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TRANSMISSION AND TREATMENT OF CUTANEOUS WARTS IN GENERAL PRACTICE

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Transmission and treatment of cutaneous warts in general practice

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TRANSMISSION AND TREATMENT OF CUTANEOUS WARTS IN GENERAL PRACTICE

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Contents

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 gymnasiums. *'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.[1] Their 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.[2] 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 filliform (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).[3] In some cases, cutaneous warts may be confused with other lesions such as epithelial cysts, corns or other benign tumours of the skin.[4] Genital warts (condylomata accuminata), mollusca contagiosa, and senile warts (sebborreic 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.[2;5;6] 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.[7] 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.[8] Only since the mid-1970s were multiple HPV types characterised.[9;10] At present, we know that papillomaviruses (PV) are a family of viruses infecting cutaneous and mucosal epithelia of vertebrates.[11] They may persist asymptomatically 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.[5] 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%.[12] At present, more than 150 human PV types have been fully sequenced.[11]
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 [13-19], gamma [14;20], and mu [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.[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, [2;21;24;25] and little is known about correlations with cure or response to treatment.[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.[3;11] Floors of swimming pools and public showers are most frequently hypothesised to be HPV reservoirs and routes for transmission of warts.[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.[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.[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%,[41-43] peaking between 5-14 years up to 24%.[44;45] Patients experience pain, irritation or cosmetic inconvenience.[46] Social interaction may even be affected in patients with widespread warts.[47] Entries in Dutch registries from general practice show that about 2% of the gen-

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

To prevent getting warts:
Do not go barefoot in public places [a,b,e]
Wear flip-flops in communal showers [d,f]
Keep feet dry [c-f]
Avoid sharing shoes, socks, or towels [d,e]
Change socks daily [e]
Do not touch someone's wart [f]
To prevent spreading warts:
Avoid scratching warts [a,c-f]
Avoid sucking fingers, or biting nails that have warts [c,d]
Do not try to cut away or burn warts yourself [e]
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 [e]
Cover the wart with a waterproof plaster when swimming [d,e]
Check children's feet periodically for warts [e]
Children with warts should not be excluded from activities such as sports and swimming, but should take measures to minimise transmission [d]

[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) [35-40]

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.[48] 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.[49] An additional yearly 17 million British pounds is spent on OTC preparations.[50] In the USA, the total yearly direct and indirect medical costs are estimated to be over 1 billion dollars.[51] 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.[50]

Natural course

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.[52] 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,[32] 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.[44] Because of the benign natural course of warts, some physicians and healthcare planners promote a wait-and-see policy.[53]

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*".[54] 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.[55] 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).[49;55] 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.*'[55] Although the evidence was scarce, topical treatment with salicylic acid showed the most

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.

Table 1.2. Overview of reported treatments for cutaneous warts.[a]

	Over-the counter	Primary Care	Secondary Care[b]
Removal	Self-removal	Excision	
		Curetage	
		Cautery	
Destruction	Cryotherapy (-50ºC)[c]	Cryotherapy (-196 ºC)[d]	Photodynamic treatment
		Silver nitrate	Pulsed dye laser
Keratolysis	Low-dose salicylic acid[e]	High-dose salicylic acid[f]	Lactic acid
		Monochloroacetic Acid	
Immunostimulation	Thuia oil		Dinitrochlorobenzene
			Intralesional Interferons
Animitotic effects			5-Fluorouracil
			Intralesional Bleomycin
Occlusion	Duct tape		
Suggestion	Prayer	Hypnosis	

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

convincing results.[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).[55] Two low-quality trials directly comparing salicylic acid and cryotherapy did not reveal differences in effectiveness.[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.[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.[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. [49]

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.

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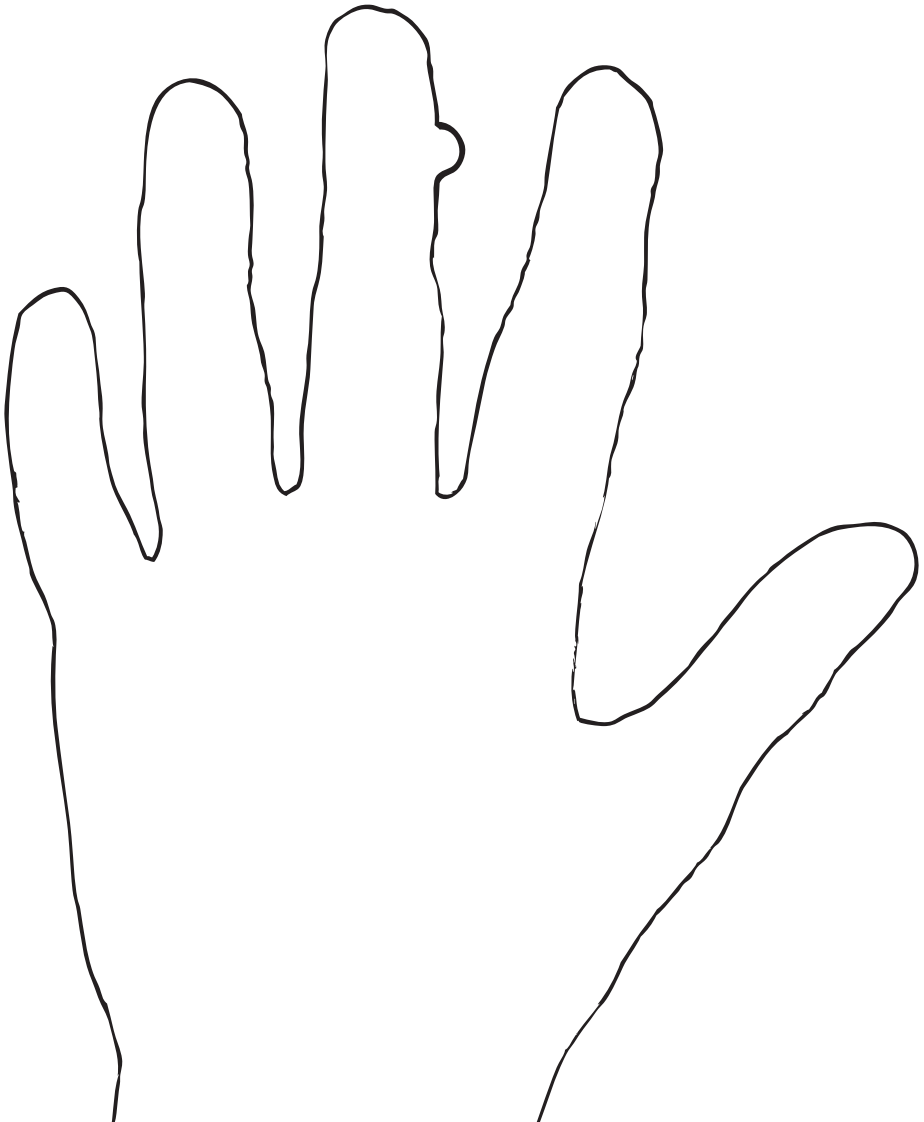

PART ONE

Transmission

CHAPTER 2

Warts in primary school children: prevalence and relation with environmental factors

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ABSTRACT

Background

Warts are very common in primary schoolchildren. However, knowledge on wart epidemiology and causes of wart transmission is scarce.

Objectives

To determine the prevalence of warts in primary schoolchildren and to examine the relation with environmental factors in order to provide direction for well-founded recommendations on wart prevention.

Methods

In this cross-sectional study, the hands and feet of 1465 children aged 4–12 years from four Dutch primary schools were examined for the presence of warts. In addition, the children's parents completed a questionnaire about possible environmental risk factors for warts.

Results

Thirty-three per cent of primary schoolchildren had warts (participation rate 96%). Nine per cent had hand warts, 20% had plantar warts and 4% had both hand and plantar warts. Parental questionnaires (response rate 76%) showed that environmental factors connected to barefoot activities, public showers or swimming pool visits were not related to the presence of warts. An increased risk of the presence of warts was found in children with a family member with warts [odds ratio (OR) 1.9, 95% confidence interval (CI) 1.3–2.6] and in children where there was a high prevalence of warts in the school class (OR per 10% increase in wart prevalence in school class 1.6, 95% CI 1.5–1.8).

Conclusions

One-third of primary schoolchildren have warts. This study does not find support for generally accepted wart prevention recommendations, such as wearing protective footwear in communal showers and swimming pool changing areas. Rather, recommendations should focus on ways to limit the transmission of wart viruses within families and school classes.

INTRODUCTION

Warts are very common in primary schoolchildren and frequently result in discomfort. However, knowledge on wart epidemiology is scarce. Available studies on wart prevalence in schoolchildren are outdated, poorly designed, or restricted to investigations of dermatology outpatients or specific ethnic groups.[1–8] With these shortcomings, the reported overall prevalence of warts ranges from 3% to 20%. One recent, high quality study carried out in Australia reported a prevalence of 22%.[9] However, based on entries in general practice registers in the Netherlands, the prevalence of warts presented to general practitioners (GPs) over a year is approximately 6% in schoolchildren.[10]

To prevent warts, official authorities such as national and municipal health services as well as GPs provide recommendations, e.g. to wear 'flip-flops' in public showers and in swimming pool changing areas.[11,12] These recommendations are based on the assumption that wart viruses are spread by contact with the floors of public showers, gyms and swimming pools. However, evidence supporting such assumptions is limited and contradictory.[7,13–18]

The aim of this cross-sectional study was to determine the prevalence of warts in primary schoolchildren and to explore whether contact with an infected environment promotes the presence of warts, thereby providing direction for evidence to base recommendations on wart prevention.

MATERIALS AND METHODS

In the summer and autumn of 2007, an extensively trained medical student (F.M.v.H.) inspected the hands and feet of all children in grades 1–8 (4–12 years of age) from four primary schools around Leiden, the Netherlands. All children were eligible, and no exclusion criteria were used. Parents were asked to give informed consent for their children and children were free to refuse during examination regardless of parental consent. The study was approved by the Medical Ethical Committee of Leiden University Medical Centre.

Location, size and number of warts were recorded on standard forms with schematic representation of hands and feet. In addition, the skin type was coded to stratify into Caucasian and non-Caucasian subgroups according to Fitzpatrick skin type.[19] Over 5% of examinations were directly supervised by experienced GPs, with no discordance in wart diagnosis.

Before examination, parents were asked to complete a questionnaire about the presence of possible environmental risk factors for warts, including a family member with wart(s),[1,3,5,15,16] number of children in the family (one vs. more),[3] walking barefoot at home, (barefoot) use of public showers,[7,17] practising gymnastics and sports barefoot,[5,15,16,18] and use of public swimming pools.[5,7,14–16,18] The examiner was unaware of the answers in the questionnaires.

Prevalences were compared with $\chi 2$ tests. Logistic regression analysis was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of all included risk factors. In subgroup analysis, ORs were calculated for children with hand warts and children with plantar warts separately.

RESULTS

The participation rate for 1526 eligible primary schoolchildren was 96%. Reasons for non-participation were lack of child or parental consent (1%) and absence of the child during the examination period (3%). Table 2.1 shows the sociodemographics of the participants. The overall prevalence of warts was 33% (485 of 1465, 95% CI 31–35%). Most of these children had only one or two warts (Table 2.1). The prevalence did not differ between sexes (P = 0.88) or between schools (P = 0.11), but did differ between Caucasian and non-Caucasian skin types (P = 0.002, Table 2.2). The prevalence of warts increased with age, from 15% in 4-year-old schoolchildren to 44% in 11-year-olds (P < 0.001, Figure 2.1). Parents' response rate to questionnaires was 76%. Children with a close family member with warts had an increased risk of having warts (OR 1.9, 95% CI 1.3–2.6) and children

Table 2.1. Characteristics of primary school children (n=1465)

Age range, years	4 - 12
Sex	
Boys	726 (50)
Girls	739 (50)
Skin type	
Caucasian	1189 (81)
Non-Caucasian	276 (19)
School	
School A, 30 classes	747 (51)
School B, 10 classes	243 (17)
School C, 8 classes	137 (9)
School D, 14 classes	338 (23)
Number of warts	
0	980 (67)
1	270 (18)
2	97 (7)
3 or 4	64 (4)
5 - 9	42 (3)
10 or more	12 (1)

Values are numbers (percentages), unless stated otherwise

Table 2.2. Prevalence of plantar warts and hand warts in primary school children according to sex, skin type and school (n=1465).

	Location of warts			
	All locations	Plantar	Hand	Combination
Overall	33 (n=485)	20 (n=287)	9 (n=136)	4 (n=62)
Sex				
Boys	33	19	11	4
Girls	33	20	8	5
Skin type				
Caucasian	35*	20	10	5
Non-Caucasian	25*	19	5	2
School				
School A	36	21	10	5
School B	30	18	9	3
School C	29	18	6	5
School D	31	18	10	3

Values are percentages. Sum of location prevalences may differ from all locations prevalence, due to rounding off

* Significant difference (p=0.002)

Figure 2.1. Prevalence of warts in primary school children (N=1465) according to wart location and age (years).

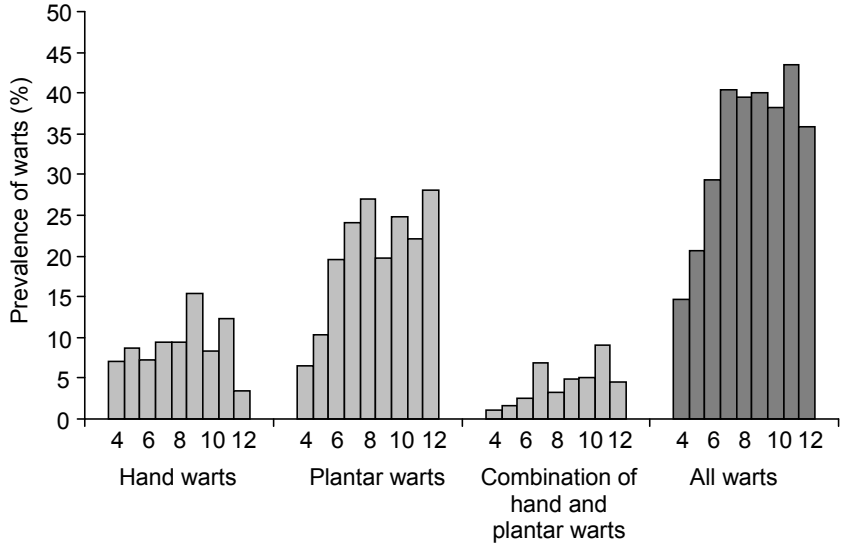

Table 2.3. Personal and environmental risk factors and their relation with the presence of warts* in primary school children, ordered by odds ratio† (N=1465)

Potential risk factor	Number of children‡	Wart prevalence (%)	Odds ratio† (95% CI)
Family member with wart(s)			
Yes	237	42	1.9 (1.3 to 2.6)
No	524	28	
Wart prevalence in school class	1465	3 to 68	1.6 (1.5 to 1.8)§
Skin type			
Caucasian	1189	35	1.6 (1.2 to 2.1)
Non-Caucasian	276	25	
Walking barefoot at home			
Yes	993	33	1.3 (0.82 to 1.9)
No	119	28	
Use of public showers			
Yes	159	38	1.3 (0.94 to 1.9)
No	892	31	
Barefoot	77	42	1.3 (0.65 to 2.4)
Footwear	72	36	
Use of public swimming pools			
Yes	895	33	1.2 (0.88 to 1.7)
No	217	29	
Practice sports barefoot			
Yes	157	33	1.1 (0.74 to 1.5)
No	950	32	
Barefoot gymnastics at school			
Yes	174	32	1.0 (0.72 to 1.4)
No	930	32	
Sex			
Boys	726	33	1.0 (0.82 to 1.3)
Girl	739	33	
Only child			
Yes	149	25	0.67 (0.45 to 0.99)
No	962	33	

* Similar outcomes were found in subgroup analysis for children with plantar warts.
† Unadjusted odds ratios are reported, adjustment for age did not change any findings.
‡ Sum of numbers per potential risk factor is ≤ 1465, due to differences in response rates (68 to 100%) to specific questions on parental questionnaire.
§ Odds ratio per 10% increase in school class wart prevalence according to logistic regression analysis.
CI, confidence interval

of families with only one child had a decreased risk of having warts (OR 0.67, 95% CI 0.45–0.99, Table 2.3). Children with a Caucasian skin type more often had warts than children with a non-Caucasian skin type (OR 1.6, 95% CI 1.2–2.1). None of the environmental factors related to barefoot activities, use of public showers or swimming pool visits showed a significantly increased risk for having warts. Wart prevalence in different school classes ranged from 3% to 68%; increasing prevalence was correlated with an increased risk of having warts (OR per 10% increase in wart prevalence in school class 1.6, 95% CI 1.5–1.8). Children with hand warts and children with plantar warts separately showed similar ORs for all potential risk factors. In particular, ORs for environmental factors related to barefoot activities did not differ between children with plantar warts and children with any warts.

According to parents' responses to the questionnaire, only 17% of children had hand or plantar warts and 4% reported warts in other locations. Parents did not report the presence of warts in 49% of children found with hand warts on physical examination and in 62% of children found with plantar warts.

DISCUSSION

This cross-sectional study on wart epidemiology reveals that one-third of primary schoolchildren have warts on their hands or feet. We did not find support for generally accepted preventive recommendations such as wearing protective footwear in public showers and in swimming pool changing areas. However, primary schoolchildren with a family member with warts or many classmates with warts have a higher risk of having warts themselves. Transmission within families and school classes probably plays an important role.

Our prevalence figures are substantially higher than in previous studies (33% vs. 3–22%), in particular due to substantially higher plantar wart prevalence.[1–9] These conflicting findings may reflect regional differences, may indicate a trend in time or may be due to variations in study design. As we presented, different observation methods will lead to different prevalences; in our study the overall prevalence was 17% by parental report and 33% by examination by experts. These unnoticed warts also explain part of the discrepancy between the prevalence of warts on examination and the proportion of schoolchildren consulting a GP for advice on treating warts (approximately 6% per year[10]).

We found an increase in the prevalence of warts with age in which the prevalence seems to level off at age 9–12 years. In accordance with others,[1,17] we found a lower prevalence in children with a non-Caucasian skin type (mostly originating from Morocco, Turkey, China, the Netherlands Antilles and Surinam).

Human papillomavirus colonization is universal and occurs very early in life. Subsequent exposure of the immune system to different, distinct wart virus subtypes during life may

promote warts to develop.[20] This multiple subtype exposure may be facilitated by barefoot activities such as swimming, using public showers and practising sports barefoot. Previous studies have indicated that these barefoot activities may relate to the transmission of wart viruses among individuals.[7,14,17,18] Based on these assumed associations, recommendations such as wearing 'flip-flops' in communal showers and covering warts when swimming were issued.[11,12] However, we could not find support for such recommendations. Our results suggest that wart viruses among children mainly transmit within families and school classes. Conceivably, besides exposure to multiple wart virus subtypes, a critical amount of localised infection load is needed to develop warts. This may be present in families and (to a lesser extent) in school classes but may not be sufficiently present in public showers, swimming pools or gyms. A genetic explanation for the higher presence of warts in some families is not likely, as the risk of warts was also higher with increasing prevalence of warts within classes. However, the cross-sectional design of our study allows us only to examine correlations between risk factors and the presence of warts. Prospective studies are needed to confirm possible causal associations.

Our study population is representative of present-day primary schoolchildren in Western Europe. It was sufficiently large and population based, with similar prevalence rates of warts across different schools and with a participation rate of 96%. We restricted examinations to hands and feet only, potentially missing warts on other parts of the body. However, a previous study showed that only 4% of all warts are located in places other than the hands or feet,[6] suggesting that we missed very few warts. Parental assessment of environmental risk factors for warts may have influenced the outcomes of our study.[7,9] However, more than half of all parents of children with warts were not aware of their children's warts.

In conclusion, warts are highly prevalent in primary schoolchildren. Preventive recommendations should focus on ways to limit the transmission of wart viruses within families or school classes. Furthermore, prospective or intervention studies are needed to demonstrate whether other preventive measures, such as covering warts within families and classes, are effective in interrupting transmission, thereby facilitating a decrease in the present-day high wart prevalence and subsequent discomfort among children.

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CHAPTER 3

Warts transmitted in families and schools: a prospective cohort

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Huisarts en Wetenschap; accepted

ABSTRACT

Background

Cutaneous warts are very common in primary schoolchildren. However, knowledge on the routes of transmission of human papillomavirus (HPV) causing warts is scarce.

Objective

This study examines the association between the degree of HPV exposure and incidence of warts in primary schoolchildren to support evidence-based recommendations on wart prevention.

Methods

In this prospective cohort study, the hands and feet of all children in grades 1-7 (aged 4-12 years) of three Dutch primary schools were inspected for the presence of warts at baseline and after 11-18 months follow-up. Data on the degree of HPV exposure included information obtained from parental questionnaires: pre-existent warts, warts in family, prevalence of warts at baseline in the class, and use of public places (e.g. swimming pools).

Results

Of the 1134 eligible children 97% participated, response rate from parental questionnaires was 77%, and loss to follow-up 9%. The incidence for developing warts was 29 per 100 person-years at risk (95% CI 26-32). Children with a Caucasian skin type had an increased risk of developing warts (HR 2.3, 95% CI 1.3-3.9). Having family members with warts (HR 2.08, 95% CI 1.52-2.86) and wart prevalence in the class (HR 1.20 per 10% increase, 95% CI 1.03-1.41) were independent environmental risk factors.

Conclusions

The degree of HPV exposure in the family and school class contributes to the development of warts in schoolchildren. Preventive recommendations should focus more on limiting HPV transmission in families and school classes, rather than in public places.

