions, but also cervical cancer and death? How will vaccination affect screening practices? How will the vaccine affect other oncogenic strains of HPV? (Haug, 2008). Only the future will show the answer to these and many other questions.

6 Innovation system analysis

In this chapter the role of the actors, institutions and network of the HPV-vaccination in the Netherlands is discussed. This research step is taken to gain insight in the development and diffusion of the technology, based from a system level perspective. The interaction of the actors, institutions and the created network determines the performance of the HPV-vaccination. And by analyzing the innovation system insight can be gained on which system factors have influenced the performance of HPV-vaccination. This research step will give an answer to the sub research question:

Which actors, institutions and networks can be defined regarding HPV-vaccination in the Netherlands?

Before the actors, institutions and network are sketched a summary of the system developments is given. The system developments are presented because different actors had a different role over time and an overview of all main developments can clarify the role of the actors over time. The discussion of the system developments is not very extensive on the general role of the actors. In the paragraph specified on the different actors, more extensive information per actor is given. The main events concerning HPV-vaccination in the Netherlands are also be depicted on a timeline.

After the main system developments are presented, information is given about all actors which are responsible for developing, producing, choosing, distributing and administrating the HPV-vaccination. This will be done by first discussing the general function of each actor and then give information on the role of the actor concerning the HPV-vaccination in the Netherlands. The actors are coupled to innovation system building blocks, defining the actors as part of the research system, industrial system, governmental system, demand side and intermediaries. Actors which have no formal role regarding HPV-vaccination are not discussed in this chapter, but are discussed in the dynamic analysis. The institutions which have influenced HPV-vaccination are mentioned as well. Finally, the linkages between the actors and the institutions are depicted in an innovation system overview. This gives insight in the innovation system the actors and institutions create.

6.1 System developments

At the basis of the innovation system is the scientific development of the HPV-vaccine. Even though fundamental research and the creation of the HPV-vaccine mainly are performed outside the Netherlands, there also has been extensive research on HPV, cervical cancer and HPV-vaccines in the Netherlands. Already in 1994 research has been performed on therapeutic vaccines (AD, 1994). This type of vaccine might cure already developed cervical cancer by inducing a strong immune response. Various universities and research groups have performed HPV and HPV-vaccination research in the Netherlands. An example of such a research group is HumaVac, which performed a clinical trial to test the effects of Cervarix on women age 26 and older (Kocken et al, 2007). Universities in Leiden en Nijmegen also have performed HPV research (LUMC, 2009; Lenselink, 2009). An important – worldwide- source of knowledge about the link between HPV and cervical cancer is the Vrije Universiteit Amsterdam. Several interviewees indicated that their HPV research is of great importance, both for cervical cancer screening, HPV DNA tests as for HPV-vaccination (Conyn, 2011; Schellekens, 2011, Interview de Kok, 2011).

In 1991 the first virus like particles of HPV type 16 and 18 were created, but it took fifteen more years before the worldwide scientific developments led to the availability of an HPV-vaccine (Schiller, 2004). The first available HPV-vaccine was Gardasil followed by Cervarix a year later. Gardasil is developed by Merck and licensed by Sanofi Pasteur MSD in Europe/the Netherlands. Cervarix is developed and licensed by GlaxoSmithKline (GSK). Both vaccines have undergone extensive clinical trials, which took place all over the world (EMA Gardasil, 2006; EMA Cervarix, 2007).

The introduction of an HPV-vaccine in the Netherlands started with market approval in Europe. The decision to approve a vaccine is made by the European Medicines Agency (EMA). Gardasil gained market approval on 20 September 2006, Cervarix gained market approval exactly a year later on 20 September 2007 (EMA Gardasil, 2006; EMA Cervarix, 2007). To gain market approval a medicine is tested on the aspects safety, quality and efficacy.

After market approval the medicine became available in the Netherlands. Girls and women could request the vaccine to their general practitioner or other healthcare professional, but had to pay the costs themselves. Few women took the vaccine in when it became available (SFK, 2007). This could be because of the high costs (around 400 euro's) of the vaccine and unfamiliarity. Efforts have been made to fund the vaccine, which was possible by reimbursing the HPV-vaccination through the drug reimbursement system (GVS) and/or adding it to the National Immunization Program (RVP). The GVS is paid through the healthcare insurance system, the vaccines in the RVP are paid by the Dutch government. Sanofi Pasteur MSD made a request to add the vaccine to the GVS in 2007. This decision is made by the Minister of Health, based on an advice from Healthcare Insurance Board (CVZ). The CVZ advised that it was better to wait till the Dutch Health Council developed an advice whether or not the vaccine should be added to the RVP (CVZ Gardasil, 2007). Also after the Health Council has developed an advice, GSK and again Sanofi Pasteur MSD, requested to add their HPV-vaccine to the GVS. In the meantime the vaccine was added to the RVP and according to the CVZ additional benefit were relatively low compared to the costs, so the CVZ advised the Minster of Health not to add the vaccine to the GVS, making this a dead end path for HPV-vaccination for now (CVZ Cervarix, 2009; CVZ Gardasil, 2009).

The Health Council published their advice regarding adding HPV-vaccination to the RVP on 31 March 2008 (Gezondheidsraad, 2008). The Health Council advised to introduce the HPV-vaccination to the RVP for twelve year old girls and to perform a catch-up campaign for girls age thirteen to sixteen. The Minister of Health followed this advice and requested the Dutch Vaccine Institute to perform a European tender. This tender, based on price and efficacy, concluded that Cervarix would be added to the RVP (GSK press release, 2008).

Since the HPV-vaccination is implemented in the RVP responsibilities are divided in the same way this is done with other vaccines. This means that first the Minister of Health, Welfare and Sport decides if a vaccine is added to the RVP, based on the advice of the Health Council. If the Minister of Health decides to add a vaccine to the RVP, the National institute for Public Health and Environment (RIVM) is responsible for the direction and execution of the vaccination program. The Dutch Vaccine Institute (NVI) supplies the vaccines and the vaccines are given by the Community Health Services (GGD) (Rijksoverheid, 2010; Informatie RVP, 2010). There has been chosen to carry out the HPV-vaccination in mass vaccination sessions by the department Youth Healthcare of the Community Health Services. The Centre for Infectious Disease Control (which is part of the RIVM) is in charge of the whole operation, supported by the Dutch GGD (Melker et al, 2009).

The catch-up campaign has been performed in the period March-November 2009. The total vaccination coverage for the catch-up campaign was 52,2% (Giesbers a, 2011). Initially the annual vaccination sessions would be held immediately after the summer holidays. However, the first vaccination round for twelve year old girls was postponed to March 2010 because of the Mexican Flu. The vaccination coverage in 2010 was 51,9% (Giesbers b, 2011). In 2011 the HPV-vaccination also has started in March (Melker et al, 2009; RIVM nieuwsbrieven, 2009-2010). Data on vaccination coverage in 2011 are not available yet, but a preliminary news report show that the attendance is around 10% higher for the first shot as in 2010 in Groningen (DVHN, 2011).

6.2 Timeline

Many different actions have been taken regarding HPV-vaccination in the Netherlands. But before a vaccine became available, knowledge development took place on an international scale. The following figure shows all major worldwide HPV-vaccination developments. Vaccine licensure took place in 2006 and 2007.

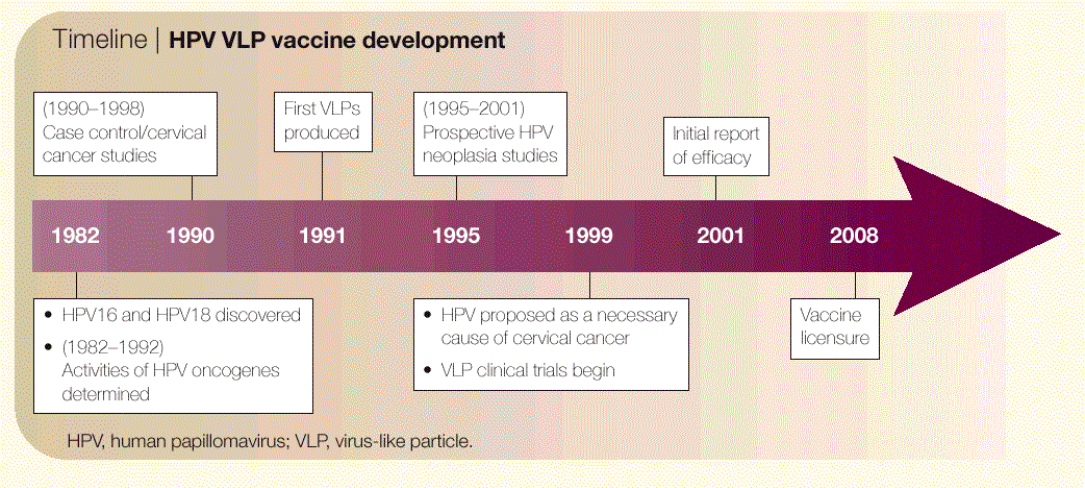

Figure 8: Worldwide HPV-vaccine development (Schiller, 2004)

Developments in the Netherlands already started long before a vaccine became available. In the next overview the most important events are shown which have influenced the HPV-vaccination in the Netherlands.

1976	Start screening program cervical cancer (RIVM, bevolkingsonderzoek, 2010)
1994	Research on a therapeutic vaccine in the Netherlands (AD, 1994)
2006 September 20	Market approval Gardasil (EMA, 2006)
2007 March 20	Minister of Health requested HPV-vaccination advice from Health Council (Gezondheidsraad, 2008)
2007 May 21	Negative advice to add Gardasil to the Drug Reimbursement System (CVZ Gardasil, 2007)
2007 September 20	Market approval Cervarix (EMA, 2007)
2008 March 31	Advice Health Council (Gezondheidsraad, 2008)
2008 July 8	Decision of Minister of Health to follow the advice of the Health Council (Kamerstuk vaccinatie, 2008)
2008 November 20	Cervarix wins tender for RVP (GSK Press release, 2008)
2009 February 23	Negative advice to add Cervarix to the Drug Reimbursement System (CVZ Cervarix, 2009)
2009 March – April	Start catch-up campaign (RIVM Newsletters, 2009)
2009 April 20	Second negative advice to add Gardasil to the Drug Reimbursement System (CVZ Gardasil, 2009)
2009 July	IGZ rapports on marketing activities SP MSD and GSK (IGZ Cervarix, 2009; IGZ Gardasil, 2009)
2009 September	Postponement vaccination girls born in 1997 because of Mexican flu outbreak (RIVM Newsletters, 2009)
2009 September	Third round HPV catch-up campaign (RIVM Newsletters, 2009)
2010 March – May	First and second round girls born in 1997 (RIVM Newsletters, 2010)
2010 September	Third round girls born in 1997 (RIVM Newsletters, 2010)
2011 March	First round girls born in 1998 (RIVM Newsletters, 2010)

6.3 Actors

The HPV-vaccination is integrated in an existing vaccination system, so most actors have experience with other vaccinations. The focus in discussing the actors is on their general role concerning vaccines/healthcare and is further specified by expending on their role and tasks related to the HPV-vaccination.

Research System

The research system cannot be seen as a well defined group of actors. Since many different universities, research institutes, governmental agencies and companies performed research on HPV-vaccination, it is not possible to mention all worldwide actors involved in HPV-vaccination research. However, scientific research is a crucial factor in the availability of HPV-vaccination in the Netherlands. Therefore global major developments will be discussed as well as all developments which have taken place regarding HPV-vaccination research in the Netherlands.

The link between Human papillomavirus and cervical cancer is first researched around 1970. The DNA of specific HPV types has been found in almost all cervical cancer cases. This has led to the discovery of high-risk HPV genotypes. The DNA of the virus has been researched, leading to information on the role of the virus to the development of cancer. This also has helped to develop new approaches for cervical cancer screening (Zur Hausen, 2002). Harald Zur Hausen, the doctor who discovered this link, received a Nobel Prize for his discovery in 2008 (Vaste Prik, 2008). A definite proof that the Human papillomavirus is a necessary cause for cervical cancer came in 1999, when Walboomers et al. published a study where previously HPV-negative cervical cancer specimens were researched, indicating that the HPV prevalence in cervical carcinomas is 99,7 % (Walboomers, 1999).

After the discovery of the link between the HPV-virus and cervical cancer, efforts in developing a preventive vaccine were made. This development started at several universities (University of Rochester, Georgetown University and the University of Queensland) and the American National Cancer Institute (NCI) (Pasmanabham et al, 2010). The NCI licensed the technology nonexclusively to MedImmune (a biotechnology company) and Merck. GSK acquired exclusive rights to the MedImmune portfolio. This has led to several patent infringements between Merck and GSK, which were partially resolved in 2005. Merck and GSK agreed to cross-license their intellectual property holdings so they both were ensured of access to the technology to produce an HPV-vaccine (Pasmanabham et al, 2010). This made it possible to produce the first vaccine against a major human cancer. The vaccines prevent the development of HPV-related cervical cancer of several high risk HPV types. But long-term follow-up studies are necessary to ensure that vaccinating woman against the majority of high risk HPV types will eventually decline cervical cancer (Zur Hausen, 2009).

The development of an HPV-vaccine also has been performed in the Netherlands. But this research was focused on developing a therapeutic vaccine and not on a preventive vaccine. A therapeutic vaccine cures cervical cancer, instead of preventing it. Already in 1994, researchers in Leiden, together with the RIVM, have put effort in producing such a vaccine. Even though the vaccine was promising in animals, it was unclear if it would have the same effect on humans (AD, 1994). Even now research is ongoing on a therapeutic vaccine in the Netherlands. Efficacy results with HPV-related vulva cancer are promising, but efficacy of the vaccine on cervical cancer is not yet known (LUMC, 2009). Since therapeutic vaccination is different from a technological, medical and societal point of view from preventive HPV-vaccination, it is not within the scope of this research. Its development is worth mentioning however, because it has helped to create knowledge and expertise about HPV (-vaccination) in the Netherlands.

Research on a prophylactic (preventive) vaccine is performed in the Netherlands as well. A research groups in the Netherlands which performed studies on preventive HPV-vaccination is HumaVac. HumaVac is a partnership between the departments of Gynecology and Pathology of the VU Medical Center Amsterdam, the departments of gynecology at Erasmus University Medical Centre in Rotterdam, Reinier de Graaf Groep in Delft/Voorburg, the University Medical Center Utrecht, and DDL Diagnostic Laboratory in Voorburg. HumaVac conducts independent scientific research and contract research regarding cervical cancer, HPV and preventive vaccination (Humavac, 2010). One of the studies HumaVac performed is the HPV-015 study, which started in March 2006. This double blinded randomized clinical study, with the Cervarix vaccine, has been performed to test the effects of HPV-vaccination in women older than 26. Previous research was focused on younger age groups; this new research should give extra information on the effects of the HPV-vaccine in a different population (Kocken et al, 2007). Also in Nijmegen at the university medical center noteworthy research has been performed. An extensive research by Charlotte Lenselink on sexual behavior, prevalence of HPV in Dutch woman and on the acceptance of an HPV-vaccine gives insight in the potential of HPV-vaccination in the Netherlands (Lenselink, 2010). A university which did not do specific research for HPV-vaccination, but performed research of major importance to investigate the link between cervical cancer and HPV is the Vrije Universiteit Amsterdam (Schellekens, 2011; Conyn, 2011)

Other research will not be discussed in this chapter, in the dynamic analysis of the innovation system all relevant literature on HPV-vaccination in the Netherlands will be analyzed, giving a more extensive overview of all scientific research related to HPV-vaccination in the Netherlands.

Industrial System

In an industrial system knowledge is translated into products. This knowledge has been created by the external research system and the firms R&D activities. There are only two companies which form the industrial system behind HPV-vaccination. There are several reasons the HPV-vaccination market consists out of only two companies. Because the technology to produce HPV 16 and 18 like VLP's is patented as well as its adjuvantia, it is not possible for other firms to freely enter the market. And because expensive clinical trials are necessary to gain market approval small firms do not have enough resources to develop and test the vaccine. The two companies which are active on the Dutch market are Sanofi Pasteur MSD and GlaxoSmithKline.

Sanofi Pasteur MSD

Sanofi Pasteur MSD is founded in 1994 as a joint venture of Sanofi Pasteur and Merck and Co (Which is known in Europe as MSD). Sanofi Pasteur MSD develops vaccines based on research of Sanofi Pasteur and Merck and makes the vaccines available for whole Europe, protecting people against infectious diseases. A substantial part of their vaccines or subcomponents is distributed in the Netherlands through the RVP (SP MSD, 2010).

Sanofi Pasteur MSD has gained market approval for Gardasil in the Netherlands in 2006 (EMA, 2006). A major difference of this vaccine compared to Cervarix, GSK's vaccine, is that it not only protects against HPV type 16 and 18, but also against HPV type 6 and 11 which cause 90% of the genital warts. There is also evidence that the vaccine gives cross-protection against other HPV-types (NVI, 2007).

At the time Gardasil became available, parents had to pay for the vaccine themselves. So Sanofi Pasteur made efforts to reimburse the vaccine or add it to the RVP. But these efforts were without success, even though several countries (Australia, Denmark) have added Gardasil in their vaccination program, Cervarix has become the vaccine which is added to the RVP in the Netherlands. This decision, made by the NVI, has led to a lawsuit. According to Sanofi Pasteur MSD the tender was not based on quality, but on price. The tender did not take the protection against genital warts into account. The judge ruled that the criteria of the tender were justified and the Minister did not had to revise his decision, keeping Cervarix as the vaccine which would be added to the RVP (Rijksoverheid, 2008).

As well as GSK, Sanofi Pasteur MSD tried to increase HPV awareness. When Gardasil became available in 2006, a website (www.beschermjedochter.nl) was launched were information was given about cervical cancer, combined with radio advertisements where a Dutch celebrity pointed women to the possibility to protect their daughters and visit the website. The Dutch society for critical vaccination (NVKP) made a formal complaint against the advertisements, stating it was a type of forbidden advertisements. The commission for the medicine advertisement code stated that the advertisements were allowed according to Dutch law (Stichting CGR, 2007). Other activities of Sanofi Pasteur MSD in the Netherlands were research on cervical cancer awareness and meetings with oncologic gynecologists according to journalist Joop Bouma (Bouma, 2008).

GlaxoSmithKline, GSK

GSK is a company which develops and distributes medicines and vaccines for treating and preventing diseases. GSK cooperates with patient and healthcare organizations, e.g. by providing training to general practitioners and pharmacy personnel. GSK is an international organization with over 100.000 employees in 116 countries in 2006 (GSK, 2010).

GSK is the producer and distributer of Cervarix, one of the two vaccines against the human papillomavirus. The vaccine has been approved in the Netherlands in 2007 (EMA, 2007) and is introduced to the RVP in 2009 after winning the tender against Gardasil from Sanofi Pasteur MSD (GSK Press release, 2008).

Cervarix is the second HPV-vaccine which has become available on the European market, and protects against HPV type 16 and 18. Research has shown there is cross protection against HPV 31 and 45. But the vaccine does not protect against HPV 6 and 11 which are the main cause of genital warts (NVI, 2007). A major difference between Cervarix and Gardasil is the adjuvant Cervarix contains, which has the name AS04. This adjuvant triggers a more sustained and stronger immune response (Bornstein, 2010). It is important to have a strong immune response because the immune response of a natural infection is not sufficient enough to protect against new infections, even with the same type (NVI, 2007). If the stronger immune response makes Cervarix more efficient in preventing cervical cancer is not certain.

In order to increase HPV awareness in the Netherlands, GSK performed several activities. These activities include funding a survey by Maurice de Hond, showing that there is a need for more information on cervical cancer. GSK also made a website to inform the public about cervical cancer and possibilities to prevent and treat the disease: http://www.baarmoederhalskankeronline.nl/. By funding the NIGYO foundation, which spreads gynecologic cancer awareness, a documentary has been aired about cervical cancer. GSK, as well as Sanofi Pasteur MSD, had extensive contacts with oncologic gynecologists before and after the introduction of the HPV-vaccine in the Netherlands (Bouma, 2008).

Even though the industrial system only exists out of two players, other developments and technologies influence the industrial system as well. Second generation HPV-vaccines might protect against more strains of HPV and thus will compete against the current generation vaccines. However, it will take several years before second generation HPV-vaccines will become available. Besides competition between the two HPV-vaccines, 'competition' is taking place against the cervical cancer screening program, HPV-DNA test and therapeutic vaccines. Even though these technologies can be used complementary, some researchers state that vaccination is undesirable because it is less cost effective as some alternatives and it might even hamper the screening program (De Kok et al, 2008). Since the scope of this research is on preventive HPV-vaccination, these technologies and their producers are not regarded as part of the system. Their interrelatedness is more extensively discussed in the dynamic analysis

Governmental System
The governmental system a very extensive part of the HPV-vaccination innovation system. Governmental agencies play a role on different aspects of the HPV-vaccination system. This is divided into actors and aspects related to the approval and funding decisions on HPV-vaccination and on actors and aspects related to implement and provide the HPV-vaccination to the target population. Besides the role of governmental agencies, politics have an influence on the HPV-vaccination as well.

Approval & Decisions
With approval and decisions all governmental actions are implied which made HPV-vaccination in the Netherlands possible. The actions of these actors do not play a role in the executing the HPV-vaccination, but without their approval and decisions large scale HPV-vaccination in the Netherlands would not be possible.

EMA/CBG
The European Medicines Agency is a decentralized body of the European Union. It exists of a European medicines network, compromising over 40 national authorities in 30 EU and EEA-EFTA countries. This includes the CBG, which is the Dutch Medicines Evaluation Board. The EMA's main responsibility is the protection and promotion of public and animal health, by evaluating and supervising human and animal medicines. The Committee for Medicinal Products for Human Use (CHMP) is responsible for evaluating the safety, efficacy and quality of new medicines before they gain market approval in the whole EU (EMA, 2010). People from the Dutch Medicines Evaluation Board took place in the CHMP's about the HPV-vaccines (Schellekens, 2011).

The final conclusion given in the EPAR (European Public Assessment Report) on Gardasil is stated as:
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Gardasil was favorable and therefore recommended the granting of the marketing authorization. The medicine has proven to prevent high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. The indication is based on the demonstration of efficacy of Gardasil in adult females 16 to 26 years of age and on the demonstration of immunogenicity of Gardasil in 9- to 15-year old children and adolescents. Protective efficacy has not been evaluated in males (EMA, 2006).

The final conclusion given in the EPAR on Cervarix is stated as:
Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Cervarix was favorable and therefore recommended the granting of the marketing authorization. The medicine has proven to prevent high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3) and cervical cancer causally related to Human Papillomavirus (HPV) types 16 and 18. The indication is based on demonstration of efficacy in women aged 15-25 years following vaccination with Cervarix and on the immunogenicity of the vaccine in girls and women aged 10-25 years (EMA, 2007).

After market approval the EMA constantly monitors the safety of medicine through a pharmacovigilance network and gathers new research results on the effects of medicines. Based on new findings the EMA can change the indication of a medicine, give safety warnings, or even withdraw a medicine from the market (EMA, 2010). An expansion of the indication of Gardasil was given in 2010, increasing the age of demonstrated efficacy in women to 45 years (EMA Gardasil, 2010).

Health Council, Gezondheidsraad
The Dutch Health Council is an independent scientific advisory. Their task is to advise the government and the parliament about public health subjects and health research (Gezondheidsraad, 2010). On 20 March 2007 the Health Council was asked to performed a research whether or not adding HPV-vaccination to the RVP was desirable (Gezondheidsraad, 2008).

The guideline for this decision is the list of seven criteria the Health Council developed in 2007 about the future of the RVP. The following criteria have to be met for the inclusion of a vaccination in a public program:
Seriousness and extent of the disease burden
1. The infectious disease causes considerable disease burden within the population.
• The infectious disease is serious for individuals, and
• The infectious disease affects or has the potential to affect a large number of people.
Effectiveness and safety of the vaccination
2. Vaccination may be expected to considerably reduce the disease burden within the population.
• The vaccine is effective for the prevention of disease or the reduction of symptoms.
• The necessary vaccination rate is attainable (if eradication/elimination or the creation of herd immunity is sought).
3. Any adverse effects associated with vaccination are not sufficient to substantially diminish the public health benefit.
Acceptability of the vaccination
4. The inconvenience or discomfort that an individual may be expected to experience in connection with his/her personal vaccination is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
5. The inconvenience or discomfort that an individual may be expected to experience in connection with the vaccination program as a whole is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
Efficiency of the vaccination
6. The balance between the cost of vaccination and the associated health benefit compares favorably to that associated with other means of reducing the relevant disease burden.
Priority of the vaccination
7. Relative to other vaccinations that might also be selected for inclusion, provision of this vaccination serves an urgent public health need at reasonable individual and societal costs.
(Houweling et al, 2010).
All these conditions have been discussed in the Health Council's advice and have been fulfilled satisfactorily, even though various remarks have been made about some of the criteria (Gezondheidsraad, 2008).

In addition two cost-effectiveness analyses have been performed for the Health Council report, using various parameters to map the effects and costs of the current screening program, HPV-vaccination and screening and HPV-vaccination combined. The analyses show that the costs are 21 000 euro and 30 000 euro respectively per QALY (Quality Adjusted Life Year) gained for screening and vaccination combined. However, these analyses are based on the commercial price of the vaccine, while the price per vaccine in a major order will be significantly lower, one of the producers already promised that the price of the vaccine would be 90 euro's per dose maximum (Gezondheidsraad, 2008). The conclusion of the Health Council is that the HPV-vaccine is cost-effective when added to the RVP. An advice on which of the two available vaccines should be preferred is not part of the analysis (Gezondheidsraad, 2008).

The Health council recommended including vaccination against HPV for twelve year old girls in the RVP. The council also advised to perform a catch-up campaign for girls ages thirteen to sixteen if the price of the vaccine is lowered (Gezondheidsraad, 2008). Because much knowledge about the

vaccination is lacking, and it will take a long time before this knowledge becomes available, the Health Council advised to accompany a possible vaccine implementation with an extensive monitoring program. This program should focus on effectiveness, duration of protection, side-effects and acceptance of the vaccination. Also relevant behavioral factors should be taken into account. This program is perceived as a necessary condition for the introduction of the HPV-vaccination (Gezondheidsraad, 2008).

Healthcare Insurance Board, College voor zorgverzekeringen, CVZ
The CVZ is both an advisory as an official system for providing health insurance policy. Pharmaceutical companies can submit a reimbursement dossier in order to gain insurance coverage of their products. The CVZ will develop an advice if a new medicine or treatment should be added to the Dutch drug reimbursement system (GVS). Following this advice, the minister of health can decide whether or not a treatment or medicine should be reimbursed by the healthcare insurance system. The CVZ has a major role in maintaining the quality, accessibility and affordability of the Dutch healthcare (CVZ, 2010). Three times, the CVZ has received a request to add an HPV-vaccine to the Dutch health insurance and three times the CVZ advised the Minister of Health not to add an HPV-vaccine to the GVS.

