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**Title:** Transmission and treatment of cutaneous warts in general practice  
**Issue Date:** 2013-09-25
CHAPTER 1

General introduction
DAILY PRACTICE

A 10-year-old girl consults general practice with a plantar wart that has persisted on her left foot for over one year. Her medical history is unremarkable. She is accompanied by her mother who always makes sure her children use flip-flop sandals in swimming pool changing areas and shoes in primary school gyms. ‘I don’t know how she got the wart, but I don’t want her to get any more and I don’t want her to give warts to other people’. When the natural course and several over-the-counter (OTC) treatments failed to help, she encouraged her daughter to visit her general practitioner (GP). Although the girl is worried about the treatment, she agreed to get rid of the wart because it is painful when running and it looks unpleasant. ‘My brother had 13 warts and was bullied by his friends and I don’t want that!’

GPs welcome patients with cutaneous warts every day. Like the girl, patients usually have two important questions:
1. How did I get the warts?
2. How do I get rid of the warts?

At first sight, these questions about this common ailment seem easy to answer. Especially because warts are known to be caused by the human papillomavirus (HPV) and several treatment options are available. However, the work presented in this thesis reveals that providing patients with evidence-based answers to these questions is not that easy. Specifically, knowledge on the transmission of warts to answer How did I get the warts?, and knowledge on the effectiveness of treatment for warts to answer How do I get rid of the warts? is still largely lacking. This general introduction provides background information about cutaneous warts, addresses the most apparent gaps in knowledge about the transmission and treatment of warts, and presents the study aims to fill these gaps.

TRANSMISSION

Definition of warts

Cutaneous warts are benign hyperkeratotic papillomas of the skin. These size ranges from a few millimetres to confluent conglomerates of several centimetres. The normal skin lines are interrupted by skin coloured to brownish-grey tumours. Small black dots may be visible, which represent capillary thrombosis. The diagnosis is established clinically; no supplementary histologic or virologic investigations are needed. Warts are classified according to localization and morphology. Common warts (verruca vulgaris) are preferentially located on the dorsa of the hands, but may also be palmar, periungual, on the face, or on other
parts of the skin. The appearance is usually cauliflower-like, but may also be smooth (verruca plana) or filiform (verruca filiformis). Plantar warts (verruca plantaris) may be single endophytic lesions located on the pressure points of the foot (myrmecia warts) or multiple confluent more superficial lesions (mosaic warts). In some cases, cutaneous warts may be confused with other lesions such as epithelial cysts, corns or other benign tumours of the skin. Genital warts (condylomata accuminata), mollusca contagiosa, and senile warts (seborrhoenic keratosis) are different types of lesions which are not dealt with in this thesis.

**Pathophysiology**

Warts are caused by the human papillomavirus (HPV). The full complexity of the relationship between warts, HPV and patient immunity is not yet fully elucidated. Skin tissue normally protects itself from viral invasion by several interrelated defence mechanisms, such as an intact stratum corneum, complement phagocytosis, and both cellular and humoral immunity. Small defects of the skin are sufficient for HPV to infect the basal epithelial layer of the skin. In contrast to an acute viral infection such as influenza (which is short-lived and induces a strong immune response with anti-viral immunity) HPV infections are more persistent. HPV evades immunologic defences through antigenic variation, genomic integration, and resides in sites not accessible to immune defences. Infection may be asymptomatic or may cause an irregular hyperplasia of the epidermis and hyperkeratosis, clinically visible as a wart. In immunocompetent patients warts do not show malignant proliferation.

**Human papillomavirus types**

It was long assumed that a single virus was responsible for all types of warts. Only since the mid-1970s were multiple HPV types characterised. At present, we know that papillomaviruses (PV) are a family of viruses infecting cutaneous and mucosal epithelia of vertebrates. They may persist asymptptomatically or cause benign as well as malignant proliferative lesions. Commonly used nomenclature in the taxonomy of PVs has a genome-based approach, because PVs are not suitable for culture techniques or robust antibody responses. PVs have circular double-stranded genomes with 8 genes. The L1 gene encodes for the principal capsid protein of the virus. Classification of PV is based on the L1 nucleotide sequence similarity: different genera share less than 60% nucleotide sequence identity, species within a genus share between 60-70%, and dissimilarity between types is at least 10%. At present, more than 150 human PV types have been fully sequenced. Types belonging to the alpha genus infecting the genital mucosa are best understood: HPV 16 and 18 are the most prevalent types in the pathogenesis of cervical cancer, and HPV 6 and 11 cause genital warts and laryngeal papillomas. In this same phylogenetic
tree of PVs, at least 15 types belonging to the alpha \textsuperscript{13-19}, gamma \textsuperscript{14,20}, and mu \textsuperscript{21} genera have been found associated to cutaneous warts. Studies on cutaneous wart-associated HPV types are scarce compared to studies on cervical dysplasia-associated HPV types.\textsuperscript{22,23} Moreover, the few epidemiological studies including more than 100 lesions were carried out in dermatologic populations and used time-consuming HPV typing methods. Specific types of infecting HPV are correlated with histological characteristics of the wart. However, correlations with clinical characteristics of patients are less obvious, \textsuperscript{2,21,24,25} and little is known about correlations with cure or response to treatment.\textsuperscript{19,26}

