Chapter 1
General Introduction

Outline

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1.
General Introduction

1.1 Historical facts on cervical cancer

Cervical cancer is the neoplastic outgrowth of cells arising from the cervix uteri. Cancer is an ancient word which has been used ever since men started describing evidence of tumours in papyruses and in lesions found in mummies. Dating back to 3,000-2,000 BC., Hippocrates (460-370 BC) gave a detailed description and classification of tumours in his documentations, including cervical cancer (Bordet, 2016).

In the mid-19th century Rigoni-Stern noticed that cervical cancer is rarely seen in celibate nuns (Rigoni-Stern, s.d.). Later on, epidemiologists in the early-20th century produced documentation in which they described that cervical cancer was commonly seen in female sex workers and women whose husbands had numerous sexual partners or were regular customers of prostitutes (Mak, 2004) (Bayo et al., 2002) and hypothesised that a transmittable agent was involved in the development of cervical cancer. Already in 1924, Dr. Hinselmann from Germany, founder of the colposcopy, worked out his method to examine the cervix (Fusco, 2008). At the same time, in February 1925, Dr. G. Papanicolaou started with a systematic study of vaginal smears collection, provided voluntarily by female workers at the New York Women's Hospital to find diagnostic criteria to diagnose cervical cancer. Both scientists were convinced that either micro- or macroscopic patterns seen in the cervix could lead to early detection of cervical cancer. Furthermore, stating that early detection and treatment could prevent death. Even at present collection of cervical cells by a brush is still the most common method used

in many countries for early detection of cervical lesions. In addition, examination of the cervix by colposcopy is worldwide used as the standard method for evaluation of women with abnormal smears. However, both methods are subjective and are associated with false positive and false negative results. In 1982 Professor H. zur Hausen and his colleagues provided the first evidence that cervical cancer was caused by Human papillomavirus type 16 (HPV) (Duèrst, 1983) (Boshart, 1984). In the course of time more so-called high risk or oncogenic HPV types associated with cervical cancer were detected. These findings have led to a better understanding of the pathogenesis of cervical cancer and a change in the approach of the diagnostic process. Today early detection of (pre)cancerous cervical lesions by means of the detection of high risk HPV (hrHPV) has proven to be more sensitive than cytology although at the cost of a slightly lower specificity (Rijkaart et al., 2012) (Arbyn et al., 2012).

In the course of time, scientists had figured out that cancer caused by HPV could be prevented by vaccinating against this virus. The development of subunit HPV vaccines were prepared based on the recombinant viral capsid protein L1, also called virus-like particles (VLPs), and started long time ago. (Schiller, 1999) The vaccines have proven great immunogenicity and also to be safe after all three phases of clinical trials. (Harro et al., 2001) The bivalent vaccine has shown 100% and 89.6% efficacy against the incidence of HPV-16 & -18 and 100% efficacy against persistent infection of both virus type. (Pagliusi, 2004) The quadrivalent vaccine was first licensed in 2006, and the bivalent vaccine in 2007. (WHO, 2017)

HPV vaccinations can be expected to make a positive contribution to the goal of eradicating cervical cancer. Three HPV vaccines are currently available on the market. Gardasil® by Merck Inc., which is a tetravalent vaccine covering two high-risk types, namely HPV-16 and -18, and two low risk types, namely HPV-6 and -11. Cervarix® by GlaxoSmithKline, is a bivalent vaccine that covers HPV-16 and -18. The third HPV nonavalent vaccine, Gardasil-9 ® by

Merck Inc., came on the market in 2015, covering HPV genotypes 6/11/16/18 and the next five most carcinogenic types which are HPV-31/33/45/52/58. At present many countries have implemented HPV vaccination. Australia is the first country which implemented HPV based vaccination with great success (Lee et al., 2017).

From a global health perspective the prevention strategy aim for cervical cancer is to switch for the detection of (pre)cancerous lesions from a subjective method like cytology to an objective HPV assay and to implement prophylactic HPV vaccines (Arbyn et al., 2012) (Castle et al., 2012). The ultimate goal of the World Health Organisation (WHO) is to eradicate cervical cancer (Bosch et al., 2013).