The first request was by Sanofi Pasteur MSD (Gardasil). The reaction of the CVZ was that pending the request to add Gardasil to the GVS, the Health Council was asked for advice about adding the vaccine to the RVP. The CVZ believed that a logic order would be to await the Health Council's advice. Also the CVZ had the view that the GVS is not the right framework for this type of intervention on population level (CVZ Gardasil, 2007).

In 2009, after the positive advice of the Health Council and the implementation of Cervarix in the RVP, Sanofi Pasteur MSD requested drug reimbursement again. Once more the CVZ advised that Gardasil should not be added to the GVS. There was insufficient support that adding the vaccine to the GVS would be an effective way of preventing cervical cancer, there was insufficient support for the validity of the proposed model in the reimbursement dossier and the proposed duration of protection was too optimistic. Also the Dutch college of general practitioners (NHG) and Health Insurances Netherlands -which gave input in the advice- find the coexistence of the HPV-vaccine in the National Immunization System and the GVS undesirable. Providing the HPV-vaccination via the RVP is most consistent with the current state of scientific knowledge (CVZ Gardasil, 2009).

GlaxoSmithKline has requested to add their HPV-vaccine to the GVS in 2009 as well. The CVZ had similar critique on the request of GSK, as on the request of Sanofi Pasteur MSD -the effectiveness is not sufficiently supported and the RVP is considered as the proper mean of providing HPV-vaccination-. This critique was expanded by stating that the evaluation by a general practitioner GSK proposed to decide whether or not vaccination is required is not a proper and effective method (CVZ Cervarix, 2009).

Minister of Health, Welfare and Sport
Minister van Volksgezondheid, Welzijn en Sport, Minister van VWS
The Minister of Health, Welfare and Sports has a role as decision maker, being the head of the Ministry of Health, Welfare and Sport. For both the RVP as for the GVS, the minister makes the decision whether or not the advice from the Health Council or CVZ should be followed (Gezondheidsraad, 2008; CVZ, 2010). Concerning the addition of the HPV-vaccine in the RVP the Minister of Health decided on 8 July 2008 that the advice of the Health Council would be adopted (Kamerstuk vaccinatie, 2008). The minister also has to report and defend the decisions that are made in parliament (Tweede Kamer, 2009).

Implementation
Other as the before mentioned governmental actors, the NVI, RIVM and GGD's are involved in the implementation and execution of the HPV-vaccination in the Netherlands and not in making policy or decisions regarding the implementation and provision of the HPV-vaccination.

Dutch Vaccine Institute, Nederlands Vaccin Instituut, NVI
The Dutch Vaccine Institute supplies the vaccines for the National Vaccine Provision, including the vaccines in the RVP (NVI, Missie en Kerntaken, 2010). The NVI has emerged from the vaccine division of the RIVM in 2003 and has over 100 years of experience with the research and production of vaccines. Because the NVI had to purchase the HPV-vaccine from pharmaceutical companies, a European tender has been set up based on (cost) effectiveness of the prevention of cervical cancer. On the basis of the offers the Minister of Health decided to purchase Cervarix for the RVP (Melker et al, 2009).

But the NVI has other tasks as well. The NVI performs research concerning vaccines for the National Vaccine Provision and is a knowledge generator and knowledge transferor on the area of vaccines and vaccinations (NVI, Missie en Kerntaken, 2010).

In the future, the role of the NVI will change. Currently, the NVI is a producer of vaccines. But because it is a small vaccine producer and requirements for vaccines are becoming stricter, it is difficult to produce vaccines at acceptable costs. The ministry of health has decided to sell the NVI production facilities to commercial parties. The purchase, distribution and storage of vaccines will rest in public hands (Toekomst NVI, 2009). The minister of health has researched if an enhanced cooperation with the National Institute of Health and Environment is of extra value. This has led to the decision to integrate the public vaccine responsibilities of the NVI with the RIVM. This integration process is ongoing and should be realized before the end of 2012 (VWS, 2010). This development will influence the system surrounding the HPV-vaccination, even though it is not yet clear what this influence will be.

National Institute for Public Health and Environment
Rijksinstituut voor Volksgezondheid en Milieu, RIVM
The RIVM is an organization which performs research, gives advice and support to the Dutch government. Every year the RIVM provides the Dutch government reports and advice about public health, healthcare, nutrition, nature, environment and disasters. The clients are the EU, United Nations, inspection agencies and various Ministries, of which the Ministry of health is the largest client (RIVM, 2010).

The Centre of infectious disease control (CIb), a division of the RIVM, coordinates the control of infectious disease in the Netherlands. The CIb focuses in effective prevention, vigilance and a quick response to disease outbreaks. The CIb supports and coordinates infectious disease control from a national and international view and directs the regional offices of the RIVM (RCP's – Regional Co-ordination of Programmes). The CIb performs scientific research and contributes to developing expertise, quality and uniformity in infectious disease control. There is a close connection with the European Center for Disease Prevention (ECDC) and the World Health Organization (WHO) and is the Dutch contact for these organizations. The head of the CIb is prof. Dr. Roel Coutinho (CIb, 2010). In figure 9 the linkages of the CIb with respect to the RVP are depicted:

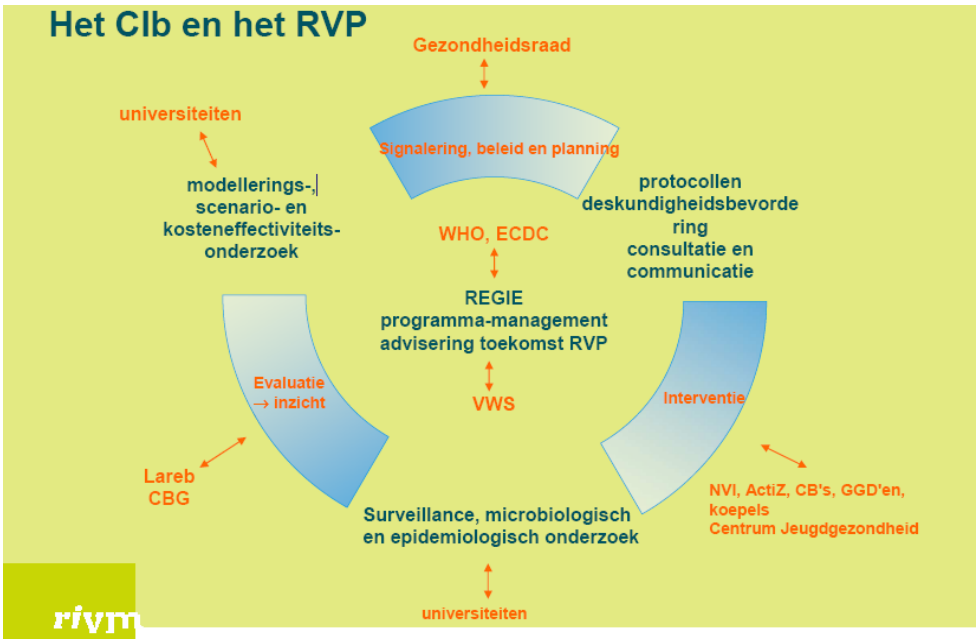

Figure 9: The role and linkages of the CIb/RVP (Conyn-van Spaendonck, 2008)

A major task of the CIb is the RVP (RVP). In 2004 the Minister decided to assign the direction and co-ordination of the RVP to the RIVM/CIb. Previously the National Association of Vaccination Administration took care of the RVP. This association is now part of the Cib, as are the regional offices of the RIVM (RCP's). The RIVM now has the responsibility to provide information about the RVP, the duty to react to questions and the responsibility to evaluate the program through epidemiological and microbiological research and safety control. The goal of this organizational transition is to maintain high vaccination coverage in the future in the Netherlands (Kamerstuk aansturing RVP, 2007).

The RIVM has provided extensive information to the public and related health organizations about the addition of the HPV-vaccination to the RVP. This includes information on the RIVM-website (http://www.rivm.nl/RVP/overzicht_ziekten/baarmoederhalskanker/). A specially designed website and slogan for the HPV-vaccination campaign in 2010 has been developed to provide information and increase awareness concerning the HPV-vaccination: www.prikenbescherm.nl.

Just as for other vaccines, the HPV-vaccination coverage is monitored by the registration system Praeventis. Doctors can report side effects by a passive system to the RIVM. In the future Lareb (The Dutch Pharmacovigilance centre) will keep track of and evaluates the side effects of vaccinations (Conyn, 2010). Research on risk factors for non participation is performed as well. It is important to know how women can be reached for HPV-vaccination, specifically the group of woman which does not respond to screening program invitations (Melker et al, 2009).

After the necessary preparations were made to invite 400 000 girls, the catch-up campaign started in March 2009. The first HPV-vaccination for the twelve-year-old girls was planned for September 2009, but was postponed because of the Mexican flu and finally started in March 2010 (Nieuwsbrieven RIVM, 2009, 2010).

Due to low vaccination coverage in 2009, the RIVM performed an interim expert evaluation and changed their communication policy in 2010, making the discussion about the vaccination more open and giving people more factual information so they can make their own decision (Zwakhals, 2010).

Community Health Services, Gemeentelijke gezondheidsdienst, GGD
The Community Health Services perform the HPV-vaccination, and all other vaccinations of children age four and older (RVP information, 2010). They do this by sending vaccination requests to the children who should take the vaccine, inviting them to go to a vaccination location to receive the vaccine.

Currently there are 29 Community Health Services in the Netherlands. All these organizations have to adapt to their local situation. This means some GGD's are in urban areas while others are more rural. Also the size and capacity of the GGD's differs. Demographic differences also influence the needs and possibilities of the GGD's. In the future the aim is to standardize the way research is performed at GGD's. The local GGD's epidemiologist should be a knowledge broker, networker, lobbyist and policy strategist (Houben, 2009).

The HPV-vaccination is carried out during mass vaccination sessions set up by the department Youth Healthcare of the Community Health Services. The centre for Infectious Disease Control has control, supported by the Dutch GGD (Melker et al, 2009). The HPV-vaccination performed by the GGD did not reach the vaccination coverage of 85% the Health Council posed in their advice, but was around 50% in 2009 and 2010 (Gezondheidsraad, 2008; Giesbers a, b, 2011). Differences in vaccination coverage per GGD vary from 38 % to 64 % in 2010 (Giesbers b, 2011). There are also big differences in vaccination levels in the municipalities of the GGD regions. The highest vaccination level is in Rucphen where 84,4% of the girls requested to take the vaccine has been vaccinated, while in Urk only 3,8% of the girls has taken the vaccination in 2010 (Giesbers b, 2011).

A last governmental aspect, which is not discussed here, is the role of the Dutch parliament and politicians. A parliamentary majority can overturn decisions made by the minister and thus have a big influence on decisions regarding HPV-vaccination, but this has not occurred. Another way the parliament has influenced the HPV-vaccination, is by debates and parliamentary questions. The role of parliament is further discussed in the dynamic analysis.

Intermediaries
Intermediaries are organizations which connect different actors in the innovation system to each other. In this role intermediaries contribute to the performance of an innovation system in making strategic decisions and fine tuning of activities.

RIVM
The RIVM can be considered as an intermediary between end users, the research system, industry and the government because of its responsibility in the execution of the National Immunization Program (Conyn, 2010). This central role makes it possible for the RIVM to diffuse knowledge, bring actors together and improve the performance of the HPV-vaccination.

Dutchbio vaccines group
The Dutchbio vaccines group (DVG) is an intermediary organization which connects pharmaceutical companies, e.g. the GSK, Sanofi Pasteur MSD and Crucell, with other vaccine related organizations, such as the NVI and TNO Pharma. (DVG Leden, 2010) Their goals are to represents the interests of the vaccine industry in the Netherlands in general as well as all other involved institutions and organizations, such as the government, pharmacists, physicians, patients, insurance companies and universities. They do this by eliminating misunderstandings regarding vaccines, make society aware of ongoing developments and threats, identify negative regulations and give shape to the standardization of vaccine research in the Netherlands (DVG Rol, 2010). The DVG had no major role in the HPV-vaccination system in the Netherlands, even though as an intermediary organization it could have played a role in the communication and choices regarding the HPV-vaccines.

Demand side

Even though the HPV-vaccination is aimed at preventing cervical cancer, and thus is given to girls, also other actors can be defined as being part of the demand side of the innovation system. This includes the Dutch government, which pays for the HPV-vaccination. Because this is part of the governmental system, the governmental actors which pay for the vaccine have been discussed in a previous chapter. In this chapter the 'final' demand side is discussed, which consists out of the targeted vaccine population and directly related people.

The intended vaccination population exists of girls before they are sexually active, decreasing the chance of being HPV infected. The protection duration of the HPV-vaccination is not yet certain and health gains are more quickly reached if older uninfected girls receive the vaccine. Therefore the vaccine is preferably given just before girls are sexually active. This has led to the advice to provide the vaccine to twelve year old girls. Research showed the vaccine to be cost effective for girls age 13 to 16 as well. These girls also were offered HPV-vaccination through the RVP.

The demand side did not play a major role in the formal system behind the HPV-vaccination. Several survey indicated that knowledge and awareness concerning HPV, HPV-vaccination and cervical cancer awareness was low (Bouma, 2008; NVKP & Radboud Universiteit, 2009). Despite an early lobby to introduce the vaccine in the RVP, public discussion about the benefits and disadvantages of a nationwide vaccination campaign started late (See dynamic analysis; Zembla, 2008).

Twelve year old girls

A big difference between vaccines provided to twelve year old girls and girls below the age of twelve is that twelve year old girls have the right of self-determination (Vaste Prik, 2008). This means the girls can choose for themselves whether or not they take the vaccine. This makes it necessary to inform both parents as well as girls about the HPV-vaccination, with the girl as final decision maker.

Girls age 13 to 16

This is also the case for girls age 13 to 16. Another aspect influencing this group is that more and more girls become sexually active, increasing the percentage of girls which already is infected with HPV type 16 or 18. This makes vaccination less effective. Because of this reduce in effectiveness the Health Council advised only to vaccinate girls up to the age of sixteen (Gezondheidsraad, 2008).

Boys

Boys are not part of the indicated vaccine population, since they do not have a cervix. Still investigations are being performed to test if including boys in HPV-vaccinations is useful. Because HPV can cause anus, mouth, throat and penis cancer in boys, they also can be harmed by the HPV-virus. But the disease burden of these cancers is considerably lower than cervical cancer (de Kok, 2011). Another advantage of vaccinating boys is that it increases herd immunity. Because of these reasons a professor, Lagro-Janssen, claimed that boys should be vaccinated against HPV (Gelderlander, 2010). Also in the in the NtvG (a Dutch medical journal) this claim has been made (van Osselen, 2011). For now, no efforts are taken in the Netherlands to provide HPV-vaccination to boys.

Parents

Even though girls have the legal right to chose for themselves whether or not they take the vaccine, parents have a big influence on this decision. Therefore information provided by the government is not only focused on young girls, but also on their parents. The site www.prikenbescherm.nl for example (which was available in 2010), was both aimed at girls and their parents or caretakers.

Medical Community

Demand for an HPV-vaccine from the medical community was mainly initiated from oncologic gynecologists (Bouma, 2008). But also other health organization had an opinion about the HPV-vaccination. The role of health organizations related to cervical cancer and HPV-vaccination is further discussed in the function analysis.

6.4 Institutions

Apart from the defined actors and their network, institutions play a role in the functioning of the HPV-vaccination system in the Netherlands. Rules and laws involved in the HPV-vaccination are the Exceptional Medical Expenses Act (AWBZ), right of self-determination, medicines advertising code and the GVS. The National Immunization Program and the rules on the role and responsibility of its involved actor are also of major importance. Norms regarding vaccine acceptance and norms about sexual behavior are informal institutions which influence the HPV-vaccination in the Netherlands.

Vaccine Funding/Exceptional Medical Expenses Act (AWBZ)

An important law to ensure HPV- vaccination in the Netherlands is the AWBZ. Healthcare cost which are not reimbursed by Health Insurances, but are too high for most people are funded by the government through the AWBZ. This includes the vaccinations in the RVP (Rijksoverheid AWBZ, 2010). However, for the HPV-vaccination an exception has been made, because of international marketing reasons the price of the vaccine has been kept secret and thus the costs are paid from the state budget of the ministry of health (Conyn, 2010). In the future all vaccines covered by the RVP are part of the state budget of the ministry of health (RIVM Nieuwsbrieven, 2010).

Right of Self-determination

As already explained in the section about the intended vaccination population, the girls who receive the HPV vaccine can choose for themselves whether or not they take the vaccine. Legally twelve year old children and their parents have to agree to medical actions. But there are two legal exceptions. If the refusal can lead to serious medical disadvantages for the child, the child can make a decision on its own. And the second exception is when the child wishes to perform the medical treatment after being well-advised, even if their parents don't agree (Vaste Prik, 2008). Because of this legislation the HPV-vaccination campaign aim is different from the information parents receive about other vaccines, both parents and their daughters have to be informed about the vaccine.

Medicines Advertising Code

In the Netherlands legislation concerning the advertisements of medicines is very strict. It is forbidden to advertise unregistered medicine, both to patients as to healthcare professionals. Advertising prescription required medicines to patients is at all time forbidden. And only when the EMA/CBG has registered a medicine, it is allowed to advertise it to healthcare professional. Advertising is defined in the broadest sense, including all oral, written and audiovisual methods to inform healthcare professionals about a medicine. There are strict guidelines how the pharmaceutical industry should communicate with healthcare professionals. This includes aspects about providing general information, providing hospitality, the supply of samples and providing benefits in cash or in kind to healthcare professionals (CGR, 2008).

Because of the Medicines Advertising Code, it was not possible for the industry to promote their HPV-vaccines to the public. Instead these companies tried to increase HPV and cervical cancer awareness. This has led to societal commotion about the influence of the pharmaceutical industry on the HPV-vaccination (Zembla, 2008). Because of this commotion and related parliamentary questions Sanofi Pasteur MSD and GSK have been inspected by the Dutch Health Inspectorate (IGZ). The reasons for these inspections were signals that these companies violated the marketing rules in the Medicines Advertising Code. The conclusions of these reports where that most of the activities of SP MSD and GSK are in line with legislation on medicine advertising. SP MSD infringed legislation by providing waiting room posters for general practitioners, giving out gifts to doctors, proving the vaccine to not indicated patient groups and providing information by several means which conflicted with the ban on public advertising. GSK infringed legislation by promotional talks to nurses, offering discounts, having an unclear service agreement with doctors, proving the vaccine to not indicated patient groups and making statements on increased effectiveness which is not part of the indication. Both companies also had contact with politicians to promote HPV-vaccination. The IGZ stated that

this way of promoting a medicine is not consistent with the ratio of the medicine advertising code (IGZ Gardasil, 2009; IGZ Cervarix, 2009).

National Immunization Program, RVP

The RVP is the vaccination program the Dutch government has founded in 1957 to protect against dangerous and sometimes deadly infectious diseases. The vaccinations are not mandatory, but over 95% of the parents vaccinate their children with the vaccines provided through the RVP. Parents do not have to pay for the vaccines themselves, with the condition that the GGD or other designated health center performs the vaccination according to the vaccination scheme (Informatie RVP, 2010).

In the following figure the whole development of the RVP is depicted.

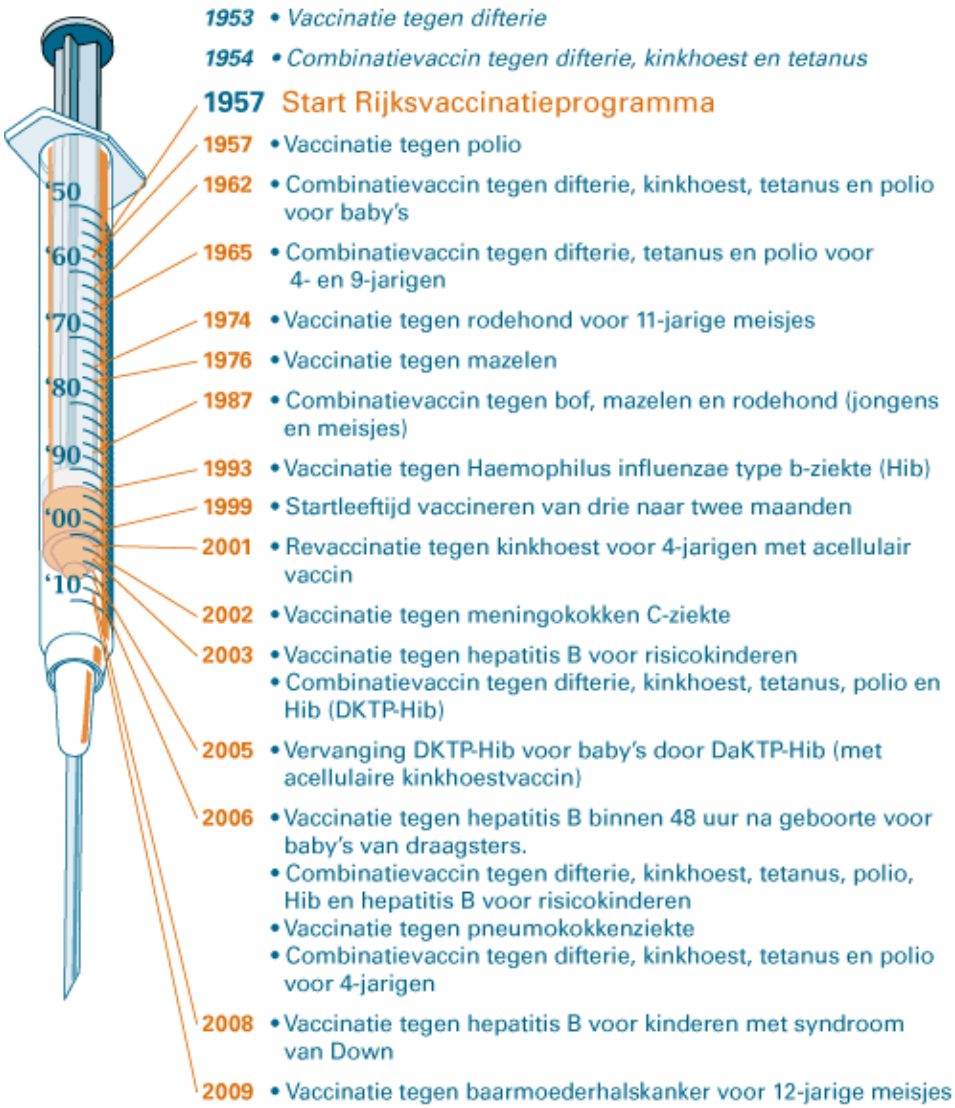

Figure 10: Developments in the RVP (RVP History, 2011)

Drug Reimbursement System
The GVS is part of the Health Insurance Law. An insured person has a right to a reimbursement for a registered drug when the Minister of Health decides to place the drug in the GVS (Farmatec, 2010). Even though the healthcare insurance board has given a negative advice to add the vaccine to the GVS, it is still possible that the HPV-vaccines will become available. In several interviews the addition of the HPV-vaccination to the GVS is discussed and addition is still an option if cost-effectiveness criteria are met (Kenter, 2011; Schellekens, 2011; Remorie; 2011).

Norms about vaccine acceptance
In general vaccine acceptation is very high in the Netherlands. In 2009, the average vaccination coverage was considerably higher than the lower limit of 90% the RIVM sees as desirable (RIVM, 2009). Even though vaccinations are not mandatory, the vaccination coverage is consistently around 95% (Informatie RVP, 2010). But continues information supply is necessary because more people doubt the necessity and safety of vaccines and anti-vaccination movements with scientifically incorrect facts are becoming more influential (Rümke, 2004).

Before the HPV-vaccination has been added to the RVP, research is performed on the acceptance by parents of the vaccine. 88% of the parents said they are willing to accept the vaccination of their daughters. The study showed that acceptance of the HPV-vaccine depended on their general vaccination acceptance and not on the knowledge of HPV and cervical cancer (Lenselink, 2010).

But reality showed this vaccination coverage is not reached. Multiple researches have been performed in the Netherlands to gain more insight which factors influence HPV-vaccination acceptance. Research showed that the main reason parents reject the vaccination is the supposed lack of safety, the chance of non-severe side-effects and the supposed lack of efficacy of the vaccine. Religion plays a minor, but significant role. The research also indicated that many parents were in doubt about making a decision to vaccinate their daughters (Van der Berg, 2010). Other research has tried to develop policy advice for future directions. Vaccine acceptance can be increased by correcting misconceptions, stimulating active processing of information and by centralize the subjective perspective of the user population needs (Paulussen, 2010). Even more research has been performed on what determines HPV-vaccination acceptance and how this acceptance can be increased (Rondy et al, 2010; Korfage et al, 2008; de Bekker et al 2010; de Boer et al, 2011).

Norms about sexual behavior
Because HPV is a virus which is mainly spread through sexual contact, norms about sexual behavior influence the success of HPV-vaccination. In the HPV-vaccination campaign little focus is put on the sexual aspects. By offering the HPV-vaccine to all twelve tot sixteen year old girls no focus is put on (future) sexual behavior. According to Peter Leusink, general practitioner and sexologist, the link between the HPV-virus and STD's should not be made. Almost everybody gets an HPV-infection in their live and it is unrealistic to think monogamy and condom use can prevent this. And a strong link between sex and getting cancer is not the right message for twelve year old girls (Vaste Prik, 2008). In contrast to Peter Leusink, the editors of the magazine from SOA-Aids Netherlands think the HPV-vaccination can be connected to a broader policy on positive attention for sexual development. This can help to reduce the stigma on STD's, for example on cervical cancer and decreases the possible misconception that safe sex and testing is of less importance (Jongen et al, 2008).

After introduction of the vaccine commotion did occur concerning the link between cervical cancer and sexual behavior. Christian professor Wolter Oosterhuis was quoted in several media that girls who remain monogamous the rest of their life do not need the HPV-vaccination (Nederlands Dagblad, 2009). This statement has been criticized because not all girls will stay monogamous and also the sexual partner of the woman has to stay monogamous. Still, studies do indicate that HPV-vaccination coverage is considerably lower among religious people (Rondy, 2010).

6.5 National Innovation System behind the HPV-vaccination

The actors and institutions and the linkages they create are represented in figure 11. The interactions of the actors are depicted in two different ways in the system overview. The formal connections are depicted with full lines. Products, knowledge and official agreements are essential for the functioning of the innovation system. Public opinion is not essential for the realization of HPV-vaccination in the Netherlands, so these interactions are depicted with dotted lines in the system overview. Still these actors are important for the performance of HPV-vaccination: according to several interviews related health organizations (e.g. general practitioners and gynecologists) have an important impact on HPV-vaccination (Interview de Kok, 2011; Kenter, 2011; van den Oetelaar, 2011; Remorie, 2011). The intermediaries, institutions and norms are shown separately since their influence is on many different parts of the system. In the next chapter events related to this system and its actors, clarifying their role over time, are analyzed according to the functions of innovation systems.

