

Cover Page



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**Title:** Transmission and treatment of cutaneous warts in general practice

**Issue Date:** 2013-09-25

## **CHAPTER 11**

### **Summary**



Cutaneous warts are caused by the human papillomavirus (HPV) and are one of the most common reasons to consult general practice, especially for children. Patients seek treatment because warts cause physical or psychological discomfort, as the case of the girl with plantar warts illustrates in **Chapter 1**. Her everyday questions *How did I get warts?* and *How can I get rid of warts?* reveal the lack of knowledge on the *transmission* and *treatment* of warts. Thus, the two general aims of this thesis are to examine risk factors for the transmission of HPV in order to provide direction for evidence-based recommendations for prevention of warts (**Part 1**), and to investigate the effectiveness of the most commonly used treatments in general practice in order to optimise treatment of warts in general practice (**Part 2**).

## Part 1: Transmission

With little evidence available on the epidemiology and transmission of warts, the aim of **Chapter 2** is to determine the prevalence of warts in an average primary school population of children and explore relations with environmental risk factors. In the observational study among four primary schools, one third of all children (n=1565) are found to have warts: 20% have plantar warts, 9% have hand warts and 4% have both. Prevalence increases with age and is lower for children with non-Caucasian skin types. Remarkably, parental questionnaires show that half of the parents of children with warts are not aware that their children have warts. Relations with risk factors suggest that transmission takes place in the family and school class, rather than in public places such on which recommendations for wart prevention focus.

Based on the cross-sectional relations with environmental factors found in Chapter 2, a model for the degree of HPV exposure (figure 3.1) is designed in **Chapter 3**. To test the model, a prospective cohort of primary school children is established by examining the children from Chapter 2 again for the presence of warts after 1 year (n=1001). The incidence rate of warts is found to be 29 per 100 person-years at risk. The transmission in the family and school class appear to be important in the development of warts; children from families with at least one family member with warts have a more than doubled risk on developing warts (hazard ration 2.1), and children in school classes with more other children with warts also have a higher risk to develop warts (hazard ratio 1.2 per 10% increase in wart prevalence in school class). Several factors related to transmission in public places do not prove to increase the risk of developing warts. These findings suggest that recommendations on the prevention of warts should focus more on limiting transmission in families and school classes rather than in public places such as swimming pools.

**Chapter 4** focuses on the HPV types responsible for the development of warts. The objective is to determine HPV type specific prevalence of warts in general practice and explore

their relations with patient characteristics. This chapter introduces the newly developed HPV typing technique for genotyping all known wart-associated HPV types collected in wart swabs. Out of 744 warts in 246 patients consulting general practice, HPV types 1, 2, 27, and 57 are most prevalent. In only 14% of warts are other HPV types detected. In contrast to the clinical profile of warts associated with 2, 27, and 57 (from the alpha genus), warts associated with HPV 1 (from the mu genus) usually occur in children, on a plantar surface, and have a short duration before presented in general practice. In 74% of patients with multiple warts, one HPV type is shared in all warts of that patient. These findings pave the way for research on HPV type-specific transmission patterns as well as HPV type-specific treatment.

## Part two: Treatment

There is no recent research available on the natural course of warts. **Chapter 5** describes the natural course of the cohort of 333 primary school children with warts at baseline. Half of all children with warts are free of warts within one year. Young age and non-Caucasian skin type are found to enhance resolution. Of all children, 20% consults general practice with their warts (mostly treated with liquid nitrogen cryotherapy or high-dose salicylic acid ointments) and a further 18% only uses over-the-counter medication (mostly dimethylether/propane cryotherapy or low-dose salicylic acid preparations). Children with large or inconvenient warts are more likely to start OTC or GP treatment. These findings on the natural course of warts provide useful information in the process of shared decision-making with parents and children to treat or not to treat warts.