1.2 The cervix uteri

The cervix is a small part of the uterus that protrudes into the vagina and is mainly composed of fibromuscular tissue (Alan et al., 2013). The cervix consists of two parts. The *ectocervix* which *i*s the outer part of the cervix on the vaginal side and is lined by non-keratinizing stratified squamous epithelium. And *the endocervix,* which is the inner part of the cervical canal on the uterine side and is lined by columnar epithelium consisting of glandular epithelial cells which secrete mucus (Dallenbach-Hellweg et al., 2006).

The squamocolumnar junction (SCJ) is the border where the ectocervix meets the endocervix. As a result of hormonal changes starting at puberty and growth of vaginal bacterial flora metaplastic squamous cells replace columnar cells at the SCJ causing the junction to migrate proximally to the endocervix (new SCJ). The transformation zone is the area between the original SCJ and the new SCJ (Herfs et al., 2013).

1.3 Human papillomavirus

Human papillomavirus (HPV) is a circular double-stranded DNA virus, that ranges from 6953 bp-8607 bp in length (Doorbar et al., 2012). They can infect the epithelium of the skin, the anogenital tract and the upper aero and digestive tract. HPV is a highly infectious virus, known as the most common sexually transmitted disease and has the capacity to cause cancer (Forman et al, 2012). Until now about 200 Human papillomavirus types were found in humans, making it one of the most extensively studied hosts (de Villiers, 2013) (Doorbar, 2005). Approximately 40 types are known to infect the genital tract. According to their oncogenic potential HPV types are subdivided into low-risk and high-risk types. 12 types of mucosal HPV types are known to cause cervical cancer and are classified as "high-risk HPV types" (HPV-16,18,31,33 45,51,52, 56, 58,59, IARC Class1) Other HPV types have been classified as "possibly high-risk" (HPV-68, IARC clas2A) or "probably high-risk"(HPV-26, 53, 66, 67, 69, 70, 73 ,82, 85 and 93 IARC class 2B) (Bouvard V. et. al, 2009), The latter group accounts for a minority (about 3%) of cervical cancers. Low-risk HPV types are associated with the development of benign lesions such as condyloma accuminata, papilloma of the respiratory tract and cutaneous warts.

The viral genome contains eight open reading frames (ORF's) and can be divided in early viral genes (E1, E2 and E4-7) and the late viral genes (L1 and L2). The early genes encode proteins which ensure that the viral genome can be reproduced, while the late proteins have a structural function and encode the structural proteins of the virus capsule, necessary for assembly of the virus. A large non-coding part referred to as the long control region (LCR) contains promoter and enhancer elements necessary for replication and transcription of the viral DNA.

E2 acts as transcription factor that regulates the viral early promoter and controls the expression of E6 and E7. Expression of E6 and E7 leads to interference with the tumour suppressor genes p53 and pRb, respectively, causing the cell cycle to become disrupted and causing instability of the cellular genome (de Villiers, 2013) (Bouvard et al., 2009).
HPV-16 and -18 are known as the two most oncogenic genotypes and are also responsible for the most cancer cases globally.

1.4 Pathogenesis of cervical cancer

For neoplastic transformation of the cervical epithelium, the cell cycle is disrupted by the interference of E6 and E7 oncoproteins with the tumour suppressor genes p53 and pRb respectively. This happens when HPV infections are not cleared by the immune system, and the infection persists. Ultimately, the viral genome might be integrated in the human genome. First the HPV genome is linearized. As a result, the regulation of the E6 and E7 genes is lost, leading to overexpression of E6 and E7 resulting in a transforming infection with dysplastic cells and finally to cancer.