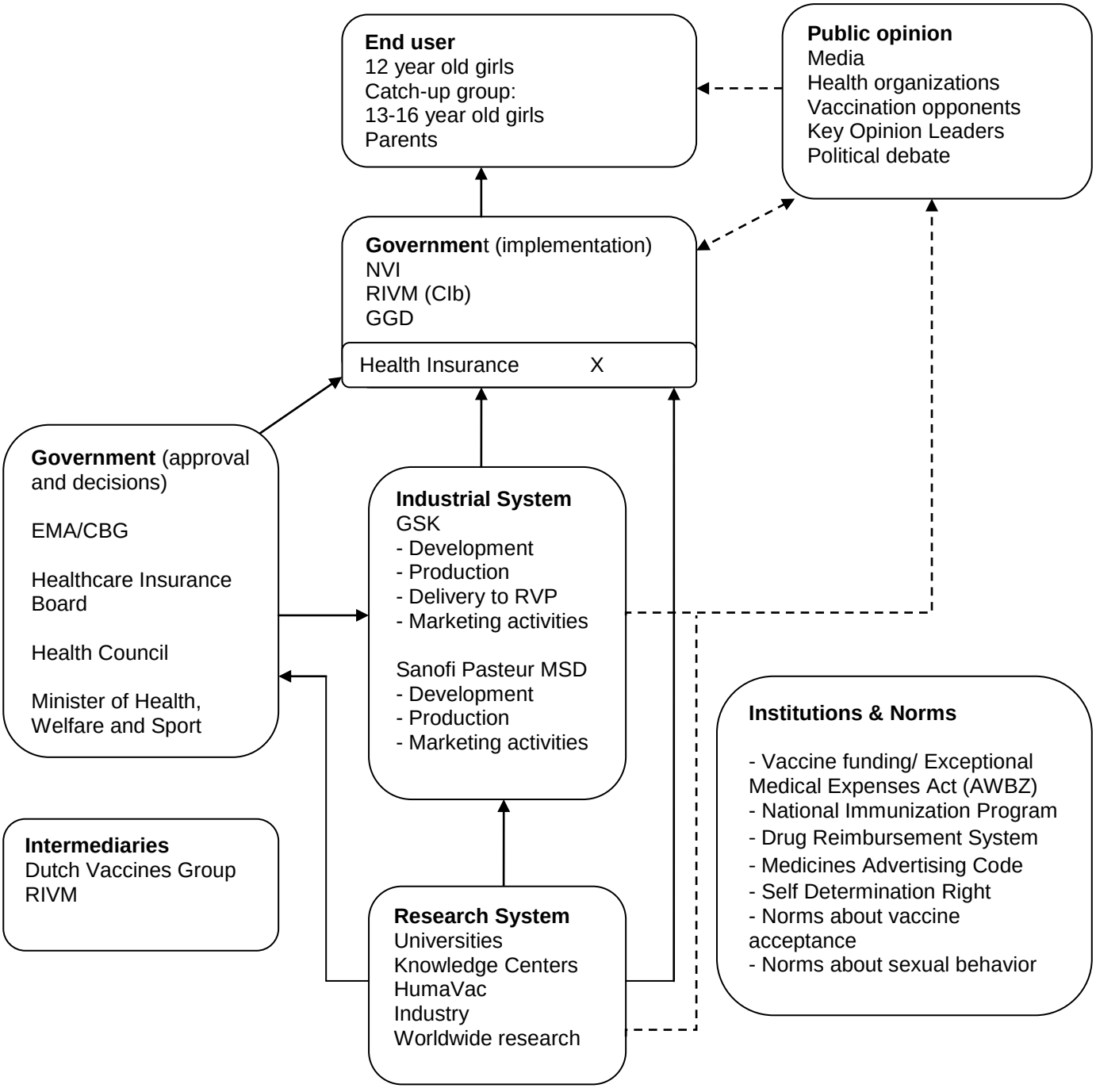

Figure 11: National Innovation System behind the HPV-vaccination in the Netherlands

7 Dynamic analysis: Functions of innovation systems

The next research step after mapping the innovation-system behind HPV-vaccination is an analysis of the system functioning. This research step is necessary because the system overview does not give insight in the performance of the HPV-vaccination innovation system. By analyzing each of the functions of the innovation system, positive and negative factors in the HPV-vaccination development can be determined. These factors will be related to the performance of the HPV-vaccination, which will be measured by looking at acceptance and vaccination coverage. The linkages between the different functions and the performance of the HPV-vaccination will be given in the conclusion chapter. So the function analysis of the system is necessary to give an answer to the central research question:
Which functions in the HPV-vaccination innovation system determine the performance of the HPV-vaccination in the Netherlands?

Besides giving an answer to the main research question the second sub question will be answered as well: *What is the influence of lock-in on the HPV-vaccination in the Netherlands?*
A separate paragraph will discuss all events where lock-in has played a role. Lock-in is regarded as the inertia of an actor or system to respond adequately to new developments, because the actor or system is focused on previous routines (David, 1985). Even though lock-in events can be linked to specific functions, there is chosen to discuss lock-in events separately and linking them directly to the performance of the HPV-vaccination. This is done because lock-in is regarded as a result and not as a cause of systemic failure (Klein Woolthuis, 2005). So lock-in is not the cause for a suboptimal performance of a certain function, but an effect of unfulfilled system elements. The effect of lock-in will be related to the depended variable 'performance of HPV-vaccination'. A more extensive explanation of the concept of lock-in is given in the theory section of this research.

All innovation system functions will be discussed one by one, describing the developments of the function over time. If sufficient events are available, the main events will be showed on a timeline to get a graphic overview of the developments related to the function. Besides the seven functions, derived from Hekkert et al. (2007), external factors will be discussed as well. External factors are events or set of events which have influenced the performance of the HPV-vaccination system but can not be classified into one of the seven functions.

Then the factors which have influenced the functions are presented in a graphical overview. Some factors have had a positive influence on specific functions while other factors have negatively influenced specific functions. Subsequently, these functions determine the performance of HPV-vaccination.

After the dynamic analysis the conclusion chapter will proceed on the findings of this chapter. In the conclusion, the results of the analysis will be related to the performance of HPV-vaccination in the Netherlands to determine the barriers and opportunities of HPV-vaccination in the Netherlands. This will give insight which functions have been of importance in the performance of the HPV-vaccination. Possible improvements in the system and for the different actors are given in the policy implications.

7.1 Functions of innovation systems

F1: Entrepreneurial activities

No entrepreneurial activities took place in the Netherlands regarding the initial developments of a preventive HPV-vaccine. The reasons no entrepreneurial activities took place are that the technology to produce HPV 16 and 18 VLP's is patented by GSK and SP MSD as well as its adjuvantia. And expensive clinical trials are necessary to gain market approval, so Dutch local operating companies do not have the possibility to freely enter the market. The worldwide entrepreneurial activities are mainly focused on two companies, Merck and GlaxoSmithKline. The main events concerning entrepreneurial activities regarding the HPV-vaccination in the Netherlands are the European market approvals of Gardasil (EMA, 2006) and Cervarix (EMA, 2007). This made it possible to offer HPV-vaccination in the Netherlands and is considered as a major entrepreneurial activity because without market approval the vaccines could not be offered in the Netherlands.

Future entrepreneurial activities will include improved HPV-vaccines. According to Diane Harper Merck is putting efforts to develop a new HPV-vaccine: *In order to remedy the lack of overall adenocarcinoma protection covered by Gardasil, a second generation pentavalent Gardasil vaccine with these missing types has been developed and is currently in clinical trials* (Harper, 2010).
Also at GSK there are thoughts to make improvements on the current HPV-vaccines (Remorie, 2011).

Other types of entrepreneurial activities did took place in the Netherlands, including clinical trials. One of these trials is the HPV-015 trial which ran from 2006 to 2009 to map the effect of the HPV-vaccination in women older than 26 (Kocken et al, 2007). Another clinical trial which took place in the Netherlands is the HPV-023 trial which looked at the effectiveness of the HPV-vaccination with co-administration with a Hepatitis B vaccination (Clinical trials, 2010). In total six different clinical trials took place or are still being performed in the Netherlands, although most of these trials only partially took place in the Netherlands. All these clinical trials were performed with the HPV-vaccine Cervarix (Clinical trials, 2010). Sanofi Pasteur MSD did not perform clinical trials, but several studies with Gardasil have been performed in multiple research centers in the Netherlands (van den Oetelaar, 2011). Clinical trials in the Netherlands are regarded as an entrepreneurial activity because they expand and diffuse scientific knowledge and familiarize Dutch doctors with HPV-vaccination and make other applications of the preventive HPV-vaccination possible in the future, both inside and outside the Netherlands.

Another event which can be regarded as entrepreneurial activity in the Netherland is the opening of a HPV-vaccine production facility in Haarlem where Gardasil is produced (MSD, 2008). This HPV-vaccine is distributed to countries in Europe, Asia and Australia. But because the Dutch government decided to add Cervarix to the RVP and not Gardasil, few of these HPV-vaccines are used on the Dutch market, only several thousand Gardasil vaccines have been sold in the Netherlands (SFK, 2007; Zembla, 2008).

F2: Knowledge development

The main resource for mapping the knowledge development regarding HPV-vaccination, both worldwide as from a Dutch perspective, is scientific literature. By analyzing the numbers of and topics in scientific literature, insight can be gained in the state of the knowledge regarding HPV-vaccination. Mapping the knowledge development over time is especially important because cervical cancer takes a long time to develop, thus long lasting, extensive research is necessary. A substantive story about the major scientific breakthroughs which have led to the HPV-vaccines is already discussed in a previous chapter. In this chapter the knowledge development on both scientific and societal aspects of the HPV-vaccination is shown over time. An in-depth analysis on Dutch HPV-vaccination knowledge development is given as well.

Knowledge about HPV-vaccination is gathered on several levels. Knowledge about the technological development, efficacy and safety of the HPV-vaccines is largely gathered from fundamental research and clinical trials. Another type of knowledge is on the societal aspects surrounding HPV-vaccination. This includes research regarding policy, acceptance and societal implications of the HPV-vaccines.
Both scientific and societal knowledge development are important to make HPV-vaccination available and successful. The scientific and technological knowledge is necessary to develop an HPV-vaccine, but researching the impact of the vaccine on a society is needed to make a successful introduction and acceptation possible. But it is not always possible to make a clear distinction between these different types of research. Cost-benefit analyses are an example of a type of research where technological and societal knowledge overlaps, since both factors such as efficacy as vaccination coverage are important.

In figure 12 the worldwide scientific developments, based on a Google scholar search results, are shown. The number of scientific articles gives an indication about the state of knowledge development. However, this overview is limited since it does not give information about the quality, outcomes and specific topics in the scientific literature. Still, it gives a general view on the intensity of HPV-vaccination research.

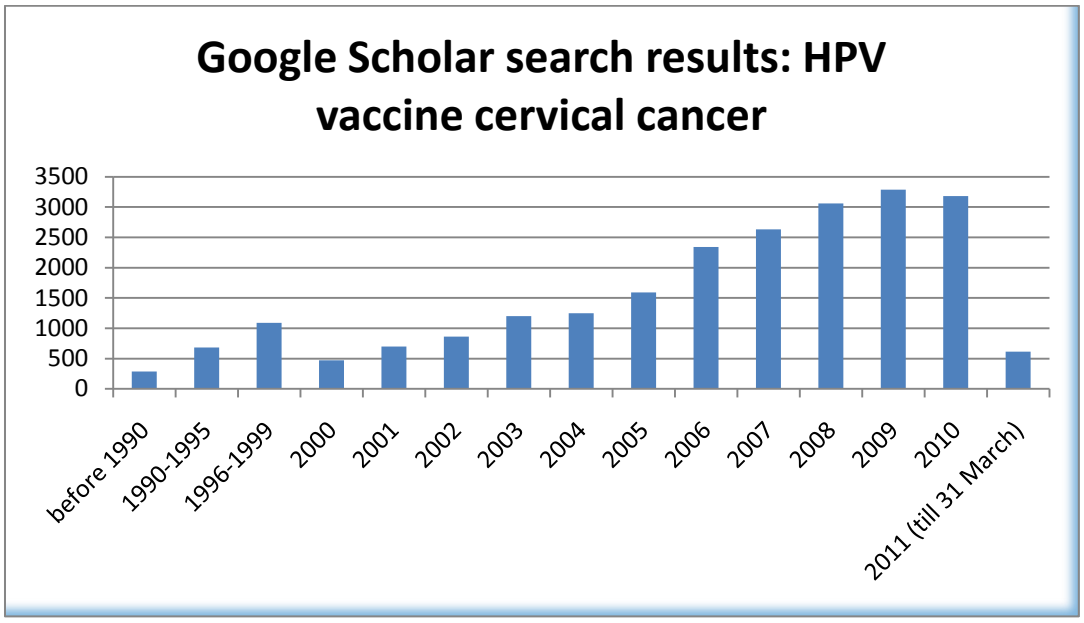

Figure 12: Number of scientific articles regarding HPV-vaccination (Google Scholar, 2010)

After a steep rise starting in 2005, the number of articles peaked in 2009 and leveled in 2010. An explanation for this rise around 2005 is the publication of clinical trials results which made market authorization possible (EPAR Gardasil 2006; EPAR Cervarix 2007). After 2007 the number of articles rose even more because research about the societal impact of vaccines became available, besides continues clinical research on efficacy and safety. It might be that this rise in articles is leveling or declining starting from 2010, because both technological as societal research might be sufficiently performed. But it is too early to give a decisive answer on how the amount of knowledge about HPV-vaccination will develop in the future and what will be major topics in this research.

Another way of gaining insight in the knowledge development of a technology is a patent analysis. However, such an analysis has not been performed; this is because few patents are related to the HPV-vaccines. And thus a patent analysis is not a representative way to map the worldwide or Dutch knowledge development of the HPV-vaccination over time. Fifteen patents concerning HPV-vaccination are issued by GSK between 1997 and 2005 and five patents are issued by Merck regarding HPV-vaccination between 1995 and 2007 (Espacenet, 2010; Search terms: HPV vaccine

Merck/HPV vaccine GlaxoSmithKline). Patents do give a view on how the two pharmaceutical companies gained access to the knowledge to produce an HPV-vaccine (Padmanabhan, 2010). Another type of knowledge development analysis is an R&D analysis, which is neither performed. Since there are just two companies and R&D spending mainly have been on expensive clinical trials an overview of R&D costs will not give insight in the knowledge development of HPV-vaccination.

Since the focus of this research is on the Dutch knowledge development regarding HPV-vaccination a separate analysis has been performed on scientific articles which focus on the Netherlands. This analysis is important because there are major differences in prevalence of cervical cancer, policy decisions and acceptance of the HPV-vaccination in the Netherlands compared to other countries, making separate studies focused on the specific Dutch situations necessary. For example, the mortality of cervical cancer in the Netherlands is the sixth lowest in whole of the EU (ECCA, 2009) and there already is a cervical cancer screening program since 1976 (RIVM bevolkingsonderzoek, 2010).

The analysis of Dutch HPV-vaccination articles is based on an extensive search via Google Scholar, the RIVM website, University websites, snowball method (looking at citations) and articles published in Dutch medical magazines. Inclusion criteria are that the article is written by an author with a scientific background, the focus in the article is on the Dutch situation (so fundamental and clinical research are not included) and that the article 'stands on itself'. This means an included article can be a commentary, but must be understandable for a reader without extensive knowledge of the previous article (so submitted letters with comments are not included).

The outcomes of this analysis are shown in figure 13. Notable is the late start of scientific literature development, before 2008 few articles which specifically focused on preventive HPV-vaccines in the Netherlands have been published. In 2008 the number of scientific articles rose steeply, so the majority of the articles is published in the year before the introduction of the HPV-vaccine in the RVP and after its introduction in the RVP. The number of articles stays around the same number until 2010. In the first quarter of 2011 a comparable amount of articles as in 2010 is published. Figure 13 shows that knowledge creation about the HPV-vaccination in the Netherlands is still ongoing.

The Health Council in 2008 is one of the most important reports in the Netherlands, because it made the application of the HPV-vaccine in the Netherlands possible and was the inducement for many other scientific articles and discussion in 2008, 2009 & 2010 (Kenter, 2011; Schellekens, 2011).

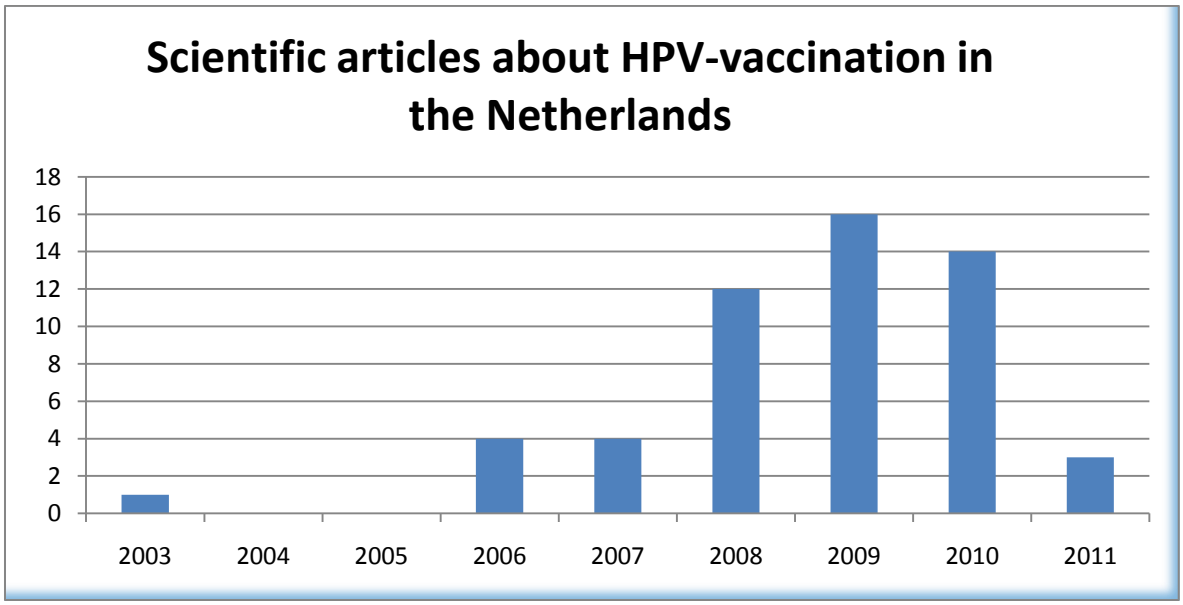

Figure 13: Number of scientific articles about HPV-vaccination in the Netherlands (See appendix A)

Because the overview does not give insight on the different subjects of the scientific research, a short summary is given on the topics which have been discussed in Dutch research.

- Cost-effectiveness analyses

In total ten articles have been published specifically about cost-effectiveness of the HPV-vaccination in the Netherlands (see appendix C). Outcomes differ a lot, depending on assumptions regarding vaccination coverage, discounting costs, efficacy and the type of model (static vs. dynamic). Most analyses indicate that the vaccine is cost-effective in the RVP, despite analyses with a negative outcome (de Kok, 2009; Postma, 2010).

- Policy research

This type of research is mainly focused on the introduction of the HPV-vaccination in the RVP and the necessity, possibilities and impact of the vaccine. The main research in this field is the Health Councils report advising to add HPV-vaccination to the RVP. Other policy research is performed by the RIVM before and after the introduction of the HPV-vaccination to guide the vaccination (de Melker et al, 2009). And scientists performed policy research to discuss the conclusions of research by the Health Council and the RIVM (de Kok et al, 2008) or to propose improvements in the system for cervical cancer prevention (van den Berg et al, 2010).

- Acceptance

Research on the acceptance of the HPV-vaccination focused on the following aspects:

  - Vaccination coverage
  - Demographic aspects
  - Determinants for HPV-vaccination acceptance

Some of this research already has been published before introduction of the HPV-vaccine, indicating high acceptance of the HPV-vaccine (Lenselink et al, 2008). After introduction, the vaccination coverage was a lot lower; therefore research has been performed on finding factors contributing to this low acceptance (Rondy et al, 2010; Paulussen, 2010; van der Berg, 2010; Korfage et al, 2008; de Bekker et al 2010; de Boer et al, 2011).

- Safety (Adverse-effects)

Only one article has been published specifically about the safety of the HPV-vaccine after introduction in the Netherlands, indicating an excellent safety profile after administration of 192.000 doses (van der Maas, 2009).

- HPV-vaccination compared to other technological developments against cervical cancer

Since several technologies influence the HPV-vaccination in the Netherlands, their influence on each other must be monitored and researched. The screening program for cervical cancer already existed over 30 years before HPV-vaccination became available and HPV-vaccination policy research is based on a combination of screening and HPV-vaccination. In the future HPV DNA tests, therapeutic HPV-vaccines and second generation vaccines are technologies which might be applied against cervical cancer, besides screening and vaccination. In 2011 a new advice from the Health Council is expected about the screening program, including HPV DNA tests (Interview de Kok, 2011; Kenter, 2011)

A topic that has been extensively discussed in the Netherlands, but is mainly researched internationally, is the effectiveness of the vaccination. Examples are the EPAR's and extensive clinical trials. But also after market approval, clinical trials are still being performed. The focus of these long running trials is on:

- Duration of protection
- Decline in CIN2+ lesions, decline in cervical cancer prevalence
- Effect of the vaccine on other cancer types
- Virus strains the vaccine protects against
- Type replacement
- Long term safety

New clinical results have become in the years after market approval. Recent findings about cross protection against more types of high risk HPV-infections and duration of protection are given in the

technological information chapter. These outcomes are important for the cost-effectiveness of HPV-vaccination. In the Netherlands research about HPV prevalence and the effect of vaccination is done as well, this was a demand by the Health Council to accompany the introduction of HPV-vaccination (Gezondheidsraad, 2008).

Therapeutic HPV-vaccination, which differs in scientific and societal aspects form preventive HPV-vaccination, also had an influence on the knowledge development of preventive HPV-vaccination in the Netherlands. A therapeutic HPV-vaccine could be effective in women which are diagnosed with cervical cancer by triggering a very strong immune response of the body against HPV infected cells. Two Dutch universities, Leiden and Groningen, have put efforts in developing a therapeutic vaccine (AD, 1994; LUMC, 2010; Riezebos-Brilman, 2008). Professors such as Cees Melief and Gemma Kenter had extensive knowledge about the role of HPV on cervical cancer and had contact with the Health Council for the preventive HPV-vaccines as well. The development of a therapeutic HPV-vaccine already started in the 1994 in the Netherlands (AD, 1994). Even now research is ongoing on a therapeutic vaccine in the Netherlands. Efficacy results with HPV-related vulva cancer are promising, but efficacy of the vaccine on cervical cancer is not yet known (LUMC, 2009). Thus no effective therapeutic HPV-vaccine is currently available. For pharmaceutical companies, the development of a therapeutic HPV-vaccine is very interesting and these companies might become involved in a later stage (Remorie, 2011). This could expand the range of treatments against cervical cancer.

A full overview of Dutch research per topic related to the HPV-vaccine can be found in appendix B.

F3: Knowledge diffusion through networks

The development of knowledge is not sufficient to make a technology into a societal success. To assure a new technology is used, understood and accepted, knowledge has to be transferred to all related actors. The knowledge diffusion of the HPV-vaccination is measured in several ways. Both diffusion events in the Netherlands as international events are important since the technological development of the HPV-vaccination took place on an international scale. The number of meetings between different actors has been counted to get an overview of knowledge diffusion events over time, this overview can be seen in figure 14. Also intermediaries and other means of knowledge diffusion are discussed to determine the performance of knowledge diffusion over time.

The following meetings have been distinguished as knowledge diffusion events which affect the HPV-vaccination system in the Netherlands: EUROGIN (European meeting on genital infection and neoplasia), ESGO congress (European Society of Gynecological Oncology), HPV-congresses, meetings between RIVM and other actors and other meetings of related actors (see appendix D for events list). A type of meetings which is not added to the overview are the Gynaecongres meetings. Still these meetings are worth mentioning. The Gynaecongres is a Dutch congress for Gynecologists about many different gynecological subjects and is held two times a year in the Netherlands, which would be depicted on the event overview very prominently, while preventive HPV-vaccination is only a minor topic during these meetings. Only one of these meetings is put in the events list, since HPV-vaccination was a major topic during this meeting.

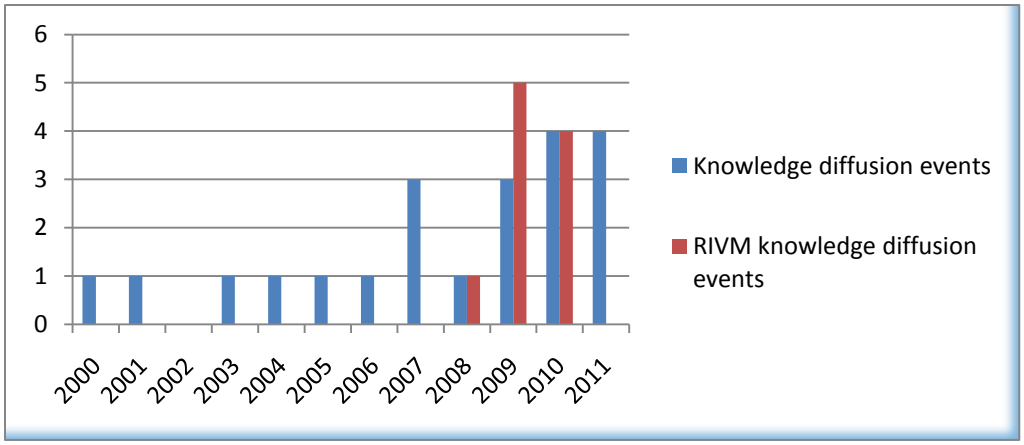

Figure 14: Knowledge diffusion events (see appendix D for type of events)

The events mainly took place in 2009 and 2010, after introduction of the HPV-vaccination in the RVP. Before 2009, only one event (in 2007) was about introduction of the vaccine in the Netherlands. The other events were all European wide events on the (scientific developments) in the field of cervical cancer and HPV-vaccination.

Besides these events, a major part of the knowledge diffusion has been performed through the RIVM, the Dutch institute for public health and environment. By having meetings, contact with the media and issuing newsletters actors were informed about the current state of affairs and knowledge about the HPV-vaccination. The newsletters are especially important for the GGD's because these letters gave information about ongoing vaccination developments. The RIVM also has been responsible for the communication to the end-users. Because of all these tasks the RIVM can be regarded as an organization which has an intermediating role between research, industry and end-user (Conyn, 2010).