### Human papillomavirus transmission

Amplification of viral DNA in the HPV infected cells of the skin results in the production of high numbers of HPV copies that potentially may infect other individuals. HPV is transmitted through direct contact with contaminated skin or via objects carrying the virus.\textsuperscript{3,11} Floors of swimming pools and public showers are most frequently hypothesised to be HPV reservoirs and routes for transmission of warts.\textsuperscript{27} However, there is no direct evidence that these places are HPV reservoirs and few studies have actually examined risk factors for HPV transmission. Moreover, existing studies have methodological weaknesses and their results are contradictory.\textsuperscript{27-34}

### Prevention

Based on consensus regarding this weak evidence on the transmission of warts, several recommendations to prevent warts have been issued through official organizations of dermatology, general practice, and public health.\textsuperscript{35-40} Recommendations to prevent getting plantar warts focus on public places, and recommendations to prevent spreading warts once you have them primarily aim at limiting the spread of warts within one individual (Table 1.1). Studies explicitly examining risk factors for developing warts could provide direction for more evidence-based recommendations.

### TREATMENT

### Burden of warts

The prevalence of warts in the general population is reported to range from 1-13\%.\textsuperscript{41-43} peaking between 5-14 years up to 24\%.\textsuperscript{44,45} Patients experience pain, irritation or cosmetic inconvenience.\textsuperscript{46} Social interaction may even be affected in patients with widespread warts.\textsuperscript{47} Entries in Dutch registries from general practice show that about 2\% of the gen-
eral population and 6% of primary school children present their warts to general practice for advice every year, ranking 11th in the list of the most common reasons for consulting general practice. Only a small proportion of these patients are referred to dermatology clinics. In the UK, similar numbers are reported, resulting in almost 2 million people visiting general practice at a cost of about 40 million British pounds per year. An additional yearly 17 million British pounds is spent on OTC preparations. In the USA, the total yearly direct and indirect medical costs are estimated to be over 1 billion dollars. In addition to the burden in the general immunocompetent population, warts are recognised as complication of long-term immunosuppression therapy with rates as high as 90% reported in patients 5 years after renal transplantation.

Table 1.1. Overview of recommendations for the prevention of cutaneous warts.

<table>
<thead>
<tr>
<th>To prevent getting warts:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not go barefoot in public places (^{a,b,e})</td>
</tr>
<tr>
<td>Wear flip-flops in communal showers (^{d,f})</td>
</tr>
<tr>
<td>Keep feet dry (^{c,f})</td>
</tr>
<tr>
<td>Avoid sharing shoes, socks, or towels (^{d,a})</td>
</tr>
<tr>
<td>Change socks daily (^{a})</td>
</tr>
<tr>
<td>Do not touch someone’s wart (^{f})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>To prevent spreading warts:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid scratching warts (^{a,c,f})</td>
</tr>
<tr>
<td>Avoid sucking fingers, or biting nails that have warts (^{c,d})</td>
</tr>
<tr>
<td>Do not try to cut away or burn warts yourself (^{a})</td>
</tr>
<tr>
<td>When paring down warts, take care not to damage surrounding skin, dispose of dead skin carefully and do not use the file for other purposes (^{d})</td>
</tr>
<tr>
<td>Cover the wart with a waterproof plaster when swimming (^{d,e})</td>
</tr>
<tr>
<td>Check children’s feet periodically for warts (^{a})</td>
</tr>
<tr>
<td>Children with warts should not be excluded from activities such as sports and swimming, but should take measures to minimise transmission (^{d})</td>
</tr>
</tbody>
</table>