1.5 HPV and cancer burden in the world

HPV is the second most common infectious agent after H. Pylori to cause cancer worldwide (Ferlay et al., 2012). The adjusted global HPV prevalence is 11.7% while this percentage varies considerably per country. Western Asia has the lowest prevalence (1.7%) and the Caribbean the highest (35.4%) (Bosch et al., 2005). Annually approximately 500,000 (ASR=14.0 per 100,000) new cases of cervical cancer are diagnosed in women worldwide and it's the cause of death in approximately 250,000 (Ferlay et al., 2012). 85% of

yearly new cases of cervical cancer are attributed to low and middle-income countries (Ferlay et al., 2015).

Besides cervical cancer, HPV is responsible for 88.0% of anal cancers worldwide with similar cancer case distribution between men and women. Furthermore, 78% of vaginal cancers are caused by HPV, whereas for penile cancer this is 50%, oropharynx 30.8%, vulva 24.9%, larynx 2.4%, oral cavity 2.2%. In case of head and neck cancers the number of attributable cases in male was remarkably higher compared to female. Also, the prevalence of HPV in oropharyngeal cancer is increasing, while the incidence of disease remains the same (De Martel et al., 2017).

The most common HPV genotypes are: -16,-18,-45,-31 of which HPV -16 and -18 are responsible for 70-75% of cervical cancers in most populations (de Sanjose et al., 2010). HPV genotype prevalence distribution may vary per region and appears to be more related to sexual behaviour than to ethnic differences.

HPV is the most important cause of cervical cancer. Poverty, lack of education, promiscuity or having a promiscuous partner, young age at sex-arche and immunosuppression (mainly in HIV patients) are associated with a higher risk for HPV infection and are also described in the literature as relevant determinants (Burchell et al., 2006) (Moscicki et al., 2006). Association between cervical cancer carcinogenesis and cofactors such as cigarette consumption, multi-parity and the use of oral contraceptives are well established. However, their precise role in affecting the risk of viral persistence is unclear (Moscicki et al., 2006) (Franco et al., 2012).

The WHO aims to eradicate cervical cancer. But, the high world incidence, prevalence and mortality rate of cervical cancer is mainly to be attributed to middle- and low-income regions (Li et al., 2010). Furthermore, implementation of prevention programmes in all parts of the world remains a challenge.

1.6 HPV and cancer burden in the Caribbean

The Caribbean region is a low-income region and cervical cancer is the second most prevalent cancer in women with a high mortality rate (ICO HPV Information Centre, 2016) (de Sanjose et al., 2010) (Guan et al., 2012). Scientists are trying to address the problem from global health perspectives, but basic issues like implementation of data registry and prevention programmes in the region remain a challenge (Banydeen et al., 2015) (Consendine et al., 2014). The Caribbean region constitutes of forty-four countries. Of these countries, 25 are geographically located in the Caribbean seas (Non-Continental Caribbean countries) and the other countries are located in North, Central and South America (Continental Caribbean countries) (Digital Library of the Caribbean dLOC). The current Caribbean population is approximately 43,714,956 with a population density of 194 per km^2 (502 people per mi^2) (Elaboration of data by United Nations, Department of Economic and Social Affairs, Population Division.). The Caribbean region is known as the place on earth with the most diversity in terms of ethnic distribution (Premdas, 1996). During the colonisation period more than 6 million enslaved people were transferred from Africa to the Caribbean. Therefore, the most predominant ethnicities seen in the Caribbean are people of African descent or a mixture of Africans with one of the many races that found their home in the Caribbean region (Premdas, 1996).

The heterogeneous diversity in the Caribbean is notable by the division in races, ethnicities, languages, religions and cultures. In this region we find immigrant societies with weak social cohesion and weak community organisation. (Knight, 1990) (Girvan, 2002) (Hillman, 2003) (Trouillot, 1992) (Premdas, 1996).

There are many reasons why it is important to understand the complexity of the Caribbean region for the objectives of the studies presented in this thesis.