Knowledge is also diffused through the hearings of the Health Council. In these hearings scientists, (governmental) agencies and companies had contact with members of the Health Council, so that the health council could have full insight in the HPV-vaccination. The following people have been consulted by the Health Council:

- dr. T. Aguado, World Health Organization, Genève
- dr. M. Arbyn, Scientific Institute of Public Health, Brussel
- dr. J Berkhof, Vrije Universiteit Medisch Centrum, Amsterdam
- dr. P. Claeys, International Center for Reproductive Health, Gent
- dr. V. Coupé, Vrije Universiteit Medisch Centrum, Amsterdam
- dr. M.A.E. Conyn-van Spaendonck, Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven
- dr. G. Garnett, Imperial College, Londen
- GSK, Rixensart: dr. P. Monteyne, dr. C.G. van Schagen, dr. H. Tamminga en dr. M. Wettendorff
- dr. K. Irwin, World Health Organization, Genève
- dr. D. Kennedy, Joint Committee on Vaccination and Immunisation, Londen
- I.M.C.M. de Kok MSc, Erasmus Universitair Medisch Centrum Rotterdam
- dr. N. Malila, Finnish Cancer Registry, Helsinki
- Nederlandse Vereniging Kritisch Prikken, Roosendaal: C. Buis, M. de Munck en H. Visser
- dr. S. Poulsen, National Board of Health, Kopenhagen
- Sanofi Pasteur MSD, Hoofddorp: dr. G. Demol, drs. C.A. Kievid en R. Tensen, arts
- Stichting Olijf, Amsterdam: J. van Leeuwen
- dr. C.A. Siegrist, Université de Genève, Genève
- dr. A. Tegnell, National Board of Health and Welfare, Stockholm
- dr. M. Zappa, CSPO Center for Study and Prevention of Cancer, Florence

(Gezondheidsraad, 2008).

Even though the producers of the HPV-vaccines have contributed a lot to the knowledge development regarding HPV-vaccination (e.g. clinical trials and funding of HPV-research in the Netherlands), little knowledge diffusion in the Netherlands took place by pharmaceutical companies. Especially knowledge diffusion to end-users is limited for a pharmaceutical company because of the Medicines Advertising Code, forbidding advertisements and the provision of information about prescription drugs (CGR, 2008). Activities to inform the public about the HPV-vaccines took place, but were regarded as controversial in several media reports (Zembla, 2008; Bouma, 2008).

On a more local level knowledge diffusion has taken place to end-users. Hospitals, doctors and GGD's have set up information evenings on their own initiative. Examples of such meetings are: http://www.sneekernieuwsblad.nl/profile/redactie/article125640.ece/sneek_infoavond_vaccinatie_baarmoederhalskanker, http://www.gezonderworden.nl/2008/09/voorlichtingsavond-vaccinatie-baarmoederhalskanker-in-azm/, http://www.gezondbrabant.nl/client/1/?websiteid=1&contentid=3078
Because there is no clear overview on these numerous meetings, they are not graphically depicted. However, their influence on local vaccination coverage might be high. In south-west Brabant, for example, vaccination coverage is perhaps higher because of meetings organized by a gynecologist. Besides meetings organized by doctors and GGD's, vaccination critics organized meetings as well. For example: http://www.martindemunck.nl/Nieuwsbrief%20april%202009.pdf and http://www.vaccinatieinformatie.nl/?p=133.

F4: Guidance of the search
Mapping the guidance of the industry and government is done by investigating goals and expectations regarding HPV-vaccination. Even though some goals overlap, governmental and industry goals are discussed separately. This is done because the guidance of governmental agencies and the pharmaceutical industry differs in purpose and time in the HPV-vaccination system.

Both pharmacy eutical companies which have developed an HPV-vaccine had the goal to get their vaccine compensated in the Netherlands and put efforts in reimbursement/governmental funding on several occasions (CVZ Gardasil 2007; CVZ Gardasil 2009; CVZ Cervarix 2009; Gezondheidsraad, 2008). To reach this goal, the pharmaceutical companies which produced the HPV-vaccines informed governmental agencies, healthcare professionals and end-users about the potential of the HPV-vaccines, to ensure that HPV-vaccination would be financed and adopted. Guidance of the search took also place by funding relevant research topics regarding HPV-vaccination in the Netherlands, such as cost-benefit analyses (see appendix B for funding information of scientific research).

Before the decision to add the HPV-vaccination to the RVP has been made, there already has been critique from vaccine producers on the guidance of the government on new vaccines in the Netherlands. According to Dutchbio, the branch organization of vaccine producers/researchers: *"The Dutch Ministry of Health lacks direction, forcing vaccine producers to perform research, which the Health Council regards as biased (Hanstede, 2007)".*
This statement was not specifically focused on the HPV-vaccine. But the problem of bias appears to apply in the introduction of the HPV-vaccination. A lot of negative media attention on the introduction of the HPV-vaccination was focused on the role of the pharmaceutical industry in the decision making process in general. This indicates that the guidance of the pharmaceutical industry by funding research had negative side-effect on the view of the public on the HPV-vaccination and the performance of the HPV-vaccination. Since this negative guidance effect had a major effect on the legitimacy of the HPV-vaccination, this factor is further discussed in the paragraph regarding creation of legitimacy.

Governmental guidance started two years before the HPV-vaccination was added to the RVP with the research of the Health Council advising if HPV-vaccination should be added to the RVP (Gezondheidsraad, 2008). This research has been performed by independent researchers based on a list of seven criteria a vaccine must meet (An English article about the seven criteria is published by Houweling et al, 2010). The advice which followed this research stated that the vaccine should be added to the RVP (Gezondheidsraad, 2008). The report also discussed how the HPV-vaccination should be guided in the future. An unconditional prerequisite to the introduction of the HPV-vaccine was the addition of a monitoring program (Gezondheidsraad, 2008). This research will give information about the efficacy of the HPV-vaccination in the long run.

The minister of Health, Ab Klink, followed this advice and expressed the desire to get a vaccination coverage for the twelve year old girls of 85% and a vaccination coverage of 70% for the catch-up campaign (VWS, 2008).

The guidance of the government in performing and monitoring the HPV-vaccination is performed by the CIb, a subpart of the RIVM, which is responsible for the vaccines in the RVP. Some goals, such as the vaccination coverage are not explicitly set up, even though estimates were made for practical reasons (Conyn, 2010). The main messages the RIVM made about the HPV-vaccination to the public were that the HPV-vaccination is a voluntary vaccination against a severe disease and that the HPV-vaccine is part of the vaccination program of the Dutch government. Other messages were that cervical cancer screening and safe sex are still important (Conyn, 2010). After the start of the HPV-vaccination, the RIVM made statements about the failure of the vaccination campaign. Roel Coutinho, head of the RIVM, stated that the vaccination campaign in 2009 did not work and a new approach would be developed in the future (Trouw, 2009). This shows that the guidance of the RIVM during the vaccination campaign did not work as desired.

Figure 15 gives an overview of all before mentioned events. Events are classified as positive or negative guidance. However, this differs from positive and negative effects of these guidance events. For example, all CVZ requests are regarded as positive guidance events (since they are goals set by the industry to make reimbursed HPV-vaccination possible), but all requests turned out negative. And even though the RIVM put more effort in the 2010 campaign, this had no major positive effect on the vaccination coverage (Giesbers a, b, 2011).

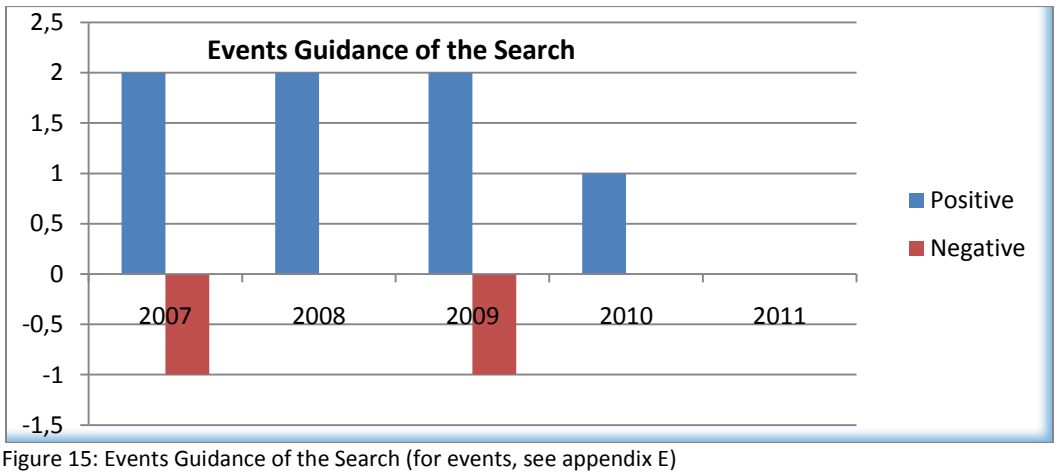

Figure 15: Events Guidance of the Search (for events, see appendix E)

Other parties have had an influence on the guidance of the HPV-vaccination in the Netherlands as well. Political statements, viewpoints of related health organizations, vaccination opponents and the media have affected the performance of the HPV-vaccination system, since many girls and parents informed themselves by other means than only the information from the RIVM (Paulussen, 2010). It is difficult to draw a clear line between guidance and creation of legitimacy, since expectations both

influence the guidance of the search, as the legitimacy of the HPV-vaccination. There is chosen to discuss these parties in the function 'creation if legitimacy' since this extensive (media) discussion is not so much based on guiding HPV-vaccination in the right direction, but more on discussing the necessity, benefits and disadvantages of the HPV-vaccination, which are aspects related to the legitimacy of the HPV-vaccination.

F5: Market formation
Different types of market formation can be distinguished for the HPV-vaccines in the Netherlands. Market formation took place by competition between HPV-vaccination and other cervical cancer prevention options, by competition between the two HPV-vaccine manufactures and market formation took place by the way the HPV-vaccination is offered to the end-user. The market-formation towards the end-user is regarded as the contact between the GGD's and twelve to sixteen year old girls.

Competition between HPV-vaccination and other technologies
A part of the market formation took place by competition between HPV-vaccination and other technologies. In order for a new technology to be successful, it has to compete with other (existing) technologies. In a market were technologies are interchangeable and users make choices on their own preferences, the emergence of a niche market for HPV-vaccination might have occurred. Then multiple technologies 'compete' side by side and depending on certain advantages each product would have its own share of the market. But because every woman is potentially at risk for cervical cancer and policy in the Netherlands is developed for equal treatment of women nationwide, a niche market did not develop.

Still the HPV-vaccination had to 'compete' with the existing screening program. Even though these technologies can be used complementary, some researchers state that vaccination is undesirable because of the success of the screening program and the uncertainties surrounding the HPV-vaccination (de Kok et al 2008; Boomsma, 2008). A major disadvantage of HPV-vaccination compared to screening is the cost per QALY, which are considerably higher for HPV-vaccination as for the screening program with the current free market price of the vaccines (see cost-effectiveness analysis in Gezondheidsraad, 2008). Another attention point is the possibility that HPV-vaccination will reduce the participation in the screening program, because women might think they are fully protected (Gezondheidsraad, 2008; Boomsma et al, 2008). But a positive effect will be that fewer women will have a positive screening test result, thus decreasing additional health costs and stress for women with a positive test result (Gezondheidsraad, 2008, Van den Berg, 2010).

The choice of the Dutch government, based on the advice of the Health Council, was to combine these two technologies, so both cervical cancer screening and HPV-vaccination are currently applied in the Netherlands (Gezondheidsraad, 2008). It is possible that this might change in the future and that the screening program will be more limited (if vaccination is successful). The boxed information on page 54 gives a more extensive overview of other preventive measures to decline the amount of cervical cancer (deaths), besides preventive HPV-vaccination.

In the future the screening program and/or HPV-vaccination might be affected by the developments of an HPV-DNA test. In the boxed text this technology is explained. According to several interviews the Health Council will soon decide upon adding an HPV-DDNA test to the screening program and most likely HPV-DNA tests will be added to the screening program (Kenter, 2011; Interview de Kok, 2011).

Screening program cervical cancer

The HPV-vaccination is not the first preventive measure against cervical cancer. Since 1976 there is an organized screening program for cervical cancer in the Netherlands. Participation is free for all women between 30 and 60 years old. Every 5 year these women receive an invitation to take a PAP smear test. This test is performed at the general practitioner and is send to a laboratory where irregular cell growth can be detected. Since the program only can detect and not prevent precancer lesions it is regarded as secundairy prevention. The government pays for this screening program and the RIVM is responsible for the national coordination. Without this screening program 400 women would die because of cervical cancer each year in the Netherlands. With the screening program around 200 women die annually because of cervical cancer (RIVM, bevolkingsonderzoek, 2010).

Of all women invited in 2007, 66% took the PAP smear test. Looking at the total five year coverage, this percentage is even higher (Van den Berg, 2010). Research indicates that cervical cancer is often related with non participation of cervical cancer screening; approximately 60% of cervical cancer cases are in the group of women which is not screened. This shows that the screening program is effective, and health gain can be increased by reaching the target population, which does not participate with the screening program (Van den Berg, 2010).

The national screening program can become one of the best sources of information on the effectiveness of the HPV-vaccination on the long run, because it registers the detected cases of cervical cancer, which is an important measurement endpoint of the vaccine's effectiveness (Van den Berg, 2010).

Because of this screening program, there has been an extensive discussion about the necessity of the HPV-vaccination and the possible effect of the HPV-vaccination on the screening program.

HPV-DNA test

As well as the Screening program, the HPV-DNA test is a form of secondary prevention against cervical cancer. Because it is not yet implemented on large scale in the Netherlands, it is uncertain how it will affect HPV-vaccination and what the effects of the HPV-vaccination are on the HPV-DNA test.

The HPV-DNA test is a new tool in the fight against cervical cancer which gives women the possibility to test for high risk HPV-infections. Women can perform this smear test at home. The test results indicate if a woman is infected with a high risk type of HPV. This can give information if further research or treatment is necessary to prevent or treat cervical cancer (Van den Berg, 2010).

By offering a test which can be performed at home a big barrier to join cervical cancer screening is reduced. Women do not have to go to a general practitioner anymore to undergo an unpleasant procedure. Research results show a home test is an effective method to increase screening participation (Van den Berg, 2010). Also the DNA test has proven to be an as good as or even better as conventional research to detect the early stages of cervical cancer. A future approach can be to combine HPV DNA screening with smear tests, e.g. by first performing an HPV-DNA test and if there is a positive test results expand the research with a smear test (Van den Berg, 2010).

The Health Council also gave advice about the HPV home test in august 2010. They gave a positive advice to the Minister of Health to perform a study involving 79 000 women which did not participate the screening program for cervical cancer. This includes two randomized trials about the HPV-DNA home test (Gezondheidsraad HPV thuistest, 2010).

Home tests are commercially offered to women in the Netherlands, for example on the website www.hpvtest.nl. Another initiative regarding home tests is Humacare, an independent foundation which offers woman information and advice about the human papillomavirus and provides home tests to women who consider HPV-vaccination (Humacare, 2010).

Competition between HPV-vaccines

Because two different vaccines are available, it is possible to comparing the two vaccines and evaluate if competition is taking place. As stated by Doctor Jacob Bornstein: *"Competition between Gardasil and Cervarix on the HPV vaccine market is based on proof of efficacy and cost–effectiveness* (Bornstein, 2010)."

Large scale study results of both vaccines show that both vaccines are safe en effective (EPAR Gardasil, 2006; EPAR Cervarix 2007). And there are differences between the vaccines. Gardasil protects against HPV 6 and 11, the major cause of genital warts. Also the vaccine has shown to be effective in preventing vulvar and vaginal precancer lesions. Cervarix on the other hand, has a higher capability of preventing HPV 45 and 52 (Bronstein, 2010), which also cause cervical cancer. Upon deciding between the two vaccines, health authorities should take the effectiveness against CIN 2+ lesions, genital warts, vaccine safety and costs into account. The age of individuals to be vaccinated is also important because the vaccine indication age group differs (Bornstein, 2010). The discussion which vaccine is better, and which endpoints should be taken into account to determine this, is still ongoing (See Chusteckam, 2009; Harper, 2009 and Haupt, 2009). In the future, even more HPV-vaccines are expected which offer broader protection at lower costs (Peres, 2011).

Competition between the vaccines took place in the Netherlands. This competition started before Cervarix was added to the RVP and was based on the date of availability, price, effectiveness and additional benefits of the vaccines. With advertisements to doctors and information campaigns to the general public the pharmaceutical companies marketed their product. The competition between the two vaccines caused controversy about possible illegal marketing activities which have been researched by the Dutch Health Inspectorate (IGZ Cervarix, 2009; IGZ Gardasil, 2009). The outcomes of these studies indicated that minor violations of the Medicines Advertising Code occurred, and suggested that both companies should make adjustments to align their marketing activities with the Medicines Advertising Code.

Competition for which vaccine would be added to the RVP was based on a tender, performed by the NVI. For the tender firms had to give extensive information about their financial standing, the registration text of the product, Good Manufacturing Practice and previous experience with vaccine delivery. The tender itself was based on the financial offer, the delivery schedule, insurance information and more criteria. The decision which firm would win the tender was based on a 100 points criterion of which price on ready-for-use-base determined 87,5 points (NVI Tender, 2008).

The outcome of this tender was that Cervarix would be the HPV-vaccine in the RVP (GSK Press release, 2008). This decision has led to lawsuit of SP MSD, stating that the additional benefit of genital wart protection was not taken into account in the tender criteria. But according to the judge, the government is free to develop their own inclusion criteria (Rijksoverheid, 2008). The price per dose for which Cervarix is provided is secret, this was a requirement of the pharmaceutical companies since multiple tenders were ongoing in different countries (Conyn, 2010). In 2012 a new tender will be held, where the vaccine price might become public.

Market formation to end-users

For the end-user, the formation of the market was mainly apparent in the way they were informed about the vaccination and by whom and where the vaccination was administered. This aspect of the market is the responsibility of the RIVM and the GGD. Specific policy was developed for the HPV-vaccination campaign. There has been chosen to perform the vaccination during mass vaccination sections by the youth healthcare department of the GGD's (de Melker et al, 2009). The campaign would be performed by the RIVM, while the GGD's contact the girls who are offered the vaccine. Aspects of the market formation which can influence the performance of the HPV-vaccination are the distance to vaccination location and the cognitive distance. Before the HPV-vaccination campaign started in 2009, several options for vaccine administration were discussed (Conyn-van Spaendonck,

2008). Both general practitioners and GGD's were considered an option. General practitioners would be a more individual way of providing the HPV-vaccination, but more expensive. And there was a good experience with the GGD for vaccinating 9-year olds. For both the catch up campaign and the RVP group there has been chosen to perform the HPV-vaccination during mass vaccination sessions by the GGD (Conyn-van Spaendonck, 2008).

If girls have doubts about the vaccination, a GGD might be regarded as impersonal for certain questions. In an opinion article in the newspaper Trouw, Jozien Bensing, professor in clinical psychology and health psychology, states that the HPV-vaccination would be more successful if it would performed by general practitioners (Bensing, 2009). Also Gemma Kenter, professor in medical oncology stated that she would like to see the HPV-vaccination covered by the healthcare insurance so that girls still can get the vaccine from their general practitioner without paying the costs for themselves (Kenter Vu, 2011).

In the future physical distance to get a vaccination centre might be of negative influence on the HPV-vaccination performance. Statements made by several GGD's during a meeting with the RIVM in November 2010 indicate that due to costs, less vaccination locations will be used in the future (RIVM Meeting, 2010). This increases the physical distance to the vaccination centre for many girls.

F6: Resource mobilization

Resource mobilization can be specified as the mobilization of financial, material and human capital to make HPV-vaccination possible. The aspect of material commodities is not an issue for HPV-vaccination, since the production of the HPV-vaccine requires materials which are sufficiently available. The aspect of human capital is neither a problem: there are sufficient people capable of distributing and administering the HPV-vaccine in the Netherlands.

Lack of capital is an issue however. In the first year an HPV-vaccine became available but was not added to the RVP, only four thousand five hundred girls chose to take the HPV-vaccine themselves (SFK, 2007). For financial resource mobilization governmental or insurance funding of the HPV-vaccine seems crucial. On several moments efforts have been made to get the HPV-vaccine reimbursed or compensated by the government or healthcare insurance. Figure 16 shows the main funding events for HPV-vaccination.

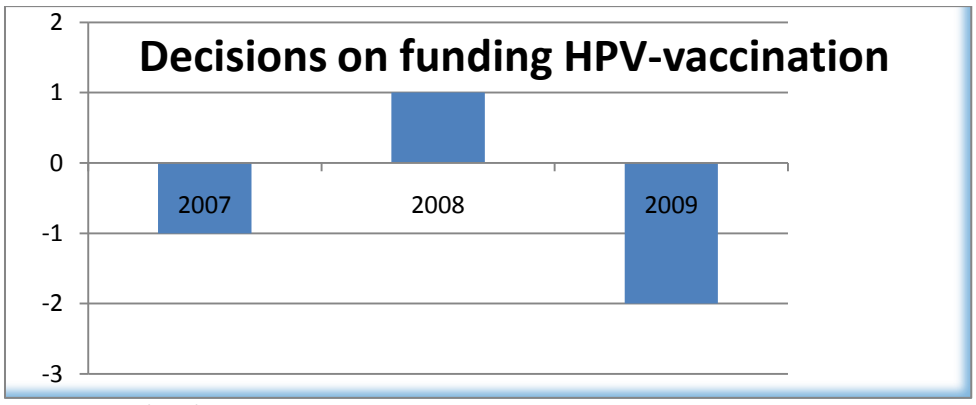

Figure 16: Funding decisions on HPV-vaccination

An important funding moment which was positive was the decision of the Minster of Health to add the HPV-vaccination to the RVP, and thus funding one of the two available vaccines. This decision was made on 8 July 2008 (VWS, 2008). Other funding moments were the –negative- advices of the CVZ on not funding the HPV-vaccination in the Netherlands (CVZ Gardasil, 2007; CVZ Cervarix, 2009; CVZ Gardasil, 2009).

Since one of the vaccines is reimbursed through the RVP, the vaccine Cervarix is available for the intended vaccination population without personal costs. But for Sanofi Pasteur MSD resource mobilization is a determining factor in the inability to make their vaccine successful, because their vaccine is not reimbursed. Still there are continues sales of Gardasil, provided through general practitioners (van den Oetelaar, 2011).

A big limitation is the secret price for mapping the financial earnings. This makes it impossible to determine the exact costs. However, an indication can be made. The maximum price promised in the health council report is 90 euro's per dose (Gezondheidsraad, 2008). And internationally there are several countries where the vaccine price is available. In Sweden the price is 22 euro's per dose (Interview de Kok, 2011). In 2010, around 52% of the girls took all three vaccines (and some girls took 1 or 2 vaccines) on a total of 95.000 girls (Giesbers b, 2011). In total around 50.000 * 3 = 150.0000 shots have been given in 2010 (a normal RVP cohort). This makes the earning to GSK for the vaccination in 2010 approximately (150.000 * 90 =) 13,5 million euro at most and (150.000 * 22 =) 3,3 million euro if the price per dose is the same as in Sweden. The total HPV-vaccination costs for the Dutch government are higher because of organizational and administration costs.

F7: Creation of legitimacy/counteract resistance to change
The last function which will be discussed is very extensive, since there has been a fierce discussion about several aspects of the HPV-vaccination in both scientific spheres as in the public media in the Netherlands. This discussion has an impact on the acceptance of the HPV-vaccination and thus on the performance of the HPV-vaccination. In the media both opponents as proponents held a lobby for/against the vaccine. In order to determine the dynamics and influence of this discussion on the performance of the HPV-vaccination the lobby events by opponents/proponents are analyzed as well as the media coverage. Lobby events are measured by mapping the statements made by proponents and opponents of HPV-vaccination.

Statements in favor/opposing HPV-vaccination
Several different organizations and people have commented on the HPV-vaccination and developed an (official) opinion about the vaccine and the vaccination campaign. In figure 17 these statements have been collected and divided into positive and negative events. The following type of events can be distinguished: opinion of health organizations, parliamentary questions, publications of scientist with widespread effects and statements and books published by vaccination opponents (see appendix F for an event overview). Statements have been collected by a LexisNexis search, interviews and by searching the websites of related health organizations and vaccination critics.

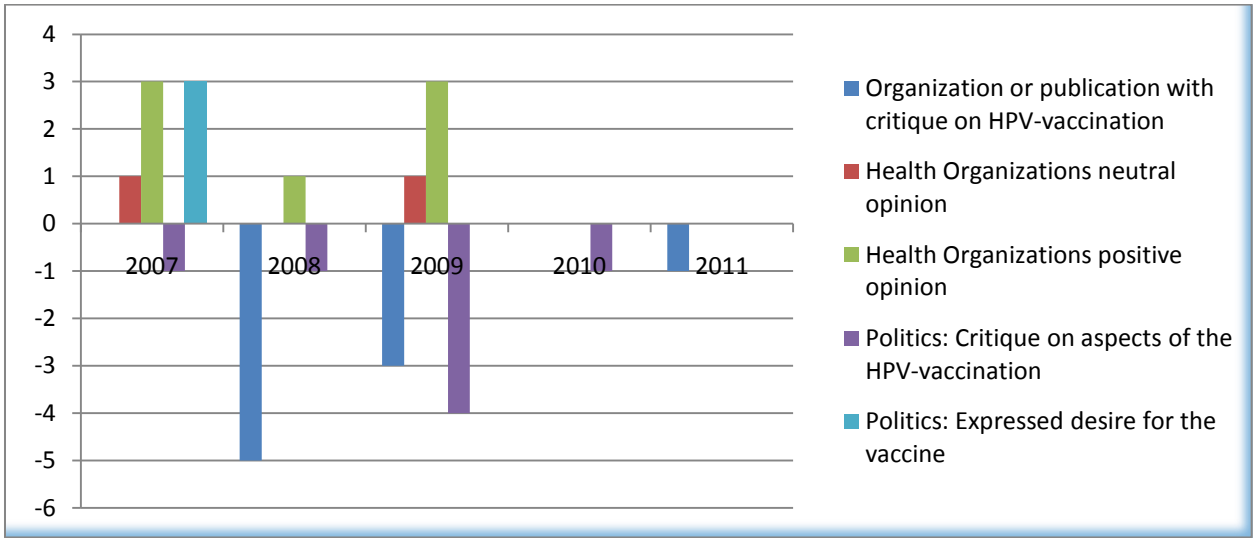

Figure 17: Overview of negative and positive events influencing the legitimacy of the HPV-vaccination.