INTRODUCTION

Cutaneous warts are benign papillomas of the skin. Warts are highly prevalent in the general population, especially among primary schoolchildren, for whom the prevalence ranges from 4-33% [1-3]. Although about 67% of warts resolve within 2 years without treatment [4], general practitioners are often consulted for treatment because of physical or psychological discomfort [5]. Based on registries in the UK and the Netherlands, the annual episode incidence rate of cutaneous warts for the age group 5-14 years in family practice ranges from 3-5 per 100 children [6;7]. However, incidence rates in the general population are unknown. Cutaneous warts are caused by infection with human papillomavirus (HPV), which is transmitted by direct contact with contaminated skin or indirectly via objects carrying the virus [8;9]. Increased exposure to HPV theoretically increases the risk of developing warts [10]. Based on studies exploring which risk factors are most important [3;11-18], recommendations to prevent warts focus on limiting the personal spread of HPV and transmission in public places. For example, the use of communal showers is considered to be a risk factor for acquiring plantar warts because wet floors are assumed to be HPV reservoirs [12]. Based on this assumption, the following type of recommendations are issued: 'Wear flip-flops in communal showers'[19], 'Cover the wart with a waterproof plaster when swimming', or 'Do not go barefoot into public places'[20]. However, data from studies on risk factors for warts are contradictory and all studies have a cross-sectional design, thus precluding determination of causal relationships. This prospective cohort study examines the incidence rate of warts in primary schoolchildren and assesses whether the degree of exposure to HPV contributes to the risk of developing warts, to provide evidence-based recommendations for wart prevention.

METHODS

Study cohort

A trained medical student inspected the hands and feet of all children in grades 1-7 from three primary schools (in/around the city of Leiden, the Netherlands) for the presence of warts. Details of the baseline examination are already published [3]. One year later, another trained medical student inspected the hands and feet of all children who were also examined at baseline (now in grades 2-8), again for the presence of warts. Parents were asked to give informed consent before both examinations. Apart from this, children were free to refuse participation during examinations. Due to practical reasons and taking into consideration the school class agenda, the follow-up period ranged from 11-18 months. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center, as well as by the boards of the participating schools.

Development of warts

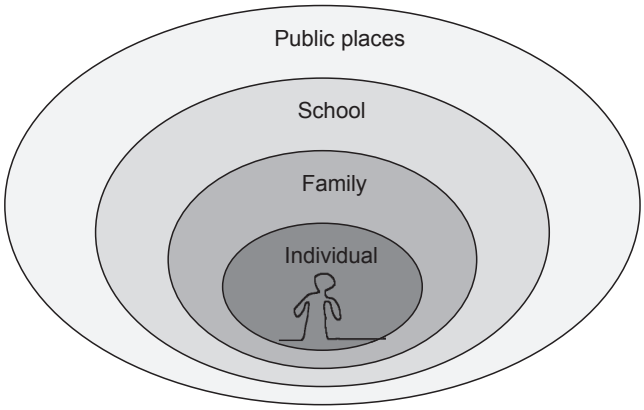
At baseline and follow-up, the type and number of warts were recorded on standard forms with schematic representation of hands and feet. A distinction was made between plantar warts (located on the soles of the feet) and common warts (located on the dorsal side of the feet or hands). Over 5% of all baseline and follow-up examinations were supervised by an experienced general practitioner, with no discordance in wart diagnosis. The examiners were unaware of the answers given in the parental questionnaires.

HPV exposure

Personal factors were recorded during baseline examination: age, sex, and skin type; the latter was coded according to Fitzpatrick to stratify into Caucasian and non-Caucasian subgroups [21]. The degree of exposure to HPV was ranked according to a conceptual model (Figure 3.1), which we operationalised by defining potential environmental risk factors for warts [3]. Information on the presence of these risk factors was obtained during baseline examination and through parental questionnaires prior to baseline examinations:

- *Individual factors*: pre-existent warts (yes vs. no);
- *Family factors*: the presence of a family member with warts (yes vs. no), walking barefoot at home (yes vs. no); [1;3;15-18]
- *School factors*: School (school A vs. B vs. C), and the prevalence of warts in school class at baseline (per 10% increase) [3], presence of warts in at least one of three closest school friends (yes vs. no);
- *Public factors*: use of public swimming pools (yes vs. no), use of public showers (yes vs. no), and practicing sports barefoot (yes vs. no) [11;14;16-18].

Figure 3.1. Conceptual model of HPV exposure [3]. The theoretical degree of HPV exposure decreases from the core outwards.



Statistical analyses

Incidence rates with 95% confidence interval (CI) were calculated, dividing the incident cases by the sum of the person-time of children at risk. An incident case was defined as a child who had developed one or more new warts at follow-up examination, irrespective of pre-existent warts. Also calculated were incidence rates stratified for plantar and common warts, and the incidence rate of new warts in children without warts at baseline.
Cox proportional-hazards model was used to identify risk factors for developing warts. First, univariate analysis was performed for the risk factors to estimate hazard ratios (HR) with 95% CI, in which $p<0.05$ was considered as significant risk factor. Multivariate analysis was performed to assess whether the degree of exposure to HPV contributed to the risk of developing warts. We included age, sex, and skin type as personal factors, as well as environmental risk factors representing the various degrees of HPV exposure: pre-existent (individual factor), presence of family members with warts (family factor), presence of warts in school class (school factor), and use of public swimming pools (public factor). In addition, an exposure sum score in which each of the four environmental risk factors equally contributed (range 0-4) was entered into the model to explore a possible dose-response effect.

RESULTS

Study cohort

The participation rate of 1,134 eligible children at baseline was 97%: 23 children (2%) were absent from school at the time of baseline examinations and 12 children (1%) did not provide parental or child consent (Figure 3.2). Loss to follow-up was 9%: 65 children (6%) left school, 23 children (2%) did not provide parental or child consent at follow-up examination, 9 children (1%) were absent at follow-up examination, and data were missing for 1 child (<1%). Median age of the 1001 children was 7 years ([range 4-12, inter quartile range [IQR] 5-9), 48% was male, 80% had a Caucasian skin type, and 33% had warts at baseline (Table 3.1). At baseline, the parents' response rate to the questionnaires was 77%.

Development of warts

The incidence for developing new warts was 29 per 100 person-years at risk (95%CI 26-32). When stratified for the type of warts, incidence rates were 14 per 100 person-years (95% CI 12-16) for plantar warts, 9 per 100 person-years (95% CI 7-11) for common warts (mostly on hands), and 5 per 100 person-years (95% CI 4-7) for a combination of plantar

Figure 3.2. Flowchart.

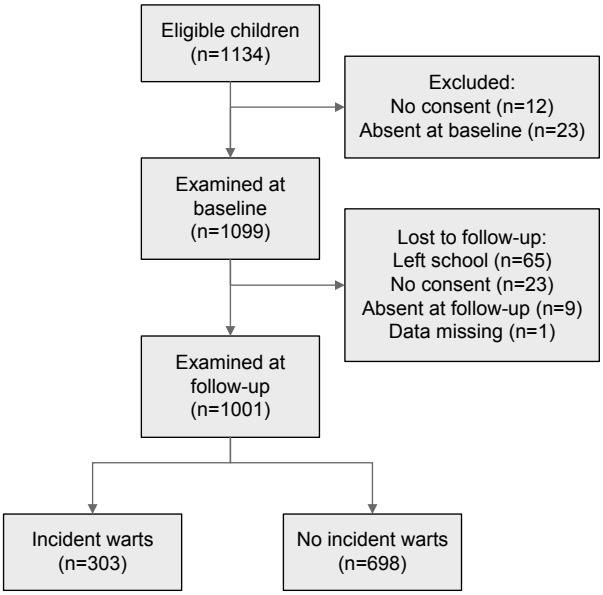


Table 3.1. Baseline characteristics of the primary schoolchildren (n=1001).

Personal	
Median age in years (range)	7 (4-12)
Male sex	485 (48)
Caucasian skin type	799 (80)
Pre-existent warts	333 (33)
Family	
Family member with wart(s)	164 (31)*
Walking barefoot at home	694 (90)*
School	
School	
A (28 classes)	618 (62)
B (8 classes)	110 (11)
C (12 classes)	273 (27)
Wart prevalence in school class ≥ 40%	372 (37)
Close school friends with wart(s)	417 (56)*
Public	
Use of public swimming pools	622 (81)*
Practice sports barefoot	160 (21)*
Use of public showers	103 (14)*

Data are presented as numbers (%), unless stated otherwise

* Total number of children per characteristic is ≤ 1001, because response rates to specific questions on parental questionnaires ranged from 68-100%.

and common warts. The median number of new warts was 1 per child (range 1-10; IQR 1-2). The incident rate in children without warts at baseline was 25 per 100 person-years (95% CI 21-30), and in children with pre-existent warts 37 per 100 person-years (95% CI 21-30) (p<0.001).

Relation with potential risk factors

Univariate analysis showed no relation with sex, but increasing age was related to increased incidence of warts (Table 3.2). There was a high incidence rate in children with a Caucasian skin type; also, several individual, family and school factors were significantly related to the development of warts (Table 3.2). Although the use of public swimming pools almost reached significance level, no significant public factors were identified.
In multivariate analysis, there was no relation with age or sex, but Caucasian skin type was a significant personal factor: HR 2.3, 95% CI 1.3-3.9 (Table 3.3). The degree of exposure, indicated by the presence of family members with warts (HR 2.1, 95% CI 1.5-2.9) and

Table 3.2. Univariate analysis of the association between the degree of HPV exposure and the incidence of warts in primary schoolchildren (n=1001).

Potential risk factor	No of cases/ person-years†	Incidence rate per 100 person-years	Hazard ratio* (95% CI)	p-value
Personal factors				
Age per year increase			1.08 (1.03-1.14)	0.003
Sex				
Girl	150 / 507	30	1	
Boy	153 / 547	28	1.1 (0.8-1.3)	0.66
Skin type				
Non-Caucasian	38 / 221	17	1	
Caucasian	265 / 832	32	1.9 (1.4-2.7)	<0.001
Degree of exposure to HPV				
Individual factors				
Pre-existent warts				
No	177 / 716	25	1	
Yes	126 / 337	37	1.5 (1.2-1.9)	<0.001
Family factors				
Family member with wart(s)				
No	90 / 396	23	1	
Yes	74 / 155	48	2.1 (1.5-2.9)	<0.001
Walking barefoot at home				
No	23 / 76	30	1	
Yes	216 / 731	30	1.0 (0.7-1.5)	0.97

Table 3.2 (continued)

Potential risk factor	No of cases/ person-years†	Incidence rate per 100 person-years	Hazard ratio* (95% CI)	p-value
School factors				
School				
A	198 / 730	27	1	
B	21 / 92	23	0.7 (0.4-1.0)	0.07
C	86 / 232	37	1.2 (0.9-1.5)	0.23
Prevalence of warts in school class				
< 40%	163 / 668	24	1	
≥ 40%	140 / 386	36	1.5 (1.2-1.9)	<0.001
per 10% increase	-	-	1.2 (1.1-1.3)	<0.001
Close school friends with wart(s)				
No	108 / 335	32	1	
Yes	132 / 440	30	0.9 (0.7-1.2)	0.54
Public factors				
Use of public swimming pools				
No	37 / 162	23	1	
Yes	202 / 645	31	1.4 (1.0-2.0)	0.065
Practice sports barefoot				
No	182 / 634	29	1	
Yes	55 / 163	34	1.1 (0.9-1.6)	0.39
Use of public showers				
No	190 / 651	29	1	
Yes	33 / 111	30	1.0 (0.7-1.5)	0.86

* Generated by univariate Cox proportional-hazards model.
† Sum of person-years per potential risk factor is ≤ 1054 (or 1053 due to rounding off), because response rates to specific questions on parental questionnaires ranged from 68-100%.

the prevalence of warts in the school class (HR 1.2 per 10% increase, 95% CI 1.0-1.4) were independent environmental risk factors for the development of warts. However, pre-existent warts was not an independent risk factor (HR 0.9, 95% CI 0.7-1.3). The use of public swimming pools showed a small non-significant risk (HR 1.17, 95% CI 0.75-1.83). A dose-response effect was present in the exposure sum score of the four environmental risk factors; the risk of warts increased by 3.5 (95% CI 2.9-4.2) per extra positive factor. In the subgroup of children with plantar warts, and the subgroup of children without warts at baseline, similar results were found.

Table 3.3. Association between the degree of exposure to HPV and the risk for developing warts in primary school children.

Factor	Hazard ratio* (95% CI)	p-value
Personal factors		
Age per year increase	1.0 (0.91-1.10)	0.99
Sex	1.2 (0.9-1.6)	0.34
Caucasian skin type	2.3 (1.3-3.9)	0.003
Degree of exposure to HPV		
Pre-existent warts	0.91 (0.7-1.3)	0.58
Family member with warts	2.1 (1.5-2.9)	<0.001
Warts in school class†	1.2 (1.0-1.4)	0.02
Use of public swimming pools	1.2 (0.8-1.8)	0.48
Exposure sum score‡	3.5 (2.9-4.2)	<0.001

* Generated by a multivariate Cox proportional hazards including age, sex, skin type and the four environmental risk factors above representing most important individual, family, school, and public risk factors.
† hazard ratio for prevalence of warts in school class per 10% increase.
‡ hazard ratio per extra positive exposure factor (range 0-4).

DISCUSSION

Summary of main findings

The incidence rate of new cutaneous warts in primary schoolchildren was 29 per 100 person-years. Exposure to HPV in families and school class was associated with the development of warts, whereas no independent associations were found for the presence of warts at baseline and public risk factors.

Strengths and limitations of the study

The development of warts was objectively established by physical inspection of hands and feet. Warts on other parts of the body were potentially missed, but account for only about 4% of all warts [22]. The causal associations between the incidence of warts and environmental risk factors were supported by the biological model of HPV exposure and the dose-response effect in our data. The sufficient numbers of children in this study with a participation rate of 97% and the presence of 20% non-Caucasian skin types (mostly originating from Morocco, Turkey, China, Netherlands Antilles and Surinam), resemble the general Dutch primary school population.[23] Although transmission patterns may differ to

some extent due to local customs, the ways of HPV exposure are probably comparable in Western countries.
A limitation of the study is that some risk factors related to HPV exposure are not considered because they are difficult to measure, for example the sharing of personal items or close contact to children with warts during specific hobbies. Although unlikely, suboptimal inter-observer agreement in assessment of warts or the parental assessment of some risk factors could have diluted associations. For example, parents could have been misinformed about the presence of warts among family members. Lastly, binary analysis of factors did not allow assessment of dose-effect relationships within factors.

Comparison with existing literature

To our knowledge, no other recent studies on incidence rates of warts in the general population are available. Based on entries in general practice registers in the UK and the Netherlands, the annual episode incidence of cutaneous warts for the age group 5-14 years in family practice ranges from 3-5 per 100 children [6;7]. The discrepancy with the much higher incidence rates we observed (29 per 100 person years) is explained by the fact that many warts are unnoticed by children and parents [3], and many warts are treated with over-the-counter medication, or not treated at all.
Studies on environmental risk factors for warts are contradictory and all have a cross-sectional design [3;11-18]. Furthermore, a validated model on the degree of HPV exposure is lacking. This is the first study with a prospective design, which also allows exploring possible causal relations. The risk factors we identified partially confirm the theoretical degree of HPV exposure in the environment: having a family member with warts was a more important risk factor than school class prevalence, which was more important than any public factor (Figure 3.1) [3]. However, pre-existing warts (expected to be the main risk factor according to the individual degree of HPV exposure), was not independently associated with the development of warts. This could be explained by the fact that, besides HPV exposure, immunogenicity and susceptibility of the host to specific HPV type are important to develop warts [10]. In other words, the immune system of the child with warts could already be triggered and might therefore be more effective against the specific HPV type the child exposes itself to. To a lesser extent, genetic aspects of the susceptibility of the child could play a role within families, but identification of school class prevalence as a risk factor confirms that HPV exposure is an important component. Future studies on HPV antibody seroprevalence and HPV typing in families/schools should provide evidence on immunogenicity and the susceptibility to specific HPV types.
Regarding public transmission, exposure to HPV was probably too low to be detected with the risk factors and number of children in this study. A possible explanation could be that some preventive measures had already been effectively carried out. Although there are

informal leaflets from public health institutions with advice on warts in the Netherlands, there are no formal regulations for persons with warts; they are neither actively banned from swimming activities nor recommended to cover their warts with plasters in public places.

Conclusion

This study reveals that the incidence of warts in primary schoolchildren is high and that cutaneous HPV is primarily transmitted via the family and school class. Current preventive recommendations mainly focus on limiting the personal spread of HPV ('Avoid scratching lesions') and reducing the risk of transmission in public places ('Wear flip-flops in communal showers')[19]. Our findings suggest that recommendations should shift towards reducing transmission among families and school classes. For example, covering warts at home potentially prevents transmission more effectively than covering warts in the swimming pool.

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CHAPTER 4

Cutaneous wart-associated HPV types: prevalence and relation with patient characteristics

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ABSTRACT

Background

Epidemiological data on cutaneous wart-associated HPV types are rare.

Objectives

To examine the prevalence of cutaneous wart-associated HPV types and their relation with patient characteristics.

Study design

Swabs were taken from all 744 warts of 246 consecutive immunocompetent participants and analysed by a broad spectrum HSL-PCR/MPG assay. Patient details including location, duration, and number of warts were recorded.

Results

No HPV DNA was detected in 49 (7%) swabs, a single HPV type in 577 (78%) swabs, and multiple HPV types in 118 (16%) swabs. HPV 2, 27 and 57 (alpha genus), HPV 4 (gamma genus) and HPV 1 (mu genus) were the most frequently detected HPV types, and HPV 63 (mu genus) was only frequently detected together with other HPV types. Less frequently detected HPV types were HPV 3, 7, 10 and 28 (alpha genus), 65, 88 and 95 (gamma genus) and 41 (nu genus). Warts containing HPV 1 showed the most distinct clinical profile, being related to children aged <12 years, plantar location, duration <6 months, and to patients with < 4 warts.

Conclusions

HPV 27, 57, 2 and 1 are the most prevalent HPV types in cutaneous warts in general population. Warts infected with HPV 1 have a distinct clinical profile.

BACKGROUND

Cutaneous warts are benign papillomas of the skin of which common warts (verrucae vulgaris) and plantar warts (verrucae plantaris) are the most common types. Up to one third of primary school children have cutaneous warts.[1] Although cutaneous warts have a benign natural history, they cause significant physical and psychological inconvenience. Therefore, patients with warts frequently consult physicians, mostly in primary care.[2,3]
Warts are caused by infection with human papillomaviruses (HPV). More than 120 HPV types, distributed over 5 genera and 16 species, have been described based on their DNA sequences.[4,5] HPV 2, 7, 27 and 57 from the alpha genus, HPV 4 and 65 from the gamma genus, and HPV 1 from the mu genus have most frequently been detected in cutaneous warts.[6-11] However, epidemiological data on cutaneous wart-associated HPV types are rare, and available studies are conducted in selected patient groups such as patients from dermatology clinics. The prevalence of cutaneous wart-associated HPV types in the general population is largely unknown.
Specific types of infecting HPV are correlated with histological characteristics and, to a lesser extent, with morphological features of warts.[12-16] Clinical characteristics other than morphological wart features may be useful to predict the prognosis and make treatment decisions. For example, the decisions of patients to consult physicians, and of physicians to start treatment, are influenced by the age of the patients as well as the location, duration, and number of warts.[3,17,18] Little is known about the relation between these patient characteristics and associated HPV genotypes.

OBJECTIVES

This study examines the prevalence of wart-associated HPV types in a large sample of patients with cutaneous warts in primary care, and explores the relation between HPV types and patient characteristics.

STUDY DESIGN

Patients and samples

We collected our samples from the warts of the participants of the Warts Randomised Treatment Study (WARTS).[17] All patients aged ≥ 4 years who attended one of the 50 participating family practices with one or more new cutaneous warts were invited to participate in this trial. We defined new warts as warts on the skin that were presented for the first

time without prior treatment from a general practitioner or dermatologist in the previous year. We excluded immune compromised patients, patients with genital warts, seborrheic warts, or mosaic warts ≥1 cm in diameter. Trained research nurses confirmed eligibility and obtained informed consent. Details on patient inclusion are already published.[17]
The protocol was approved by the medical ethical committee of the Leiden University Medical Center. The research nurses took swabs from each single wart by firmly rubbing a pre-wetted cotton-tipped stick over the surface of the wart five times. This swab technique adequately detects HPV types present in wart scab as well as wart biopsy.[19] Only when warts were too close to take separate swabs, was a single swab taken from the cluster of warts. We considered multiple warts as a cluster when the distance between warts was ≤1 cm. All swabs were stored in 1 ml of saline solution.

HPV identification

We used a newly developed broad spectrum PCR/MPG assay for genotyping all known wart-associated HPV types from the alpha- (HPV 2, 3, 7, 10, 27, 28, 29, 40, 43, 57, 77, 91 and 94), gamma- (HPV 4, 65, 95, 48, 50, 60 and 88), mu- (HPV 1 and 63) and nu-genus (HPV 41) to determine HPV distribution. This sensitive and specific assay (HSL-PCR/MPG assay; Labo Biomedical Products BV, Rijswijk, the Netherlands) has been described and evaluated by de Koning et al.[20] In short, 10 µl of the saline solution was used in the single-step HSL-PCR, generating a biotinylated amplimer of 76-84 bp from the L1 region. Subsequently, simultaneous identification of the 23 HPV genotypes was performed with bead-based xMAP suspension array technology. Negative samples were not analysed any further. All PCR reactions were carried out with all precautions to avoid contamination described by the manufacturer. Negative PCR and genotyping controls were incorporated and remained negative upon analysis with the HSL-PCR/MPG assay.