\(^a\) Dutch College of General Practitioners (NHG)  
\(^b\) Dutch Association of Dermatologists (NVDV)  
\(^c\) Dutch Communal Health Service (GGD)  
\(^d\) National Health Service (NHS)  
\(^e\) British Association of Dermatologists (BAD)  
\(^f\) American Academy of Dermatology (AAD)  

The duration of warts persisting without treatment ranges from a few months to over a decade. The most cited study on the natural course of cutaneous warts reported two thirds of patients free of warts after 2 years. However, that study was conducted in 1963 among an institutionalised mentally disabled population. Another study conducted in
1959 with a complete resolution after one year of 57% only included hand warts in Dutch primary school children, and a cohort of 11-year-old British children concluding follow-up in 1993 showed a 5-year resolution of 93%; however, this latter study did not provide data on short-term follow-up. Because of the benign natural course of warts, some physicians and healthcare planners promote a wait-and-see policy.

**Treatment of warts**

The first documented problems related to the treatment of warts were reported in the 1st century AD in the medical encyclopaedia ‘De Medicina’ by Aulus Cornelius Celsus: “The myrmecia are held by very broad roots, and so cannot be excised without causing a large wound”. Nowadays, physicians still hesitate to perform surgical excision of a wart because of the complications of the procedure in combination with possible recurrence after treatment. The fact that warts also resolve spontaneously over time has fuelled beliefs in all kinds of folklore to get rid of warts (Figure 1.1).

Even today, a variety of OTC medications, GP treatments and specialist therapies are available (Table 1.2). The number of different methods alone indicates that none of the treatments is considered generally effective. In 2006, the extensive Cochrane systematic review on topical treatments for cutaneous warts concludes: ‘There is a considerable lack of evidence on which to base the rational use of topical treatments for cutaneous warts’. Although the evidence was scarce, topical treatment with salicylic acid showed the most

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**Figure 1.1.** Fragment from The adventures of Tom Sawyer by Mark Twain, 1876.

“Say – what is dead cats good for, Huck?”
“Good for? Cure warts with.”
“No! Is that so? I know something that’s better.”
“I bet you don’t. What is it?”
“Why, spunk-water. . . You got to go all by yourself, to the middle of the woods, where you know there’s a spunk-water stump, and just as it’s midnight you back up against the stump and jam your hand in and say:
‘Barley-corn, barley-corn, injun-meal shorts,
Spunk-water, spunk-water, swaller these warts,’
and then walk away quick, eleven steps, with your eyes shut, and then turn around three times and walk home without speaking to anybody. Because if you speak the charm’s busted… Sometimes I take ’em off with a bean.”
“Yes, bean’s good. I’ve done that.”
“Have you? What’s your way?”
(...)

HUCKLEBERRY FINN.
convincing results.\textsuperscript{56-60} Pooled data from five trials showed a cure rate of 117/160 patients (73%) after salicylic acid treatment compared with 78/162 (48%) in controls, which translates to a risk ratio of 1.6 (95% CI 1.2-2.2).\textsuperscript{55} Two low-quality trials directly comparing salicylic acid and cryotherapy did not reveal differences in effectiveness.\textsuperscript{59;61} Therefore, the Cochrane review proposes: ‘The most urgent need is for a trial to compare topical salicylic acid, cryotherapy and placebo in primary care’. This recommendation was an important starting point for the research in this thesis.

In addition to the widely available cryotherapy and salicylic acid, several specialised treatments are available in a hospital setting (Table 1.2). Evidence for these treatments is limited and large-scale use in primary care is not feasible. However, an exception may be monochloroacetic acid (MCA) which is a powerful irritant used by dermatologists and podiatrists for several decades.\textsuperscript{62;63} A trial from the UK and two small unpublished pilot studies from the Netherlands showed promising results of MCA in primary care with few side effects.\textsuperscript{64-66}