Figure 17 shows that in 2007 mainly positive statements about the vaccine have been expressed, which changed drastically in 2008 and 2009. Even though several positive statements about the vaccine have been made public, mainly critical parliamentary questions and statements have been expressed. In 2010 and 2011 hardly any new statements about the vaccine have been made, but the statements that have been made, were negative.

It is important to stress that these events are snapshots and might not represent the current opinion of the people/organization. Another important side note is the difference between statements against adding HPV-vaccination to the RVP and statements discouraging the use of the vaccine. Most scientific critique did not state that girls should not take the vaccine, but stated that the vaccine should not have been implemented in the RVP yet. This was the intention of the article in the NtvG of de Kok et al. in 2008 (Interview de Kok, 2011). Some vaccination opponents however, explicitly stated that girls should not take the vaccine. In the following paragraphs the different statements are discussed.

A scientific discussion on the justification of adding the HPV-vaccination to the RVP took place after the Health Council's report (Gezondheidsraad, 2008). Some researchers disagreed with this decision to add the vaccine to the RVP and wrote a critical article about this decision, stating that five out of seven criteria for the addition of a new vaccine were not met (de Kok et al, 2008). This article was first published in the Dutch Journal of Medicine (NtvG), but also has been displayed on various websites of HPV-vaccination critics (www.nvkp.nl, www.verontrustemoeders.nl) and mentioned numerous times in media reports. This article is widely regarded as very influential, in every interview the value and impact of this article has been discussed (Kenter 2011; Schellekens, 2011; Interview de Kok, 2011; van den Oetelaar, 2011; Remorie, 2011). The article has caused much confusion (Conyn, 2011).
A part of the researchers behind the article in the NtvG wrote a new cost benefit analysis, stating that even under favorable assumptions the HPV-vaccination would not be cost-effective (de Kok et al, 2009). However, if the Dutch guidelines for discounting costs would be followed, the outcome of the research would be that the vaccination is cost effective (Postma, 2010). A problem with cost effectiveness analyses is that it is difficult to state which parameters and QALY's should be the guiding principle. Another research which is extensively discussed in the media is in the article by Boomsma et al. in 2008 (see the boxed text on page 59) which led to newspaper headlines such as "Vaccinating young girls leads to more deaths" (AD, 2008).

Organizations which can not be classified as health organizations, but still made statements about the vaccine are the DES Centrum and Lindeboom Institute. The DES Centrum (DES was a medicine with terrible negative side effects for children of mothers taking DES) stated that they are not against HPV-vaccination, but implementing vaccination nationwide should be based on solid scientific research, while there are many points of critique (DES Centrum, 2008). A more recent negative statement is from the Lindeboom Instituut, a study centre based on a Christian philosophy together with the NVP (Dutch Patient Society), a Christian based patient society. The directors of these institutes state that the HPV-vaccination should be stopped and never should have been provided through the RVP in the first place (Groenewoud et al, 2011).

The following paragraphs discuss statements made by related health organizations, vaccination opponents/critics and political discussion about the vaccine.

Opinions regarding HPV-vaccination of related health organizations
Because the Human Papillomavirus is an infection which is mainly spread through sexual contact, can develop into cervical cancer and the vaccine is given to twelve year old girls, many different health organizations are indirectly involved in the HPV-vaccination, because of its influence on their goals and expertise. All of these organizations are positive or neutral about using the vaccine after it is added to the RVP, even though some have several remarks. The date the opinion is published is of influence on the content of the remarks. Some opinions are given before the vaccine has been added to the RVP. This means those opinions are not up to date. Still these opinions are relevant since they give an indication about the attitude of health organizations regarding HPV-vaccination.

Dutch College of General Practitioners, Nederlands Huisartsen Genootschap, NHG
In 2007 the NHG declared that general practitioners should have a cautious approach to girls requesting vaccinations pending the advice of the Health Council (Huisarts Wet, 2007).
When the Health Council advised to add the HPV-vaccine to the RVP, their opinion was expanded. The NHG endorses the decision of the Health Council, so they support HPV-vaccination for twelve year old girls, as well as the catch-up campaign for girls age thirteen to sixteen (NHG, 2009).

However, there is also critique from general practitioners. Articles by Bakker (2008) and Boomsma et al. (2008) were critical about the vaccination, focusing on high costs and decline of the effectiveness of screening. The article of Boomsma et al. created a lot of commotion, because of an error factor hundred in the calculations. Remarks about the research parameters and proposed effects of the HPV-vaccine have been discussed in letters send to the magazine where the article was published. This has lead to an epilogue of the authors, where they acknowledge the mistakes made in the article, stipulate that they do trust the integrity and independence of the members of the health council and regret that the article has clouded the discussion about the introduction of the HPV-vaccination (Boomsma et al, 2008).

Dutch society for Pediatrics, Nederlandse vereniging voor Kindergeneeskunde, NVK
The Dutch society for pediatrics developed an advice in 2007 indicating that individual vaccination requests could be granted if people accept the financial aspect (being that people have to pay the full vaccine price themselves). The vaccination is regarded as being useful and safe (NVK, 2007). After the vaccine has been added to the RVP, no new opinion has been created.

Dutch Society of Obstetrics and Gynecology
Nederlandse Vereniging voor Obstetrie en Gynaecologie, NVOG
The NVOG supports the advice of the Health Council to add the HPV-vaccination to the RVP. The NVOG does not agree with negative media reports. And the NVOG stresses that the assumption that HPV-vaccination will decrease participation of Pap smear test is not scientifically supported (NVOG, 2007).

Olijf Foundation, Stichting Olijf
The Olijf Foundation is a peer group of woman with cervical cancer. Their opinion about the HPV-vaccination is that the aim has to be to add the vaccine to the RVP, if the Health Council first researches all possible aspects. The Olijf Foundation also has sent a letter to the Minister of HWS, expressing this desire. Besides the creation of societal support, good information and involving patient organizations with the formation of the Health Council advice, the Olijf Foundation stipulates that cervical cancer screening still has to continue (Vaste Prik, 2007).

SOA-Aids Netherlands, SOA-Aids Nederland
SOA-Aids Netherlands states that protection with a safe and effective vaccine is an important strategy in controlling an STD. Experience with other vaccination programs show that implementation deserves attention to realize sufficient uptake. The current vaccine is promising, and will have a big impact on morbidity and mortality of cervical cancer in the Netherlands. Thus SOA-Aids Netherlands agrees with the advice of the Health Council. But several questions still have to be answered now the HPV-vaccination is introduced (SOA-Aids Nederland, 2008).

Ruby & Rose, NIGYO: Nationaal initiatief gynaecologische oncologie.
NIGYO is a foundation which put efforts in creating funds to support research concerning gynecological cancer. Leon Massuger, founder of NIGYO and professor in gynecological oncology is a strong advocate for HPV-vaccination. He is shocked by all the negative commotion surrounding the vaccine. He states that the campaigns which advice not to take the vaccine are based on rumors (VOX, 2009). A journalist of the newspaper Trouw had comments on the foundation. NIGYO has received a gift of 48.000 Euro from GSK in the past, which NIGYO used to sponsor a documentary about cervical cancer (Bouma, 2008).

Dutch Cancer Society, KWF Kankerbestrijding
The Dutch cancer society regards the HPV-vaccination as a contribution to the fight against cancer. Because there is uncertainty about the duration of protection, the cancer society expects that the government informs the public about ongoing developments (KWF, 2010).

Dutch Cancer Institute
Nederlands Kanker Instituut – Antoni van Leeuwenhoek Ziekenhuis, NKI-AVL
The Dutch Cancer institute states that there are many reports in the media about the HPV-vaccine. Also employees of the Dutch Cancer Institute appear in media reports (e.g. Radar, 2009). This has given a lack of clarity about the official opinion of NKI-AVL. The NKI-AVL states that they do not discourage the use of the vaccine (NKI, 2009).

Vaccination opponents/critics
In the Netherlands, several vaccination action groups have given their opinion about the HPV-vaccine. These action groups mainly operate via the internet and do not have any connection to official health organizations, even though they use scientific research as an information source.

The main actor in the lobby against vaccination is the NVKP, the Dutch society for critical vaccination. The NVKP is very critical about vaccinations in general, but have put extra focus on the HPV-vaccination. The opinion about the HPV-vaccination of the NVKP is that they regret the decision of the minister of Health to implement the HPV-vaccine in the RVP (NVKP, 2010). The NVKP calls the vaccination against cervical cancer for twelve year old girls a health experiment. This statement already has been made in 2008, in the following year their file about the HPV-vaccination has been altered and expanded (the statements expressed here are from their HPV-dossier from 2010).
The NVKP claims the scientific debate about the HPV-vaccination is still open. The relation between the HPV-virus and the development of cervical cancer has not been proven convincingly. The NVKP states that there are too many uncertainties making it irresponsible to expose young girls to the risks of vaccination. They claim this opinion is shared by several leading scientists (NVKP, 2010).
Instead of vaccination on large scale, good information should be given about the risk factors increasing the chance of cervical cancer. Consumers have the right to balanced information. This includes objective information about cervical cancer and on the usefulness, risk, effectiveness and side effects of the vaccination (NVKP, 2010).

In 2009 there was a dispute between professor Coutinho (RIVM) and the NVKP. In a letter addressed to the NVKP he stated that the information the NVKP is spreading is wrong and is not based on scientific knowledge. The NVKP responded by stipulating that only few examples of critique have been mentioned and that the fables are based on the work of other researchers. The NVKP points out that the major part of the information on their website is not criticized by Coutinho. Furthermore the NVKP does not agree with the argument of Coutinho that their information harms the health of women. The dispute is expanded by the discussion of a list of fables and facts about the HPV-vaccination the RIVM has published. The NVKP has given a reaction about the statements on this list, stating that the NVKP does not support all the fables in the list such as the claim that the vaccine causes cancer. But still the NVKP disagrees with the RIVM about the HPV-vaccination (NVKP, 2009).

Another fierce opponent is Désirée Röver, medical research journalist. Articles by her hand are on several anti-vaccination websites. She claims that Nobel Prize winner Bertrand Russell has described in detail how vaccines induce a partial lobotomy and create a zombie population (Röver, 2007). She also has a strong opinion about the HPV-vaccine Gardasil. She does not think this vaccine prevents cervical cancer, but thinks it is probably a disguised sterilization agenda (Röver, 2007). When the HPV-vaccine was added to the RVP she advised girls not to take any vaccine and to stay very far away from the HPV-vaccines. Furthermore she states that the HPV-vaccines are based on genetically modified virus parts, which can create a genetic modified host, being able to switch genes causing infertility, auto immunity and cancer (Röver, 2009).

A well attended website which frequently published articles on the HPV-vaccination is www.verontrustemoeders.nl. The websites contains many different health claims, with a lot of focus on vaccines and the HPV-vaccine in particular. Anneke Bleeker is the main authors on this website, and started the site after she read about the HPV-vaccination in a book about alternative cancer therapies (Trentelman, 2008). Based on this book and her own research and experiences, she wrote her own book in 2009 about vaccinations (Bleeker, 2009). In 2010 and 2011 she was also active in the providing articles and news about the HPV-vaccination (see: www.verontrustemoeders.nl/hpv.html).

An extensive research of a vaccination opponent is the book *'The hidden danger of vaccinations – especially for young children'* by Kuiper-Van den Bos (Kuiper, 2009). She claims that many children are damaged or deceased because of vaccines. She mentions that the HPV-vaccines will be given to younger children in the future and will be combined with Hepatitis B vaccine. The aluminum in the vaccines will lead to a depletion of calcium, phosphorus and vitamin D (Kuiper, 2009).

There are also various other websites and people which have warned girls and parents about the vaccine. Some websites contain claims which are better or worse founded as some of the websites and people discussed above, but the number of websites and claims is too extensive to discuss them all. The before mentioned are of main importance and give an overview of the opinion of vaccination critics on HPV-vaccination.

Politics

The role of politics is defined different from the role of related governmental agencies and the role of the minister as decision maker. With politics the remarks, parliamentary questions, discussion and lobby in the Dutch parliament are meant. These political actions are not directly of influence on the way HPV-vaccination is performed in the Netherlands, but do influence the image and future decision process of the HPV-vaccination and thus are part of the creation of legitimacy.

When the former Minister of Health, Ab Klink, decided to add an HPV-vaccine to the RVP, the topic has been discussed in the parliament (Tweede Kamer, 2009).This discussion in the parliament about the implementation of the HPV-vaccination in the RVP is very diverse and extensive. Many members of parliament have critique on the way the vaccine is introduced and want to discuss these matters with the parliament and the Minster of Health (from now on referred to as minister).

Ms. Kant (SP) has critique on the independence of the advice of the Health Council, making it difficult to assess the decision of the Minister. She has full trust in the Health Council, but she does not want the appearance that the Health Council is not independent. She wants that the Minister sets up another commission which will develop a new advice about the implementation of the vaccine. Ms. Schermers (CDA) points out that the CDA always wanted to await the advice of the Health Council before making a decision, even though the Minister has been pressured by the parliament to make preparations to implement the vaccine before the advice was finished. The CDA shares the opinion of the Minister that the Health Council has made it clear enough that the advice has been developed according to strict procedures.

This statement leads to a discussion about the independence of the health council. The next speaker, Mr. Zijlstra (VVD), still thinks that it is a good thing, that the vaccination has been added to the RVP. However, there is a lot of negative publicity, about the lobby, but also about the safety and efficacy of the vaccine. He wants to know if this negative publicity is well founded. Ms. Wiegman-van Meppelen Scheppink (ChristenUnie) states that the ChristenUnie likes to stay reserved concerning these matters, the decision to implement a vaccine should not be based on political preferences. However, she would like to stand still on the utility and necessity of the vaccination during the parliamentary discussion.

Also Ms. Sap (Groenlink) has questions about the usefulness and functioning of the vaccine, the role of the Health Council and the role and lobby of the pharmaceutical industry. Even though Groenlinks initially was one of the initiators in introducing the vaccine, they now regret this and would like to turn back the decision to request implementation of the vaccine. Ms. Agema (PVV) wonders if research has been performed why some women cannot surmount the HPV-infection, instead of providing an expensive vaccine. It seems that the Minister has fallen victim of an effective lobby of drug companies. Also the PVV requests that the Minister will wait with the vaccination campaign and rethinks implementing this vaccine in the RVP. Ms. Arib (PvdA) declares that the PvdA is in favor of adding the HPV-vaccination to the RVP and agrees with the advice of the Health Council to make vaccination available for every girl.

When all members with remarks have given their opinion a discussion takes place, which is mainly focused on the independence of the Health Council. After this discussion the Minster of Health, Ab Klink, responds to all the commotion. He explains that the safety and efficacy of the vaccine is extensively tested on European level. The Health Council has calculated that vaccination will save 125 lives, which is an important reason to add HPV-vaccination to the RVP. When the HPV-vaccination is added to the RVP, it will be closely monitored, including side effects. The minister also explains the connection of the Health Council with the pharmaceutical industry. He mentions that the research is performed by request of the industry, but in a scientific setting, with so called ‘unrestricted grants’. The research should be performed in a way that outcomes, research questions and means of publication are not influenced by the industry.

After the minister has given his contribution, the discussion about the role of the industry in the decision to add the vaccine to the RVP continues and is expand to the role of the industry in decisions made by the health council in general (Tweede kamer, 2009).

The full discussion is even more extensive, but this summary shows that the introduction of the HPV-vaccination in the RVP is extensively discussed in parliament. Major parts of the discussion are not focused on the HPV-vaccination, but are about the independence of the Health Council and the lobby of pharmaceutical companies. It is questionable how these discussions, which are broader than the introduction of the HPV-vaccination, have influenced the debate.

Besides the parliamentary discussion, several parliamentary questions have been asked regarding the HPV-vaccination over time (Kamerstukken, 2007 -2009). Ten of these parliamentary questions have been answered by the Minister of Health. The subjects of the questions vary and one Member of Parliament often asks questions about multiple subjects at once. Several questions are about the implementation of the vaccine in the RVP (Kamerstukken 20-03-2007, 05-06-2007, 04-12-2007). Some questions are about uncertainties concerning efficacy and safety of the vaccine and practical problems with its implementation (Kamerstukken 15-08-2008, 02-06-2009, 12-10-2009).The main subject of other questions is about the advertisement campaign the pharmaceutical industry and governmental agencies have performed (Kamerstukken 14-05-2007, 18-03-2009, 15-06-2009, 06-05-2010). This political discussion is still open and it is unclear how this discussion has affected the HPV-vaccination in the Netherlands.

Media analysis

Besides the before mentioned events, there has been a lot of discussion in the media about several aspects of the HPV-vaccination, e.g. on the role of the pharmaceutical industry, the (cost-) effectiveness of the vaccination, the research by the RIVM, girls who could win iPods if they took all three shots, GGD doctors which refused giving the vaccination and so on. The before mentioned statements from health organizations, researchers, vaccination opponents and politicians influenced the media reports as well. To map the HPV-vaccination discussion in the media an analysis of the media coverage is performed. But first the general role of the media and means of media coverage are discussed.

Media is a broad definition of all means which transfer information. This includes radio, TV, internet and written media (Van Dale, 2010). In the Netherlands written media, radio and television are legally protected against government control on content. Programs and newspapers are not judged on their content on beforehand, so censorship is forbidden. The responsibility of the content is in the hands of the broadcasters or publishers (CvdM, 2010).

In order to explain the importance of the media attention a short comparison is made of the coverage on the introduction of the HPV-vaccination to previous vaccines. During previous vaccine introductions no extensive discussion between opponents and proponents took place. The Meningococcal C vaccination in 2002 for example was very successful (de Melker, 2003). This vaccine was quickly adopted and led to an immediate decrease of Meningococcal C related disease (de Melker, 2003). A big difference is the amount of media attention between meningococcal C vaccination and the HPV-vaccination. There are 157 articles in national newspapers about 'meningokokken' and 'vaccin', while there are 495 articles about 'baarmoederhalskanker' and 'vaccin' (LexisNexis search in 2011). Even though this does not give insight in the direction of the discussion, it gives an indication of the amount of media attention about the HPV-vaccination.

Besides TV (Zembla, 2008; Radar, 2009, Nova, Netwerk, several news programs), radio (news, discussion programs), newspapers & magazines (practically all newspapers had extensive coverage on the vaccination) a lot of HPV-vaccination related information can be found on the internet. On many websites readers could give comments on the articles and on HPV-vaccination in general. For this research no extensive analysis of comments on the internet has been performed. The following links can be used as examples of the fierce discussion which took place on the internet:

http://www.scholieren.com/weblog/chat-stel-al-je-vragen-over-het-hpv-vaccin/
A chat between Marina Conyn and (mainly) teenagers about the vaccine
http://www.spitsnieuws.nl/archives/binnenland/2011/03/elke_vrouw_hpvvaccin.html
A more recent article, with comments by readers
http://cryptocheilus.wordpress.com/2009/02/10/hpv-prik-en-bescherm/
A weblog with a scientific discussion about the vaccines
http://www.argusoog.org/?s=HPV+vaccinatie&x=0&y=0,
http://www.wanttoknow.nl/?s=HPV+vaccinatie
Websites with many posts about the vaccine, including many comments by people with their own articles and websites with information about the HPV-vaccine
http://www.youtube.com/watch?v=atk3L3u8LxE
A Youtube movie where the RIVM is depicted as Nazi's
http://www.youtube.com/watch?v=EiLGrL7vhPE
Another Youtube movie with negative stories about the vaccine

Acceptation of the HPV-vaccination is strongly influenced by the media reports and social communication on the internet. Because of media reports about incidents and deaths after HPV-vaccination several countries had a major discussion about the safety of the HPV-vaccine. These media activities can influence the vaccination campaigns negatively, decreasing acceptance and vaccination coverage. There is also the possibility of mass hysteria effects, occurring during vaccination campaigns (Van den Berg, 2010). So even though 'the media' does not have an formal role in HPV-vaccination innovation system, the scope and viewpoint on the HPV-vaccination in media reports has a major influence on the performance of the HPV-vaccination in the Netherlands

A media analysis performed by Paul Sikkema showed that in 2009 the media coverage was mainly negative and few reports were positive. In 2010 around two thirds of the media coverage was neutral while still few media reports were positive about HPV-vaccination (RIVM Meeting, 2010). For this research a new newspaper analysis is performed. The analysis in figure 18 maps the cumulative media coverage of the HPV-vaccination in the Dutch national newspapers Trouw, Volkskrant and Telegraaf based on a LexisNexis search. The reason these newspapers are chosen is that the Volkskrant and Telegraaf are the largest newspapers in the Netherlands, the combination of the newspapers represents a broad spectrum of the Dutch society ('left' and 'right') and that these newspapers, especially Trouw, had extensive media coverage about the HPV-vaccination. An overview of all the articles can be found in appendix H.

The data is collected between 2005 and 2010. Even though there already have been articles on HPV-vaccines as early as 1994, these articles were on the therapeutic HPV-vaccine and articles about the preventive HPV-vaccine in 2000-2002 were about clinical research and not on the potential of these vaccines in the Netherlands. All newspaper articles have been labeled positive or negative based on their content and are cumulatively represented in figure 18, each dot in the graph represents an article.

Positive articles can be divided into positive opinions about the vaccine, positive research outcomes or positive performance of the vaccine (such as high vaccination coverage). Negative articles were articles with a negative opinion, negative research outcomes or negative performance of the vaccine (such as a low acceptance). Articles which were neither negative nor positive have not been added to the analysis and articles where HPV-vaccination was only a minor topic (e.g. when it was used as an example for lack of trust in the government) were not used as well.

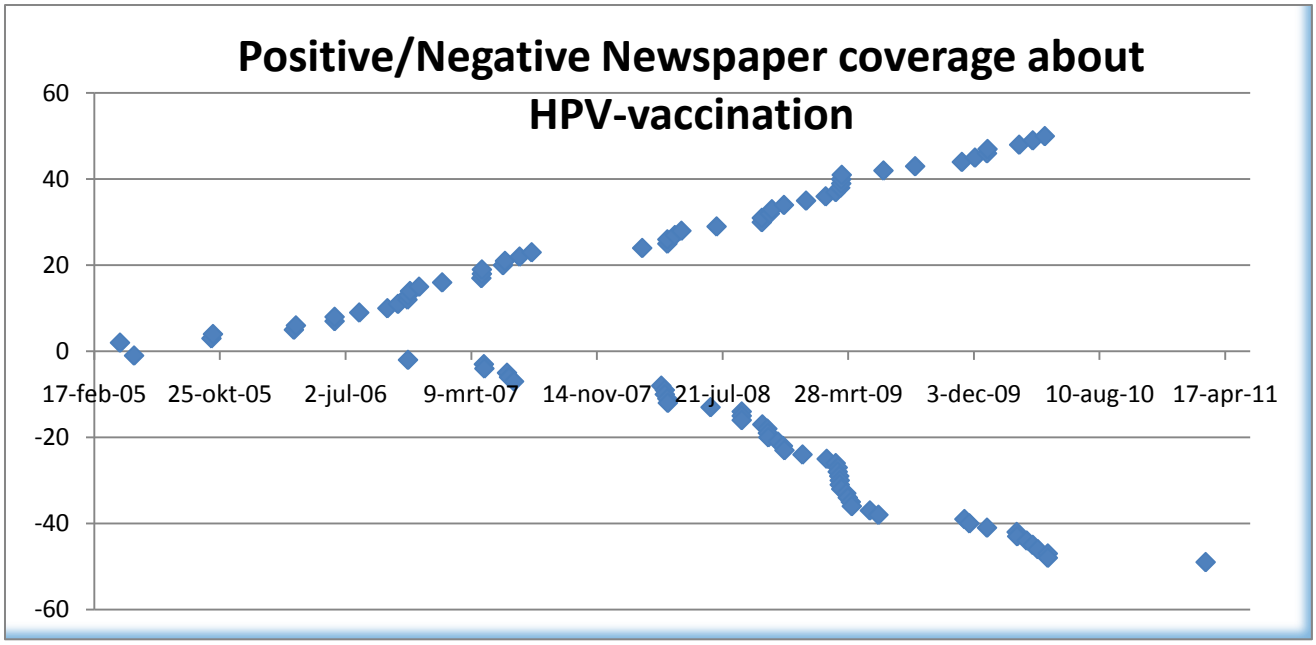

Figure 18: Cumulative HPV-vaccination newspaper articles in the Trouw, de Volkskrant and Telegraaf.

To better understand the number of positive and negative articles and the moment these articles have been published, a short overview is given in figure 19 of important HPV-vaccination related events/reports which have been discussed in depth in the before mentioned newspapers and other media.

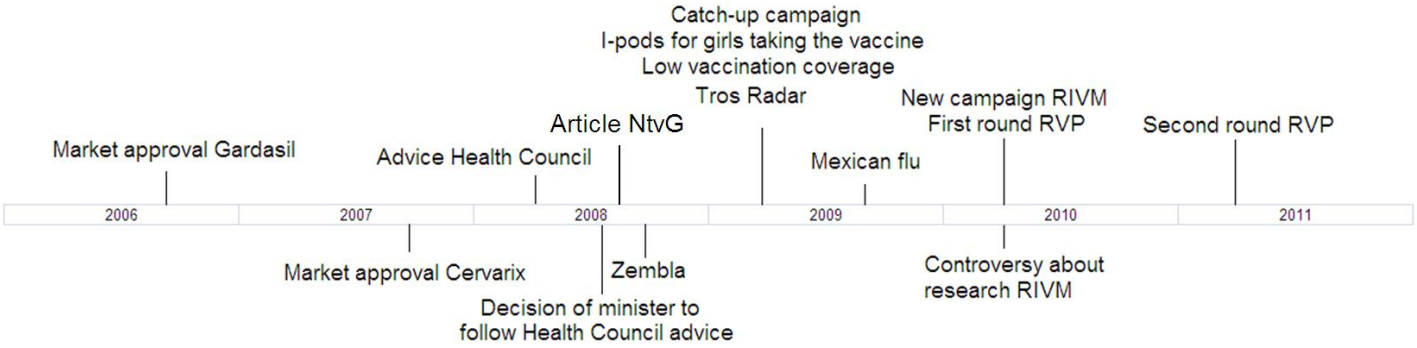

Figure 19: Major events which have been discussed in the media

Looking at figure 18, the media-analysis shows that before the advice of the health council to add the HPV-vaccination to the RVP, media articles were mainly positive about the vaccine. But starting in March 2008, more and more negative media articles about the HPV-vaccination were published. During the catch-up campaign (March 2009) there was much more negative media coverage than positive media coverage. After March 2009, less media articles were published. During the new HPV-campaign in 2010 a lot less HPV-related news was published, but still there were more negative articles then positive articles about the HPV-vaccination. After the campaign in 2010 the discussion about the HPV-vaccination on the internet is still ongoing, even though there is little media attention anymore. After April 2010 only one article specifically focused on HPV-vaccination has been published in the researched national newspapers. This is because there are no new major developments regarding HPV-vaccination in the Netherlands and the RIVM has put efforts in correctly informing the media about incorrect resources for news about the HPV-vaccination (RIVM Meeting, 2010).