Patient characteristics

We recorded the following characteristics: sex (male vs. female); age (4-11 years vs. 12-20 years vs. 21 years and older); location of warts (plantar warts [warts on the soles of the feet] vs. common warts [warts on other locations than soles of the feet, mostly hand warts]); duration of warts at the time of investigation (≤6 months vs. >6 months); number of warts per patient (<4 vs. ≥4 warts); part of cluster of warts (yes vs. no); inconvenience caused by warts (pain, irritation, or cosmetic inconvenience; yes vs. no). For statistical purposes and clear presentation of results, the characteristics were dichotomised with cut-off values closest to the median.

Statistical analysis

Prevalence with 95% confidence interval (CI) was calculated for warts associated with a single HPV type and for warts associated with multiple HPV types. We used warts with a single HPV type in our primary analysis. All HPV types were stratified according to dichotomised patient characteristics. We considered a number of <30 warts per HPV type too small to reliably investigate their relation with patient characteristics. For the most prevalent HPV types, proportions of warts per characteristic were compared using 95% CI. In the sensitivity analyses, prevalence and clinical profiles were calculated with a proportional weighting attribution, which includes information about warts with multiple types.[21-23] For example, in a wart with multiple types consisting of HPV 2 and HPV 4 where prevalence in single types is 22% and 5%, respectively, using the proportional attribution, the case would be split between the two types with the prevalence in single types used as reference: 22/27 for HPV 2 and 5/27 for HPV 4.
To explore the different types involved in warts with multiple HPV types, we compared observed numbers of specific 2-type combinations with expected numbers, which were obtained by multiplying the prevalence of both HPV types in warts with a single type, multiplied by the total number of warts. We also repeated analyses of prevalence and clinical profiles with patients instead of warts as unit of analysis, and assessed concordance of HPV types within patients with multiple warts calculating the proportions of patients sharing one HPV type in all warts.

RESULTS

Patients and samples

Of the 250 included patients, 246 provided wart swabs for HPV testing. The swabs of 4 patients were lost in transport to the laboratory. Median age was 13 (range 4-73) years and 59% of the participants were female (Table 4.1). At study entry, 91 patients (37%) had one wart, 117 (58%) had 2-5 warts, and 38 (15%) had 6 or more warts. Sixty patients (24%) had at least one cluster of warts. Furthermore, 103 patients (42%) had plantar warts only, 108 (44%) had common warts only, and 35 (14%) had both plantar and common warts. All 744 warts from these 246 patients were analysed: 373 plantar warts (50%) located on the soles of the feet, and 371 common warts (50%) of which 75% was located on hands and 25% on the rest of the body.

Table 4.1. Patient characteristics of the study population (n=246)

Sex	
Female	150 (58.9)
Male	96 (41.1)
Age	
4-11 years	107 (43.5)
12-21 years	45 (18.3)
21+ years	94 (38.2)
Location of warts	
Plantar warts only	103 (41.9)
Common warts only	108 (43.9)
Plantar as well as common warts	35 (14.2)
Duration of oldest wart	
< 6 months	100 (40.7)
≥ 6 months	146 (59.3)
Number of warts	
1	91 (37.0)
2	47 (19.1)
3	33 (13.4)
4	24 (9.8)
5	13 (5.3)
6 or more	38 (15.4)
Presence of wart cluster	60 (24.4)
Warts cause inconvenience*	184 (74.8)

Data are numbers of patients (%)
* Pain, irritation, or cosmetic inconvenience

HPV type prevalence

From the 744 swabs, 49 (7%) were negative for HPV DNA, 577 (78%) were positive for a single HPV genotype, and 118 (16%) swabs contained DNA of multiple HPV types. In total, 217 warts (29%) were part of a cluster, of which 27 clusters providing 69 warts had been swabbed with a single swab because warts were too close to take separate swabs. In these swabs, the proportion of swabs with multiple HPV types was equal to the proportion in all swabs (also 16%).

Table 4.2 presents the prevalence of HPV types in all HPV-positive warts. Most prevalent HPV types in warts with a single HPV type were HPV 27 (24%), HPV 57 (22%), HPV 2 (22%), and HPV 1 (19%). Their combined relative contribution was 86% (95% confidence interval (CI) 83-88%). Furthermore, HPV 4, HPV 65, HPV 28, HPV 3 and HPV 10 were each present in 1-5% of swabs, and HPV 7, HPV 63, HPV 41 and HPV 95 in <1%. The prevalence

Table 4.2. Human papillomavirus (HPV) types in all HPV-positive warts, according to a single or multiple HPV type present (n=695).

HPV type*	Warts with single HPV type			Warts with multiple HPV types						All warts		
	number of warts with single type (n=577)	%	95%CI	number of warts with two types (n=94)	number of warts with three types (n=20)	number of warts with four types (n=4)	all warts with multiple types† (n=118)	%	95%CI	proportional weighting attribution (n=695)‡	%§	95%CI
27	137	23.7	20.5-27.4	35	7	3	45	38.1	29.9-47.1	162	23.3	20.3-26.6
57	126	21.8	18.7-25.4	26	3	-	29	24.6	17.7-33.1	145	20.9	18.0-24.0
2	125	21.7	18.5-25.2	45	10	3	58	49.2	40.3-58.1	166	23.9	20.9-27.2
1	107	18.5	15.6-21.9	29	9	2	40	33.9	26.0-42.8	130	18.7	16.0-21.8
4	29	5.0	3.5-7.1	27	10	1	38	32.2	24.4-41.1	36	5.2	3.8-7.1
65	14	2.4	1.5-4.0	5	5	-	10	8.5	4.7-14.9	15	2.2	1.3-36
28	13	2.3	1.3-3.8	2	1	-	3	2.5	0.9-7.2	14	2.0	1.2-3.3
3	10	1.9	0.9-3.2	-	-	-	-	-	-	10	1.4	0.8-2.6
10	8	1.4	0.7-2.7	5	-	-	5	4.2	1.8-9.5	8	1.2	0.6-2.3
7	3	0.5	0.2-1.5	-	-	-	-	-	-	3	0.4	0.1-1.3
63	2	0.3	0.1-1.3	10	10	4	24	20.3	14.1-28.5	2	0.3	0.1-1.1
41	2	0.3	0.1-1.3	2	3	3	8	6.8	3.5-12.8	2	0.3	0.1-1.1
95	1	0.2	0.0-1.0	1	-	-	1	0.9	0.1-4.6	1	0.1	0.0-0.8
88	-	-	-	1	2	-	3	2.5	0.9-7.2	0	0.0	0.0-0.5

HPV types 29,77,94, 40,43,91,48,50,60 were tested, but not identified in wart swabs

* One of multiple HPV types involved in warts with multiple types

† The mean number of HPV types per wart is 2.2 (264/118) for warts with multiple HPV types, and 1.2 (841/695) for all warts

‡ Rounded off in whole numbers

§ Sum of percentages ≠ 100% due to rounding off

of HPV types in all warts according to the proportional attribution was comparable to the prevalence in warts with a single HPV type (Table 4.2).

HPV type and patient characteristics

Table 4.3 presents data on the relation between patient characteristics and the detected HPV types in warts associated with a single HPV type. The four most prevalent HPV types were related to specific clinical profiles (Figure 4.1). Warts with HPV 1 showed the most distinct clinical profile, being related to children aged <12 years, plantar location, duration <6 months at the time of investigation, and to patients with < 4 warts. For these characteristics, the 95% CI for HPV 1 did not overlap the 95% CI of all warts, nor the CI of the other most prevalent HPV types. Warts with HPV 27 and warts with HPV 57 had a similar clinical profile which slightly differed from warts with HPV 2: HPV 27/57 were related to patients aged ≥12 years, especially to patients aged 21+; HPV 2 was related to location on the hands (Table 4.3). Less frequently detected HPV types were found in warts with short as well as long duration.

Warts with multiple HPV types

In warts associated with multiple HPV types (n=118), HPV 4 and HPV 63 were also involved in >20% in addition to the highly prevalent HPV 27, 57, 2 and 1 (Table 4.2). Warts with double HPV types (n=94) were observed less frequently than expected (Appendix 4.1). The combination of HPV 2 and 4 (n=18), and the combination of HPV 1 and 27 (n=18) were the most prevalent. In all observed combinations, one of the four most prevalent HPV types was present, with the exception of the combination HPV 65 and 28 (n=1). Remarkably, the combination of HPV 1 and 57, and the combination of HPV 1 and 2 were not observed, while combinations with HPV 63 (n=10) were more prevalent than expected. Patient characteristics of warts with combinations of multiple types did not reveal significant profiles (data not shown).

Patients with multiple warts

When patients were used as unit of analysis, HPV prevalence (Appendix 4.2) and clinical profiles (data not shown) were in line with the results in warts. In 74% of patients with multiple warts (n=150), all warts shared one HPV type. In a further 23% of patients with multiple warts some but not all warts shared one HPV type. As an example for this, a 6 year old boy had a plantar wart associated with HPV 65 and two hand warts, of which one was also associated with HPV 65 but the other with HPV 57. Within all clusters of warts (n=82), the HPV positive warts shared one HPV type, with the exception of one plantar cluster of 3 warts, where in one wart HPV 27 was detected and in the other two warts HPV 57 was detected.

Figure 4.1: Patient characteristics of warts in relation to the four most prevalent HPV types (n=577). X-axis represents the mean proportion in all warts. Differences between proportions are considered significant when 95% CIs of proportions do not overlap.

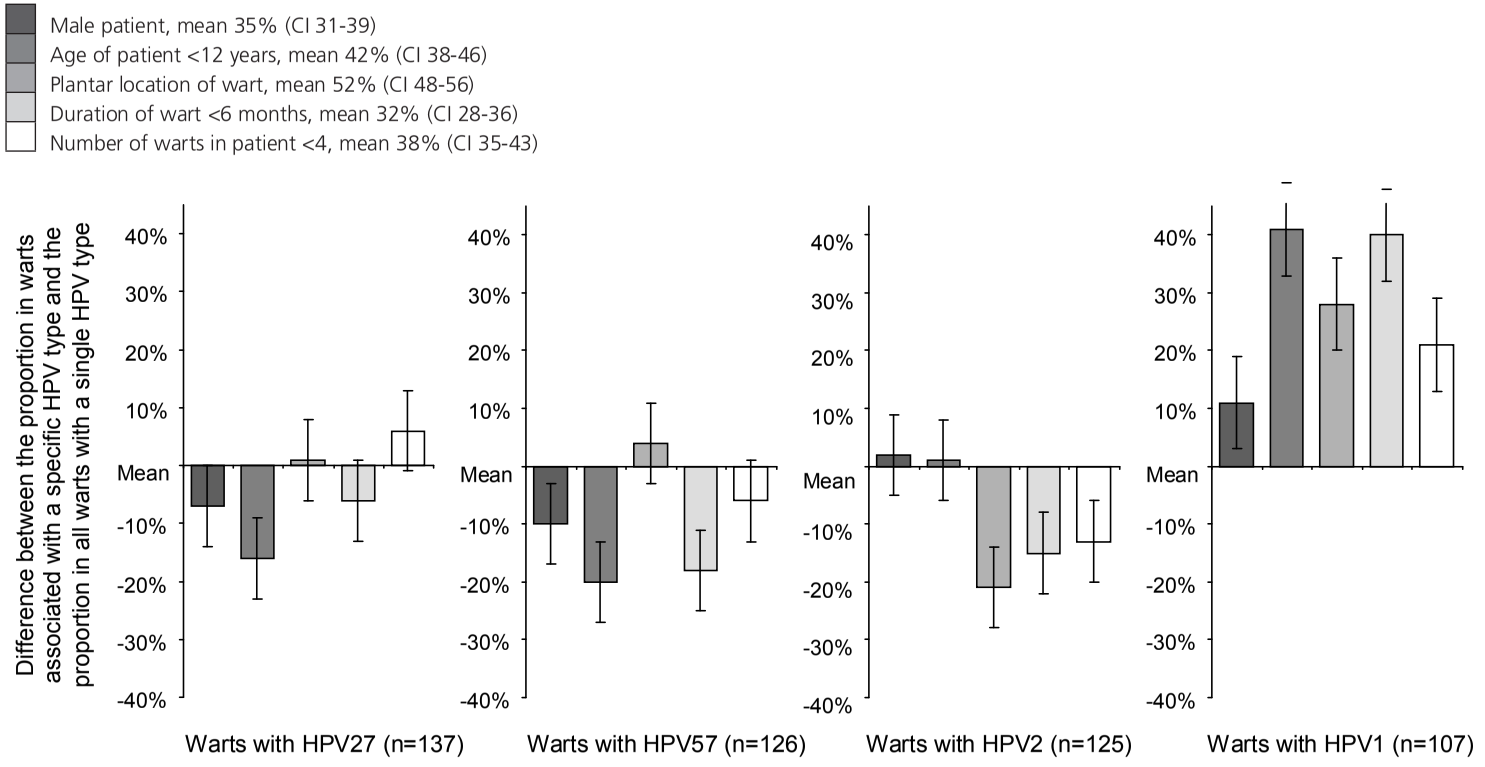

Table 4.3. Clinical profiles of all identified HPV types in warts with single HPV type (n=577).

	Alpha							Gamma			Mu		Nu	All warts (n=577)
	Species 2			Species 4			Species 8	Species 1			Species 1	Species 2	Species 1	
Patient characteristic	HPV3 (n=10)	HPV10 (n=8)	HPV28 (n=13)	HPV2 (n=125)	HPV27 (n=137)	HPV57 (n=126)	HPV7 (n=3)	HPV4 (n=29)	HPV65 (n=14)	HPV95 (n=1)	HPV1 (n=107)	HPV63 (n=2)	HPV41 (n=2)	
Male	3 (30)	0 (0)	4 (31)	46 (37)	39 (28)	32 (25)	3 (100)	19 (66)	7 (50)	1 (100)	49 (46)	0 (0)	0 (0)	203 (35)
Age 4-11 years	3 (30)	0 (0)	4 (31)	54 (43)	36 (26)	28 (22)	0 (0)	19 (66)	10 (71)	0 (0)	89 (83)	0 (0)	0 (0)	243 (42)
12-20 years	0 (0)	0 (0)	0 (0)	51 (41)	44 (32)	38 (30)	0 (0)	1 (3)	1 (7)	0 (0)	8 (7)	2 (100)	0 (0)	145 (25)
21+ years	7 (70)	8 (100)	9 (69)	20 (16)	57 (42)	60(48)	3 (100)	9 (31)	3 (21)	1 (100)	10 (9)	0 (0)	2 (100)	189 (33)
Plantar location	0 (0)	0 (0)	0 (0)	39 (31)	72 (53)	70 (56)	0 (0)	18 (62)	10 (71)	0 (0)	86 (80)	2 (100)	2 (100)	299 (52)
<6 months duration	0 (0)	0 (0)	0 (0)	21 (17)	35 (26)	18 (14)	3 (100)	21 (72)	5 (36)	1 (100)	77 (72)	2 (100)	0 (0)	183 (32)
<4 warts in patient	0 (0)	0 (0)	0 (0)	31 (25)	60 (44)	40 (32)	3 (100)	9 (31)	12 (86)	1 (100)	63 (59)	1 (50)	2 (100)	222 (38)
Part of cluster	2 (20)	5 (63)	7 (54)	47 (38)	26 (19)	55 (44)	2 (67)	11 (38)	0 (0)	0 (0)	20 (19)	0 (0)	0 (0)	175 (30)
Inconvenience*	7 (70)	8 (100)	11 (85)	101 (81)	112 (82)	91 (72)	3 (100)	27 (93)	7 (50)	1 (100)	89 (83)	1 (50)	2 (100)	260 (80)

Data are numbers (percentages)

* Pain, irritation, or cosmetical inconvenience

DISCUSSION

Main findings

In the present study, HPV 27, 57, 2 and 1 were the most prevalent HPV types. In only 14% of warts other HPV types were detected. The clinical profile of warts associated with HPV 1 from the mu genus differed from those associated with HPV 27, 57 and 2 from the alpha genus. Warts with HPV 1 usually occurred in children, preferentially on a plantar surface, and had a short duration before presentation to the physician. In 74% of patients with multiple warts, one HPV type was shared in all warts of that patient.

Comparison with literature

Three other large HPV prevalence studies analysing cutaneous wart-associated HPV types have been conducted, all in selected dermatology populations.[6,8,9] In these studies, different HPV type prevalences were reported. For example, the prevalence of HPV 1 was reported to be 44% by Hagiwara et al., 27% by Iftner et al., and 4% by Rubben et al., compared to 19% in the present study. These differences may be due (in part) to regional differences, or to patient selection. Our study was conducted in primary care, in which patient selection is less likely to have occurred than, for example, in a dermatology department. Alternatively, this discrepancy may be explained by the use of different HPV detection and typing methods in each study.

The observation that HPV 1 is related to young patients, plantar location, and short duration is in line with others.[9,16] Furthermore, in the prevalence studies, the higher the proportion of plantar warts, the higher the reported prevalence of HPV 1.[6,8,9] However, Hagiwara et al., Chen et al., and Tomson et al. found no relation with age.[6;7;11] The reasons for this are not clear, but may be influenced by their study population with a very low prevalence of HPV 2/27/57[6,7] or HPV 1.[11]

In the current study, the presence of multiple HPV types was detected in 16% of all swabs, which is more than reported in other studies;[6,9,20,24,25] this is probably due to our HSL-PCR/MPG method which is specifically capable of detecting multiple HPV types per sample.[20] These warts with multiple HPV types were analysed separately from the warts with a single HPV type, since combining them would dilute associations with patient characteristics and reduce the clarity of interpretation. In addition to the highly prevalent HPV 27, 57, 2 and 1 in warts with a single type, HPV 4 and 63 were also frequently detected in warts with multiple types. We hypothesise that in a wart in which multiple HPV types are detected, usually only one HPV type will be responsible for the development of the wart. This is supported by evidence on the clonal origin of warts,[26] and by a recent study which found that within a defined cervical intraepithelial neoplastic lesion, only one HPV type is present.[27] In the latter

study, analysis was done on dissected lesional cells for which biopsies were needed. For the present primary care population, however, non-invasive swabs of the lesion were used and the sensitive HSL-PCR/MPG could have picked up a passenger HPV type present on the skin.[28,29] We could not use the relative abundance of HPV types, because the HSL-PCR/MPG technology is not a quantitative method. Results presented by De Koning et al. support that HPV types identified in wart swabs are representative for the HPV type present in the wart biopsy by showing a very high concordance (96%) between the HPV type detected in the wart swabs and wart biopsies: comparing HPV types on different sites, 24/25 wart swabs, 19/25 perilesional swabs and 9/25 normal epithelium swabs were identical to the wart biopsy. In the perilesional and normal epithelium swabs 3 and 2 multiple infections were detected and 2/25 and 11/25 were HPV negative, respectively.[19] Alternatively, a co-infection of single cells with multiple HPV types could be responsible for the development of some warts with multiple types;[24] for completeness, the results of sensitivity analysis including the warts with multiple types were comparable.

Strengths and limitations

The present study population was a large non-selected sample of patients with first presentation of single or multiple warts in primary care. However, HPV type prevalence could be different in the general population since HPV types causing warts with little inconvenience are underrepresented in primary care. Only 7% of all swabs were negative for HPV DNA. The HSL-PCR/MPG was designed to amplify all HPV types previously found in cutaneous warts as well as related types from the same viral species.[4] Viral loads below the detection limit of the assay, other or unknown HPV types, or not yet described variants of the types included in the assay may be involved in these negative swabs. Also, lesions (e.g. callus) could have been misdiagnosed as warts or residual hyperkeratotic lesions following HPV clearance could have been sampled; however, no histological investigation of the warts was made. Also, no data on mosaic warts were collected, since this was one of the exclusion criteria.

Implications

This is the first large study combining a comprehensive genotyping assay analysing all known cutaneous wart-associated HPV types and simple non-invasive swabs to collect viral DNA. This could be of special interest if specific HPV infections prove to be associated with clearance or response to specific treatments. In that case, HPV genotyping or HPV type assessment based on clinical profiles may become relevant for daily practice.

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Appendix 4.1. Specific combinations of HPV types in warts with two types (n=94)

HPV types*	27	57	2	1	4	65	Total
27							130 - 35
57	37 - 6						124 - 26
2	37 - 8	34 - 10					124 - 45
1	32 - 18	29 - 0	29 - 0				108 - 29
4	8 - 2	8 - 1	8 - 18	7 - 6			34 - 27
65	4 - 0	4 - 0	4 - 2	3 - 2	1 - 0		16 - 5
28	4 - 0	4 - 0	4 - 1	3 - 0	1 - 0	0 - 1	16 - 2
3	3 - 0	3 - 0	3 - 0	2 - 0	1 - 0	0 - 0	12 - 0
10	2 - 0	2 - 3	2 - 1	2 - 1	0 - 0	0 - 0	8 - 0
7	1 - 0	1 - 0	1 - 0	1 - 0	0 - 0	0 - 0	4 - 0
63	1 - 1	1 - 4	1 - 3	0 - 2	0 - 0	0 - 0	3 - 10
41	1 - 0	1 - 1	1 - 1	0 - 0	0 - 0	0 - 0	3 - 2
95	0 - 0	0 - 1	0 - 0	0 - 0	0 - 0	0 - 0	0 - 1
88	0 - 0	0 - 0	0 - 1	0 - 0	0 - 0	0 - 0	0 - 1

Data are numbers of combinations Expected (multiplying prevalences of both HPV types in warts with a single type multiplied by the total number of warts) – Observed.