Apart from treatment effectiveness, other arguments such as side effects, treatment burden, patient satisfaction, and costs also influence treatment choices in practice, especially because patients with warts are often children. Moreover, specific subgroups of patients could be identified, allowing to distinguish patients with high treatment response from patients who will not benefit from treatment.\textsuperscript{49}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
 & Over-the counter & Primary Care & Secondary Care\textsuperscript{b} \\
\hline
Removal & Self-removal & Excision & \\
 & & Curetage & \\
 & & Cautery & \\
Destruction & Cryotherapy (-50\degree C)\textsuperscript{c} & Cryotherapy (-196 \degree C)d & Photodynamic treatment \\
 & Silver nitrate & Pulsed dye laser & \\
Keratolysis & Low-dose salicylic acid\textsuperscript{a} & High-dose salicylic acid\textsuperscript{f} & Lactic acid \\
 & & Monochloroacetic Acid & \\
Immunostimulation & Thuia oil & Dinitrochlorobenzene & \\
 & & Intralesional Interferons & \\
Animotic effects & & 5-Fluorouracil & \\
 & & Intralesional Bleomycin & \\
Oclusion & Duct tape & & \\
Suggestion & Prayer & Hypnosis & \\
\hline
\end{tabular}
\caption{Overview of reported treatments for cutaneous warts.\textsuperscript{a}}
\end{table}

\textsuperscript{a} This overview does not aim to be complete, but illustrates the variety of widely available treatments.
\textsuperscript{b} In addition to treatments also used in primary care.
\textsuperscript{c} Dimethylether/propane cryotherapy.
\textsuperscript{d} Liquid nitrogen cryotherapy, applied by cotton bud, application pen, or sprayer.
\textsuperscript{e} Low dose = 17\% or lower concentration ointments.
\textsuperscript{f} High dose = 30-50\% concentration ointments
OUTLINE OF THIS THESIS

Aims

Fuelled by the most apparent gaps in knowledge on the transmission and treatment of warts, the aims of this thesis are:

1. To examine risk factors for the development of warts and gain a deeper understanding of the transmission of the wart-associated human papillomavirus in order to provide direction for evidence-based recommendations for wart prevention;
2. To investigate the effectiveness and side effects of commonly used treatments in general practice and identify subgroups of patients with a favourable treatment response in order to optimise treatment in general practice.

These two aims are the backbone of the thesis; in addition, several secondary aims were formulated. However, all aims share the view of a general practitioner and the intention to fill in the gaps of knowledge on the transmission and treatment of warts. To achieve these aims studies are conducted in different populations, which are briefly described below.

Part one: Transmission

In a prospective cohort of primary school children, hands and feet are examined at baseline and at follow-up to collect epidemiological data on their warts and evidence on wart transmission. In Chapter 2, the baseline data from this study cohort represent the prevalence of common and plantar warts in primary schoolchildren. Through parental questionnaires, parental awareness of their children’s warts, as well as cross-sectional relations with environmental risk factors, is explored. Based on these findings and on the theoretical degree of HPV exposure, a model for risk factors for the development of warts is tested in Chapter 3 to provide direction for evidence-based patient information on the prevention of warts. To study HPV types more directly than through risk factors for transmission, a newly developed HPV typing technique for genotyping all known wart-associated HPV types is introduced. The objective of Chapter 4 is to investigate which specific HPV types cause warts in a primary care population. In addition, the relation between specific HPV type and patient characteristics is explored.

Part two: Treatment

For the study in Chapter 5, the cohort of primary school children with warts at baseline is used to acquire data on the resolution of warts after one year. This study investigated factors related to enhanced resolution of warts and aims to describe all OTC as well as GP-delivered treatments used by school children. In Chapter 6, a survey among Dutch GPs
shows which treatments are most frequently used for warts in practice. In addition, the study explores GPs’ motivation for these choices and compares the choices with favoured treatments based on currently available evidence.

The following three chapters present results from two subsequent Warts Randomised Treatment Studies (WARTS). Both WARTS studies are pragmatic, multicenter, randomised trials in immunocompetent patients presenting new warts in general practice. The three-armed WARTS-1 compares the effectiveness of liquid nitrogen cryotherapy, salicylic acid self-application and a wait-and-see policy (Chapter 7). It also reports on side effects, treatment burden and patient satisfaction, and presents subgroup analysis for common and plantar warts, for children under the age of 12 years, and warts with a duration over 6 months. With the knowledge gained from WARTS-1, the WARTS-2 study compares the effectiveness and side effects of monochloroacetic acid with cryotherapy in common warts, and with cryotherapy combined with salicylic acid in plantar warts (Chapter 8). Using the newly developed HPV typing technique from Chapter 4 and the trial population from Chapter 7, the interaction between subgroups based on specific HPV type infecting the wart and treatment response is explored in Chapter 9.

Final chapters

The aim of the general discussion in Chapter 10 is to bring the findings back to daily practice, to present explanations for the observed effects, and to provide recommendations for future research. Chapter 11 summarises the contents of all chapters and Chapter 12 contains a summary in Dutch.
REFERENCES