7.2 External factors

Besides the events which can be linked to the functions of innovation systems, other events occurred which influenced the performance of the HPV-vaccination in the Netherlands which cannot be linked to the functions of innovation systems.

Mexican Flu (Vaccination)

Due to the Mexican Flu Vaccination the vaccination campaign for twelve year old girls has been postponed from September 2009 to March 2010 (Nieuwsbrieven RIVM, 2009). What the effect of this postponement was is hard to say. Perhaps the HPV-vaccination of 12 year old girls went better or worse when it started in September. Another aspect of the Mexican flu besides the postponement of the HPV-vaccination was the media commotion around this vaccine. Both the way the government handled the HPV-vaccination as the vaccination against the Mexican flu have been discussed together as examples that the government does not have the best intentions for its civilians (Schothorst, 2010). So the vaccination against the Mexican Flu might have had a negative effect on the image of the HPV-vaccination.

General view of the media & public on the pharmaceutical industry

The discussion about the trust of pharmaceutical industry is broader than the HPV-vaccine. The branch organization of innovative pharmaceutical companies held a debate in 2009 discussing the relation of the media with the pharmaceutical companies (Nefarma, 2009). The conclusions of this debate and the accompanied research were that a better relation between the media and pharmaceutical industry is necessary. The pharmaceutical industry is regarded as a closed world, with little space for journalist with critique. Both sides should be more aware of their responsibilities toward consumers. Both in the pharmaceutical industry as in journalism there is the desire to have a more open, intensive relationship. Only if Dutch pharmaceutical companies consider their reputation as important as their sales, the image of the pharmaceutical companies will be good (Nefarma, 2009). It might be that in the perception of the public, the HPV-vaccine became the scapegoat for the bad reputation of the pharmaceutical industry in general.

Lack of trust in the government/health authorities

Research has been performed on the communication of the RVP, both on internal as external communication (Cihangir, 2010; Schothorst, 2010). According to the Dutch Social and Cultural Planning Office vaccinations are generally well trusted, even though there is little trust in the government (Schothorst, 2010). The research indicated that civilians have more trust in official information resources than in informal information resources, however the way the government has communicated about the HPV-vaccination has not convinced everybody that the government does have the best intentions for its civilians (Schothorst, 2010). The internal communication of the government with health care professionals about vaccination is regarded much more positive, in general professionals involved in vaccinations are positive about the information supply (Cihangir, 2010). On 2 March 2011 a documentary about decision to vaccinate a daughter aired where the difficulty of making a choice and the importance of trust stood central (Nevejan, 2011). It is difficult to make a scientifically founded conclusion on the role of trust in the performance of the HPV-vaccination, but a lack of trust in health authorities does seem a major problem for the success of HPV-vaccination.

7.3 Lock-in

In this chapter the concept of lock-in is discussed with regard to the HPV-vaccination in the Netherlands to answer the second sub question:

What is the influence of lock-in on the HPV-vaccination in the Netherlands?

Lock-in exists of the inertia of actors or the system to respond adequately to HPV-vaccination because of routines. Even though cases of lock-in can only be discussed in retrospect, signs of lock-in can be found before a technology is implemented.

A short answer to this sub question would be that lock-in did not occur on system level, since HPV-vaccination has been implemented in the Netherlands within 2,5 years a vaccine became available and the Health Council continuously researches different strategies in prevention cervical cancer. Still several examples regarding lock-in in the innovation system behind HPV-vaccination can be determined. Some have been mentioned before introduction of the HPV-vaccination (Hanstede, 2007; Asveld et al, 2008). Other aspects of lock in have been discussed in retrospect. The following paragraphs discus examples of lock-in of parts of the innovation system.

A research from the Rathenau institute expressed potential problems with inertia of the RIVM because the RIVM did not focus much on normative aspects behind the HPV-vaccination (Asveld et al, 2008). That the campaign in 2009 did not work as intended is acknowledged by the RIVM. Roel Coutinho, head of the RIVM, stated that the campaign for the HPV-vaccination was too old-fashioned (Trouw, 2009). The communication about the vaccine from the RIVM was not able to overcome the impact of negative comments in social media and in the fierce public discussion. The new campaign in 2010 still was not able to increase the acceptance of the vaccine much.

As mentioned in a previous chapter, Han Hanstede of the Dutch Vaccines Group stated that: *"The Dutch Ministry of Health lacks direction, forcing vaccine producers to perform research, which the Health Council regards as biased (Hanstede, 2007)".* For the HPV-vaccination, independent institutes or the Dutch government were not the main financiers of several researches (e.g. cost-benefit analyses), which have been done with financial support of the pharmaceutical industry. And the financial ties of researchers with the pharmaceutical industry have been discussed very negatively (Zembla, 2008). Previously the Dutch government was the main developer and producer of the vaccines in the RVP, but now vaccine development is done by the pharmaceutical industry. The Dutch government has to follow these developments and respond to them when necessary, elsewise vaccination research in the Netherlands might be locked in on pharmaceutical industry funding.

The refusal to add HPV-vaccines to the drug reimbursement system can also be considered as an example of lock-in. Perhaps the RVP has been seen as a golden standard, being the reasons that HPV-vaccination is not added to the drug reimbursement system. Even though the negative advices of CVZ were based on several different arguments (e.g. lack of convincing cost-effectiveness) lock-in on the RVP might have caused that adding HPV-vaccines to the drug reimbursement system is not examined to the full extent. However, it is not possible to estimate this effect on value, since other factors play a role in the drug reimbursement advice as well, such as costs.

Even though media events can be linked to the function 'Creation of legitimacy', there can be argued that the HPV-vaccination became a media hype where emotional, false and incomplete arguments played a major role, around the start of the vaccination in 2009. Other media took over the reports, creating a lot of commotion about the HPV-vaccination. The public opinion about the vaccine became negative because of this commotion. Even though media attention is considerably lower in 2010 and 2011, it might be that the the public opinion now is locked-in on this negative attitude, without looking at new knowledge concerning HPV-vaccination.

A last case, where lock-in can be argued as a factor, is the resistance of scientist involved in the screening program. These scientists argued that implementation of HPV-vaccination in the RVP was not justified, partially because of the successful screening program (de Kok et al, 2008). So these scientists focused on an existing technology as standard. Even though their critique was backed up with valid arguments and a different interpretation of research findings, it might be that their focus was locked-in on the existing technology to prevent cervical cancer, without fully looking at the possibilities of HPV-vaccination. However, it also can be argued that HPV-vaccination proponents were 'locked-in' on vaccination, without looking at the other methods of preventing cervical cancer.

7.4 Performance of HPV-vaccination

In order to assess the influence of the function performance on the HPV-vaccination, it is necessary to measure the performance of the depended variable as well. This is mainly done by looking at vaccination coverage, but other endpoints are mentioned as well.

Before the start of the HPV-vaccination, research was already performed to investigate HPV-vaccination acceptance. This research, performed in 2006, showed that 88% of parents would accept HPV-vaccination for their child (Lenselink, 2008).

The vaccination coverage in reality is much lower. In 2009 the catch-up campaign for 13 to 16 year old girls has been performed. The girls who rejected the invitation in 2009 still could take the vaccination in 2010. In total 52,2% of the 13 to 16 year old girls took all three vaccines, 3,3% took two vaccines, 1,9% took one vaccine and 42,5% took no shot at all (Giesbers a, 2011). During the first RVP-campaign for twelve year old girls in 2010, 51,9% of the girls took all three shots (Giesbers b, 2011), however in the course of 2011 this number can become higher because of girls which still have to take the third vaccination. The second RVP round in 2011 is currently ongoing, no official data is yet available, but first signs indicate an increase of the vaccination coverage. In Groningen the vaccination coverage is around 65% in 2011 for the first shot, while last year 58,6% of the girls took all three shots (GGD Groningen, 2011, Giesbers b, 2011)

Looking at figure 20 & 21, it becomes clear that there are big differences in vaccination coverage per municipality. Especially in big cities, the Bible belt (a diagonal line between Zeeland and the Veluwe) and Twente the vaccination coverage is low. It is difficult to say why vaccination coverage is lower in big cities. Low vaccination coverage in the Bible belt is common because of religious objections, even though for HPV-vaccination the coverage is considerably lower. In Twente several GGD's offered free iPods for girls taking all three shots, which has been negatively discussed. It seems the iPod offer lowered vaccination coverage instead of improving it. Around Roosendaal in Noord-Brabant, high vaccination coverage can be found; this might be because of information evenings organized by a gynecologist (BN de Stem, 2009).

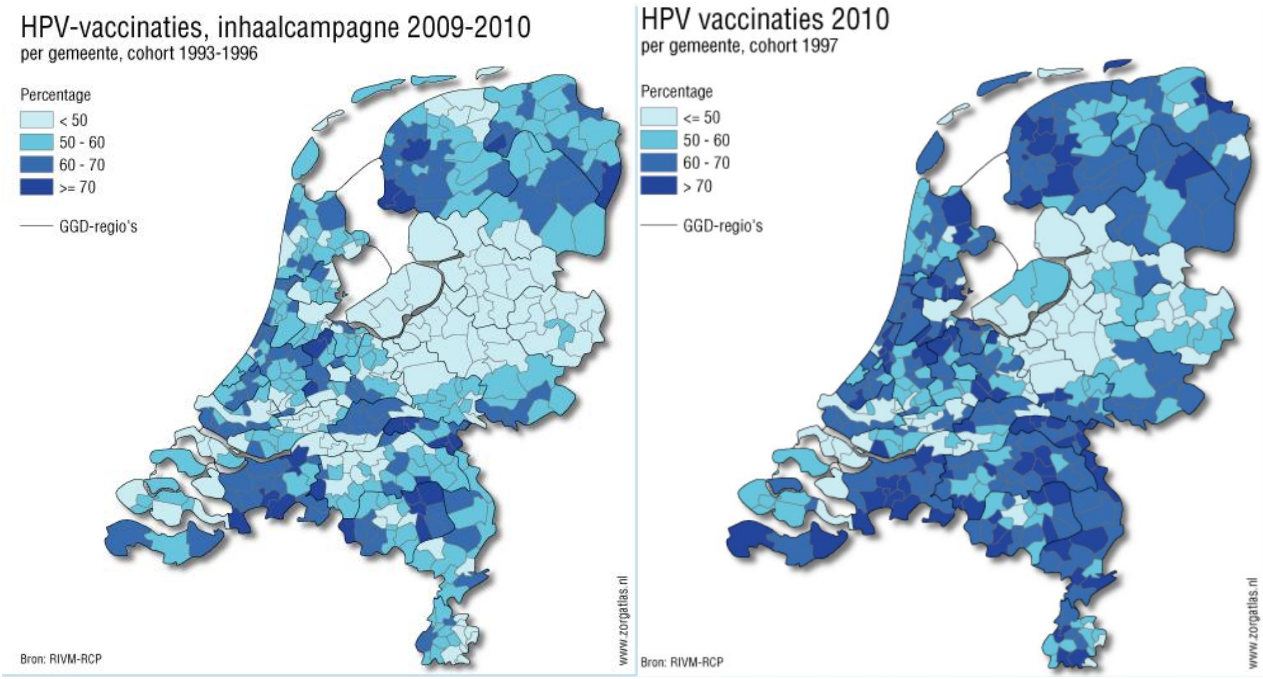

Figure 20 & 21: HPV-Vaccination coverage per municipality (Giesbers a, b, 2011).

HPV-vaccination performance from a financial perspective for the pharmaceutical companies is much lower than initially expected. Because Gardasil is not funded, there are hardly any sales and the sales for Cervarix to the RVP are much lower because of the low vaccination coverage.

Even though several medical professionals and scientists have made critical remarks about the vaccine, almost all doctors are positive about the HPV-vaccination. Most of the general practitioners would vaccinate their own daughter, while only 2% has comments about the vaccination, according to a survey done by the Association of General Practitioners (LHV, 2009)

A last performance endpoint is the future effect of HPV-vaccination on cervical cancer and other types of cancer. According to the Health Council HPV-vaccination will reduce the number of deaths caused by cervical cancer with 100 to 125 (Gezondheidsraad, 2008). This is based on a vaccination coverage of around 85%, considerably higher than the current coverage. And the eventual decline of HPV-related cancers is heavily dependent on factors such as duration of protection, vaccine efficacy, dominant HPV-types, sexual behavior, risk factors (e.g. smoking), interaction with screening program & HPV-DNA test and many other factors. Looking at the HPV-vaccination performance based on clinical research, results concerning protection against precancer lesions and duration of protection are positive. Publications after the large clinical trials have various positive outcomes. The vaccines give cross protection against several HPV subtypes, including types which are difficult to find with PAP smear tests and both vaccines give protection for at least 8,4 years (Harper, 2010; Frazer, 2011).

A restriction for the eventual success of HPV-vaccination on the reduction of cancer in the Netherlands is the low vaccination coverage among girls with a low socioeconomic status (Rondy et al, 2010). Their chance of getting cervical cancer is considerably higher (IKST, 2008). When comparing the rates of cervical cancer per region with the vaccination coverage, it becomes clear that in the regions where HPV-vaccination could have the biggest effect, coverage is low. For example, in region Rotterdam the cancer rate is 10,6 per 100.000 women in 2008, compared to 8,4 per 100,000 woman in 2008 nationally. The vaccination coverage in Rotterdam is 26,5% for the complete series in 2010 compared to 51,9% nationwide (IKCNET, 2011; Giesbers b, 2011). Another problem related to the eventual decline of cervical cancer in the Rotterdam region is that cervical cancer screening attendance is also lower then the national attendance. The difference is minimal however, with a screening attendance of 65,9 % in the Rotterdam region against 67,4 % nationawide (Mulder, 2010).

7.5 Hampering and promoting factors

Based on the innovation system analysis, the dynamic analysis and the interviews insights have been gained on the opportunities and barriers of HPV-vaccination over time. Figure 22 shows the main factors which have influenced the functions of innovation systems. Subsequently these functions have influenced the performance of HPV-vaccination.

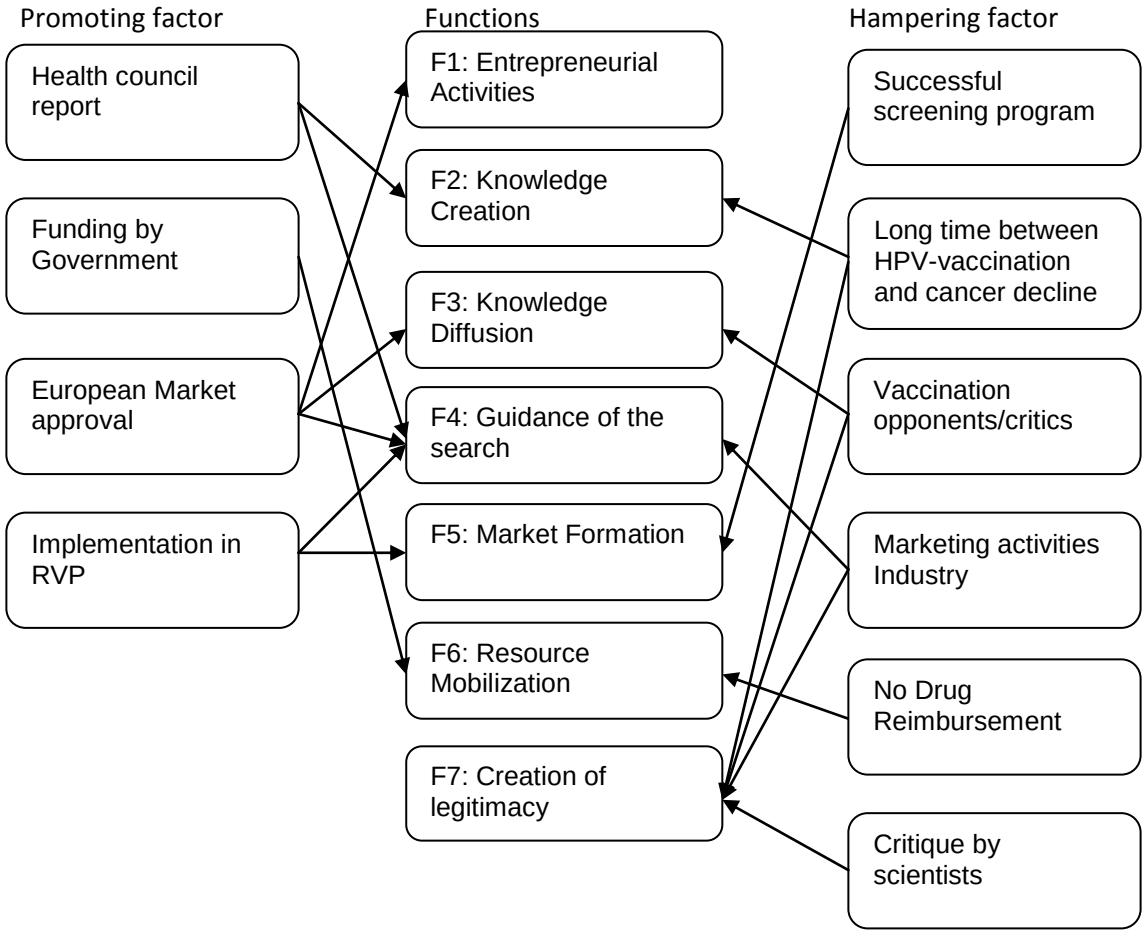

Figure 22: Overview of hampering and promoting aspects on Innovation systems (Schuttelaar, 2007)

The market approvals of the vaccines and health council report have been regarded as important guidance events of the pharmaceutical companies and the government (Kenter, 2011; Schellekens, 2011; van den Oetelaar, 2011; Remorie; 2011). However, the marketing activities of pharmaceutical companies have been considered as hampering for guidance of the HPV-vaccination and creation of legitimacy. Several interviewees expressed in minor or major extend that the marketing activities were not always conducive in increasing the success and acceptance of HPV-vaccination (Kenter, 2011; Conyn, 2011; Remorie, 2011; Schellekens, 2011; Interview de Kok, 2011).

Many factors have had a negative influence on creation of legitimacy. The critique by scientist, expressed in public media is considered as major factor in the discussion about the HPV-vaccination (Kenter, 2011; Conyn, 2011; Schellekens, 2011; van den Oetelaar, 2011). The influence of vaccination opponents/critics also had a negative effect on the legitimacy of HPV-vaccination even though this is not regarded as influential as the critique by scientists. However, these groups have spread incorrect data out of personal conviction, which has hampered knowledge diffusion about HPV-vaccination (Schellekens, 2011).

8 International comparison

In this chapter a comparison is made between the Dutch HPV-vaccination innovation system and the HPV-vaccination innovation system in other countries, specifically England. This will answer the sub question: *Which functions explain the differences in the performance of the HPV-vaccination innovation system in England compared to the Netherlands?*
The comparison is on specific aspects of the innovation system of England. This is done to focus on the most relevant differences of the HPV-vaccination innovation system between countries. The comparison helps to generalize the results. Before a comparison is made between England and the Netherlands some general information about HPV-vaccination in other countries is given.

Besides the national policy of many different countries, international policy has been developed on scenarios for HPV-vaccination. Both the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) have looked at HPV-vaccination on an international scale (WHO, 2007; ECDC, 2008). Worldwide there are high differences in cervical cancer rates, the highest being in Africa below the Sahara and the lowest in developed countries (WHO, 2007). Looking at Europe, HPV-vaccination is already introduced in Belgium, Denmark, Germany, France, Greece, Italy, Luxemburg, Portugal, Spain, Sweden, the United Kingdom and Norway in 2008 (ECCA, 2009).

Vaccination coverage in other European countries
In many other countries that provide HPV-vaccination, coverage is as low as or even lower as in the Netherlands. For example the vaccination coverage in France in 2008 was 24%, 56% in Italy in 2009 and 30% in Portugal in 2009 (Dorleans, 2010). Finland has chosen for a different approach on HPV-vaccination as most other European countries (see overview in ECCA, 2009). In Finland there is chosen to await a nationwide vaccination campaign and perform a phase IV study first. In this study HPV vaccination in both sexes is evaluated, with more than 30 000 participants (Nelson, 2009). One of the reasons Finland has chosen for this approach is because cervical cancer is a very minor health problem in Finland, with the lowest cervical cancer rates of Europe (ECCA, 2009). The Dutch health council also has discussed the possibility of a phase IV study, but did not chose for this option because there were doubts where and how such a study should be performed (Kenter, 2011).

Comparison between the Netherlands and England
A country which is worth studying more in depth is England. In England HPV-vaccination has reached a higher coverage as in the Netherlands. The provided HPV-vaccine is Cervarix, just as in the Netherlands, and the routine vaccination is given through a school-based program. In England HPV-vaccination has been introduced around the same time as in the Netherlands, with the first vaccination round starting in September 2008 (Sheridan et al, 2010). In the Netherlands vaccination started in March 2009.

In school year 2008-2009 84,1% of the twelve year old girls took all three shots (Sheridan et al, 2010). The catch-up campaign was less successful however, in 2008-2009 eighteen year olds could take the vaccine at their general practitioner, 47,4% completed the series of three shots. The total vaccination coverage of all girls born from 1 September 1990 to 31 August 1997 performed in school year 2008-2009 and 2009-2010 reached 72,4% of the girls for at least one shot and 60,4% of the girls took all three shots (Sheridan et al, 2010). An overview of the vaccination coverage is given in figure 23, giving an indication of the HPV-vaccination system performance.

	Netherlands 2009	Netherlands 2010	England 2008/2009	England 2009/2010
Catch-up	52,2%		47,4%	54,4%
Routine Cohort		51,9%	84,1%	76,4%

Figure 23: Vaccination coverage Netherlands & England (Based on Giesbers a, b, 2011; Sheridan et al, 2010)

Knowledge development
Looking at national knowledge development before the start of the vaccination program cost-effectiveness analysis showed that both the quadrivalent and the bivalent vaccine are cost effective, with duration of vaccine protection as key variable (Jit et al, 2008). Additional benefits of the quadrivalent vaccine against genital warts showed that the price of the bivalent vaccine should be 13-21 pounds cheaper to make it preferable. Other than in the Netherlands, no fierce scientific discussion about the implementation and use of the vaccine took place, affecting the vaccination performance.

Guidance of the search
The guidance of the search from both the pharmaceutical industry as from the NHS (National Health Service) was much stricter in England compared to the Netherlands. Policy of pharmaceuticals was aimed at starting with disease awareness so the public was informed about the vaccination and responses were ready to stifle controversies before they started and to respond to factually inaccurate news reports (Bourne, 2008). Because there has been extensive previous experience with anti-vaccination sounds in England, the English health authorities were prepared for potential problems. Previous anti-vaccination controversies were about the pertussis vaccine and the MMR-vaccine, both discussions led to decrease of vaccination coverage and increase of vaccine preventable diseases and deaths (Gangarosa et al, 1998; Deer, 2004). According to Dr O'Mahony and Dr Taylor, healthcare professionals have been told by the NHS to say nothing publicly that would damage the current vaccine program, such as discussing the choice of Cervarix over Gardasil (O'Mahony et al, 2011). This shows that there was a strict guidance from the government on communication about the HPV-vaccination in England.

Market formation
Just as in the Netherlands competition between GSK and SP MSD took place in England through a tender with a secret price. Also in England, Sanofi Pasteur MSD objected to the outcome of the tender. This did not happen with a lawsuit, but with a media response regretting the choice of the government stating that Gardasil '*provided unmatched cervical cancer protection*'. GlaxoSmithKline issued a complaint, which was granted since clinical data did not endorse this claim (PMCPA, 2008). The controversy about which vaccine is preferable still continues with doctors claiming that the genital wart protection of Gardasil is a reason to choose this vaccine instead of Cervarix (O'Mahony et al, 2011). But there is no indication that this discussion has led to a lower performance of the HPV-vaccination campaign in England.
Another difference in market formation is the school based program in England for routine cohorts (Sheridan et al, 2010). The difference between the school-based cohorts and the catch-up campaign at general practitioner cohorts (vaccination coverage of 84,1% against 47,4%) indicate that a school based program gives a much higher vaccination coverage (ECCA, 2009).

Creation of legitimacy/Counteract resistance to change
Several major events influenced the HPV-vaccination performance in England. When HPV-vaccination was about to start, Jade Goody, a Big Brother celebrity, was diagnosed with cervical cancer. On news reports she openly advocated cervical cancer screening and HPV-vaccination in minor extent. This led to an immediate increase in screening program performance and had a possible positive effect on HPV-vaccination uptake (although there is no previous data to make a comparison with) (Elliot, 2009). This effect also shows that a general focus on cervical cancer both increases screening as vaccination uptake. In the future this might be important because a lot of critique of HPV-vaccination has been on the possible decline of screening attendance. It seems that women are willing to choose both screening as HPV-vaccination to protect themselves against cervical cancer.

A tragic event concerning HPV-vaccination was the death of a 14 year old girl in England in September 2009, who died only a couple of hours after receiving her HPV-vaccination (Rose, 2009). As a safety precaution the vaccine batch was suspended, but extra research showed that she died from a large chest tumor, unrelated to the vaccine. In the Netherlands this news could have been disastrous, but in England the negative effect on the vaccination program and the coverage were small.

This short comparison of HPV-vaccination in England and the Netherlands shows that the biggest differences between England and the Netherlands are on the guidance of the search, market formation to end-user and Creation of legitimacy. Similarities are that the technology and clinical knowledge available in England are the same as in the Netherlands and in both countries the vaccine is provided for free through a nationwide vaccination program. An explanation for the difference in the performance of HPV-vaccination can be found in the stricter guidance of the government, which had a positive influence on the creation of legitimacy. The way the vaccine is provided also seemed to have a positive impact on the performance of HPV-vaccination.

A development worth mentioning is the exchange of information between the RIVM with the English Health Protection Agency and the Department of Health. These parties have contact with each other about the communication of the vaccination program towards the end-user (Conyn, 2011). The RIVM also has contact with Scandinavian health authorities about HPV-vaccination, but communication about vaccines is something which mainly has been discussed with England. In England there is continuous monitoring of the attitudes towards vaccinations (Conyn, 2011). In this way Dutch governmental agencies learn lessons from vaccination campaigns in other countries and vice versa.