* HPV types are ordered according to prevalence in warts with a single type.

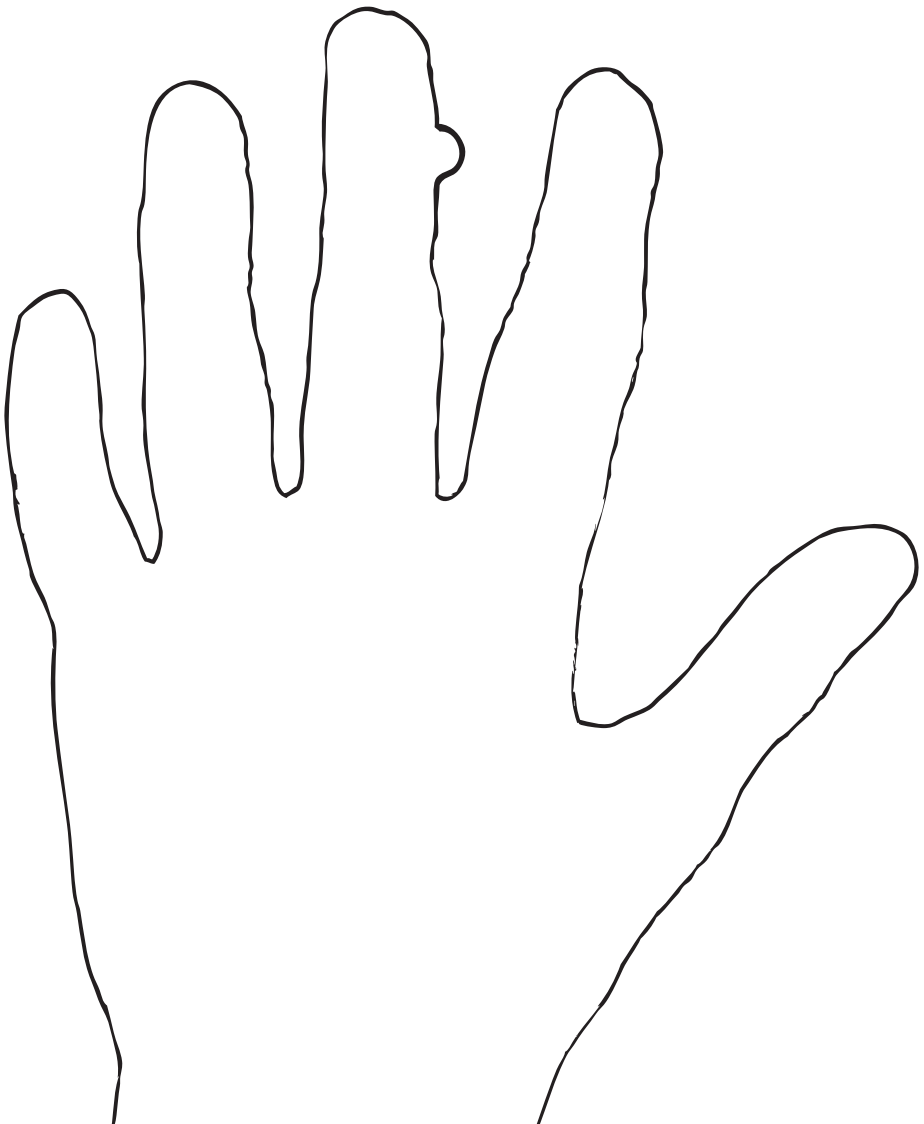
Appendix 4.2. Human papillomavirus (HPV) types in 236 patients* with single or multiple warts, with a single or multiple HPV type present.

HPV type	Patients with single wart		Patients with multiple warts		All patients		
	patients with warts with a single type (n=79)	patients with warts with multiple types (n=7)	patients with warts with a single type (n=76)	patients with warts with multiple types (n=74)†	total (n=236)	%	95%CI
27	23	3	19	35	80	33.9	28.2-40.2
57	12	1	14	35	62	26.3	21.1-32.2
2	11	2	18	33	64	27.1	21.8-33.1
1	25	6	18	24	73	30.9	25.4-37.1
4	5	3	2	17	27	11.4	8.0-16.1
65	2	-	2	11	15	6.4	3.9-10.2
28	-	-	1	3	4	1.7	0.7-4.3
3	-	-	1	1	2	0.8	0.2-3.0
10	-	-	-	3	3	1.3	0.4-3.7
7	-	-	1	-	1	0.4	0.1-2.4
63	-	1	-	12	13	5.5	3.2-9.2
41	-	-	-	3	3	1.3	0.4-3.7
95	1	-	-	1	2	0.8	0.2-3.0
88	-	-	-	2	2	0.8	0.2-3.0
Mean number per patient	1 (79/79)	2.3 (16/7)	1 (76/76)	2.4 (180/74)	1.5 (361/236)		

HPV types 29,77,94, 40,43,91,48,50,60 were tested, but not identified in wart swabs

* In 10 of 246 patients (4%), all swabs were negative for HPV DNA.

† Due to different HPV types in warts with a single type, or due to multiple HPV types in a single wart.



PART TWO

Treatment

CHAPTER 5

Natural course of cutaneous warts among primary schoolchildren: a prospective cohort

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ABSTRACT

Purpose

Because cutaneous warts resolve spontaneously and available treatments often fail, general practitioners and patients may consider a wait-and-see policy. We examined the natural course of cutaneous warts and treatment decisions in a prospective observational cohort of primary school children.

Methods

The hands and feet of children aged 4-12 years from three Dutch primary schools were inspected for the presence of warts at baseline and after a mean follow-up of 15 months. Parental questionnaires at follow-up provided information on inconvenience caused by warts and treatments used.

Results

Of the 1134 eligible children, 1099 participated (97%) of which 366 (33%) had cutaneous warts at baseline. Overall, loss to follow-up was 9% and response from parental questionnaires was 83%. The complete resolution rate was 52 per 100 person-years at risk (95% CI 44-60). Age (hazard ratio 1.1 per year decrease, 95% CI 1.0-1.2) and non-Caucasian skin type (hazard ratio 2.0, 95%CI 1.3-2.9) were related to higher resolution rates. During follow-up, 38% of children with warts at baseline decided to treat warts: 18% used over-the-counter treatment, 15% treatment in general practice, and 5% used both. Initiation of treatment was related to warts ≥1cm in size and parent-reported inconvenience caused by warts.

Conclusions

Half of primary school children with warts will be free of warts within one year. Young age and non-Caucasian skin type enhance resolution. Children with large or inconvenient warts are more likely to start treatment. These findings will be useful in the process of shared decision-making with parents and children.

INTRODUCTION

Cutaneous warts are caused by the human papillomavirus (HPV). Small defects of the skin are sufficient for HPV to infect the basal layer of the skin which may lead to benign hyperkeratotic papillomas.[1] Warts are very common in the general population, especially among children. The prevalence of warts among primary school children is reported to be 22-33%,[2;3] while the annual prevalence based on consultations in general practice is about 6%.[4;5] This difference indicates that only a proportion of children seeks medical advice or treatment for warts.

Liquid nitrogen cryotherapy and salicylic acid application (30-50%) are the most frequently used treatments for warts by general practitioners (GPs).[6] Less potent over-the-counter (OTC) cryotherapy or salicylic acid (usually 17%) treatments are offered in pharmacies without prescription.[7] Because warts resolve spontaneously and available treatments often fail, especially in the case of plantar warts,[8-10] a 'wait-and-see' policy may be considered in treatment decisions.[11] However, studies on the natural course of warts are scarce and outdated.[12-14]

Therefore, the present study examines the natural course of cutaneous warts and treatment decisions in a prospective observational cohort of primary school children.

METHODS

Study cohort and procedures

At baseline we included all children in grades 1-7 from three primary schools in/around the city of Leiden, the Netherlands. A trained medical student inspected the hands and feet of all children for the presence of warts. A previous publication reports on the details of the baseline examination.[3] One year later, another trained medical student examined the hands and feet of all children with warts at baseline (now in grades 2-8), again for the presence of warts. Mean follow-up was 15 months, with a range of 11-18 months due to practical reasons and taking into account school vacations. Parents were asked to give informed consent before both examinations. Apart from this, children were free to refuse participation during examinations. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center, as well as by the boards of the participating schools.

Presence of warts

At baseline and follow-up, the type and number of warts were recorded on standard forms with schematic representation of the hands and feet. A distinction was made between plantar warts (located on the sole of the feet) and common warts (located on the hands

or the dorsal side of the feet). Complete resolution was defined as a child with no warts at follow-up examination. A wart was considered resolved when it was no longer visible (skin favour and skin lines were re-established) and could no longer be palpated by hand. Over 5% of both the baseline and the follow-up examinations were supervised by experienced GPs, with no discordance regarding wart diagnosis or resolution.

Factors enhancing resolution

During baseline examination, the following factors were recorded:

- Demographic factors: age (split on the median: 4-7 years vs. 8-12 years), sex (girls vs. boys), and skin type (coded according to Fitzpatrick to stratify into Caucasian vs. non-Caucasian subgroups).[15]
- Wart factors: type (plantar vs. common warts), number of warts (single vs. multiple warts), size of wart (<1 cm vs. ≥1 cm).

Treatment decisions

Prior to follow-up examination, parents were asked to complete a questionnaire about the inconvenience caused by warts present at any time during the follow-up period and which treatments were initiated for these warts. The following factors were recorded:

- Inconvenience of warts: type of inconvenience (pain, irritation, unsightly, opinion of others), and amount of inconvenience (on a scale from 0 [no inconvenience] to 4 [considerable inconvenience]);
- Initiated treatment: GP involved (OTC treatment vs. GP treatment), specific treatment (cryotherapy vs. salicylic acid application vs. others),

Statistical analyses

Resolution rates with 95% confidence interval (CI) were calculated, dividing the children with complete resolution by the sum of the person-time of children at risk (person-years at risk). For calculating person-time at risk, the date of resolution was considered to be halfway the follow-up period. In addition, we calculated resolution rates stratified for plantar and common warts, as well as the resolution rate when only baseline warts were considered, i.e. new warts which developed during the follow-up period were disregarded. Cox proportional hazards models were used to identify factors enhancing resolution. Univariate analysis was performed for demographic, wart, and treatment factors to estimate hazards ratios (HR) with 95% CI. Multivariate analysis with all factors was performed to assess which relations were independent. In subgroup analysis, HRs were calculated for children with plantar warts separately. In addition, a logistic regression model was used to

explore factors related to the decision to treat warts. Odds ratios (OR) with 95% CI were calculated for demographic, wart, and inconvenience factors.

RESULTS

Study cohort

At baseline, the participation rate of 1134 eligible children was 97%: 23 children (2%) were absent from school at the time of baseline examinations, and for 12 children (1%) parental or child consent was not given. At baseline, 366 children had warts upon examination (33%). During follow-up, 33/366 (9%) were lost to follow-up: 24 children (7%) left school and for 9 children (2%) parental or child consent was not given for the follow-up

Table 5.1. Baseline characteristics of the primary school children with warts included in the follow-up (n=333)

Median age in years (range)	8 (4-12)
Sex	
Boys	162 (49)
Girls	171 (51)
Skin type	
Caucasian	284 (85)
Non-Caucasian	49 (15)
School	
School A, 28 classes	219 (66)
School C, 8 classes	27 (8)
School D, 12 classes	87 (26)
Type of warts	
Common warts	100 (30)
Plantar warts	192 (58)
Both common and plantar	41 (12)
Number of warts	
1 wart	191 (57)
2 warts	63 (19)
3 to 5 warts	52 (16)
6 warts or more	27 (8)
Size of warts	
No warts ≥1 cm	209 (63)
Wart ≥1 cm	124 (37)

Values are numbers (%), unless stated otherwise

examination. At baseline, the median age of the 333 children included in the follow-up was 8 years (interquartile range [IQR] 5-10 years), 49% was male, and 15% had a non-Caucasian skin type, originating from Morocco, Turkey, China, the Netherlands Antilles or Surinam (Table 5.1). In total, 42% of the children had common warts, 70% plantar warts, 43% multiple warts, and 37% had a wart ≥1 cm in size.

Resolution of warts

The complete resolution rate was 52 per 100 person-years, 95% CI 44-60. When newly-developed warts were not considered, the resolution rate of baseline warts was even higher: i.e. 90 per 100 person-years (95% CI 79-100). These numbers were similar for both common warts and plantar warts.

Table 5.2. Univariate analysis of the association of demographic and wart factors at baseline with the resolution of all warts in primary school children

Potential risk factor	No. of cases/ Person-years	Resolution rate per 100 person-years	Hazard ratio* (95% CI)	p-value
Demographic factors				
Age in years				
8-12	80 / 176	45	1	
4-7	82 / 137	60	1.5 (1.1-2.0)	0.015
Per year decrease			1.12 (1.04-1.20)	0.003
Sex				
Girls	76 / 164	46	1	
Boys	86 / 149	58	1.3 (0.9-1.7)	0.13
Skin type				
Caucasian	129 / 274	47	1	
Non-Caucasian	33 / 39	85	2.0 (1.3-2.9)	0.001
Wart factors				
Type				
Common	50 / 94	53	1	
Plantar	96 / 181	53	1.0 (0.7-1.4)	0.88
Both common and plantar	16 / 38	42	0.7 (0.4-1.2)	0.19
Number				
Single wart	90 / 184	49	1	
Multiple warts	72 / 129	56	1.1 (0.8-1.4)	0.71
Per extra wart †			1.03 (0.96-1.10)	0.43
Size				
≥1 cm	55 / 117	47	1	
<1 cm	106 / 194	55	1.2 (0.9-1.6)	0.29

* Generated by univariate Cox proportional hazards model.

Factors enhancing resolution

Young age (HR 1.1 per year decrease, 95% CI 1.0-1.2) and non-Caucasian skin type (HR 2.0, 95% CI 1.3-2.9) enhanced the resolution of warts, whereas the type, number or size of the warts did not predict resolution (Table 5.2). Multivariate analysis showed almost comparable results with the only difference being that, in this model, an increase in the number of warts slightly enhanced the resolution (HR 1.1 per extra wart, 95% CI 1.0-1.2, p=0.039). Subgroup analysis of children with plantar warts and the analysis only considering warts present at baseline yielded similar results as primary analysis considering all warts including warts that developed during follow-up.

Treatment decisions

According to parental questionnaires with a response of 276/333 (83%), 73 children (26%) reported inconvenience caused by warts and 106 (38%) children were treated with OTC or GP treatments during follow-up (Table 5.3). Two children were referred to

Table 5.3. Reported inconvenience caused by warts and initiated treatments according to parental questionnaires* (n=276)

Any inconvenience caused by warts	73 (26)
Pain	23 (8)
Irritation	28 (10)
Unsightly	38 (14)
Bothered by opinion of others	10 (4)
Initiated treatment	106 (38)
OTC treatment only	49 (18)
GP treatment only	41 (15)
GP as well as OTC treatment	16 (5)
Specific OTC treatments‡	
Dimethylether/propane cryotherapy	28 (10)
Low dose (17%) salicylic acid	37 (13)
Duct tape	2 (1)
Other	12 (4)
GP treatments‡	
Liquid nitrogen cryotherapy	49 (18)
High dose (40-50%) salicylic acid	14 (5)
Other	3 (1)

* Response to parental questionnaires was 276/333 (83%)
† Initiated treatments were comparable for common warts and plantar warts
‡ More than one option possible: 23 children reported more than one type of inconvenience, 13 children used more than one OTC treatment, and 9 children used more than one GP treatment.

Table 5.4. Associations of personal and wart factors at baseline and reported inconvenience with the decision to treat warts during follow up (n=276)

	Odds ratio* (95% CI)	p-value
Demographic factors		
Age (per year increase in age)	1.1 (0.9-1.2)	0.33
Female sex	1.3 (0.8-2.1)	0.28
Caucasian skin type	1.6 (0.8-3.2)	0.24
Wart factors		
Plantar location	1.1 (0.7-2.0)	0.66
Number (per extra wart)	1.1 (1.0-1.2)	0.080
Size ≥1 cm	3.2 (1.9-5.3)	<0.001
Warts not resolved at follow-up†	2.0 (1.2-3.3)	0.012
Inconvenience caused by warts§		
Yes	38 (16-90)	<0.001
Degree of inconvenience‡	11 (5.6-23)	<0.001
Pain	21 (4.8-91)	<0.001
Irritation	27 (6.3-118)	<0.001
Unsightly	20 (6.7-57)	<0.001
Opinion of others	16 (2.0-126)	0.010

* Generated by univariate logistic regression model.
† Proxy for long-lasting warts
‡ OR per unit on a scale from 1 (little inconvenience) to 4 (considerable inconvenience).
§ Reported retrospectively by parents

a dermatologist. Initiated treatments were comparable for common warts and plantar warts. Children treated during the follow-up period had worse resolution rates than the non-treated children: HR for all treatments 0.6 (95% CI 0.4-0.8); for GP treatments 0.7 (95% CI 0.4-1.1) and for OTC treatment only 0.5 (95% CI 0.3-0.8).

The decision to initiate treatment of warts during follow-up (OTC and GP treatment combined) was not related to age, sex, skin type, or type of wart at baseline, but was related to the size of the wart at baseline (OR ≥1 cm vs. <1 cm 3.2, 95% CI 1.9-5.3), long-lasting warts (OR not resolved vs. resolved warts at follow-up 2.0, 95% CI 1.2-3.3), and the reported inconvenience caused by warts (OR inconvenience vs. no inconvenience 38, 95% CI 16-90, Table 5.4). Multivariate analysis with all of the above factors showed comparable results.

DISCUSSION

Summary of findings

Half of all primary school children with warts will be free of warts after one year. Among young children and children with non-Caucasian skin type, resolution rates are even higher. During follow-up, 38% of children/parents decided to treat warts, a decision that was related to bigger size of warts and increased inconvenience caused by warts.

Comparison with other studies

The most cited study on the natural course of cutaneous warts reported 113/168 (67%) of patients free of warts after 2 years.[12] None of the participants were treated during follow-up; however, that study was conducted in 1963 in an institutionalised mentally disabled population. Another study conducted in 1959 with a complete resolution after one year of 77/136 (57%) only included hand warts in Dutch primary school children,[13] and a more recent cohort of 11-year-old British children showed a 5-year resolution of 337/364 (93%) but did not provide data on a shorter follow-up.[14] Despite all the methodological limitations, the natural course in these latter studies is roughly in line with that in our study. Although the full complexity of the relationship between the persistence of warts and immunologic responses is not yet fully elucidated,[16] the current study shows that age and ethnic factors play a role in the resolution of warts. In agreement with others, the location and size of warts do not seem to influence the resolution rate.[12;13] Associations with the number of warts are not consistent in other studies and the present study could not provide clear evidence on this issue either. [10;12;13]

Strengths and limitations

This study with a participation rate of 97% represents the natural course of warts in a current primary school population in Western Europe. Although the data did not allow to draw conclusions on time to resolution or wart growth, resolution rates after one year were objectively established by physical inspection of hands and feet. Warts on other parts of the body were potentially missed, but they only account for less than 4% of all warts.[17] Information on initiated treatments was collected because treatment effects might play a role in the observed resolution rates. In agreement with a study among Australian school children,[2] about one third of children with warts had sought treatment, for which a wide range of OTC and GP treatments were available. The remaining two thirds decided to refrain from treatment, or were simply not aware of the presence of warts. The parental questionnaires before baseline examination at least showed that approximately half of

all children had warts that had not been noticed earlier by their parents.[3] The present study shows that family practice yearly only encounters 20% of all children with warts. These children have larger and more inconvenient warts with poorer resolution rates than children who did not seek treatment. However, further interpretation of these findings is limited because selection and recall bias are probably involved. We had no information on the duration of warts at baseline; moreover, retrospectively, the parents of children with persistent warts may more easily have recalled treatments and inconvenience than the parents of children with resolved warts. In a recent randomised controlled trial in a GP population the resolution rate in children after a wait-and-see policy of 3 months was 29% (95% confidence interval 17% to 45%).[10]

Implications

A child with warts has a 50 percent chance of still having warts after waiting a year, despite any treatments. Warts in young children and children with Caucasian skin types will resolve faster. These findings will be useful in the process of shared decision-making with parents and children. Patients and GPs should weigh the benign natural course, the side effects of treatments and costs on the one hand, and the effectiveness of treatments and the risk of spreading warts on the other. Future research needs to more precisely establish time to resolution of warts and identify subgroups of patients with relatively low natural resolution rates and high treatment response.

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CHAPTER 6

Current choices in the treatment of cutaneous warts: a survey among Dutch general practitioners

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ABSTRACT

Background

General practitioners (GPs) apply several treatments for patients with cutaneous warts. Available evidence recommends salicylic acid application.

Objective

We investigated whether current choices of GPs in the treatment of warts are in agreement with available evidence.

Methods

A nationwide random sample of 700 Dutch GPs received a postal questionnaire on their choices in the treatment of warts. In addition, factors that influence these choices, their view on the effectiveness of treatments, and their view on the natural history of warts were assessed.

Results

The questionnaire was returned by 280 GPs (40%). Cryotherapy was first choice treatment in 73% of GPs for hand warts, in 49% of GPs for plantar warts, and in 72% of GPs for warts on other locations. Salicylic acid application or the combination of cryotherapy and salicylic acid were used less frequently, followed by an wait-and-see policy and (electro) surgery. Most important factors influencing their treatment choice were GPs' routine and GPs' views on effectiveness.

Conclusion

In contrast to available evidence, most GPs apply cryotherapy as first choice treatment of cutaneous warts. Pragmatic high-quality trials on the effectiveness of wart treatments conducted in primary care might solve this discrepancy between evidence and practice.