Sexual practices and habits may vary between regions based on the social and cultural background. Caribbean people are defined as persons with a complex mixed identity having low social economy resources and sometimes extreme poverty. The region is an attractive holiday destination and known for sex-tourism (Dominguez, 2010) (Agard-Jones, 2011). In order to investigate the most effective way to implement primary (vaccination) and secondary (screening) prevention in local Caribbean healthcare systems, it is important to really understand this region with all its complexities, which are closely connected to its historical events.

A good understanding of the aforementioned may lead to a better and more effective approach with regard to the next two aspects, which are essential and necessary to solve the cervical cancer problem. First is the commitment by government policy makers and private partners who are responsible for the management of the logistics in healthcare programmes. The second is the commitment by the population that must respond by actively participating in healthcare programmes. Thus, creating an awareness within the population of this urgent health issue and the preventive measures being offered. At the same time people need to have sufficient confidence and trust in the national healthcare system. Both play an important role in the willingness to participate. A dysfunction in one of previous aspects will lead to failure in the programme's purpose and this will lead to negative consequences in healthcare, finance and economic fields.

HPV and cancer in the Caribbean. In the Caribbean region, an up-to-date cancer registration and implementation of epidemiology registration protocols, remains a challenge (Consedine et al., 2014) (Banydeen et al., 2015) (Luciani, 2015). A total of 18 non-Latin Caribbean countries were included in a cervical cancer situational analysis report in 2013. Five countries namely: Belize, the Cayman Islands, Guyana, St. Vincent and the Grenadines and

Suriname, responded as having a cervical cancer policy in place. Seven countries (Belize, the Cayman Islands, Dominica, Guyana, Jamaica, St. Vincent and the Grenadines and Trinidad and Tobago) reported having an organized cervical cancer screening programme. Beside Haiti, all countries reported that they offer Pap smears. VIA screening (visual inspection with acetic acid) was reported by eight countries namely: Belize, Cayman Islands, Guyana, Haiti, St Kitts & Nevis, St Vincent & the Grenadines, Suriname and Trinidad & Tobago. Population based HPV testing within the public health system was reported in four countries namely: Barbados, Bermuda, Cayman Islands, Trinidad & Tobago. (Martin et al., 2013) According to the official Pan American Health Organisation (PAHO) report, (*Regional strategy and plan of action for cervical cancer prevention and control. Final report of the 29th Pan American sanitary conference 69th session of the regional committee of the WHO for the Americas. Washington, D.C., USA, 25-29 September 2017)*, seven Caribbean islands reported having implemented HPV vaccination as part of their National Immunisation Plan. Of these seven islands, four (Bahamas, Barbados, Puerto Rico and Trinidad) implemented vaccination for both genders. Additionally, Bonaire also has a National Immunisation Programme that includes the HPV vaccine. Bonaire is a Caribbean island with a secondary prevention programme, however it's not mentioned in the PAHO report.

1.7 Cervical cancer and its prevention on Curaçao

Curaçao is an island located in the southern Caribbean about 40 miles north of the coast of Venezuela and a country in the Dutch Kingdom, with a population size of 157,000 [CBS estimate 2016]. The majority of the residents are of Afro-Caribbean descent or a mix of European and Afro-Caribbean descent [CBS 2012]. A cancer registry was initiated on Curaçao in 1977 by

dr. S.C. Freni covering the former Netherlands Antilles, excluding Aruba, and remains located at the Pathology Department of the central laboratory of the Analytic Diagnostic Centre on Curaçao.
The pathology department on Curaçao served the other islands of the former Netherlands Antilles namely St. Maarten, Saba, St. Eustatius and Bonaire (until the status change in 2010).