9 Conclusions

The aim of this research was to find the factors which have led to the low performance of HPV-vaccination system in the Netherlands using innovation system theory. Based on the results of the innovation system analysis, dynamic analysis and the findings from the interviews, conclusions are developed answering the main and sub research questions. Before the main research question "*Which functions in the HPV-vaccination innovation system determine the performance of the HPV-vaccination in the Netherlands?"* will be answered, the first two sub questions are answered. After the main research question is answered, a separate paragraph discusses the answer to the third sub question concerning policy implications. The answers to the research questions are stated in bullet points before a more extensive answer is given. In the bullet points the main findings are summarized to get a quick overview of the research findings.

The first sub question which will be answered is:
Which actors, institutions and network can be defined regarding HPV-vaccination in the Netherlands?
The following can be concluded:

- All system building blocks are present to make HPV-vaccination possible
- The RIVM plays a central role as responsible actor for performing HPV-vaccination and as an intermediary actor
- Related health organizations have a major influence on the HPV-vaccination system
- Before the vaccine was introduced in the RVP, information from a independent institute might improve the communication towards the general public

Sub question one was answered by analyzing the building blocks of the HPV-vaccination innovation system in the Netherlands. Figure 11 represents the innovation system behind HPV-vaccination in the Netherlands. A central role in the system is played by the RIVM, which has contact with many different actors and is responsible for the execution of the HPV-vaccination in the Netherlands. The most important institution in the system is the National Immunization Program (RVP), managed by the RIVM. Other actors which affect the performance of the HPV-vaccination, but are no formal players in the system are the related healthcare professionals, such as general practitioners and gynecologists. All essential building blocks to form a functioning innovation system are present. An intermediary organization between vaccine producers might be helpful in giving full, unbiased and open (technological) information toward other actors and end-users before a vaccine is added to the RVP. In the current HPV-vaccination system, mainly pharmaceutical companies spread information about the vaccine, which has been discussed negatively in the media. An example of such an intermediary organization would be a national institute of clinical excellence, where knowledge about new medicines is discussed and spread. The RIVM has this role now the vaccine is added to the RVP, but for new technological developments and other vaccine innovations an intermediary organization could bridge the knowledge gap between the pharmaceutical industry and other actors, without putting focus on the interests and marketing activities of pharmaceutical companies.

The second sub question is:
What is the influence of lock-in on the HPV-vaccination in the Netherlands?
The following can be concluded:

- No lock-in on a specific technology occurred (screening and vaccination co-exist)
- Communication about the vaccine was too old-fashioned and focused on the way previous vaccination campaigns were performed
- The main focus in the system is on the RVP, while other means of providing the vaccine are possible as well

The results regarding lock-in show that even though several examples of lock-in have been found, lock-in does not have played a major role in the HPV-vaccination innovation system in the Netherlands. This is concluded based on the interviews and the dynamic analysis which showed that

the system and its actors were able to make HPV-vaccination possible, without being fully focused on previous technologies. The HPV-vaccination is implemented within 2,5 years after the first vaccine became available, so the adoption of this technological innovation has taken place rather quickly. Improved vaccines are being developed, so technological lock-in also does not seem a problem. However, lock-in can be seen as a factor on several aspects of the system. Actors such as the RIVM and pharmaceutical companies have performed some of their activities regarding the HPV-vaccination based on previous routines, without realizing the newness of the institutions, end users and technology behind the HPV-vaccination. This effect was most evident during the vaccination campaign in 2009 which was locked in on giving dull, scientific information, which was successful during previous vaccination campaigns. But efforts to improve communication are performed. Lock-in on the RVP could also be present, since the vaccine is not offered through the drug reimbursement system. However, the vaccine might be provided through the drug reimbursement system in the future. So if all involved actors continuously inform themselves about ongoing developments and consider adapting their activities on new situations, (HPV-) vaccinations will be performed more successful, then during the start of the HPV-vaccination, without being locked-in on suboptimal routines.

The third sub question is:
Which functions explain the differences in the performance of the HPV-vaccination innovation system in England compared to the Netherlands?
The following can be concluded:

- The international comparison showed that guidance of the search, creation of legitimacy and market formation had a positive impact on the performance of the HPV-vaccination innovation system in England

In the comparison of the Dutch HPV-vaccination innovation system with the system in England, the importance of guidance of the search and creation of legitimacy is observed. Nationwide HPV-vaccination is introduced around the same time in England, but more successful. Stricter guidance of the government during the introduction of the vaccine led to few negative statements about the vaccine, while creation of legitimacy was positively influenced by Jade Goody effect. The market formation in England is an important function as well, school based vaccination seems to have a positive impact on the performance of HPV-vaccination.

Finally the main research question is answered:
Which functions in the HPV-vaccination innovation system determine the performance of the HPV-vaccination in the Netherlands?
The following can be concluded:

- The performance of HPV-vaccination expressed in vaccination coverage is low
- Creation of legitimacy/counteract resistance to change (F7) is the most important function in determining the performance of HPV-vaccination innovation system
- A turning point happened halfway 2008 and a negative attitude predominated the HPV-vaccination during the catch up campaign in 2009, resulting in a low vaccination coverage
- Knowledge development and diffusion (F2 & F3), Guidance of the search (F4) and Market formation (F5) were not sufficiently accounted for to legitimize HPV-vaccination towards the general public

The most important function in determining the performance of HPV-vaccination in the Netherlands seems to be 'Creation of Legitimacy/Counteract resistance to change'. This function is of most importance because negative statements and negative media attention expressed during the vaccine introduction had a negative impact on the public opinion and the vaccination coverage, even though the vaccine is offered for free to the end users.

But other functions and the interrelatedness of functions are important as well in determining the performance of the HPV-vaccination in the Netherlands. Mainly guidance of the search, market formation, knowledge development & diffusion, creation of legitimacy and their interrelatedness are important. The dynamic analysis showed that knowledge development and knowledge diffusion started late in the Netherlands and mainly occurred after the health council advice to offer HPV-vaccination in the RVP was published. The market formation between technologies has led to a lot of discussion about the speed at which the vaccine is introduced and the market formation towards end-users combined with the expressed lack of guidance of the government led to a low performance of HPV-vaccination system.

The role of the different functions has shifted over time and therefore two graphical overviews are developed to show the functional patterns at two moments in time. There is a major difference between the situation before August 2008 (around then resistance against the vaccine started) and the situation in the period thereafter, when a fierce public discussion about the vaccines occurred. Figure 24 & 25 show functional patterns in these two situations. These overviews are based on the motors of innovation system (Suurs, 2009) and research on methods to represent Innovation Systems (Eveleens et al, 2010).

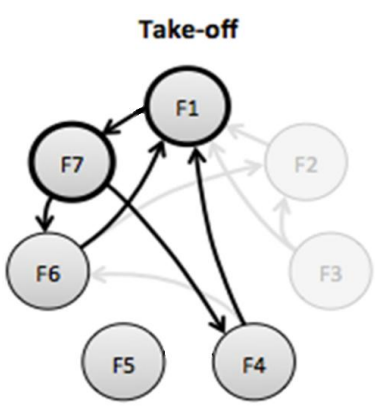

Figure 24: Functional patterns in the HPV-vaccination innovation system (Based on Eveleens et al, 2010)

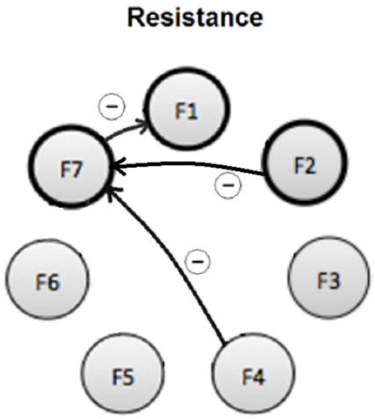

Figure 25: Functional patterns in the HPV-vaccination innovation system

Figure 24 based on a framework from Eveleens et al. (2010). The framework shows a phase where widespread use of an innovation is initiated. The situation regarding HPV-vaccination in the period from 2006 to the first half of 2008 is comparable with figure 24. There was an expressed desire for the vaccine, initiating guidance events and resource mobilization, making widespread use of the vaccine possible. The theoretical performance of the vaccine was high at that time, research indicated that 88% of parents would vaccinate their daughter. Starting in the second half of 2008 a new situation occurred where resistance against the vaccine became dominant. In this phase, an expressed lack of knowledge to justify a nationwide vaccination campaign combined with insufficient guidance caused a negative creation of legitimacy. This negative creation of legitimacy had a negative effect on the entrepreneurial activities and the performance of HPV-vaccination.

The current situation regarding HPV-vaccination is similar to figure 25. Guidance of the government and knowledge development have improved but a low creation of legitimacy remains a problem for the performance of HPV-vaccination in the Netherlands, this might be because public opinion is still locked-in on the situation which occurred end 2008. This shows that there is a relation between the functions of innovation systems and lock-in: when widespread use of a technology is not legitimized, this has a negative impact on the performance of an innovation and it is difficult to alter this negative view to a more positive opinion.

9.1 Policy recommendations

In this sub chapter possible steps are discussed to increase the performance of HPV-vaccination and the innovation system behind HPV-vaccination. This answers the last sub question:
How can the performance of the innovation system behind HPV- vaccination in the Netherlands be improved?

- Improvements are already ongoing
- Major system alterations are not necessary: the current system has the potential for a high performance of HPV-vaccination
- Focus on acceptation is of most importance, despite that technological and policy improvements can increase the performance of HPV-vaccination as well
- Earlier involvement of the RIVM or another governmental agency in communication about the vaccine, both toward healthcare professionals and the general public, is desirable
- New knowledge should be wider diffused
- Lobby from pharmaceutical companies should be performed more cautiously
- Media and politicians should be less driven by emotions and hypes
- Offering HPV-vaccination through the drug reimbursement system may improve the performance of HPV-vaccination

It is important to stress that the actors in the innovation system behind HPV-vaccination in the Netherlands are continually working on improvements in the years after the HPV-vaccination have been implemented in the RVP. The fierce debate about the vaccine has faded and both governmental agencies and pharmaceutical companies have learned important lessons from HPV-vaccination in the Netherlands. This is both observed in de dynamic analysis as in the interviews with key actors.

The Innovation System analysis and dynamic analysis, which are supported with statements from the interviews, indicate that no major system alterations are necessary to improve the performance of HPV-vaccination in the Netherlands. The low performance is regarded as a result of actors not acting adequately on the newness of HPV-vaccination, while little critique was given on how the system behind HPV-vaccination is structured.

The dynamic analysis and interviews show that the focus point of policy improvements should be on the acceptance of HPV-vaccination. System alterations such as a different way of providing the vaccine only will be successful if the vaccine is generally accepted by the Dutch public. Due to the bad start of HPV-vaccination in the Netherlands a long term strategy is necessary to make HPV-vaccination widely accepted (Conyn, 2011; van den Oetelaar, 2011; Remorie, 2011). A shift in the public opinion about the vaccine takes time.

Still there are many steps which already can be taken. Several alterations are possible to make HPV-vaccination more successful. The following paragraphs discuss possible measures to improve the innovation process for (HPV-) vaccination in the future. Some improvements are focused on the system while others are focused on a specific actor.

Information to healthcare professionals, the end users and general media should receive a more continuous input about new clinical and societal research outcomes. Knowledge development and diffusion is continuously taking place in scientific environment, while more societal application of research outcomes seems desirable. The vast amount of research which determines factors explaining the acceptance of HPV-vaccination and discusses policy to increase the acceptance should be diffused more widely so more practical applications of this research are applied. And misconceptions about the effectiveness, safety and duration of protection still are present in parts of the public, while much more knowledge is available since the decision to implement HPV-vaccination in the RVP in 2008 (e.g. Harper et al, 2010; Frazer, 2011). When more knowledge becomes available

over time and the protection against cervical cancer of HPV-vaccination is confirmed, acceptance will increase (Kenter, 2011).

The RIVM is the most appropriate actor for knowledge diffusion and already has put these efforts on the right track (Conyn, 2011). The RIVM would be best suited for the provision of new information since it is the responsible actor for performing HPV-vaccination in the Netherlands, has an intermediary role between scientific research and end-users and does not have a financial interest in increasing vaccination coverage. General practitioners can play a role as well in providing independent information (Kenter, 2011). In the future the RIVM has plans to give contributions about vaccinations on conferences to general practitioners (Conyn, 2011).

Guidance from the government should start at an earlier stage in the future. For other vaccines, which are not (yet) added to the RVP, this step is already taken by providing information about these vaccines on the RIVM website (Conyn, 2011). Still the role of the RIVM has to stay limited before a decision on adding a vaccine to the RVP is made, since this is the responsibility of the Health Council and the Minister of Health to develop new vaccination policy. Guidance from the RIVM should not only focus its knowledge provision to doctors involved in performing the vaccinations in the RVP, general practitioners, gynecologists and other involved healthcare professionals should be given information as well, so a wide field of healthcare professionals is properly informed (Conyn, 2011). This also prevents public discussions by scientists or healthcare professionals taking place when a vaccination is about to start, since opposing views are discussed at an earlier stage (Conyn, 2011). A specific problem for the HPV-vaccination still remains that many different healthcare professionals (general practitioners, immunologists, cancer-experts, gynecologists, experts in sexually transmitted diseases and epidemiologists) have a view and specific knowledge about the impact of HPV-vaccination. But with central direction of the RIVM all the wishes of these parties can be discussed collectively. How the government should deal with vaccination resistance groups is difficult to say, although correctly responding to statements of these groups and monitoring vaccination resistance can help developing policy on how to handle with vaccination resistance. When a response to these groups is necessary, it is important not to make a judgment on their statements, but to give a factual reply (Lips, 2010).

Another policy alteration could be a more open decision making process by the Health Council, to increase public support for vaccinations (Schellekens, 2011). This process can become more open by making the meetings and votes advising what should be done with a new vaccine open to the general public. But this approach might have its drawbacks, since emotions can play a role during such a public discussion. According to Gemma Kenter, member of the Dutch Health Council, the current way of developing an advice is a way which makes the clearest discussion between advisors possible, including all pros and cons (Kenter, 2011).

The role of the pharmaceutical industry during the introduction of HPV-vaccination in the Netherlands has been discussed very negatively. Currently there are hardly any marketing activities concerning HPV-vaccination by pharmaceutical companies (Remorie, 2011; van den Oetelaar, 2011). More restraint in pressuring public, politicians and organizations in introducing a new vaccine seems desirable. The lobby by pharmaceutical companies gave a fierce backlash, while the decision making process was already started in March 2007 when the Minister of Health requested an advice from the Health Council. This does not mean that no input should be given from pharmaceutical companies. By responding to controversies about marketing activities and product safety and efficacy in an open and factual way, the image of the pharmaceutical companies can be improved, while currently people have little trust in the pharmaceutical industry.
It is important in this respect to clarify to the public that interests of the pharmaceutical companies are strictly divided from the interests of governmental agencies. During the campaign in 2009 several people stated that the whole vaccination was of interest to the pharmaceutical industry, while it

should be clear that this does not play a role in the RVP (Conyn, 2011). Now the HPV-vaccine is added to the RVP it still is important that future marketing activities of all related actors should be carefully considered. Contacts between competing companies and other actors are desirable (despite colliding interest): the actions of one actor can have a major impact on the performance of the HPV-vaccination in general. A problem is how pharmaceutical companies should market their new vaccines: disease awareness campaigns and lobby to healthcare organizations and politicians seemed to have counterproductive effects on the societal support for the vaccine. But it can be argued that without marketing activities, it would have taken much more time before a decision was made about adding the vaccine to the RVP.

The role of the media in HPV-vaccination in the past has been a subject of discussion. Even though it is evident that the media should report critique from prominent researchers, the effects of this critique can be of major influence on public health. Therefore careful and complete coverage of the subject is important, for example by covering the reply on the critique as well. This has not always been the case with media coverage about HPV-vaccination. The same applies to people which spread their message through the media, previous critique on vaccination campaigns in England shows that this critique has an impact on the vaccination coverage, people spreading their message to the general public should be aware of this effect. Lessons are that the RIVM has to act more pro-active on potential discussions. This might be done in future vaccination campaigns by giving press briefings so media can create a dossier about a subject (Conyn, 2011).
In the parliament HPV-vaccination has been discussed extensively, while most representatives are not substantively informed about HPV-vaccination and respond to signs in the media and society, rather than feedback from scientists (van den Oetelaar, 2011; Conyn, 2011; Interview de Kok, 2011). Also politicians have been partially influenced in their activities by the lobby of the pharmaceutical industry (Schellekens, 2011). Halbe Zijlstra, a former VVD representative, has critique on his co-representatives, stating that members of parliament should be careful with their critique on the vaccination campaign, especially when the willingness to vaccinate drops (Zijlstra, 2010).

A system alteration is the possible addition of one or both HPV-vaccines to the drug reimbursement system. Efforts to get the vaccine reimbursed already have been performed in 2007 and 2009, without success. But this possibility remains open. Since HPV-vaccination does not reach all women to which it is recommended and prices of the vaccines are declining, provision of the HPV-vaccines through the drug reimbursement system remains an option. In practice this would mean that girls could request the vaccine from their general practitioner or other healthcare professional and costs are covered by their healthcare insurance. Multiple people have expressed the potential benefit of adding the HPV-vaccine to the drug reimbursement system, provided that the vaccine is cost-effective (Kenter, 2011; Schellekens, 2011; Remorie, 2011). The current free market price of the vaccine (125 euro) is not considered cost-effective for the Dutch situation, but this price can change. According to Marina Conyn, responsible for the RVP, HPV-vaccination outside the target population of the RVP can be useful in individual cases, e.g. for girls which are not yet sexually active and are born before 1993. The HPV-vaccine could be added to the drug reimbursement system if it is cost-effective for these groups. Then vaccination of groups outside the RVP, on basis of an individual consideration, could take place by their general practitioner or other doctor (Conyn, 2011). Vaccination at the general practitioner is better suited for individual doubts and questions of girls which are confused about the risks and benefits of the vaccine, increasing the trust in HPV-vaccination (Bensing, 2009).

An opportunity on the short term to inform the public about the HPV-vaccines is during the new advice regarding HPV DNA test. This advice by the health council will be published halfway 2011, expectations are that HPV DNA tests will be added to the HPV prevention program (Interview de Kok, 2011, Kenter, 2011). This might be a good moment to reflect on the HPV-vaccination in the media, to ensure that full and correct information about the efficacy and safety of HPV-vaccination is spread.

10 Discussion

In this final chapter the research design, the theoretical relevance of this research, research outcomes and future research opportunities are discussed.

The goal of this research was not to make conclusions on whether or not HPV-vaccination is implemented in the RVP at the right moment and for the right reasons. Even though the decision to add HPV-vaccination in the RVP is an important event in the dynamics of the HPV-vaccination innovation system in the Netherlands, this decision itself is not discussed. The addition of the HPV-vaccination in the RVP is approached as a given fact. This research is neither meant to conclude if an individual benefits from the HPV-vaccine or not. The study assumes that increasing the performance of HPV-vaccination (expressed in vaccination coverage) is desirable.

Concerning the research quality of the followed methodology and the obtained results the construct validity, internal validity, external validity and reliability are discussed

Construct validity is established by having correct operational measures for the concepts being studied (Yin, 2003). Construct validity has been accounted for by discussing all relevant actors, literature and events regarding HPV-vaccination in the Netherlands. A big pitfall for construct validity is the fierce public discussion which has taken place in the Netherlands with both strong opponents as proponents for HPV-vaccination. Therefore it was of importance to give a correct and neutral overview of all events. This is done by describing actors and events in a factual and complete way. Subjective descriptions of actors and events are avoided, by literally quoting statements. By giving a full overview of both statements in favor as against HPV-vaccination, bias in the measurement of the functions is reduced as much as possible. Another way bias is reduced is done by interviewing both critics as proponents for HPV-vaccination, such as Inge de Kok and Gemma Kenter. In this way various data sources are used to cross check information on actors and events. An extensive list of references is used and during the last interviews no new information altering the outcomes of the dynamic analysis became available, indicating that a data collection is complete. Still, chances are that a number of relevant resources are missed, for example scientific articles or statements which have had an impact on a specific part of the population.

Internal validity is establishing a causal relationship, whereby certain conditions are shown to lead to other conditions (Yin, 2003). It is difficult to state if internal validity is met, since the relations between the functions and the performance of HPV-vaccination are assumptions based on existing innovation theory and no previous application of innovation system theory on vaccination innovation system performance has been performed, making it difficult to state whether the proposed relations are correct. However, the vast amount of empirical data concerning HPV-vaccination in the Netherlands made it possible to create well founded conclusions about the relations proposed in the theory. To explain the relation of the functions of innovation systems to events, a list of hampering and promoting factors has been developed to give insight in how specific events or factors are linked to the functions of innovation systems. And because of the extensive information on the different functions of innovation systems, it was possible to apply motors of innovation systems to further explore the relation between different functions. By discussing the cumulative causation of the different functions and relating this causation to the performance of HPV-vaccination, internal validity is increased.

The internal validity of the proposed relation between lock-in and performance of HPV-vaccination is harder to measure. The outcomes of lock-in in this research are limited since HPV-vaccination is available in the Netherlands for only five years and it might take more time to determine whether the innovation system behind HPV-vaccination is locked-in on routines which hamper its

performance. In this research, examples of lock-in have been found, but efforts to alter these suboptimal routines are already taking place. The relation of lock-in and functions of innovation systems can be researched more extensivly in future research.

External validity establishes the domain to which a study's finding can be generalized (Yin, 2003). External validity can be assessed by comparing the theory and outcomes of this research to similar cases, e.g. the Hepatitis B vaccination or HPV-vaccination in other countries. The external validity of this research is tested by the comparison between HPV-vaccination in the Netherlands and HPV-vaccination in England, indicating which functions determine the performance of HPV-vaccination in general. This has increased the generalizability of the research. The short comparison shows that creation of legitimacy is of main importance for a high performance of HPV-vaccination for other cases as well. So for other innovations, lessons can be learned on resistance to the nationwide application of a technology. If society turns against a technology, it is very difficult to overcome this resistance. Therefore it is important not to overpressure the application of a technology when opposition still wants to have their say in the debate. When a big part of the end users and general public have turned against a technology, it takes more time for the technology to become successful.

A limitation of the external validity is that technological and societal aspects surrounding HPV-vaccination can not easily be compared with other innovations or with HPV-vaccination in other countries, this makes it more difficult to generalize this research. The external validity can be further tested in the future by making a comparison with similar innovations, HPV-vaccination abroad or by performing a new function analysis for HPV-vaccination when the system is longer in its place and more information about certain aspects of HPV-vaccination is gathered. Such an extensive comparison can conclude if the proposed relations between the theoretical concepts and the performance of HPV-vaccination system can be seen in general or that the conclusions in this research are more case specific.

Reliability can be established by demonstrating that the operations of a study can be repeated with the same results (Yin, 2003). The reliability of this research is tested in multiple ways. An extensive references list helps to assure that all events related to HPV-vaccination in the Netherlands are taken into account. Besides these references, feedback from thesis supervisors and interviews has made the results more reliable and made triangulation of the results possible. Problems with the reliability are the numerous newspaper and website references, where people might have been misquoted and information might have been misinterpreted or exaggerated by the writer of an article. A problem with the overviews in the dynamic analysis (see appendix A to J) are possible missed events which could have changed the outcomes of the event overviews.
Having an internship at the producer of the HPV-vaccine which is implemented in the National Immunization Program has been a risk for bias and thus might have an effect on the reliability of the research. GlaxoSmithKline has a financial interest in a more successful HPV-vaccination, increasing the sales of Cervarix. But the research has not been commissioned by GSK, all references come from public resources (making the research reproducible) and no guidance is put on the research results and conclusions by GSK supervisors. There can be argued that research outcomes would have been different if no internship, or if an internship at another involved actor was performed and during the interview phase I have encountered critique based on my internship at GSK.

Discussing the value of this research to innovation theory in general can give insight in its contribution to the field of innovation theory. An extensive scan of previous literature showed that studying the innovation system behind a vaccine is a new application of innovation system theory. Innovation System research on medical technologies has been performed before (e.g. Schuttelaar, 2007), but never on a specific medicine or vaccine. So this research can be seen as a test for the general applicability of the functions of innovation systems in the medical field. However, current knowledge on innovation system approach has its limitations because the market for vaccines is

different as for sustainable technologies (a field where innovation system theory is applied more often). Focus points for successful innovation are not the same for all technologies. A big difference seems the lack of incremental innovations; only after large clinical trials a new vaccine is approved, which has an influence on the functions entrepreneurial activities and market approval. This had its impact on the methodology of the research, common function indicators such as the creation of niche markets or number of new entrants could not be used.

Several broader topics for future research are proposed. A complete comparison between the dynamics in the Dutch HPV-vaccination innovation system with other countries would increase the value and generalizability of applying a technological innovation systems approach to the vaccine field. Further research could be on the innovation system developments regarding all technologies in the prevention and treatment of cervical cancer in the Netherlands. Then, not only HPV-vaccination would be studied, but also the developments in other means of primary prevention (sexual education/abstinence), secondary prevention (the screening program, HPV-DNA tests) and treatment of (precursors of) cervical cancer. In the entire field of cervical prevention and treatment numerous developments have occurred over the last decades and these developments influence each other. To fully understand the nature of medical innovations the developments and relations of these technologies can be studied. A big difference with this research would be that the scope is not on a single technology, but on many different technologies, all with the same goal. So the study would not be on a Technological Innovation System, but on a *Sectoral* Innovation system, the sector being cervical cancer prevention and treatment. The shift in dominant technologies to prevent cervical cancer can be considered as creative destruction. Creative destruction is the process if transformation that accompanies radical innovation (Schumpeter, 1942).

Another new type of research could be performed if HPV-vaccination would be offered through the drug reimbursement system. This would mean a shift in the paradigm of vaccine provision in the Netherlands. Instead of a programmatic approach, such as the RVP, the vaccines would be provided in a demand-driven environment, even though financing still would be collective. Figure 26 shows how these alterations would mean a shift from quadrant 1 to quadrant 2. This quadrant system, sketched in 2007, discusses future possibilities for vaccine provision. Future vaccines might not only be in quadrant 1 (the vaccines in the RVP) or 4 (e.g. travel vaccines) but might be offered in settings fitting quadrant 2 or 3 as well. This opens possibilities for a niche experiment, for example by testing the effect of demand driven in a specific part of the Netherlands. This can show the effects of this measure and thus paves the road for other ways of providing HPV-vaccination in the Netherlands.