INTRODUCTION

Up to one third of primary school children have cutaneous warts.[1] The prevalence of warts presented to general practitioners (GPs) over a year is approximately 2% in general population, and adds up to 6% in school children. Warts rank 11th in most frequently presented complaints and diseases in general practice.[2;3] However, subsequent wart treatment causes annoying side effects and often is as effective as a wait-and-see policy. As a consequence, different treatment modalities are applied.[4]

Previous studies carried out nearly 2 decades ago showed that in general practice, if available, liquid nitrogen cryotherapy was most frequently applied. When cryotherapy was not available, topical salicylic acid was prescribed or patients were referred to dermatology clinics.[5,6] However, after these studies were conducted wart management has changed considerably. Firstly, availability of liquid nitrogen has increased extensively and many general practices now have wart clinics in which cryotherapy is implemented. Secondly, the recent Cochrane review on topical treatments for warts concludes that, although evidence is sparse and conflicting, salicylic acid is the most effective treatment option.[7] As a result, present guidelines recommend salicylic acid as first choice treatment of warts.[8,9]

We performed a survey on choices in the treatment of warts among GPs in the Netherlands in order to investigate whether current practice is in agreement with current evidence. We also explored GPs' views on effectiveness of treatment and natural history of warts in order to explicate their treatment choices.

METHODS

Preparation

In April 2006 we enrolled GPs with different backgrounds for explorative semi-structured individual interviews on wart management. The interviews were moderated by two researchers. Field notes were discussed by all authors and translated into hypotheses. Sufficient information for this process was gathered after five interviews (2 female and 3 male GPs, experience ranging from 8 years to 20 years, working in single-handed, duo or group practice). Based on the results from these interviews, we constructed the postal questionnaire.

In June 2006, the postal questionnaire was sent to a random sample of 700 GPs from the GP register of the Netherlands Institute for Health Services Research (NIVEL).[10] Three weeks after initial mailing, GPs who had not returned the questionnaire received a reminder.

Questionnaire

We clearly defined that all questions concerned patients with cutaneous warts, i.e. common warts or plantar warts, excluding genital warts or molusca contagiosa. We asked GPs to estimate the percentages of patients treated with each of the various treatments in their practice (adding up to 100% in total), separately for patients with hand warts, plantar warts, and other warts (warts on parts of the skin other than hands or feet). GPs could choose from the following treatments: cryotherapy, salicylic acid, combination of cryotherapy and salicylic acid, a wait-and-see policy, (electro) surgical removal, or another specific treatment.[4]

We assessed factors which influence GPs in these treatment choices, i.e. routine, scientific evidence, financial considerations, the balance between effectiveness and side effects, colleagues' opinions, and practical/organizational considerations. In addition, we assessed the views on effectiveness of different treatments and their views on the natural history of warts. We graded these opinions using statements in the questionnaire according to 5 point rating scales. These answers were later dichotomised into 'effective' ('very effective' and 'effective' combined) and 'not effective' ('absolutely not effective', 'not effective' and 'moderately effective' combined) for GPs' views on effectiveness of different treatments and into 'agree' ('agree' and 'strongly agree' combined) and 'not agree' ('do not agree or disagree', 'disagree' and 'strongly disagree' combined) for GPs' views on the natural history of warts, because five categories did not reveal additional information over two categories.

Statistical analysis

We compared main characteristics of participating GPs with main characteristics of all Dutch GPs.[10] Results are displayed as percentages with corresponding 95% confidence intervals (CI). We used Chi-square tests to compare categorical data. Data were analyzed with SPSS Version 16.0 and Episheet, Version 2003.[11]

RESULTS

GPs' response rate was 40% (280/700). Participating GPs covered a practice population of approximately 550,000 citizens, and were representative for the Dutch population of GPs (Table 6.1). In total, only 9% (95%CI 6-13%) of GPs did not have liquid nitrogen available, and 20% (95%CI 16-26%) did not use salicylic acid (Table 6.2). GPs estimated that 5% of their patients with warts were referred to dermatologic or surgical outpatient clinics.

Cryotherapy was most often used as GPs' first choice treatment for all warts, followed by salicylic acid application and cryotherapy/salicylic acid combination therapy (Table 6.3).

Table 6.1: Characteristics of participating GPs compared to all Dutch GPs.

Characteristics	Participating GPs (n=280)	All Dutch GPs[10] (n=8495)
Male	60 (54-66)	66 (65-67)
Mean age in years (SD)	46.6 (8.7)	47.9 (8.3)
GP in urban practice	86 (82-90)	88 (87-88)
GP working in		
Single-handed practice	31 (26-36)	25 (24-26)
Duo practice	30 (25-35)	30 (29-31)
Group practice	40 (34-45)	45 (44-46)

Data are % of general practitioners (GPs) (95% confidence intervals), unless stated otherwise.

Table 6.2: Aspects of wart management in general practice (n=280).

Assistant regularly provides	
Oral information	82 (77-86)
Written information	17 (12-22)
Liquid nitrogen available in practice*	
Continuously	36 (30-41)
Intermittently	56 (50-61)
No	9 (6-13)
Salicylic acid prescription used	
Solution 31-50%	23 (18-28)
Solution ≤ 30%	57 (51-62)
No	20 (16-26)
Mean percentage (SD) of treatments applied by	
Practice assistant	68 (36)
General practitioner	32 (34)

Numbers are % of general practitioners (GPs) (95% confidence intervals), unless stated otherwise.
Data is missing for 52 GPs in information data, none in nitrogen availability data, 5 GPs in salicylic acid use, and 1 GP in implementation data.
* Sum of percentages is not equal to 100% due to rounding off.

Treatments with salicylic acid were more frequently applied in plantar warts compared to hand warts or other warts. For all warts, only 5-7% of GPs used a wait-and-see policy as first choice and only few GPs used monochloroacetic acid[12] or duct tape[13] as first choice treatment. In other warts, 26 GPs (10%) used (electro) surgery as first choice.
Several factors influenced GPs' treatment choice: of all GPs (n=280, missing data in n=8 to n=23 per factor), 59% (95%CI 53-65%) was influenced by routine, 46% (95%CI 40-52%) by the balance between effectiveness and side effects, 29% (95%CI 24-35%) by evidence, 25% (95%CI 20-30%) by colleagues' opinions, 21% (95%CI 17-27%) by practical/organizational considerations, and 5% (95%CI 3-8%) by financial motives. Of all GP's, 71% (95%CI 65-76%) considered cryotherapy to be effective versus 55% (95%CI

Table 6.3. GPs' first choice treatment of warts depending on location (n=280).

	Location of warts					
	Hand (n=278)		Plantar (n=276)		Other locations (n=266)	
First choice treatment	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Cryotherapy	204	73 (68-78)	136	49 (43-55)	192	72 (67-77)
Combination of cryotherapy and salicylic acid	45	16 (12-21)	82	30 (25-35)	23	9 (6-13)
Salicylic acid	30	11 (8-15)	50	18 (14-23)	32	12 (9-16)
Wait-and-see	19	7 (4-10)	15	5 (3-9)	22	8 (6-12)
(Electro)surgery	4	1 (1-4)	8	3 (1-6)	26	10 (7-14)
Monochloroacetic acid	8	3 (1-6)	10	4 (2-7)	5	2 (1-4)
Duct tape	0	0 (0-1)	3	1 (0-3)	2	1 (0-3)

Data are numbers of general practitioners (GPs) and % of GPs (95% confidence intervals). Data is missing for 2 GPs in hand, 4 GPs in plantar, and 14 GPs in other warts. Sum of GPs is >280 and sum of percentages is >100% per location of warts, because 10-14% of GPs reported to apply two or three different treatments equally frequent.

49-61%) for salicylic acid, 66% (95%CI 60-71%) for the combination therapy, and 47% (95%CI 41-53%) for a wait-and-see policy (Table 6.4). The GPs using cryotherapy as first choice treatment more often considered cryotherapy to be effective than GPs not using cryotherapy as first choice treatment ($p<0.001$).

According to 82% (95%CI 77-86%) of GPs warts are self-limiting and according to 34% (95%CI 29-40%) of GPs warts are very contagious. The percentages of GPs agreeing with these two statements did not differ between the GPs with a wait-and-see policy as their

Table 6.4. Perceived effectiveness of different treatments according to GPs' personal experience (n=280)

	GPs personal experience		
Treatment	Effective	Not effective	No experience with treatment
Cryotherapy*	71 (65-76)	27 (22-32)	3 (1-5)
Combination of cryotherapy and salicylic acid	66 (60-71)	15 (11-20)	19 (15-24)
Salicylic acid	55 (49-61)	39 (33-45)	6 (4-10)
Surgical removal	42 (36-48)	37 (31-43)	21 (16-26)
Monochloroacetic acid	25 (20-31)	23 (18-28)	52 (46-58)
Duct tape	12 (9-16)	26 (21-32)	62 (56-67)
Homeopathy	3 (1-5)	59 (53-65)	38 (33-44)
Wait-and-see	47 (41-53)	45 (39-51)	9 (6-13)

Numbers are % of general practitioners (GPs) (95% confidence intervals). Data is missing for 1 to 15 GPs per treatment.

* Sum of percentages is not equal to 100% due to rounding off.

first choice and GPs with active treatments as their first choice (p=0.83 and p=0.20, respectively), and did also not differ between the GPs who considered a wait-and-see policy to be effective and those who considered a wait-and-see policy not to be effective (p=0.076 and p=0.26, respectively). A majority of all GPs (73% (95%CI 68-78%)) reported to advise patients with warts to wait-and-see when the inconvenience caused by warts is limited.

DISCUSSION

Summary of main findings

Cryotherapy is the first choice treatment of warts among Dutch GPs. Salicylic acid is used less frequently, and often in combination with cryotherapy. GPs' treatment choices are guided by their routine and their views on effectiveness, rather than evidence or opinions on the natural history. Although GPs most often choose active treatments, they prefer a wait-and-see policy when inconvenience caused by warts is limited, because they believe warts are self-limiting.

Strengths and limitations of this study

This is the first quantitative study on choices in the treatment of warts after cryotherapy became widely available in primary care and after the Cochrane review on topical treatments of warts has been published.[7] Our sample of GPs was large and representative for all Dutch GPs. Moreover, we think that our results contain patterns that are likely to be similar in other countries in which patients with warts are primarily treated in general practice and liquid nitrogen is widely available.

A limitation of our study is the response rate of 40%. Although our response rate is comparable to response rates of surveys among GPs in literature,[14] and our responders in general did not differ from all Dutch GPs in general, the high preference for cryotherapy might be due to some selection bias. Perhaps, GPs interested in wart treatment and cryotherapy have responded more often. On the other hand, recall bias (cryotherapy is often applied by practice assistants and out of sight from GPs) and social desirability bias (overestimation of influence by evidence, underestimation of financial motives) could have played a role. However, GPs practice can not be evaluated in a more careful way then we did.

Evidence versus practice

Ideally, treatment practice reflects available evidence on effectiveness. According to the recent Cochrane review on topical treatments for warts, evidence favours the use of sali-

cylic acid.[7] In contrast, our survey shows that GPs prefer cryotherapy over salicylic acid. The recent NHS Health technology Assessment's qualitative study on opinions with regard to the treatment of warts shows a similar trend as our survey: health professionals' opinions towards cryotherapy were quite positive and opinions towards salicylic acid were fairly negative.[15] This discrepancy between evidence and practice can be explained in different ways. Firstly and most importantly, recommendations on the treatment of warts favouring salicylic acid[8,9] do not have a firm evidence base, since they are based on small, low quality studies. Direct comparison between cryotherapy and salicylic acid in the two available randomised studies did not show a difference in effectiveness.[16,17] In absence of clear and direct evidence, GPs' confidence in the effectiveness of cryotherapy could represent the actual competence of cryotherapy. As a consequence, we conclude in accordance with the Cochrane review that more randomised trials are needed.[7] Secondly, increasing availability of liquid nitrogen could have led to increasing demand for cryotherapy among patients.[6] GPs tend to act upon patient's personal ideas and treatment preferences when the natural history of the disease is favourable. Although GPs prefer a wait-and-see policy when the inconvenience caused by warts is limited (as shown in our study), they may comply with the patient's demand for cryotherapy nonetheless. Lastly, it has been suggested that GPs prefer cryotherapy because they financially profit from its implementation.[18] In our survey, however, only 5% of GPs report that financial reasons influence their treatment choice.

Implications for future research

This survey clearly shows the discrepancy regarding the treatment of warts between available evidence and current practice. This may partly be due to the low quality of the underlying evidence which is a common phenomenon in minor ailments.[19] Although non-adherence to guidelines based on low quality evidence is of limited clinical importance for practice, it is of high importance for clinical research. Only pragmatic high-quality trials in primary care can solve this problem.

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CHAPTER 7

Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: a randomised controlled trial

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ABSTRACT

Background

Cryotherapy is widely used for the treatment of cutaneous warts in primary care. However, evidence favours salicylic acid application. We compared the effectiveness of these treatments as well as a wait-and-see approach.

Methods

Consecutive patients with new cutaneous warts were recruited in 30 primary care practices in the Netherlands between May 1, 2006, and Jan. 26, 2007. We randomly allocated eligible patients to one of three groups: cryotherapy with liquid nitrogen every two weeks, self-application of salicylic acid daily or a wait-and-see approach. The primary outcome was the proportion of participants whose warts were all cured at 13 weeks. Analysis was on an intention-to-treat basis. Secondary outcomes included treatment adherence, side effects and treatment satisfaction. Research nurses assessed outcomes during home visits at 4, 13 and 26 weeks.

Results

Of the 250 participants (age 4 to 79 years), 240 were included in the analysis at 13 weeks (loss to follow-up 4%). Cure rates were 39% (95% confidence interval [CI] 29%–51%) in the cryotherapy group, 24% (95% CI 16%–35%) in the salicylic acid group and 16% (95% CI 9.5%–25%) in the wait-and-see group. Differences in effectiveness were most pronounced among participants with common warts (n = 116): cure rates were 49% (95% CI 34%–64%) in the cryotherapy group, 15% (95% CI 7%–30%) in the salicylic acid group and 8% (95% CI 3%–21%) in the wait-and-see group. Cure rates among the participants with plantar warts (n = 124) did not differ significantly between treatment groups.

Interpretation

For common warts, cryotherapy was the most effective therapy in primary care. For plantar warts, we found no clinically relevant difference in effectiveness between cryotherapy, topical application of salicylic acid or a wait-and-see approach after 13 weeks. (ISRCTN42730629)

INTRODUCTION

Cutaneous warts are common.[1–3] Up to one-third of primary school children have warts, of which two thirds resolve within two years.[4,5] Because warts frequently result in discomfort,[6] 2% of the general population and 6% of school-aged children each year present with warts to their general practitioner.[7,8] The usual treatment is cryotherapy with liquid nitrogen or, less frequently, topical application of salicylic acid.[9–12] Some physicians choose a wait-and-see approach because of the benign natural course of warts and the risk of side effects of treatment.[10,11]

A recent Cochrane review on treatments of cutaneous warts concluded that available studies were small, poorly designed or limited to dermatology outpatients.[10,11] Evidence on cryotherapy was contradictory,[13–18] whereas the evidence on salicylic acid was more convincing.[19–23] However, studies that compared cryotherapy and salicylic acid directly showed no differences in effectiveness.[24,25] The Cochrane review called for high-quality trials in primary care to compare the effects of cryotherapy, salicylic acid and placebo.

We conducted a three-arm randomised controlled trial to compare the effectiveness of cryotherapy with liquid nitrogen, topical application of salicylic acid and a wait-and-see approach for the treatment of common and plantar warts in primary care.

METHODS

Participants

Between May 1, 2006, and Jan. 26, 2007, 30 family practices from the Leiden Primary Care Research Network in the Netherlands invited all patients aged four years and older who attended the clinic with one or more new cutaneous warts to participate. We defined new cutaneous warts as those on the skin that were diagnosed in family practice and had not been treated by a physician or dermatologist in the previous year, regardless of previous self-treatment with over-the-counter medication. We excluded immunocompromised patients and patients with genital warts, seborrheic warts or warts larger than 1 cm in diameter. Patients who fulfilled the inclusion criteria and agreed to participate were visited at home by a trained research nurse, who confirmed their eligibility. Informed consent (child as well as parental informed consent for participants less than 18 years of age) was obtained, and baseline characteristics were collected.

Study design and randomization

We stratified patients by location of warts: plantar (warts on the soles of the feet) or common (warts on the hands or other locations).[26] Participants who had both plantar and common warts were stratified according to where the majority of their warts were located. We used opaque, sealed envelopes that were numbered based on a computerised randomization list delivered by an independent statistician to conceal allocation. After stratification by location of warts and by number of warts (< six warts v. ≥ six warts), random allocation of participants to treatment groups was done without blocking. The study protocol was approved by the medical ethical committee of the Leiden University Medical Center.

Treatment protocols

One of us (K.Z) trained all participating general practitioners and assistants working in their practices in the three 13-week treatment protocols, which were designed to reflect best practice. [10,24] Training consisted of a one-hour interactive practical session, during which all tools and techniques were demonstrated; real warts were not used in the demonstrations. For cryotherapy, we used a high-intensity regimen of one session every two weeks until all warts were completely gone. During each session, the participant received three serial applications in which a wad of cotton wool saturated with liquid nitrogen was moved around on the wart. Each application was executed until a frozen halo of 2 mm around the base of the wart appeared (usually after 2–10 seconds).

For the topical application of salicylic acid, we used a white petroleum jelly containing 40% salicylic acid. We chose this concentration to provide a stronger treatment than over-the-counter products, which usually contain 17% salicylic acid. Participants assigned to this group were asked to apply the salicylic acid every day until the warts were completely gone. They were instructed to cover the surrounding skin with tape to protect healthy skin and apply the salicylic acid on top of the wart with another piece of tape. Before each subsequent daily application, they used a file to pare the softened surface area of the wart. Participants assigned to the wait-and-see group were informed about the benign natural course of warts and were advised not to undergo treatment (apart from over-the-counter medication) for at least 13 weeks.

After the 13-week treatment period, all participants who still had warts could switch to another treatment according to their own preferences. Participants were free to use over-the-counter medication during the entire follow-up period but were asked to report all usage.

Outcome measures

Trained research nurses assessed outcomes during home visits at 4, 13 and 26 weeks of follow-up, independently of the treating physicians. A wart was considered cured if it was no longer visible (skin colour and skin lines were reestablished) and could not be palpated anymore by hand. The primary outcome measure was the proportion of participants whose warts were all cured at 13 weeks. Research nurses assessed side effects, newly developed warts (which were not included in the primary outcome assessment) and adherence to treatment. Treatment adherence was considered adequate if participants had received cryotherapy at least every three weeks, had self-administered salicylic acid at least four days per week and had not undergone any cointervention (treatment of warts other than over-the-counter medication).

In addition, participants were asked to rate treatment burden using a 10-point scale (1 = no burden, 10 = the worst imaginable burden). A scores of six or higher was considered to reflect a substantial burden. Participants rated treatment satisfaction using a five-point scale (one = very unsatisfied, five = very satisfied); those with a score of four or five were considered to be satisfied.

Research nurses, general practitioners and participants were not blinded to treatment allocation. For quality control, 5% of the assessments were directly supervised by experienced general practitioners (J.E. and K.Z.).

Statistical analysis

We chose a sample size that would provide 80% power, at a significance level of 5%, to detect an absolute increase in the cure rate of 20% between the two active treatment groups. Based on a literature review, we expected salicylic acid to be most effective, with a 70% cure rate.[10,11] A total of 91 patients were required per treatment arm.

We used the $\chi 2$ test for all comparisons of cure rates and percentages. In our primary analysis, we compared cure rates between the three treatment arms on an intention-to-treat basis. We also calculated relative risks, risk differences and numbers needed to treat for cryotherapy versus salicylic acid, cryotherapy versus wait-and-see approach, and salicylic acid versus wait-and-see approach.

In secondary analyses, we compared cure rates between the three study arms (a) with patients lost to follow-up considered not cured, (b) after excluding patients who had both plantar and common warts, (c) at 26 weeks' follow-up, (d) using individual warts as the unit of analysis instead of patients and (e) per protocol cure rates based on reported treatment adherence.

Subgroup analyses were pre-planned for location of warts (common wart group v. plantar wart group), age clusters (4– 12 years v. ≥ 12 years), number of warts per participant, and

duration of warts (≤ six months v. > six months). We formally tested for effect modification of treatment by location of warts using a logistic regression model.
Lastly, we compared the percentages of patients with side effects and considerable treatment burden between the two active treatment arms, and the percentages of patients satisfied with treatment between the three arms.
An abridged version of our study protocol can be found at www.controlled-trials.com/ISRCTN42730629/warts.

RESULTS

Patient characteristics

Of 303 patients recruited, we excluded 53, mainly because they had already received treatment in the previous year or refused to participate (Figure 7.1). We randomly assigned the remaining 250 participants to the cryotherapy (n = 80), topical salicylic acid (n = 84) and wait-and-see (n = 86) groups. Baseline characteristics did not differ significantly between the groups (Table 7.1). Seven per cent of the participants reported that they had received treatment for warts more than one year before enrolment; 35% reported that they had treated their warts with one or more of the following over-the-counter medications or methods in the past with no success: dimethyl ether propane cryotherapy (18%), ointment containing salicylic acid at a concentration lower than the study ointment (12%), cutting away the warts themselves (6%) and other alternatives (6%). At study entry, 34% of the participants stated that they preferred cryotherapy, 35% salicylic acid and 4% a wait-and-see approach (no preference given by 27%). Of the 250 participants, 122 (49%) were stratified into the common wart group and 128 (51%) into the plantar wart group. In the common wart group, 103 participants (84%) had warts on their hands, 19 (16%) had them on parts of the body other than hands or soles of the feet, and 13 (11%) also had plantar warts. In the plantar wart group, 22 participants (17%) also had common warts. Baseline characteristics were similar between the common and plantar wart groups except for age distribution and duration of warts.