Cervical cancer was the second most common female cancer in the Netherlands Antilles with a crude[1] annual incidence of 23.5 in the period of 1968-1973 and 20.3 in the period of 1974-1979 (Freni et al., 1981). In 1988 Dr. Wildschut, a gynaecologist on Curaçao, noted an increase in the number of cervical cancer cases reported between the period 1973-1977 and 1978-1982. To verify this assumption an analysis was performed, in which they also looked at possible factors that might have influenced this increase. The absolute increase was mainly due to a change in age distribution of the female population of Curaçao, and thus not to an actual increase in the incidence of cervical cancer (Wildschut et al., 1988).
The availability of opportunistic screening for cervical cancer probably enabled the decrease of cervical cancer incidence on Curaçao. In the period 1983-1998 incidence of cervical cancer on Curaçao was 14.3 per 100,000 women (Bax et al., 2004). This was low compared to other areas in the region but relatively high compared to other western countries.[2] The last reported incidence of cervical cancer on Curaçao was 16.0 in the period 2009-2011 (ASR World). At present, during our analysis, cervical cancer is the fourth most common cancer among women on Curaçao, with a preliminary incidence

[1] *The figures of Freni represent 5 islands, so a population of Ca. 200,000 and are not age standardized (ASR World). Meaning that the figures from the different studies in this section must be interpreted carefully because they are not standardized to each other.*
[2] *The figures of Bax et al. (2004) represents only the local population of Curaçao*

of 12.0 per 100,000 women (ASR World) between 2013-2016 [Data source: ADC Curaçao].

Due to the small numbers of cervical cancer cases (15-20) reported annually on Curaçao, and to minimize the influence of fluctuations it is suggested in the monitoring of cervical cancer incidence to focus on the trend, whether this remains the same or if there is a decline. (Table 1.1). Most of the reported cases are in the age group 60-74 (Table 1.1). The lack of early detection, which can be achieved by means of screening programmes, may explain the higher incidence in older patients.

Table 1.1
Number of cases of cervical cancer Curaçao 2013-2016

Age-group	№ of cases	Female person years
15-29	4	57,334
30-44	11	65,260
45-59	15	81,114
60-74	20	54,041
75 +	10	23,077
Total	**60**	280,826

Data source: Department of pathology
Analytic Diagnostic Centre (ADC).

Prevention care is a field that is continuously growing and developing on Curaçao. This was also the case in 2013 at the start of this scientific study, when attention was directed at the issue of HPV and cervical cancer being a public health concern, both among the general population and by caregivers. The island has a well-organised youth vaccination programme. However,