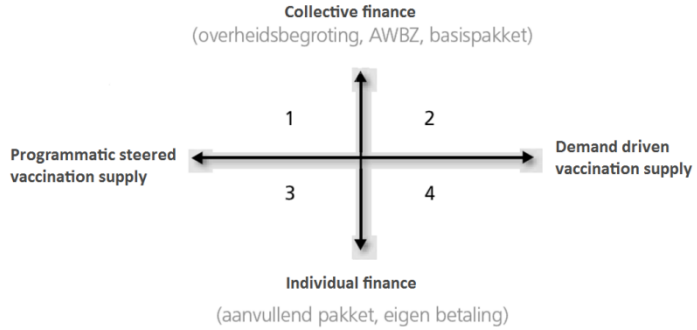

Figure 26: Quadrant system vaccinations in the Netherlands (DVG, 2007)

The intention of this research was to give insights to the reader in the system surrounding HPV-vaccination in the Netherlands. Even though it is possible that people still differ in opinion about the most important factors explaining the low performance of the HPV-vaccination innovation system, the findings are a helpful tool to determine the possibilities for HPV-vaccination in the future and indicate which potential failures can arise when introducing a new vaccine.

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Appendix

Appendix A: Google Scholar search results: HPV vaccine cervical cancer

before 1990	285
1990-1995	682
1996-1999	1090
2000	473
2001	699
2002	862
2003	1200
2004	1250
2005	1590
2006	2340
2007	2630
2008	3060
2009	3290
2010	3180
2011 (till 31 March)	613

Appendix B: Scientific articles about HPV-vaccination in the Netherlands

Yellow articles have been made possible through grants by GSK

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2008	Korfage et al, Women show mixed intentions regarding the uptake of HPV vaccinations in pre-adolescents: A questionnaire study, European Journal of Cancer, volume 44, issue 9, 2008.
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2009	de Kok I. M. C. M., Ballegooijen van M., Habbema J. D. F., Cost-effectiveness analysis of Human Papillomavirus Vaccination in the Netherlands, JNCI, 2009.
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Appendix D: Knowledge diffusion events

Year	Month	Organization	Subject	Reference
2000	April	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2001	October	Leader meeting	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2003	April	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2004	October	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2005		ESGO meeting	Istanbul ESGO meeting	http://www.esgo.org/Meetings/Pages/PastEvents.aspx
2006	April	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2007		ESGO meeting	Berlin ESGO meeting	http://www.esgo.org/Meetings/Pages/PastEvents.aspx
2007	February	CBG (MEB, Health Council,	Workshop on HPV vaccines	CBG MEB

		RIVM-Cib)		
2007	October	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2008	November	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2008	May	RIVM	Ontwikkelingen RVP; in het bijzonder HPV-vaccinatie	PAOG Maastricht
2009	February	RIVM	Vakgroepbijeenkomst communicatieadviseurs	Nieuwsbrieven
2009	March	RIVM	Communicatiebijeenkomst RIVM en GGD	Nieuwsbrieven
2009	March	RIVM	Expertmeeting Voorlichtingscampagne	Nieuwsbrieven
2009	April	RIVM	Bijeenkomst met GGD'en	Nieuwsbrieven
2009	February	Nefarma	De relatie tussen media en farma	Nefarma
2009		ESGO meeting	Belgrade ESGO congres	http://www.esgo.org/Meetings/Pages/PastEvents.aspx
2009	May	HPV Congres	HPV Congres	http://www.hpv2009.org/
2009	November	NVFG	Presentatie vanuit NVFG	http://www.nvfg.nl/images/sturm7/20091103Vaccin4Conyn.pdf
2010	February	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2010		Rathenau Institute	Voorwaarden voor vaccineren	http://www.rathenau.nl/themas/project/voorwaarden-voor-vaccineren.html
2010	November	RIVM/GGD	Afsluiting HPV-campagne	Nieuwsbrieven
2010	January	RIVM/GGD	Over verleden, heden en herstart van de HPV-vaccinatiecampagne	Nieuwsbrieven
2010	February	RIVM	Bijeenkomst van de expertpool	Nieuwsbrieven
2010	March	RIVM	Persbijeenkomst	Nieuwsbrieven
2010	July	HPV Congres	HPV Congres	http://hpv2010.org/main/
2010	November	RCP Oost	12e Papendal Symposium Baarmoederhalskankerpreventie	www.pathology.nl/
2011	May	EUROGIN	EUropean Research Organisation on Genital Infection and Neoplasia	http://www.eurogin.com/
2011	September	HPV Congres	HPV Congres	http://hpv2010.org/main/
2011	March	Het meisje en de Prik	Debat over HPV-vaccinatie en vertrouwen	http://www.debalie.nl/artikel.jsp?articleid=368904
2011	September	ESGO meeting	ESGO international Meeting	http://www.esgo.org/Meetings/Pages/ESGOMeetings.aspx

Appendix E: Guidance of the search events

Events Guidance of the Search		Positive	Negative
2007	CVZ request Gardasil	1	
2007	Campaign beschermjedochter.nl	1	
2007	Lack of direction (Hanstede, 2007)		-1
2008	Health Council Advice	1	
2008	Vaccination coverage goal (Ministerie VWS, 2008)	1	
2009	CVZ request Gardasil	1	
2009	CVZ request Cervarix	1	
2009	Failed Campaign RIVM (Trouw, 2009)		-1
2010	New campaign RIVM	1	

Appendix F: Lobby events (references of statements are discussed in the function analysis)

	Postive	**Negative**	**Neutral**
2007			NHG
2007	NVK		
2007	NVOG		
2007	Olijf		
2007	Kamervragen 20-3-2007		
2007		Kamervragen 14-05-2007	
2007	Kamervragen 5-6-2007		
2007	Kamervragen 4-12-2007		
2008	SOA-Aids		
2008		NVKP	
2008		Boek Trentelman	
2008		Kamervragen 15-8-2008	
2008		DES Centrum	
2008		Onvoldoende gronden HPV-vaccinatie	
2008		HPV-vaccinatie weinig zinvol	
2009	KWF		
2009	NHG		
2009	NIGYO		
2009			NKI-AVL
2009		Kamervragen 18-3-2009	
2009		Kamervragen 2-6-2009	
2009		Kamervragen 15-6-2009	
2009		Kamervragen 12-10-2009	
2009		Boek Desiree Rover	
2009		Boek Anneke Bleeker	
2009		Boek Kuiper-Van den Bos	
2010		Kamervragen 6-5-2010	
2011		Lindeboom instituut	

Appendix G: Resource mobilization events

No funding Gardasil CVZ (CVZ Gardasil, 2007)		2007	-1
Funding Cervarix through RVP (GSK Press release, 2008)		2008	1
No funding Cervarix CVZ (CVZ Cervarix, 2007)		2009	-1
No funding Gardasil CVZ (CVZ Gardasil, 2009)		2009	-1

Appendix H: Newspaper analysis

7-mei-05	-1	Zou vaccinatie baarmoederhalskanker echt terugdringen?
3-nov-06	-2	Alleen collectief inenten helpt tegen baarmoederhalskanker; nieuw vaccin
3-apr-07	-3	Klacht tegen fabrikant van kankervaccin; 'BN'er praat vrouwen angst aan'
4-apr-07	-4	'Terughoudend zijn met kankervaccin'
19-mei-07	-5	Baarmoederhals Nederland loopt niet bepaald voorop met toelating nieuw kankervaccin
23-mei-07	-6	Vaccin Gardasil niet in basispakket
2-jun-07	-7	Het papillomavirus is overal, baarmoederhalskanker is dat niet;
21-mrt-08	-8	Verboden reclame voor kankervaccin op school
28-mrt-08	-9	Farmaceuten sponsoren tv-programma's; Commissariaat stelt onderzoek in
28-mrt-08	-10	De felle lobby voor een vaccin
2-apr-08	-11	Vaccin is nog geen garantie tegen kanker; Baarmoederhalskanker
3-apr-08	-12	Maagdenprik is overdreven
27-jun-08	-13	Inspectie kritisch over vaccin arbodienst
28-aug-08	-14	Vraagtekens bij inenting meisjes
28-aug-08	-15	'Maagdenprik tegen kanker komt te vroeg'
28-aug-08	-16	'Vaccinatie meisjes te snel besloten'
8-okt-08	-17	Te koop: Europese patiëntenlobby
18-okt-08	-18	Experts Gezondheidsraad kregen geld vaccinmakers; Schijn van belangenverstrengeling
19-okt-08	-19	Pharma-inval verwelkomd
20-okt-08	-20	Kant wil debat over agressieve marketing vaccinmakers
8-nov-08	-21	Fabrikant: Keuze Klink voor kankervaccin kost extra doden
18-nov-08	-22	Bedrijf verliest geding om vaccinkeuze
21-nov-08	-23	Prik maakt onderzoek baarmoederhals niet overbodig
27-dec-08	-24	Zwanger worden op z'n Chinees; Jaaroverzicht Ook 2008 was een jaar vol wetenschappelijke flauwekul, flaters en misverstanden
13-feb-09	-25	Boos om duur vaccin
3-mrt-09	-26	ANGSTMAILS tegen 'kankerprik'; Inenting meisjes 13-16 jaar nu van start
7-mrt-09	-27	Haagse meisjes moeten opnieuw een prik halen
7-mrt-09	-28	Het effect is niet bewezen
10-mrt-09	-29	BAARMOEDERHALSKANKER onrust vaccin houdt aan; Is het glas nu halfleeg of halfvol?
11-mrt-09	-30	Inenting van jonge meisjes tegengewerkt
11-mrt-09	-31	Ook kritiek op vaccin in wetenschap
14-mrt-09	-32	Meisjes halen de prik om een dagje vrij te zijn; Column. Economieleraar Ferry Haan hoort in zijn derde klas de argumenten om wel of niet een vaccinatie tegen baarmoederhalskanker te gaan halen. Die snijden nogal weinig hout.
24-mrt-09	-33	Over de 'maagdenprik' wordt paniek gezaaid
27-mrt-09	-34	Nee tegen prik, nee tegen gezag
2-apr-09	-35	RIVM: 'Vaccinatiecampagne mislukt'
4-apr-09	-36	Eerst de 'meidenprik' beter organiseren, dan pas nieuwe vaccinaties;
10-mei-09	-37	Prik met klein risico en onzeker resultaat;
27-mei-09	-38	Artsen weigerden meidenprik te geven
14-nov-09	-39	Naar wie moeten we luisteren?; achtergrond het tanende geloof in de wetenschap
24-nov-09	-40	Bestand tegen heel veel negatieve energie; dinsdagprofiel Anneke Bleeker

29-dec-09	-41	Overheid heeft emoties rond inenten te lang belachelijk gemaakt;
26-feb-10	-42	Farmaceut in de fout; Producent vaccin baarmoederhalskanker overtrad de marketingregels
27-feb-10	-43	Wellicht boete voor fabrikant vaccin baarmoederhalskanker
18-mrt-10	-44	Fabrikant fout bij aanprijzen kankervaccin; Inspectie zint op maatregelen
30-mrt-10	-45	RIVM betreurt ophef rond onderzoek meidenprik; Kamer bezorgd over seksuele enquête en 'opslag DNA'
9-apr-10	-46	Vrolijk foldertje neemt twijfels over noodzaak van vaccinatie niet weg
29-apr-10	-47	Weer lage opkomst vaccinatie meisjes
29-apr-10	-48	Helft meisjes haalt prik
9-mrt-11	-49	Meisjes bedanken massaal voor prik
5-feb-05	1	Kankervaccin meisjes
9-apr-05	2	Vaccin op komst tegen baarmoederhalskanker ; TUMOR
8-okt-05	3	Vaccin voor kanker in baarmoeder
11-okt-05	4	Vaccin tegen baarmoeder- halskanker
21-mrt-06	5	Vrouwen voor een PRIKJE...
25-mrt-06	6	Eindelijk een vaccin tegen baarmoeder- halskanker
10-jun-06	7	Amerikaans vaccin tegen baarmoederhalskanker
10-jun-06	8	Nieuw vaccin cervix-kanker
29-jul-06	9	Nog dit jaar vaccin cervixkanker
23-sep-06	10	EU keurt vaccin goed tegen baarmoederhalskanker
14-okt-06	11	Dit vaccin maakt kankervirussen monddood;Preventie Veelbelovend middel wordt wellicht verplicht ingezet tegen baarmoederhalskanker
2-nov-06	12	Inenten meisjes tegen kanker aan baarmoederhals
3-nov-06	13	Vaccinatie tegen baarmoederhalskanker
7-nov-06	14	Verlossende prik tegen baarmoederhalskanker
25-nov-06	15	Alternatief voor uitstrijkje redt levens; baarmoederhalskanker
10-jan-07	16	Trage goedkeuring vaccins kost te veel mensenlevensdag
29-mrt-07	17	Duitse meisjes krijgen kankervaccin als eerste
30-mrt-07	18	Minister besluit dit jaar nog over kankervaccin
30-mrt-07	19	'Haast met vaccin tegen baarmoederhalskanker'
11-mei-07	20	Keelkanker wordt vaak veroorzaakt door orale seks;
15-mei-07	21	België adviseert vaccinatie baarmoederhalskanker
13-jun-07	22	Vaccineer vrouwen nu het mogelijk is
7-jul-07	23	'Klacht Kritisch Prikken niet gegrond'
12-feb-08	24	Prik tegen baarmoederhalskanker
2-apr-08	25	'Inenting zinvol voor meisjes van twaalf jaar'
2-apr-08	26	'Meisjes inenten tegen kanker'
17-apr-08	27	Mijn dochters krijgen die maagdenprik, punt uit
30-apr-08	28	Vrouwen zien 'maagdenprik' wel zitten
9-jul-08	29	Klink: Prik tegen baarmoederhals- kanker vanaf 2009
7-okt-08	30	Hoogmoed wordt afgestraft; Wetenschap 'Boevenstreek' van onderzoeker Gallo kost hem de Nobelprijs voor geneeskunde
7-okt-08	31	Nobelprijs Geneeskunde gaat naar ontdekkers van twee ziektevirussen
23-okt-08	32	Gezondheidsraad: Advies vaccins was onafhankelijk
27-okt-08	33	Vaccin beschermt ook oudere vrouw; Aantal gevallen van baarmoederhalskanker kan fors omlaag. KWF weet niets van Amerikaans onderzoek
20-nov-08	34	Inenten 12-jarige meisjes vanaf 2009
3-jan-09	35	Vaccin tegen kanker is geen miskleun
11-feb-09	36	Massale inenting tegen baarmoederhalskanker
3-mrt-09	37	Ik vertrouw het advies van de minister'; Ondanks twijfel toch lange rijen voor inenting tegen baarmoederhalskanker
12-mrt-09	38	"Heb vertrouwen in meidenprik!";
14-mrt-09	39	Was er voor andere vormen van kanker ook maar een vaccin;

14-mrt-09	40	Je dochter wel uit laten gaan maar geen vaccinatie geven
15-mrt-09	41	Viroloog ROEL COUTINHO bezorgd over gevolgen van 'hetze' tegen vaccin baarmoederhalskanker "Ons doel staat geheel los van belangen van genees-middelen- industrie"
6-jun-09	42	'Maagdenprik' helpt ook oudere vrouw
8-aug-09	43	ANTI-VACCINATIE-EXTREMISTEN Aanvoerster hetze tegen griepprik blijkt discipel van sinistere complottheoriën "Ik weet dat er mensen rondlopen die deze aardbol een stuk rustiger willen maken..."
9-nov-09	44	Kans op ernstige bijwerking 'miniem'; Onderzoekers weerspreken verhalen over hersenschade en onvruchtbaarheid door vaccin
5-dec-09	45	Vaccin helpt langer tegen baarmoederhalskanker
29-dec-09	46	Campagne moet prik aan de meid brengen; Accent baarmoederhalskanker
30-dec-09	47	Afgeschrikt
3-mrt-10	48	Trendy campagne voor vaccinatie
30-mrt-10	49	Opnieuw meisjes voor prik opgeroepen
23-apr-10	50	Aantal patiënten met anuskanker is in twintig jaar tijd verdubbeld

Telegraaf
Trouw
Volkskrant

Appendix I: Interview overview

Overview of meetings and interviews		Organisation & affiliation	Transcript size
30-nov-10	Afsluiting HPV-campagne 2009-2010	RIVM, meeting between GGD's and RIVM	1178 words
9-dec-10	Interview Marina Conyn	RIVM, program manager RVP	2464 words
17-feb-11	Lezing Jannes Koetsier	Gezond Verstand Avond, doctor and vaccination critic	1700 words
17-feb-11	Interview Rolf Remorie	GSK, commercial manager vaccines	4692 words
1-mrt-11	Interview Huub Schellekens	Professor University Utrecht, member CBG	4877 words
2-mrt-11	De Prik en het Meisje	De Balie, documentary about the vaccine	n.a.
8-mrt-11	Interview Marina Conyn	RIVM, program manager RVP	4674 words
10-mrt-11	Interview Inge de Kok	Erasmus UMC, scientific researcher	6132 words
17-mrt-11	Interview Willem van den Oetelaar	Sanofi Pasteur MSD, manager PR and public affairs	4326 words
8-apr-11	Interview Gemma Kenter	AMC, oncological gynecologist	4952 words

Appendix J: Interview questions

This overview shows the main interview questions (in Dutch), depending on specific knowledge, questions are altered, erased or added.

Actorspecifieke vragen

- Hoe zou u uw rol omschrijven in het systeem achter de HPV-vaccinatie?
  (Wat zijn de verrichtingen, doel en verantwoordelijkheden van de partij)?
- Op welke momenten heeft u een rol gespeeld bij de HPV-vaccinatie in Nederland?
  (voor introductie, tijdens introductie, na introductie, op elk moment)?

1e interviewonderdeel, systeemoverzicht

Vragen

- Zijn alle relevante partijen in het systeem achter de HPV-vaccinatie genoemd?
- Zo nee, welke partijen mist u?
- Ontbreken er instituties (normen, wetten, waarden, regels) die van invloed zijn op de HPV-vaccinatie?
- Zo ja, welke instiuties ontbreken er?
- Vindt u het overzicht een correcte weergave van de verbanden tussen de partijen?
- Zo nee, welke verbanden moeten anders?
- Vindt u de systeemkaart volledig of mist u nog aspecten in het overzicht?

2e interviewdeel, dynamiek van het systeem.
De dynamiek van het systeem zal gaan over verschillende aspecten van de HPV-vaccinatie. De vragen gaan over belangrijke gebeurtenissen en hoe die de HPV-vaccinatie beinvloed hebben.

Mijn eerste vragen gaan over ondernemersactiviteiten. Daarbij wordt gekeken naar verrichtingen van ondernemers om de technologie toe te passen en te bevorderen.
De gebeurtenissen die daarin hebben plaatsgevonden zijn klinische trials in Nederland, 6 in totaal. De opening van een productiefaciliteit van Gardasil en markttoelating van Gardasil (2006) en Cervarix (2007).

- Weet u nog andere vormen van ondernemersactiviteit die in Nederland hebben plaatsgevonden?
- Welke nieuwe ondernemersactiviteiten verwacht u in de toekomst (andere producenten, 2e generatie vaccins)?

Mijn volgende vragen gaan over kennisontwikkeling, waarbij zowel technolgische/klinische kennis als kennis van goed beleid/maatschappelijke aspecten aan bod komt. Ook maak ik een onderscheid tussen wereldwijde kennis en Nederlandse kennis.
Belangrijke gebeurtenissen internationaal gezien zijn: Link HPV en BMHK, ontwikkeling VLP's, klinische trials, markttoelating. Belangrijke gebeurtenis nationaal: Rapport gezondheidsraad..

- Welke wereldwijde kennis-ontwikkelingen zijnin uw ogen het belangrijkst geweest voor de ontwikkeling en toepassing van de HPV-vaccinatie (onderzoeksresultaten, technologische ontdekkingen)?
- Welke Nederlandse kennis-ontwikkelingen zijn er belangrijk bij de HPV vaccinatie?
- Is er in u ogen een gebrek aan kennis over de HPV-vaccinatie in Nederland die de het succes van de vaccinatie belemmerd?
- Zo ja, wat voor soort onderzoek moet er in de toekomst gedaan worden om de hiaten in te vullen?

Kennisdiffusie gaat over het verspreiden en toepassen van kennis. Het RIVM wordt daarbij gezien als centrale partij in de kennisdiffusie in Nederland.
Bijeenkomsten waar kennis werd gedeeld en verspreid vond voornamelijk op Europees niveau plaats en pas in 2009 vonden bijeenkomsten door het RIVM plaats.

- Weet u nog bijeenkomsten over de HPV-vaccinatie waarin kennis is verspreid?
- Welke bijeenkomsten of contacten tussen partijen ziet u als belangrijk in de verspreiding van kennis over de HPV-vaccinatie?
- Welke partijen hebben hoofdzakelijk kennis over de HPV-vaccinatie verspreid naar andere partijen/het publiek in Nederland?
- Op welke manieren denkt u dat het beste kennis over HPV-vaccinatie verspreid kan worden naar gerelateerde partijen en de doelgroep voor het vaccin?

De volgende vragen gaan over de keuzes en de rol van de producenten van het HPV-vaccin en de Nederlandse overheid in het implementeren van de HPV-vaccinatie in nederland.
De farmaceutische industrie heeft vaccinatie bevorder door onderzoek te financieren, artsen en eindgebruikers voor te lichten en door te proberen het vaccin vergoed te krijgen.

- Wat ziet u als belangrijke gebeurtenissen in de begeleiding van de producenten in het implementeren van de HPV-vaccinatie in Nederland?
- Hoe vindt u dat de producenten van het HPV-vaccin in Nederland de toepassing van het vaccin in Nederland hebben begeleid?
- Wat zouden de producenten beter kunnen hebben gedaan/kunnen doen?

De Nederlandse overheid is op verschillende manieren betrokken geweest bij de invoering van het HPV-vaccin: GR-advies, besluit tot toevoeging RVP, streven vaccinatiegraad, voorlichting, uitvoering.

- Wat ziet u als belangrijke gebeurtenissen in de begeleiding van de overheid in het implementeren van de HPV-vaccinatie in Nederland?
- Hoe vindt u dat de Nederlandse overheid/overheidsinstanties de invoering van de HPV-vaccinatie in Nederland hebben begeleid?
- Wat zouden de Nederlandse overheid/overheidsinstanties beter kunnen hebben gedaan/kunnen doen?

De volgende vragen gaan over de markt van het HPV-vaccin, daarbij is zowel 'concurrentie' met andere technologien als tussen producenten gaande. Ook de manier waarop de markt naar de eindgebruikers is opgezet is van belang.

- Ziet u de verschillende vormen van BMHK-preventie als aanvullend op elkaar of ziet u de verschillende preventiemogelijkheden ook als 'concurrenten' van elkaar?
- Hoe denkt u dat de mogelijkheid om met andere technologien BMHK te voorkomen/behandelen de HPV-vaccinatie heeft beinvloed?
- Wat zijn uw verwachtingen (huidige systeem, screening, HPV DNA test en HPV-vaccinatie) voor het succesvol voorkomen van BMHK?

Concurrentie producenten/vergoeding van het vaccin

- Wat vindt u van de manier waarop concurrentie tussen Gardasil en Cervarix plaatsvond (hoofdzakelijk Tender)?
- Ziet u de huidge vorm van financiering van de HPV-vaccinatie als de beste manier om het vaccin te vergoeden?
- Welke andere manieren van financiering ziet u als mogelijkheden voor de HPV-vaccinatie?

Markt naar de 'eindgebruiker' toe

- Wat vindt u van de keuze om de HPV-vaccinatie uit te laten voeren door de GGD in massavaccinatiesessies?
- Waar moeten de GGD en het RIVM op letten bij aanbieden van het vaccin?
- Denkt u dat de HPV-vaccinatie beter op een andere manier aangeboden had kunnen worden?
- Zo ja, hoe?

De volgende vragen gaan over gebeurtenissen die de lobby voor en tegen het vaccin bepalen. Hierbij wordt zowel gekeken naar statements van gerelateerde organisaties als naar berichten in de media.

- Welke statements voor of tegen de invoering van de HPV vaccinatie door invloedrijke partijen ziet u als belangrijk?
- Welke mediagebeurtenissen (TV-uitzendingen, uitspraken van voor of tegenstanders in kranten) ziet u als belangrijk in de discussie over de HPV-vaccinatie?
- Vind u dat de discussie over het HPV-vaccin op een goede manier en op het juiste moment heeft plaatsgevonden?
- Zo nee, wat was er dan mis met deze discussie en hoe had deze discussie beter gekund?
- Wat vindt u van de
    - Rol van wetenschappers?
    - Rol van de media?
    - Rol van de politiek?
    - Rol van gezondheidsorganisaties?
    - Rol van vaccinatie-critici?

Actorspecifieke vragen deel 2

- Zou u uw rol in het verleden anders hebben ingevuld met de kennis van nu?
- Zo ja, hoe?
- Hoe ziet u uw de rol in de toekomst bij de HPV-vaccinatie?

Algemene vragen + Lock-in

- Denkt u dat sommige partijen teveel hebben gehandeld uit gewoonte en daardoor niet adequaat hebben gehandeld bij de HPV-vaccinatie?
- Weet u voorbeelden van zulke beperkingen bij bepaalde partijen (geef eerst eigen voorbeelden)?
- Hoe denkt u dat in de toekomst te voorkomen is dat door gewoontes niet goed gereageerd wordt op potentiele problemen?

- Welke gebeurtenissen hebben volgens u het meest bijgedragen aan de huidige vaccinatiegraad/acceptatie van de HPV-vaccinatie?
- Wat zijn sterke punten voor de HPV-vaccinatie (zowel technologische gezien, als gericht op beleid)?
- Wat zijn zwakke punten/belemmeringen voor de HPV-vaccinatie (zowel technologische gezien, als gericht op beleid)?
- Welke oplossingen zijn er in uw ogen om de HPV-vaccinatie in Nederland meer succesvol te maken?

- Welke aspecten van de invoering van het HPV-vaccin ziet u als leerproces voor de invoering van andere vaccins?

Buitenland

In Engeland en Denemarken is de HPV-vaccinatie succesvoller ingevoerd, in andere landen is de invoering van het HPV-vaccin juist minder succesvol geweest dan in Nederland (IJsland, Duitsland). Indien u bekend bent met situaties in het buitenland wil ik u daar graag enkele vragen over stellen.

- Welke overeenkomsten ziet u tussen Nederland en andere landen bij de invoering van de HPV-vaccinatie?
- Welke verschillen ziet u tussen Nederland en andere landen bij de invoering van de HPV-vaccinatie?
- Welke land zie u als voorbeeld waar op een goede wijze met de HPV-vaccinatie is omgegaan?
- Hoe zouden de partijen in Nederland lering kunnen trekken uit de situatie in andere landen?
- Ziet u iets in meer voorlichting/samenwerking op Europees niveau?

Overig

- Heeft u nog vragen of opmerkingen over de HPV-vaccinatie in Nederland?
- Heeft u nog vragen of opmerkingen over mijn onderzoek?
- Weet u nog andere partijen/personen binnen deze partijen die u mij aanraad om te interviewen?