Follow-up and treatment adherence

At 13 weeks, 10 participants (4%) were lost to follow up (8 refused further participation, 1 had entered by error because the wart was diagnosed as a seborrheic wart, and 1 was lost for unknown reasons). Overall, 48 (20%) of the remaining 240 participants stopped the assigned treatment protocol (see Appendix 7.1). During the 13-week follow-up period, 61 participants (25%) had one or more new warts; no participants were referred to dermatology outpatient clinics.

Figure 7.1. Flowchart.

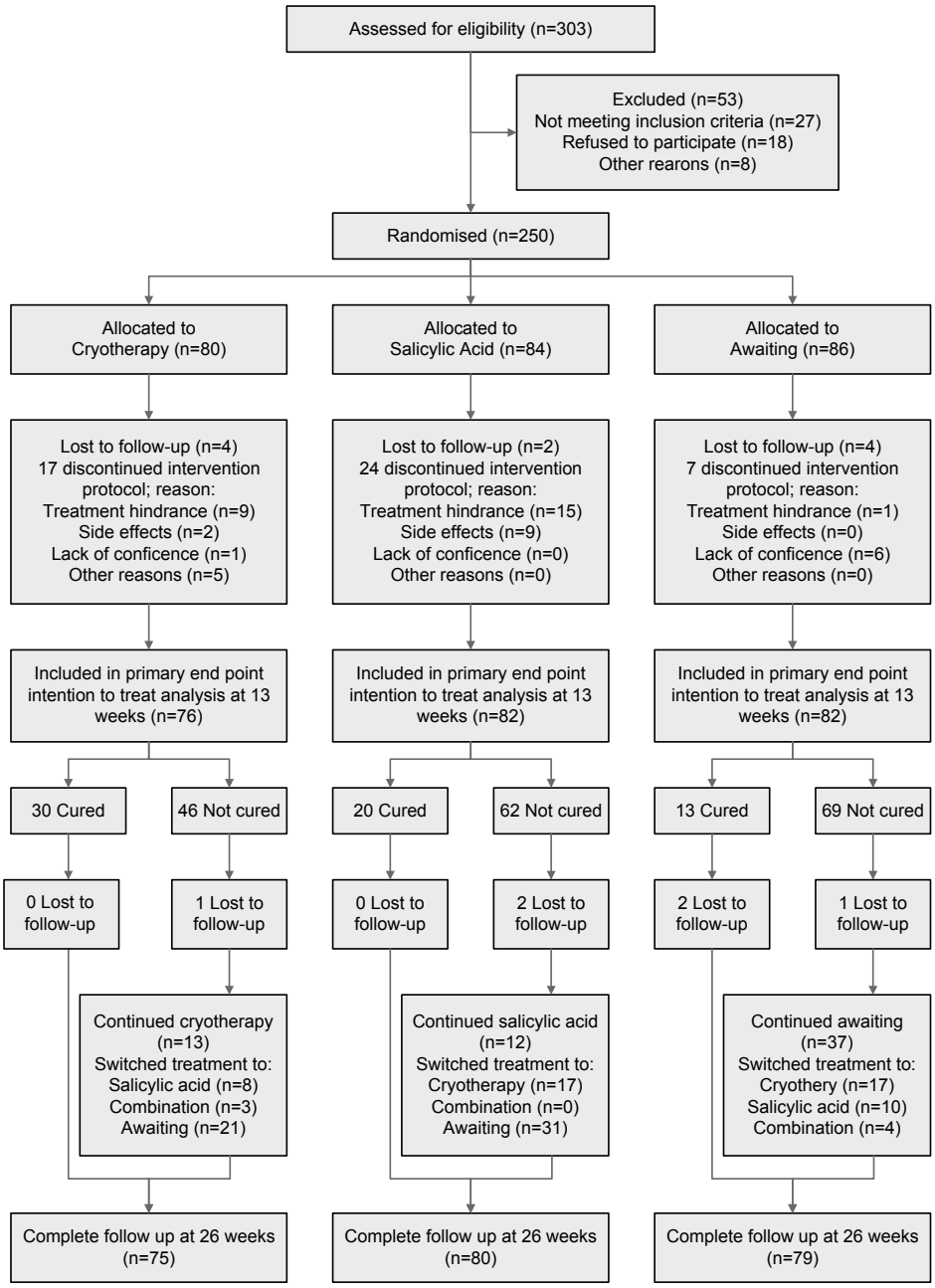

Table 7.1. Participant characteristics at baseline (n=250)

	Treatment arm		
	Cryotherapy (n=80)	Salicylic acid (n=84)	Awaiting (n=86)
Female sex	45 (56)	54 (64)	50 (58)
Age groups			
4 to 12 years	33 (41)	36 (43)	39 (45)
≥ 12 years	47 (59)	48 (57)	47 (55)
Number of warts (median, IQR)	2 (1 to 3)	2 (1 to 4)	2 (1 to 5)
Size of warts in millimetre (median, IQR)	4 (3 to 5)	4 (3 to 5)	4 (3 to 5)
Hindrance*	55 (69)	63 (75)	70 (81)
Location†			
Common wart group	41 (51)	40 (48)	41 (48)
Plantar wart group	39 (49)	44 (52)	45 (52)
Wart duration			
< six months	31 (39)	37 (44)	34 (40)
≥ six months	49 (61)	47 (56)	52 (61)‡
Treatment preference at baseline			
Cryotherapy	33 (41)	24 (29)	29 (34)
Salicylic Acid	22 (28)	33 (39)	32 (37)
Awaiting	6 (8)	2 (2)	2 (2)
No preference	19 (24)‡	25 (30)	23 (27)

Values are number of participants (percentage of participants) unless stated otherwise. IQR = Inter Quartile Range.

* Presence of pain, irritation or esthetical annoyance.

† We stratified randomization according to location, but we did not sample according to stratification (number of participants with common warts and number of participants with plantar warts were equivalent by chance).

‡ Sum of percentages is ≠ 100 due to rounding off.

Effectiveness of treatment

At 13 weeks, the cure rates were 39% (95% confidence interval [CI] 29%–51%) after cryotherapy, 24% (95% CI 16%–35%) after salicylic acid and 16% (95% CI 9.5%–25%) after the wait-and-see protocol, for a relative risk of 1.6 (95% CI 1.0–2.6) for cryotherapy versus salicylic acid. Because the effectiveness of treatments differed between the common wart group and the plantar wart group (*p* for interaction 0.007), we report outcomes for all patients as well as by location of warts (Tables 7.2 and 7.3).

In the common wart group, cryotherapy was most effective, with a cure rate of 49% (95% CI 34%–64%) at 13 weeks (Tables 7.2 and 7.3). Further stratification by age and by duration of warts gave similar findings.

Table 7.2. Overall effectiveness of treatments at 13 weeks, stratified according to location of warts (n=240)

		Treatment arm						P-value*
		Cryotherapy		Salicylic acid		Awaiting		
		n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
All participants (n=240)								
All		30/76	39 (29 to 51)	20/82	24 (16 to 35)	13/82	16 (10 to 25)	0·001
Age groups	4 to 12 years	16/31	52 (35 to 68)	15/36	42 (27 to 58)	11/38	29 (17 to 45)	0·056
	≥ 12 years	14/45	31 (20 to 46)	5/46	11 (5 to 23)	2/44	5 (1 to 15)	0·001
Wart duration	< six months	19/30	63 (46 to 78)	14/37	38 (24 to 54)	10/32	31 (18 to 49)	0·012
	≥ six months	11/46	24 (14 to 38)	6/45	13 (6 to 26)	3/50	6 (2 to 16)	0·012
Common wart group (n=116)								
All		19/39	49 (34 to 64)	6/39	15 (7 to 30)	3/38	8 (3 to 21)	<0·001
Age groups	4 to 12 years	6/12	50 (25 to 75)	2/12	17 (5 to 45)	1/15	7 (2 to 25)	0·010
	≥ 12 years	13/27	48 (31 to 66)	4/27	15 (6 to 32)	2/23	9 (2 to 27)	0·001
Wart duration	< six months	10/12	83 (55 to 95)	2/11	18 (5 to 48)	2/13	15 (4 to 42)	0·001
	≥ six months	9/27	33 (19 to 52)	4/28	14 (6 to 31)	1/25	4 (<1 to 20)	0·006
Plantar wart group (n=124)								
All		11/37	30 (17 to 46)	14/43	33 (20 to 47)	10/44	23 (13 to 37)	0·46
Age groups	4 to 12 years	10/19	53 (32 to 73)	13/24	54 (35 to 72)	10/23	43 (26 to 63)	0·54
	≥ 12 years	1/18	6 (<1 to 26)	1/19	5 (<1 to 25)	0/21	0 (0 to 15)	0·34
Wart duration	< six months	9/18	50 (29 to 71)	12/26	46 (29 to 65)	8/19	42 (23 to 64)	0·63
	≥ six months	2/19	11 (3 to 31)	2/17	12 (3 to 34)	2/25	8 (2 to 25)	0·77

Values are number of participants cured / number of participants in intention to treat analysis at 13 weeks, and percentages of participants cured (95% confidence intervals). A participant is cured when all warts present at baseline are gone.

* 2-sided chi-square, comparing three treatment groups.

Table 7.3. Relative measures of effect between the three treatment arms, depending on location of warts (n=240)

	Relative Risk (95%CI)	Risk Difference (95%CI)	NNT* (95%CI)†
All participants (n=240)			
Cryotherapy versus Awaiting	2.49 (1.41 to 4.41)	0.24 (0.10 to 0.37)	4 (3 to 10)
Salicylic Acid versus Awaiting	1.54 (0.82 to 2.88)	0.09 (-0.04 to 0.21)	12 (-27 to 5)
Cryotherapy versus Salicylic Acid	1.62 (1.01 to 2.59)	0.15 (0.01 to 0.29)	7 (3 to 145)
Common wart group (n=116)			
Cryotherapy versus Awaiting	6.17 (1.99 to 19.16)	0.41 (0.23 to 0.59)	2 (2 to 4)
Salicylic Acid versus Awaiting	1.95 (0.52 to 7.24)	0.07 (-0.07 to 0.22)	13 (-15 to 5)
Cryotherapy versus Salicylic Acid	3.17 (1.42 to 7.07)	0.33 (0.14 to 0.53)	3 (2 to 7)
Plantar wart group (n=124)			
Cryotherapy versus Awaiting	1.31 (0.63 to 2.73)	0.07 (-0.12 to 0.26)	14 (-8 to 4)
Salicylic Acid versus Awaiting	1.43 (0.72 to 2.87)	0.10 (-0.09 to 0.29)	10 (-11 to 4)
Cryotherapy versus Salicylic Acid	0.91 (0.47 to 1.76)	-0.03 (-0.23 to 0.18)	35† (-4 to 6)

* Number needed to treat for benefit (95% confidence intervals), i.e. number of patients needed to get specific treatment in order to cure one more patient of all warts. When negative, the value becomes the number needed to treat for harm.

In the plantar wart group, the cure rate at 13 weeks did not differ between the treatment arms (Tables 7.2 and 7.3). Further stratification revealed that cure rates were considerably lower among participants 12 years and older than among younger participants. Also, cure rates were lower among participants whose warts had been present for six or more months at baseline than among those whose warts had been present for a shorter duration (Table 7.2).

Sensitivity analysis

The results at 26 weeks were concordant with the results at 13 weeks (see Appendix 7.2). The same was true when we considered that all patients lost to follow-up were not cured, or when we excluded participants with both common and plantar warts from the analysis. Per-protocol analysis and analysis of the cure rate of individual warts at 13 weeks showed the same significant results as our primary analysis (see Appendix 7.3 and 7.4).

Side effects and treatment satisfaction

In both wart groups, participants experienced more side effects after cryotherapy than after topical salicylic acid application (Table 7.4). In the common wart group, 31% (95% CI 19%–46%) of the participants reported considerable treatment burden after cryotherapy and 54% (95% CI 39%–68%) after salicylic acid treatment (p = 0.040). Furthermore,

Table 7.4. Reported side effects at 13 weeks in the active treatment groups, stratified according to location of warts (n=152)

	Treatment arm		P-value*
	Cryotherapy (n=37)	Salicylic acid (n=38)	
Common wart group			
Number of side effects			0·012
0	5 (14)	8 (21)	
1	8 (22)	19 (50)	
2, 3 or 4	24 (65)	11 (29)	
Type of side effects			
Pain	29 (78)	5 (13)	<0·001
Blistering	22 (59)	2 (5)	<0·001
Scarring	8 (22)	-	0·003
Skin irritation	6 (16)	27 (71)	<0·001
Skin pigmentation	3 (8)	2 (5)	0·62
Bleeding after filing	-	6 (16)	0·012
Crust	3 (8)	-	0·075
Plantar wart group	(n=37)	(n=40)	
Number of side effects			<0·001
0	3 (8)	14 (35)	
1	14 (38)	19 (48)	
2, 3 or 4	20 (54)	7 (18)	
Type of side effects			
Pain	31 (84)	4 (10)	<0·001
Blistering	16 (43)	5 (13)	0·003
Scarring	1 (3)	-	0·298
Skin irritation	6 (16)	21 (53)	0·001
Skin pigmentation	3 (8)	2 (5)	0·58
Bleeding after filing	-	1 (3)	0·34
Crust	1 (3)	-	0·30
Other minor side effects	4 (11)	4 (10)	0·91

Values are number of participants with side effect (percentage of participants with side effect). Data were missing for three participants with common warts and three participants with plantar warts.
* 2-sided chi-square, comparing two treatment groups.
† Five out of nine participants with scars reported that their scars had disappeared at 26 weeks.

69% (95% CI 53%–82%) of participants were satisfied with treatment after cryotherapy, as compared with 24% (95% CI 13%–39%) after salicylic acid treatment and 22% (95% CI 12%–38%) after the wait-and-see protocol ($p < 0.001$). In the plantar wart group, there were no differences in treatment burden or satisfaction between the three treatment groups.

INTERPRETATION

In this pragmatic three-arm randomised controlled trial conducted in family practices, we found that cryotherapy was the most effective therapy for common warts (mainly on hands), with 49% of patients cured after 13 weeks. Despite the fact that cryotherapy caused more frequent and more severe side effects than topical salicylic acid application, patients were most satisfied when treated with cryotherapy. For plantar warts, we found no clinically relevant difference between the treatment arms. Regardless of treatment, children with plantar warts showed relatively high cure rates (about 50%), whereas plantar warts in adolescents and adults were highly persistent (cure rates of about 5%).

Although our overall relative risk of 1.5 between salicylic acid treatment and the wait-and-see protocol was similar to the relative risk of 1.6 from pooled data in the recent Cochrane review, our overall cure rates of 24% in the salicylic acid group and 16% in the wait-and-see group were lower than the cure rates of 73% and 48% in the Cochrane review at similar follow-up.[10,11] This marked difference is most likely due to variation in study design and study population. Our primary care setting, pragmatic design, wide inclusion criteria, excellent follow-up and intention-to-treat analysis led to results that were easy to interpret and directly applicable to daily practice in primary care. In contrast, the two other studies comparing cryotherapy and salicylic acid treatment, which involved dermatology outpatients, excluded patients who had more than five warts, those with warts on locations other than the location under investigation, and non-attending or noncompliant patients (in our study 20% of participants included in the analysis were non-compliant).[24,25] Other factors may also be at play, such as age of the patients and duration of warts before treatment, which our study showed to be significantly associated with cure rates.

Our follow-up at 26 weeks showed that the effects of treatment of common warts were sustainable. In the plantar wart group, in contrast to statistically equal effectiveness at 13 weeks, both of the active treatments might have higher cure rates than a wait-and-see approach in the long term. These findings suggest that the effect of active treatments on plantar warts is delayed or that more aggressive treatment is needed because of the callosity overlying the warts.[14]

Limitations

As in daily practice, salicylic acid was applied by the participants themselves, which could reduce effectiveness compared with treatments applied by health professionals. However, we explicitly recorded participants' adherence to standardised treatment protocols, and intention-to-treat cure rates were concordant with results of the per-protocol analyses.

The participating patients and family practices were aware of the treatment allocations, because the pragmatic study design and treatment options did not secure realistic blinding.

Furthermore, the research nurses who assessed outcomes were aware of the treatment allocations, because the appearance of the skin after treatment usually revealed the specific treatment and because the large proportion of children often spontaneously reported the specific treatment.

Conclusion

Although earlier evidence favoured topical salicylic acid application over cryotherapy for the treatment of cutaneous warts, the results of our randomised controlled trial provides evidence to support the use of cryotherapy over salicylic acid treatment, for common warts only. For plantar warts, we found no clinically relevant difference between cryotherapy, salicylic acid treatment or a wait-and-see approach after 13 weeks.

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Appendix 7.1. Treatment adherence

Overall, 48 (20%) participants discontinued treatment protocol after 13 weeks (Figure 7.1), of which 32 (13%) did not receive treatment adequately, and 16 (6.7%) used a co-intervention in addition to treatment protocol (table). In addition, ten participants reported the additional use of OTC medication such as low-dose salicylic acid-containing ointments, dimethylether propane cryotherapy, and Thuja-oil. Stratification in the common wart and plantar wart group did not reveal additional information.

Adherence to treatment protocol at 13 weeks (n=240)

	Treatment arm		
	Cryotherapy, n=76	Salicylic acid, n=82	Awaiting, n=82
Adhered to treatment protocol	59 (78)	58 (71)	75 (91)
Permitted additional use of OTC treatment°	3 (4)	1 (1)	6 (7)
Discontinued treatment protocol	17 (22)	24 (29)	7 (9)
Category of discontinuation			
Did not receive treatment adequately^	14 (18)	18 (22)	-
Used co-intervention	3 (4)*	6† (7)	7 (9)‡
Reason for discontinuation			
Treatment burden	9 (12)	15 (18)	1 (1)
Side effects	2 (3)	9 (11)	-
Lack of confidence	1 (1)	-	6 (7) §
Other reason	5 (7)§	-	-

Values are number of participants (percentage of participants).

* Participants had used salicylic acid application.

† Participants had used cryotherapy.

‡ Three participants had used cryotherapy, two salicylic acid, and two a combination of both.

§ Sum of percentages ≠ total due to rounding off.

° Such as low-dose salicylic acid-containing (17%) ointments, dimethylether propane cryotherapy, or Thuja-oil.

^ Participants did not receive treatment adequately when cryotherapy had been applied less than every three weeks, or when salicylic acid had been administered less than four days per week.

Appendix 7.2. Outcomes at 26 weeks.

At 26 weeks, another six (2%) were lost to follow-up (four refusing further participation, one moving out of the region and one for unknown reasons). After the 13 week protocols, participants that had not been cured were free to switch therapies (or continue the same). They reported to have most frequently switched to or continued a wait-and-see policy for the next 13 weeks (47% in cryotherapy, 52% in salicylic acid, and 54% in wait-and-see). Stratification in the common wart and plantar wart group did not reveal additional information. In all participants combined and in the common wart group, the differences found at 13 weeks persisted for the next 13 weeks (table). In the plantar wart group, the cure rates increased in cryotherapy and salicylic acid arms, but did not change considerably in wait-and-see group (table)

Effectiveness of treatments at 26 weeks*, stratified according to location of warts (n=234)

	Treatment arm						P-value†
	Cryotherapy		Salicylic acid		Awaiting		
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	
All participants (n=234)	42/75	56 (45 to 67)	32/80	40 (30 to 51)	20/79	25 (17 to 36)	<0.001
Common wart group (n=113)	24/38	63 (47 to 77)	12/38	32 (19 to 47)	10/37	27 (15 to 43)	0.001
Plantar wart group (n=121)	18/37	49 (33 to 64)	20/42	48 (33 to 62)	10/42	24 (13 to 39)	0.022

Values are number of participants cured / number of participants analyzed at 26 weeks, and percentages of participants cured (95% confidence intervals). A participant is cured when all warts present at baseline are gone.
* After the 13 week protocols, participants were free to switch to any other therapy.
† 2-sided chi-square, comparing three treatment groups.

Appendix 7.3. Per-protocol analysis of effectiveness of treatments at 13 weeks, stratified according to location of warts (n=192)

	Treatment arm						P-value*
	Cryotherapy		Salicylic acid		Awaiting		
	n	% cured (95%CI)	n	% cured (95%CI)	n	% cured (95%CI)	
All participants (n=192)	26/59	44 (32 to 57)	18/58	31 (21 to 44)	11/75	15 (8.4 to 24)	<0.001
Common wart group (n=88)	18/30	60 (42 to 75)	4/24	17 (6.7 to 36)	1/34	3 (<1 to 15)	<0.001
Plantar wart group (n=104)	8/29	28 (15 to 46)	14/34	41 (26 to 58)	10/41	24 (14 to 39)	0.66

Values are number of participants cured / number of participants in per-protocol analysis, and percentages of participants cured (95% confidence intervals). A participant is cured when all warts present at baseline are gone.
* 2-sided chi-square, comparing three treatment groups.