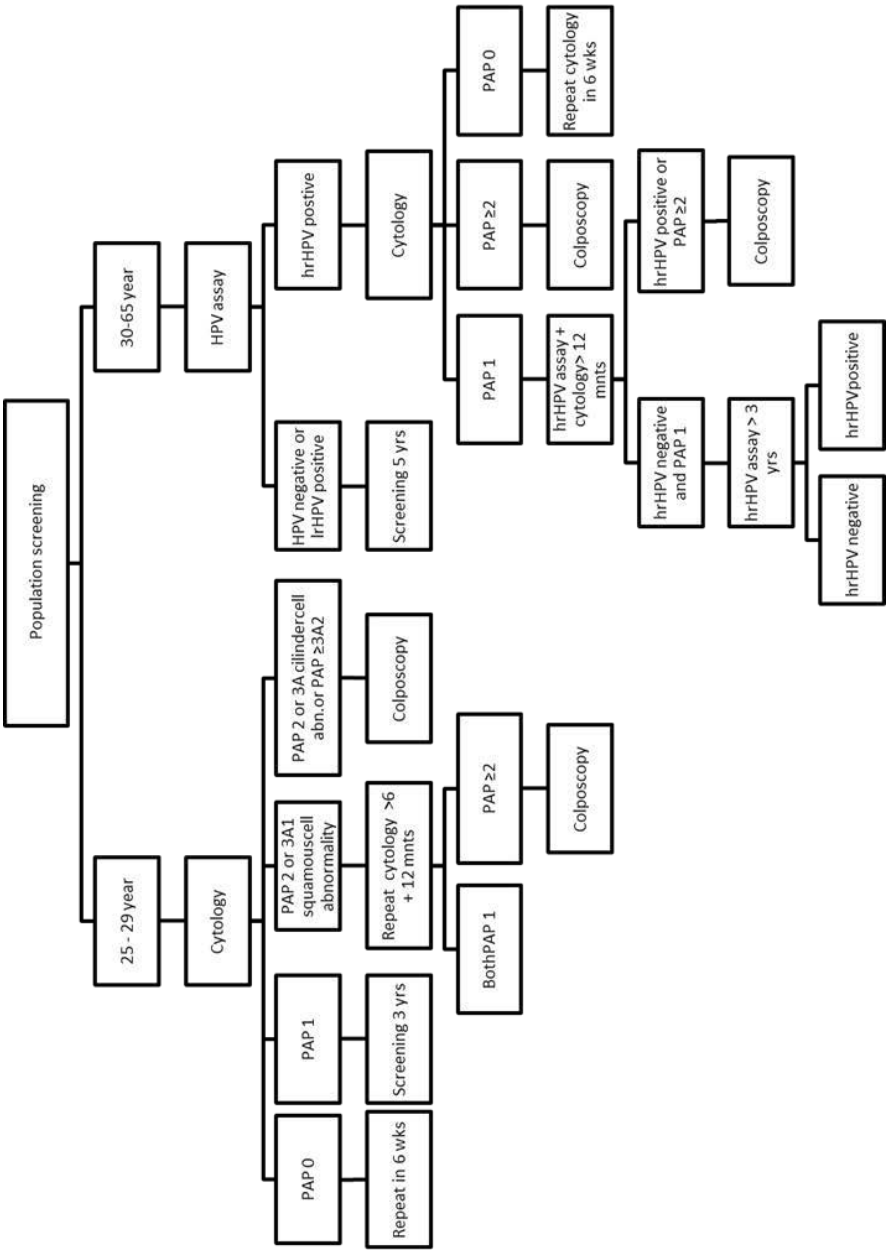
HPV vaccination, which is an important primary prevention, had not yet been implemented. Today both prophylactic vaccines bi and tetravalent are available on the island, but only administered and covered privately/on personal initiative and expenses.

The current population screening started on 01-06-2016, under the direction of Fundashon Prevenshon (FP). Women in the age group of 25-65 years of age receive a written invitation at their home address, inviting them to participate in the screening for cervical cancer.

The woman can choose to do this at her GP's office or she can pay a visit to FP where a registered nurse collects the sample. People who are eligible for screening, but for some reason have not received an invitation, can also visit FP or their GP and ask for the possibility to be screened.

For women younger than 30 years old only cytology screening of the cervix is performed, meaning the cervix is analysed for the presence of abnormal cells. In the population group between 30-65 years, HPV testing with triage testing for cytology is done. The samples are tested for the presence of HPV at the Medical Laboratory Services (MLS) Curaçao. Samples that need further cytology analysis are sent to the Netherlands. The cytology results are sent back to FP. FP follows up by sending the results to the GPs, who have the responsibility to communicate the results to the patients who have been tested. Figure 1.1 shows the flowchart used for screening and referral on Curaçao.

Figure 1.1 Flowchart of screening for cervical cancer Curaçao



Flowchart designed by Dr. I. Gomes Bravio, Gynae-Oncologist, St. Elisabeth Hospital, Curaçao