A wide range of options is available for wart treatment. Before the studies of this thesis were conducted, salicylic acid seemed to be the most effective treatment option in literature even though the available evidence was sparse and conflicting. **Chapter 6** aimed to investigate whether the choices of GPs in the treatment of warts were in agreement with this available evidence. A nationwide random survey among 280 Dutch GPs showed that cryotherapy was the first choice treatment for common as well as plantar warts. Salicylic acid was used less frequently and often in combination with cryotherapy. A wait-and-see policy was preferred by less than 20% of GPs and monochloroacetic acid by only 3%. Thus, cryotherapy is preferred in practice while salicylic acid is preferred in the available evidence. This discrepancy may be partly due to the low quality of the underlying evidence.

**Chapter 7** presents the results of the first Warts Randomised Treatment Study (WARTS-1). This multicenter, pragmatic trial compares the effectiveness of liquid nitrogen cryotherapy, salicylic acid self-application and a wait-and-see policy in immunocompetent patients presenting new warts in general practice (n=250). Remarkably, treatment response differs

considerably for patients with common warts and patients with plantar warts. For common warts, cryotherapy is the most effective treatment (49% of patients cured after 3 months) with acceptable side effects, the lowest treatment burden and highest patient satisfaction. For plantar warts, both active treatments are not relevantly more effective than a wait-and-see policy (23% of patients cured after 3 months). Plantar warts are considerably more persistent among adolescents or adults than among children.

In the search for a more effective first-line treatment, **Chapter 8** presents the second Warts Randomised Treatment Study (WARTS-2). With the knowledge gained from WARTS-1 that the response to treatment differs for common and plantar warts, WARTS-2 is conducted as a multicenter, pragmatic, parallel group trial. The effectiveness and side effects of monochloroacetic acid (MCA) are compared to cryotherapy (the most effective treatment from WARTS-1) for patients with common warts, and compared to cryotherapy combined with salicylic acid for patients with plantar warts. It concludes that MCA is a good alternative for cryotherapy for common warts. The effectiveness of MCA (43% of patients cured after 3 months) is comparable to the effectiveness of cryotherapy, but MCA avoids pain during treatment. This could be appealing for treatment in children who often fear the pain during cryotherapy. For plantar warts, MCA (46% of patients cured after 3 months) is preferred over cryotherapy combined with SA (39% of patients cured after 3 months) based on effectiveness, side effects and treatment burden.

Because we know from the above trials that the usual treatments of warts fail for about half of all patients, it seems useful to identify subgroups of patients that will better respond to specific treatment. **Chapter 9** aims to explore the relation between specific HPV type infecting the wart and the response to treatment. For common warts, specific HPV type did not turn out to be relevant for practice, because most common warts were associated with the HPV types 2, 27, and 57, which show comparable response to treatment. For HPV 1-associated plantar warts the probability of cure after a wait-and-see policy was 8 times higher than for HPV 2, 27, and 57-associated plantar warts. When treated, salicylic acid is more effective than cryotherapy for both HPV 1-associated plantar warts and HPV 2, 27, and 57-associated plantar warts. Thus, HPV testing of warts is a new direction to optimize treatment of plantar warts.

The general discussion in **Chapter 10** brings the conclusions of this thesis back to daily practice. The most important finding to answer *How did I get the warts?* is that warts are mostly transmitted in families and school class. To address *How can I get rid of the warts?* patients should be informed about the benign natural course, the limited effectiveness of available treatments and its side effects. Subsequently, a shared decision should be made to either wait and see, or start treatment: cryotherapy or monochloroacetic acid for

common warts, monochloroacetic acid or a combination of cryotherapy and salicylic acid for plantar warts. Finally, the most important recommendation of this chapter is to develop a decision tool for the treatment of warts supported by the occupational group of general practitioners for the optimal use of the available knowledge for patients with warts. This tool can guide patients whether or not to visit general practice for treatment, and advise physicians which treatment to use for specific groups of warts or patients.