Appendix 7.4. Overall effectiveness of treatments at 13 weeks according to the number of individual warts cured (n=737)

	Treatment group						P-value*
	Cryotherapy		Salicylic acid		Awaiting		
	n	% cured (95% CI)	n	% cured (95% CI)	n	% cured (95% CI)	
All warts (n=737)	96/202	48 (41 to 54)	78/273	29 (24 to 34)	59/262	23 (18 to 28)	<0.001
Common warts (n=366)	66/104	63 (54 to 72)	30/146	21 (15 to 28)	10/116	8.6 (4.7 to 15)	<0.001
Plantar warts (n=371)	30/98	31 (22 to 40)	48/127	38 (30 to 46)	49/146	34 (26 to 42)	0.73

Values are number of individual warts cured / number of individual warts in intention to treat analysis at 13 weeks, and percentages of individual warts cured (95% confidence intervals). A wart is cured when wart is gone visually as well as palpably.
* 2-sided chi-square, comparing three treatment groups.

CHAPTER 8

Role of monochloroacetic acid application for common and plantar warts in primary care: a randomised controlled trial

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Submitted

ABSTRACT

Background

Cryotherapy or salicylic acid (SA) application for the treatment of cutaneous warts often fails. The aim of this study is to compare the effectiveness of topical monochloroacetic acid (MCA) with cryotherapy in patients with common warts, and with cryotherapy combined with salicylic acid (SA) in patients with plantar warts.

Methods

Consecutive patients with new common or plantar warts were recruited in 53 general practices in the Netherlands. Patients were randomly allocated to office-applied MCA or liquid nitrogen cryotherapy every two weeks for patients with common warts, and to MCA or cryotherapy combined with daily SA self-application for patients with plantar warts. The primary outcome was the proportion of patients in whom all warts were cured at 13 weeks, as assessed by trained research nurses during home visits. Secondary outcomes included treatment adherence, side effects and treatment satisfaction.

Results

Loss to follow-up was 2%. In the common wart group (185 participants), cure rates were 43% (95% confidence interval [CI] 34-54) for MCA and 54% (95% CI 44-64) for cryotherapy. In the plantar wart group (221 participants), cure rates were 46% (95% CI 37-56) for MCA and 39% (95% CI 31-48) for cryotherapy combined with SA. MCA caused less pain than cryotherapy, especially during treatment. Cryotherapy combined with SA was associated with considerable treatment burden.

Conclusion

For common warts, MCA is an effective alternative for cryotherapy to avoid pain during treatment. For plantar warts, office-applied MCA is preferred over cryotherapy combined with SA, based on effectiveness, side effects and treatment burden. (Dutch trial registration: NTR1771)

INTRODUCTION

Cutaneous warts are highly prevalent benign papillomas of the skin.[1] Because they have an unsightly appearance and cause pain,[2] 2% of the general population and 6% of school children yearly present their warts in family practice.[3] Worldwide, the usual treatments are cryotherapy and/or salicylic acid (SA).[4] The 2012 update of the Cochrane review on the treatments for cutaneous warts did not draw firm conclusions since data on the effectiveness of cryotherapy and SA remain contradictory.[5] However, that review highlighted the apparent difference in response to treatment between common warts (mostly located on hands) and plantar warts (located on the sole of the foot). Our recent randomised controlled trial showed that for common warts cryotherapy is more effective than a wait-and-see policy or SA treatment.[6] Nevertheless, cryotherapy did not cure half of all patients with common warts and was the cause of several side effects such as pain, blistering and scarring. For plantar warts, the trial showed that both cryotherapy and SA monotreatments were not effective; this was confirmed by another large trial.[7] However, there is some evidence for the treatment of plantar warts that SA combined with cryotherapy could be more effective than either treatment alone.[8,9]

In addition to these widely used treatments for warts, several specialised treatments such as pulsed dye laser or intralesional bleomycin are available in a hospital setting. Evidence for these treatments is limited and large-scale use in primary care is not feasible.[10] However, an exception may be monochloroacetic acid (MCA) which is a powerful irritant that has been used by dermatologists and podiatrists for several decades.[11,12] 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.[13-15] It should be stressed, however, that treatment with MCA should only be administered by experienced healthcare professionals. Therefore, we conducted a multicenter, randomised, parallel group trial to compare the effectiveness and side effects of MCA with the most effective usual treatments, i.e. in common warts compared to cryotherapy, and in plantar warts compared to cryotherapy combined with SA. Since the protocol was similar to our first trial, this also gave the opportunity to compare these treatments with cryotherapy and SA monotreatments and a wait-and-see policy.[6]

METHODS

Patient inclusion, study design and outcome assessment were identical to our previous trial to allow comparison between the treatment arms of the two trials. For details on the methods of the previous trial, including treatment protocols, we refer to the original publication.[6]

Participants

Between September 2009 and September 2010, 53 general practices in the Leiden region of the Netherlands invited all patients aged 4 years and older with one or more newly diagnosed common or plantar warts to participate. We excluded patients that were treated by a physician or dermatologist in the previous year, as well as pregnant, breast-feeding or immunocompromised patients, and patients with genital warts, seborrheic warts or warts ≥ 1cm in diameter. A trained research nurse visited eligible patients at home, confirmed eligibility, obtained informed consent (both child and parental consent for patients aged ≤ 18 years), provided information on warts and wart treatment, and collected baseline characteristics for a maximum of 10 warts per patient.

Study design and randomization

Patients were assigned to two parallel groups: the plantar wart group (patients with warts on the soles of the feet) or the common wart group (patients with warts on hands or other locations). Patients with both common and plantar warts were assigned according to the type of the majority of warts and, in case of equal numbers, according to the warts causing the most discomfort. After stratification based on the number of warts (< 6 vs. ≥ 6 warts), we randomly allocated patients to MCA treatment or cryotherapy in the common wart group, and to MCA treatment or cryotherapy combined with SA in the plantar group. All warts of one patient received the allocated treatment irrespective of location. Opaque, sealed envelopes delivered by an independent statistician based on computerised randomization secured concealment of allocation. The study protocol was approved by the Medical Ethical committee of the Leiden University Medical Center.

Treatment protocols

Allocated treatments were reported to patients' own general practices where the treatments were explained and carried out. In addition to written protocols, one of the authors (PE) trained all participating general practitioners (GPs) and their practice assistants by visiting the practices and demonstrating all tools and techniques in a one-hour interactive session. All patients were instructed not to use any other treatments other than the allocated treatment during the 13-week protocols.

For topical application of MCA in the common and plantar wart group, the research pharmacy provided practices with a saturated concentration of 76%. The GP or practice assistant applied the MCA every two weeks until all warts were completely cured. The removal of callosity and protection of surrounding skin with petroleum jelly preceded each application of MCA solution on the wart with a cotton swab. In case not all applied MCA

was absorbed by the wart, excess MCA was removed with a tissue. After application, the wart was covered with tape and patients were instructed to keep the wart dry for at least 12 hours. We refer to http://www.youtube.com/watch?v=cTzkPCZaGW8 for an instruction video.

For cryotherapy in the common wart group, three subsequent freeze-thaw cycles were applied in the general practice every two weeks until all warts were completely cured. One cycle consisted of application of a wad of cotton wool saturated with liquid nitrogen on the wart until a frozen halo of 2 mm around the base of the wart appeared (usually 2-10 seconds per application). For the cryotherapy combined with SA in the plantar wart group, the above protocol for cryotherapy was applied, combined with daily self-administration of petroleum jelly containing 40% SA until all warts were completely cured. Patients were instructed to daily pare softened surface area of the wart with a file, cover the surrounding skin with tape for protection of healthy skin, and apply SA on top of the wart with another piece of tape.

Outcome assessment

Independently of the treating physician, trained research nurses assessed outcomes during home visits at 4 and 13 weeks follow-up. The visit at 4 weeks was mainly to verify and support adherence to the treatment protocol. The primary outcome measure was the proportion of patients with all common and plantar warts cured at 13 weeks. A wart was considered cured if it was no longer visible (skin favour and skin lines reestablished) and could not be palpated any more. Secondary outcome measures included reported side effects, treatment adherence, treatment burden, and treatment satisfaction. We considered adherence adequate if patients did not use treatments other than the allocated treatment, had received MCA at least every three weeks and kept the wart dry at least 8 hours after applications, had received cryotherapy at least every three weeks, and had self-administered SA at least 3 days a week. Patients rated treatment burden (yes vs. no) and treatment satisfaction on a 5-point scale (1 = very unsatisfied, 5 = very satisfied); those with a score of 4 or 5 reported to be satisfied. Research nurses, GPs and participants were not blinded to treatment allocation.

Statistical analysis

We calculated sample sizes for the common wart and plantar wart group separately, which would provide 80% power at a significance level of 5% to detect a clinically relevant absolute increase in cure rate of 20% for the MCA arms. Considering a 50% cure rate in the cryotherapy arm of the common wart group and a 30% cure rate of a wait-and-see policy in the plantar wart group,[6] 91 patients were required per treatment arm for each

wart group. Assuming a loss-to-follow of 10%, we needed 200 patients for the common wart group and 200 patients for the plantar wart group.

In primary analysis, we calculated cure rates including 95% confidence intervals (CIs) to compare treatment arms. For the common wart group MCA and cryotherapy arms were compared, and for the plantar wart group MCA and cryotherapy combined with SA arms were compared. These treatment arms were also compared to the cryotherapy, SA, and wait-and-see arms in the respective groups of patients from our previous trial with identical design.[6]

In addition, we compared the secondary outcomes (percentages of patients with side effects, considerable treatment burden, and the percentages of patients satisfied with treatment) between arms using the χ^2 test. Furthermore, subgroup analyses on effectiveness were pre-planned for age clusters (4-12 years vs. ≥ 12 years), number of warts per participant, and duration of warts (≤ 6 months v. > 6 months). In sensitivity analyses, we compared cure rates between treatments arms per wart group (a) with patients lost to follow-up considered not cured, (b) using per protocol analysis based on adequate treatment adherence, (c) after excluding patients who had both plantar and common warts, (d) only including the warts on the hands in common wart group, and (e) with individual warts instead of patients as unit of analysis.

RESULTS

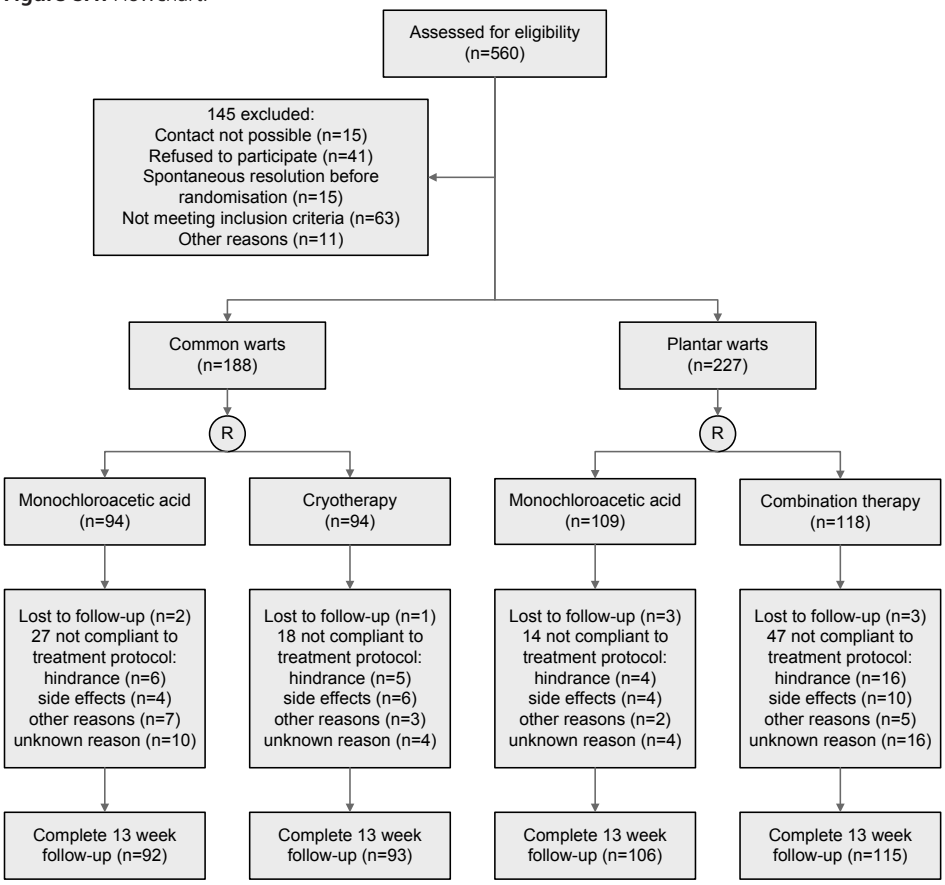
Patient characteristics

Of the 560 initially selected patients with warts, 145 were excluded mainly because they had already been treated in the past year or they did not want to participate (Figure 8.1). The remaining 415 patients were stratified into the common wart group (n=188) and the plantar wart group (n=227) before randomization. Within both groups, baseline characteristics did not differ between treatment arms (Table 8.1), and also did not differ from the baseline characteristics of the previous trial (data not shown).[6] For the common wart group, median age and median duration of warts were higher than in the plantar wart group. In total, the study contained 790 plantar warts and 611 common warts, of which 526 warts (86%) were located on hands and 85 warts (14%) were located on other body sites.

Follow-up and treatment adherence

At 13 weeks, 3 patients from the common wart group and 6 patients from the plantar wart group were lost to follow-up because they refused further participation or could no longer be contacted (Figure 8.1). Of the remaining 406 patients, 106 (26%) did not fully

Figure 8.1. Flowchart.



comply with treatment protocol; 92 did not adhere to minimal treatment frequencies and 14 started other treatment in general practice in addition to the protocol. The cryotherapy combined with SA arm showed lowest adherence to treatment protocol (68/115, 59%); the most frequently reported reason was treatment burden such as time-consuming visits to the general practice and daily hassle with SA and tape (Figure 8.1). During follow-up, only one patient was referred to a dermatologist because the wart was growing larger than 1 cm in spite of treatment and the patient had considerable pain.

Effectiveness of treatment

For the common wart group, the cure rate at 13 weeks of MCA was 43% (95% CI 34-54) which was comparable to the cure rate of cryotherapy of 54% (95% CI 44-64, p=0.16) (Table 8.2). When the treatment arms were compared with the treatment arms of the previous trial,[6] both cryotherapy and MCA were more effective than the wait-and-see

Table 8.1. Baseline characteristics of patients with common warts and patients with plantar warts (n=415).

	Common wart group		Plantar wart group	
Characteristic	MCA (n=94)	Cryotherapy (n=94)	MCA (n=109)	Cryotherapy with SA (n=118)
Sex, female	54 (57)	43 (46)	69 (63)	76 (64)
Age, median (IQR)	14 (9-44)	16 (8-42)	10 (7-29)	11 (6-38)
Age, years				
4-12	35 (37)	35 (37)	59 (54)	60 (51)
≥ 12	59 (63)	59 (63)	50 (46)	58 (49)
Number of warts, median (IQR)	2 (1-4)	1 (1-3)	1 (1-3)	2 (1-4)
Number of warts				
1 up to 5	83 (88)	79 (84)	94 (85)	97 (82)
6 or more	11 (12)	15 (16)	16 (15)	21 (18)
Size of warts, mm, median (IQR)	4 (3-6)	4 (3-6)	4 (3-5)	4 (3-5)
Both common and plantar warts	13 (14)	10 (11)	17 (16)	21 (18)
Duration of warts, mo, median (IQR)	12 (6-24)	12 (4-24)	6 (3-24)	6 (3-24)
Duration of warts, mo				
< 6	20 (21)	30 (32)	47 (43)	52 (44)
≥ 6	74 (79)	64 (68)	62 (57)	66 (56)
Hindrance of warts*	64 (68)	76 (81)	90 (83)	99 (84)
Previous self-treatment†	37 (40)	30 (32)	45 (41)	46 (39)
OTC cryotherapy	18 (19)	17 (18)	26 (24)	23 (19)
OTC salicylic acid	20 (21)	16 (17)	24 (22)	18 (15)
Other self-treatment	5 (5)	5 (5)	11 (10)	15 (13)
Treatment preference at baseline				
MCA	33 (35)	41 (44)	48 (44)	45 (38)
Cryotherapy	7 (7)	8 (8)	-	-
Cryotherapy+SA	-	-	14 (13)	14 (12)
No preference	54 (58)	45 (48)	47 (43)	59 (50)

Values are numbers (%) unless stated otherwise; mo = months IQR = Interquartile range, OTC = over-the-counter, MCA = monochloroacetic acid, SA = salicylic acid.

* Presence of pain or esthetic annoyance

† More than one self-treatment possible

policy or SA treatment (Figure 8.2). Stratification by age or by duration of warts yielded similar findings (Table 8.2).

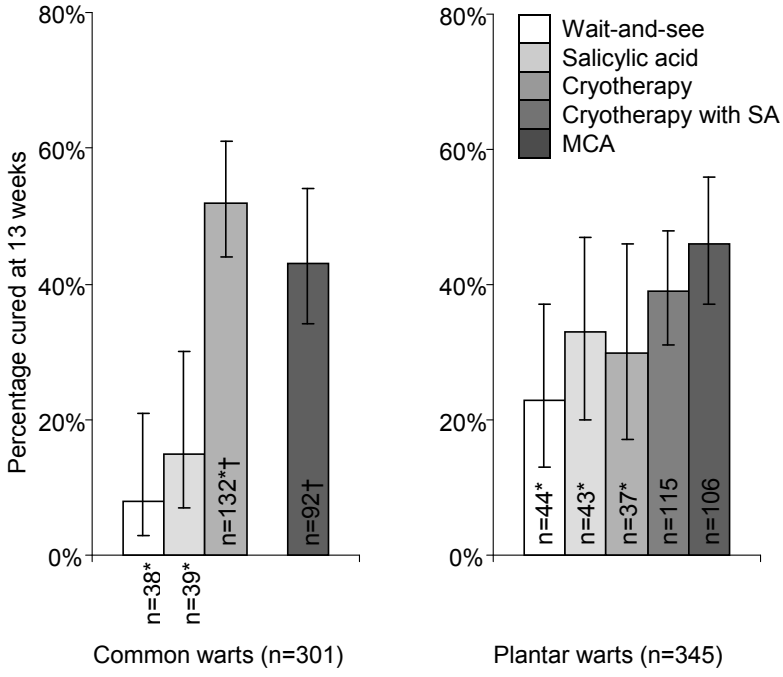
For the plantar wart group, the cure rate at 13 weeks of MCA was 46% (95% CI 37-56) which was comparable to the cure rate of cryotherapy combined with SA of 39% (95% CI 31-48) (p=0.29) (Table 8.2). When these treatment arms were compared with the treatment arms of our previous trial,(6) all CIs of the active treatment groups of MCA, cryo-

Table 8.2. Effectiveness of treatments for patients with common warts (n=185) and patients with plantar warts (n=221).

	Common wart group				Plantar wart group			
	MCA		Cryotherapy		MCA		Cryotherapy with SA	
Variable	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)
All patients	40/92	43 (34-54)	50/93	54 (44-64)	49/106	46 (37-56)	45/115	39 (31-48)
Age, years								
4-12	15/34	44 (29-61)	20/35	57 (41-72)	39/57	68 (56-79)	34/59	58 (45-69)
≥ 12	25/58	43 (31-56)	30/58	52 (39-64)	10/49	20 (11-34)	11/56	20 (11-32)
Duration of warts, months								
< 6	13/19	68 (46-85)	22/30	73 (56-86)	30/46	65 (51-77)	34/51	67 (53-78)
≥ 6	27/73	37 (27-48)	28/63	44 (33-57)	19/60	32 (21-44)	11/64	17 (10-28)

Values are numbers of participants cured/number of participants in intention-to-treat analysis at 13 weeks, and percentages of participants cured with 95% CI. A participant was considered cured when all warts present at baseline had disappeared at follow-up. MCA = monochloroacetic acid, SA = salicylic acid, CI = Confidence interval

Figure 8.2. Effectiveness of treatments with 95% confidence intervals of the current trial and the previous trial at 13 weeks for patients with common warts and patients with plantar warts (n=646). * Patients originate from previous trial. † Patients originate from current trial



therapy combined with SA, and cryotherapy and SA monotreatments overlapped (Figure 8.2). Compared to a wait-and-see policy, MCA for plantar warts was the only treatment reaching the predefined clinically relevant risk difference (RD 23%, 95% CI 8-39; RR 2.0, 95% CI 1.1-3.6) (see Appendix 8.1).

All sensitivity analyses were in line with primary analysis (see Appendix 8.2). The cure rate of cryotherapy combined with SA in the plantar wart group was increased in the per protocol analysis (60%, 95%CI 48-71), but remained comparable with the cure rate of MCA (53%, 95%CI 43-63).

Side effects and treatment satisfaction

Pain was the most frequently reported side-effect for all treatment arms (Table 8.3). We found a lower proportion of patients reporting pain *during* MCA application compared to cryotherapy for both common and plantar wart groups. However, similar proportions of

Table 8.3. Side effects reported during the 13-week follow-up per treatment group (n=406).

	Common wart group			Plantar wart group		
	MCA (n=92)	Cryotherapy (n=93)		MCA (n=106)	Cryotherapy+SA (n=115)	
Treatment pain	70 (76)	85 (91)	*	80 (76)	92 (80)	
During application	8 (9)	77 (83)	*	17 (16)	85 (74)	*
After application	69 (75)	74 (80)		77 (73)	76 (66)	
Pain score, median (IQR)	4 (2-6)	6 (4-7)	*	4 (2-6)	5 (3-7)	*
Other side effects						
Number of other side effects						
none	33 (36)	26 (28)		43 (41)	55 (48)	
1	24 (26)	43 (46)		38 (36)	40 (35)	
≥2	35 (38)	24 (26)		25 (24)	20 (17)	
Type of other side effects						
Blistering	36 (39)	58 (62)	*	36 (34)	33 (29)	
Wound	12 (13)	9 (10)		3 (3)	2 (2)	
Infection	4 (4)	2 (2)		2 (2)	1 (1)	
Scar	8 (9)	8 (9)		4 (4)	0	
Pigmentation	7 (8)	3 (3)		6 (6)	6 (5)	
Irritation of skin	25 (27)	12 (13)	*	18 (17)	34 (30)	*
Burning sensation	12 (13)	2 (2)	*	10 (9)	0	*
Itching	12 (13)	1 (1)	*	16 (15)	5 (4)	*
Other minor side effects	0	2 (2)		5 (5)	2 (2)	

Values are numbers (%) unless stated otherwise; IQR = Interquartile range, MCA = monochloroacetic acid, SA = salicylic acid.