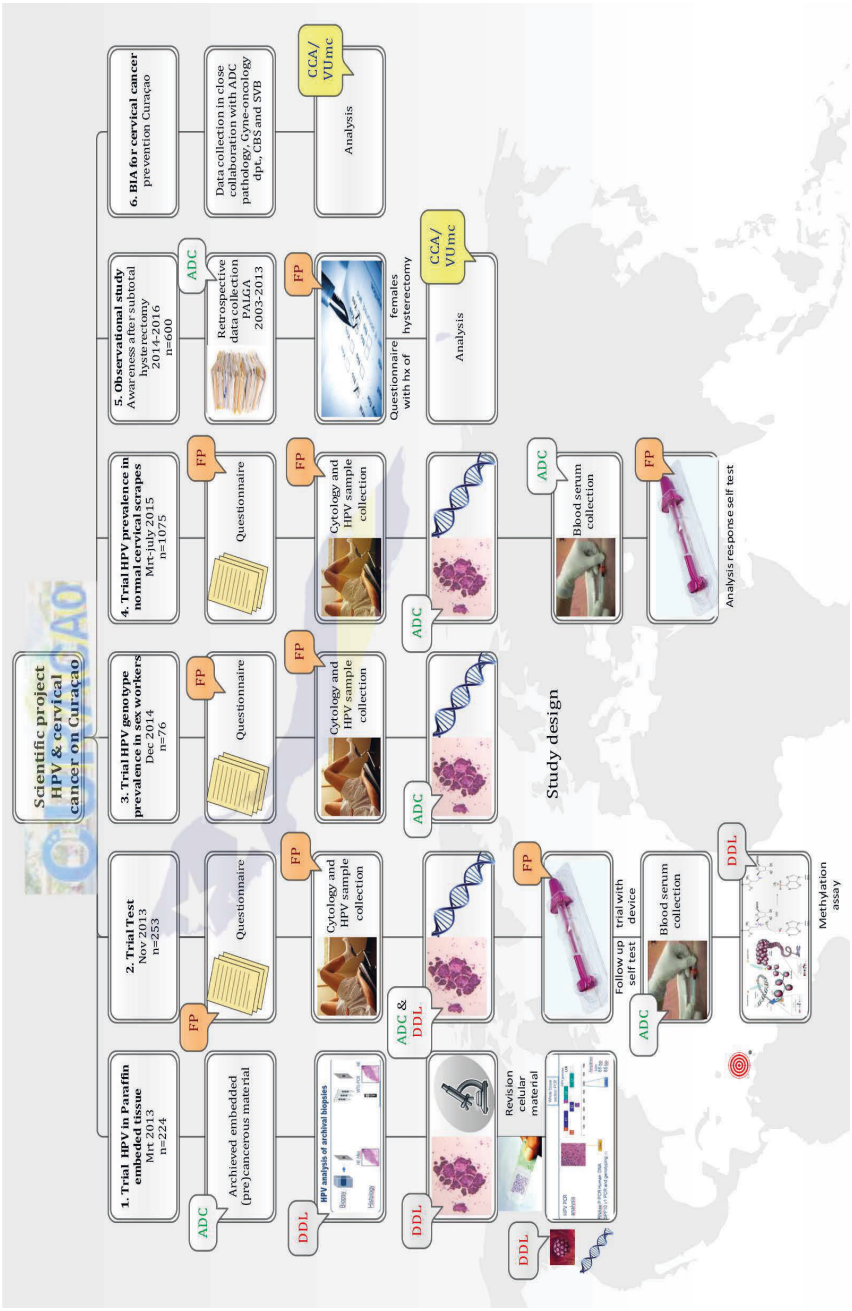
Currently there are 81 GPs in family practice and in addition there are 15 other registered GPs, who work either as insurance physician, company doctor, observer or doctor for a specific group (Snoeijs et al., 2012). Not all healthcare providers involved with screening are following the guidelines as stipulated and implemented by FP in June 2016. Some of them are still sending their smear samples to the National Pathology Department, which was the procedure before FP started with the screening programme.
According to the National Department of Pathology 60 new cases of cervical cancer were registered in 2013-2016. The most common registered cervical cancer type is squamous cell carcinoma which occurs at an average age of 52 years.

A decrease in the national screening registration has been noticed since 2016. An explanation for this could be that 2016 is the year in which FP initiated the population screening programme. The Pap smears collected through this programme are sent to the Netherlands for cytological analysis and are not automatically registered within the national screening registration. To maintain a quality of data registry on cervical cancer and to make sure that the information is complete on a national level, it will be necessary to centralise the registration like it was before and/or make adjustments if deemed necessary. It is also important that all healthcare professionals involved with the phases of cervical cancer cycle, are committed to work towards a uniformed practice throughout the whole process.
The WHO/PAHO have developed and stipulated guidelines and (mandatory) requirements with regards to implementation of prevention programmes. Some of the elements included in the guidelines and/or requirements are the assignment of a programme coordinator, a quality assurance process, including quality indicators and supervision of the set-up of the information system for programme monitoring and evaluation in accordance with pre-

determined indicators. Adherence to these guidelines and requirements are beneficial to the programme in terms of efficiency and efficacy.

Financial resources play an important role in the implementation of a screening programme. The finances of the healthcare system on the island are split up in two parts: private and public resources (Varlack, 2014). The public finances are administered by the social insurance institution being the Sociale Verzekeringsbank (shortly SVB). The annual report of the SVB for 2016 indicates that the government financed healthcare with ANG 260 million in 2016 and ANG 261 million in 2015 (Antillean Guilders). The total costs covered in 2016 and 2015 amounted to ANG 494 million and ANG 454 million respectively (Sociale Verzekeringsbank, 2017).

Figure 1.2 Study design HPV and cervical cancer research on Curaçao



1.8 Outline of the thesis

This research is an initiative of and was commissioned by Fundashon Prevenshon (FP). The research project started in January 2013 and consists of 6 parts which are illustrated in figure 2. The data collected for the study date back to the period before the start of the population-based screening. Documents from the WHO on the implementation of prevention programmes, policy for cervical cancer and guidelines for conducting scientific research in this field, were used as a template for the study design. The aforementioned third-party documents were used as reference for this study. The results are intended to be supportive in decisions to be made for both policy and guidelines concerning the prevention of cervical cancer on Curaçao.

Chapter one gives an overview of available literature on the role of the Human papillomavirus (HPV) in cancer worldwide, in the Caribbean and on Curaçao.

To understand the behaviour and reaction to screening invitations we describe in Chapter two a qualitative and quantitative analyses of data on health and social determinants of the female population on Curaçao, obtained from questionnaires used for this scientific project. We analysed the results and compared these with published data in the field of health and social sciences on Curaçao and in the Caribbean region.

To get insight in the awareness of women about the status of their cervix after hysterectomy we analysed in *Chapter three* the proportion of supravaginal hysterectomies in the period 2003-2013 and looked at the number of cervical stump carcinomas. In addition, we handed out a questionnaire to females with a history of hysterectomy who participated voluntary, aiming to analyse the level of awareness in this group. It appeared that the women were not aware that the cervix was still preserved. They had assumed that the cervix had been

removed automatically, which is the reason that these women discontinue their screening for cervical cancer.

To find out which type of vaccine should be used on Curaçao we describe in Chapter four a study that we performed on paraffin embedded tissue from cervical (pre)cancerous material, where we analysed the most prevalent HPV types in cervical cancer on Curaçao.
The results show that compared to the world population the prevalence of HPV type 16 and 18 in cervical cancer is lower and consequently the contribution of the HPV genotypes 31, 45, 51, 52 and 58 is higher.

In *Chapter five* the prevalence of HPV in the general population of on Curaçao is described. To our knowledge, this is the only HPV prevalence data in the Caribbean region obtained from a randomly selected female population with HPV type prevalence distribution in four age groups.
Results of this analysis describe a high HPV prevalence in a population of randomly selected women in four age groups (25-65 years) from Curaçao.
Women with multiple sex partners are known to have a higher risk to develop cervical cancer, implicating that sex workers are more at risk.

Chapter six provides information about an analysis of HPV-genotype prevalence in cervical scrapes and related risk factors of Female Sex Workers (FSW) working in a legal brothel with routinely medical monitoring in comparison with women not working in the sex industry. The results show that HPV prevalence was not different from women not working in the sex industry, probably because FSW were more aware of STD and better educated in sexual health issues than non-FSW.

In *Chapter seven* we summarise and discuss our findings and give recommendations for implementing vaccination and screening on Curaçao based on our research findings and financial data collected from Curaçao.

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