* $p<0.05$

patients reported pain *after* treatment. MCA showed a pain-free period after MCA application (median 1 h, IQR 10 min-7 h), whereas the pain during application for cryotherapy was immediately followed by post-application pain. Median duration of pain for all treatment arms was 1 day (IQR 2 h-3 days). The median overall treatment pain score was lower for MCA than for cryotherapy arms (Table 8.3). In the common wart group, the percentage of patients reporting treatment burden was comparable for MCA (34%, 95% CI 25-46) and cryotherapy (37%, 95% CI 27-47, p=0.76). In the plantar warts group, treatment burden was lower for MCA (30%, 95% CI 22-39) than for cryotherapy combined with SA (47%, 95% CI 38-56, p=0.009). The percentage of patients satisfied with their treatment was comparable between treatment arms and between common and plantar groups (overall 64%, 95% CI 59-68).

DISCUSSION

Summary of findings

This pragmatic randomised controlled trial in primary care showed that for common warts both MCA application and cryotherapy are effective treatments. Pain caused by MCA starts about one hour after application compared to the immediate, more intensive pain caused by cryotherapy. For plantar warts, MCA was the only treatment with a clinically relevant risk difference (23%) compared to a wait-and-see policy. Cryotherapy combined with SA also seemed effective, especially in patients compliant to treatment protocol, but caused considerable side effects and treatment burden.

Comparison with other literature

In line with the recently updated Cochrane review on cutaneous warts, the present trial was separately powered for patients with common warts and patients with plantar warts because of evident differences in response to treatment. However, in that review MCA was not investigated due to the insufficient number of trials to include. Apart from a few descriptive studies,[11,12] we found only one trial on MCA in warts.[13] That study reported that MCA combined with SA treatment resulted in a cure rate of 66% compared to 16% for placebo after 6 weeks in patients with plantar warts; however, only 59 patients were included and a MCA crystal was taped on the wart for one week. We also found two unpublished pilot studies showing that MCA saturated solution every 2 weeks was more effective than SA, and as effective as cryotherapy but with less reported pain.[14,15] Our data confirm the modest benefit for SA in plantar warts reported by the Cochrane review, but only significant when pooled. This benefit is probably enhanced when combined with

cryotherapy, but the clinical relevance of the risk differences compared with a wait-and-see policy remains questionable.

Strengths and limitations

With the pragmatic design in a primary care setting, almost complete follow-up and intention-to-treat analysis, our findings are directly applicable to daily practice. The baseline characteristics of our two subsequent trials with identical designs were similar. A sound comparison between the treatment arms across the two trials was confirmed by comparable outcomes of the two cryotherapy arms in the common wart groups.
Treatment options did not secure realistic blinding of patients and practices. Research nurses were also not blinded, because they assessed side effects, treatment burden and treatment adherence in addition to outcome assessment during home visits.
Although MCA has been locally used by podiatrists and dermatologists for treatment of warts for decades, it is not routinely obtainable in pharmacies.[11] However, it could easily become widely available at low costs if the demand increases, because MCA is produced on a large scale for the chemical industry and agriculture.[16] When carefully administered, MCA is safe for topical use on skin lesions. However, because of the strong corrosive capacity of the acid it should be stored in small quantities. It is not suitable for self-application and should always be administered by a healthcare professional.[17] In our trial, the most serious side effects MCA caused were blistering (36% of patients) and superficial wounds (8% of patients). Chemical wounds were caused by the application of too much MCA or spilling MCA on healthy skin. However, cryotherapy caused even more blistering in common warts and comparable numbers of wounds. Full-thickness chemical burns and joint deformity have been described in case reports when MCA was not carefully applied, i.e. high concentration of MCA with a long application period or large application surface.[18,19] Systemic effects may be expected when a body surface up to 5% is exposed to an 80% solution of the acid.[20]

Implications

The present trial establishes MCA as an effective treatment option for cutaneous warts. For common warts MCA is an effective alternative for cryotherapy to avoid pain during treatment. This might be appealing for treatment in children who often fear the pain during cryotherapy. For plantar warts, MCA is preferred over cryotherapy combined with SA based on effectiveness, side effects and treatment burden.
Nevertheless, optimal treatment for both common and plantar warts only cures around 50% of patients. Therefore, subgroups of patients that respond to current treatments need to be identified and new treatments should be investigated. Ultimately, an evidence-based decision tool should be developed that assists physicians in their decision concerning which treatment to use for specific patient groups.

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Appendix 8.1. Relative measures of effect comparing the treatments of the two trials with a wait-and-see policy* for patients with common warts (n=301) and patients with plantar warts (n=345).

	Common wart group		Plantar wart group	
Treatment*	Relative risk (95%CI)	Risk difference % (95%CI)	Relative risk (95%CI)	Risk difference % (95%CI)
Salicylic acid	2.0 (0.52-7.2)	7 (-7;22)	1.4 (0.72-2.9)	10 (-9;29)
Cryotherapy	6.6 (2.2-20)	44 (32-56)	1.3 (0.63-2.7)	7 (-12;26)
Cryotherapy with SA	-	-	1.7 (0.95-3.1)	16 (1-32)
MCA	5.5 (1.8-17)	36 (22-49)	2.0 (1.1-3.6)	23 (8-39)

MCA = monochloroacetic acid, SA = salicylic acid, CI = Confidence interval
* Data for wait-and-see policy, SA and cryotherapy in the plantar wart group originate from our previous trial; data for MCA and cryotherapy combined with SA originate from the present trial; data for cryotherapy in the common wart group are combined from our previous and present trial.

Appendix 8.2. Sensitivity analyses for the effectiveness of treatments for patients with common warts (n=185) and patients with plantar warts (n=221).

	Common wart group				Plantar wart group			
	MCA		Cryotherapy		MCA		Cryotherapy with SA	
Analysis	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)	n/N	% (95%CI)
Primary intention to treat analysis	40/92	43 (34-54)	50/93	54 (44-64)	49/106	46 (37-56)	45/115	39 (31-48)
Patients lost to follow-up considered not cured	40/94	43 (33-53)	50/94	53 (43-63)	49/109	45 (36-54)	45/118	38 (30-47)
Per protocol analysis based on treatment adherence	38/65	58 (46-70)	45/75	60 (49-70)	49/92	53 (43-63)	41/68	60 (48-71)
Patients with both common and plantar warts excluded	36/79	46 (35-57)	49/83	59 (48-69)	45/90	50 (40-60)	43/94	46 (36-56)
Only patients with warts located on hands	38/81	47 (36-58)	42/83	51 (40-61)	-	-	-	-
Individual warts instead of patients as unit of analysis*	145/249	58 (52-64)	170/265	64 (58-70)	150/296	51 (45-56)	155/359	43 (38-48)

Values are numbers cured/total number in treatment arm, and percentages cured with 95% confidence interval (CI). MCA = monochloroacetic acid, SA = salicylic acid.
* The total number of 514 common and 655 plantar warts in analysis at 13 weeks is lower than the reported total of 611 common and 790 plantar warts, because outcomes of individual warts were reported for a maximum of 10 warts per patient.

CHAPTER 9

HPV type in plantar warts predicts natural course and treatment response: secondary analysis of a randomised controlled trial

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ABSTRACT

Background

Cryotherapy is effective for common warts, but for plantar warts available treatments often fail.

Objectives

Within a pragmatic randomised controlled trial, we examined whether subgroups of common and plantar warts have a favourable natural course or response to treatment based on wart-associated HPV type.

Study design

Consecutive patients with new common or plantar warts were recruited in 30 Dutch family practices. Patients (n=250) were randomly allocated to liquid-nitrogen cryotherapy, 40% salicylic acid self-application, or wait-and-see policy. Before treatment, swabs were taken from all separate warts and analyzed by a broad spectrum HPV genotyping assay. At 13 weeks, cure rates with 95% confidence intervals of common and plantar warts on intention to treat basis were compared between treatment arms for the different wart-associated HPV types.

Results

In total, 7% of swabs tested negative for HPV DNA and 16% contained multiple types, leaving 278 of 371 common swabs (75%) and 299 of 373 plantar swabs (80%) with a single type for analysis. After wait-and-see policy, cure rates were 2/70 (3%, 95% confidence interval 1-10) for HPV 2/27/57-associated common warts, 4/58 (7%, 3-16) for HPV 2/27/57-associated plantar warts, and 21/36 (58%, 42-73) for HPV 1-associated plantar warts. After cryotherapy, cure rates were 30/44 (68%, 53-80), 6/56 (11%, 5-21), and 15/23 (65%, 45-81); after salicylic acid 16/87 (18%, 12-28), 15/60 (25%, 16-37), and 24/26 (92%, 76-98), respectively.

Conclusions

HPV type influenced the natural course and response to treatment for plantar warts. HPV testing potentially optimises wart treatment in primary care.

BACKGROUND

Cutaneous warts are benign papillomas of the skin of which common warts (verrucae vulgaris) and plantar warts (verrucae plantaris) are most common.[1,2] Up to one-third of all primary schoolchildren have warts, of which two-thirds resolve spontaneously within 2 years.[3,4] Since warts frequently result in discomfort,[5] 2% of the general population and 6% of schoolchildren present warts to their general practitioner (GP) for treatment,[6,7] at a reported cost of £40 million per year in the UK.[8] A range of treatment options are available, [9,10] the most common being liquid-nitrogen cryotherapy or topical salicylic acid application.[11] For common warts cryotherapy showed to be most effective, but for plantar warts available treatments often fail.[12,13] Because of the benign natural course and limited effectiveness, side effects and costs of treatments, some physicians promote a wait-and-see policy.[8;14-16] Definition of subgroups that will better respond to specific treatment could improve treatment results, reduce costs, and limit the burden of side effects.[17]

Warts are caused by infection with human papillomavirus (HPV). More than 120 HPV types, distributed over 5 genera and 16 species, have been described based on their DNA sequences.[18,19] Development of the HSL-PCR/MPG (hyperkeratotic skin lesion – polymerase chain reaction / multiplex genotyping) assay has recently paved the way for large-scale cutaneous wart-associated HPV typing.[20] HPV 2, 27, and 57 from the alpha genus, and HPV 1 from the mu genus are the most prevalent types detected in cutaneous warts.[21-27] Since specific HPV types are related to clinical characteristics such as type of wart (common or plantar) and age of the patient, we questioned whether these HPV types could influence the natural course or response to treatment.[27]

OBJECTIVES

Within a randomised controlled trial comparing liquid nitrogen cryotherapy, topical salicylic acid application, and a wait-and-see policy, we examined whether subgroups of common and plantar warts have a favourable natural course or response to treatment based on wart-associated HPV type.

STUDY DESIGN

This study is a secondary analysis within the WArts Randomised Treatment Study (WARTS, trial registration ISRCTN 42730629). For detailed information on study design and treatment protocols we refer to the publication of the original trial.[12]

Patients and samples

All patients from 4 years of age and older who attended one of the 30 participating general practices between May 1st 2006 and January 26th 2007 with one or more new cutaneous warts were eligible. We defined new cutaneous warts as common or plantar warts on the skin that were diagnosed in general practice and were presented for the first time without treatment from a physician or dermatologist in the previous year, regardless of previous self-treatment with over-the-counter (OTC) medication, and excluded immunocompromised patients. Trained research nurses visited the patients at home to confirm eligibility and collect baseline characteristics, including number, size, location and duration (<6 versus ≥6 months) of warts.

Randomisation

We stratified patients by number of warts (<6 versus ≥6 warts) and type of warts (plantar [warts on the soles of the feet] versus common [all other locations, mainly on the hands]). Patients who had both plantar and common warts were stratified according to where the majority was located. All warts of patients with multiple warts received the same treatment.

Treatments

We trained all GPs and assistants in the three 13-week protocols, which were designed to reflect best practice.[10] In the cryotherapy protocol, we used a high intensity regimen of one session every two weeks until all warts were completely gone. In the salicylic acid protocol, salicylic acid 40% in a vaseline album solution was self-administered every day. In the wait-and-see protocol, participants were informed about the benign natural course of warts and were advised not to undergo treatment for at least 13 weeks.

Outcome assessment

The trained research nurses assessed wart cure during home visits at 13 weeks of follow-up, independently of the treating general practice. A wart was considered cured if the wart had visually disappeared (skin colour and skin lines re-established) and could no longer be palpated by hand.

HPV identification

At baseline, the nurses took swabs from each single wart by firmly rubbing a wetted cotton-tipped stick over the surface of the wart five times. This swab technique adequately detects HPV types compared to wart scab or biopsy.[28] We considered multiple warts as a cluster when the distance between warts was less than 1 cm. Only when warts were too close to take separate swabs, a single swab was taken from the cluster. All swabs were stored in 1 ml of saline solution.

To determine HPV type, a broad spectrum PCR-MPG assay was used for genotyping all known wart-associated HPV types from the alpha (HPV2, 3, 7, 10, 27, 28, 29, 40, 43, 57, 77, 91 and 94), gamma (HPV4, 65, 95, 48, 50, 60 and 88), mu (HPV1 and 63) and nu genus (HPV41). This sensitive and specific assay (HSL-PCR/MPG assay; Labo Biomedical Products BV, Rijswijk, The Netherlands) has been well described and evaluated.[20] In short, 10 µl of the saline solution was used in the single-step HSL-PCR, generating a biotinylated amplimer of 76-84 bp from the L1 region. Subsequently, simultaneous identification of the 23 HPV genotypes was performed with bead-based xMAP suspension array technology.

Statistical analysis

Baseline characteristics of the patients and warts, as well as all outcomes, were stratified for common and plantar warts. Because HPV type is associated with separate warts, we used warts instead of patients as unit of analysis. The primary outcome measure was the crude cure rate of separate warts associated with a single HPV type per treatment arm per specific wart-associated HPV type at 13 weeks on an intention-to-treat basis. The software package SPSS, PASW Statistics, release 17.02 was used.

We only compared cure rates for HPV types which had at least 10 warts per treatment arm. To identify subgroups of common and plantar warts that have a favourable natural course, cure rates of wait-and-see arms were compared between specific HPV types using 95% confidence intervals (CIs). To examine subgroups that have favourable response to treatment, cure rates of treatment arms were compared within specific HPV types using 95% CIs, relative risks and risk differences.

In addition, per-protocol analysis was performed based on reported treatment adherence. To explore whether we had created a specific subgroup of warts by including only warts with a single HPV type, we compared cure rates of warts negative for HPV DNA and cure rates of warts with multiple HPV types with cure rates of warts with single HPV type within treatment arms.

RESULTS

Patients and samples

In the original trial, 250 patients with 391 common and 379 plantar warts were included.[12] No swabs were available from 20 common and 6 plantar warts (13 warts belonged to four patients without consent for swabs, and 13 swabs were lost in transport to the laboratory). A total of 45 common and 4 plantar warts (7%) swabs tested negative for HPV DNA, and 48 common and 70 plantar warts (16%) contained multiple HPV types per swab, leaving 278 common warts (75%) and 299 plantar warts (80%) with single HPV type for analysis. A further 6 patients with 7 common and 8 plantar warts (3%) warts were lost to follow-up (Figure 9.1). Patients were evenly distributed over treatment arms, but by chance the cryotherapy arm contained less warts than the salicylic acid and wait-and-see arm for common warts (p=0.003) as well as plantar warts (p=0.069).

Baseline characteristics of patients with complete follow-up showed that, in the common wart group (n=103), 54 patients (56%) were female, median age was 16 (range 4-73) years, and median number of warts was 2 (interquartile range [IQR] 1-4). In the plantar wart group (n=110), 68 patients (62%) were female, median age was 11 (range 4-69) years, and median number of warts was also 2 (IQR 1-4). In total, 91 patients had common warts only, 90 had plantar warts only, and 32 had both common and plantar warts.

Figure 9.1. Flowchart.

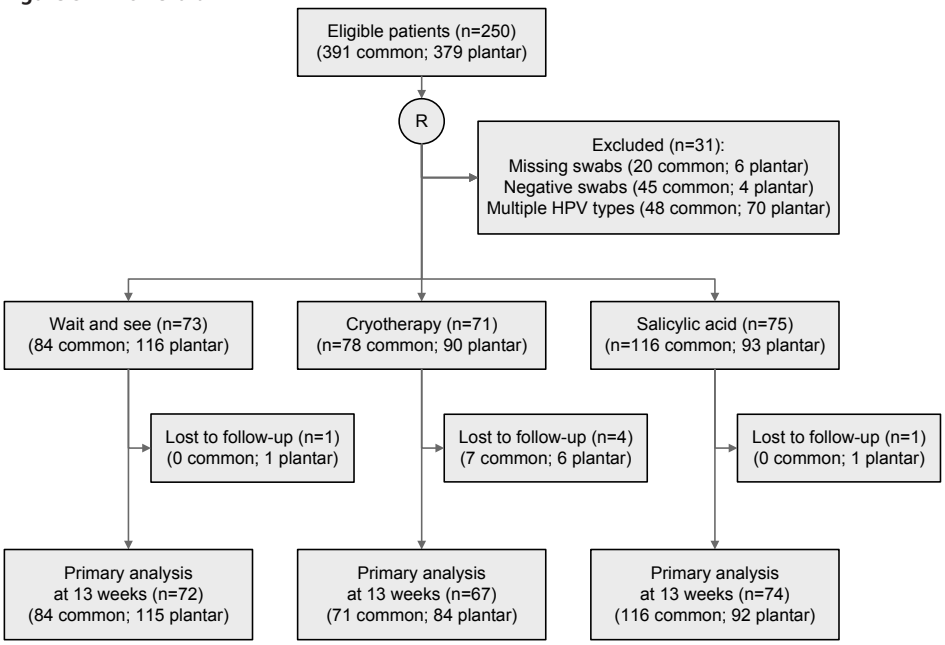


Table 9.1. Characteristics of warts associated with a single HPV type (n=562).

	Common warts (n=271)	Plantar warts (n=291)
Associated HPV type*		
HPV 1	20 (7)	85 (29)
HPV 2	80 (30)	35 (12)
HPV 27	65 (24)	71 (24)
HPV 57	56 (21)	68 (23)
Other HPV types	50 (18)	32 (11)†
Location		
Sole of the foot	-	291 (100)
Dorsum of the foot	26 (10)	-
Hand	211 (78)	-
Rest of the body	34 (13)	-
Wart duration <6 months	56 (21)	125 (43)
Size of wart in millimetre (median, IQR)	3 (4-5)	3 (4-5)

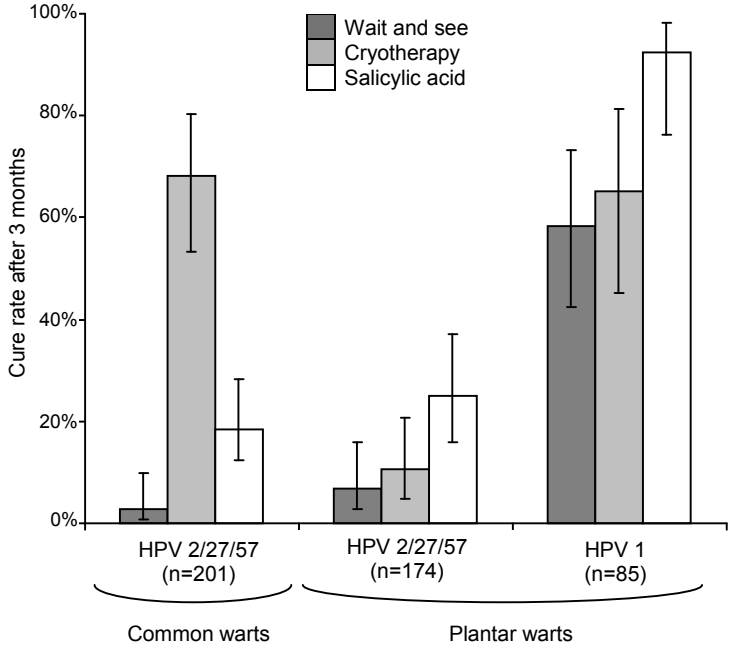
Values are numbers (percentage of warts) unless stated otherwise.
* HPV3, 10, 28, 2, 27, 57 and 7 from the alpha genus, HPV4, 65, and 95 from the gamma genus, HPV1 and 63 from the mu genus, and HPV41 from the nu genus.
† Sum of percentages is ≠ 100 due to rounding off.

The patients had a total of 271 common warts and 291 plantar warts (Table 9.1). The common warts were mainly located on hands (78%). The combined contribution of the four most prevalent HPV types (HPV 1, HPV 2, HPV 27 and HPV 57) was 82% in common and 88% in plantar warts. For detailed information on the HPV type prevalence and their relation with patient characteristics we refer to a recent publication.[27]

HPV types and wart cure

Only the three most prevalent types (HPV 2, 27, and 57) for common warts, and the four most prevalent types (HPV 2, 27, 57, and 1) for plantar warts had sufficient numbers (>10) to compare treatment arms (Appendix 9.1). Since the CIs of cure rates of the three highly prevalent HPV types 2, 27, and 57 from the alpha genus species 4 overlapped for common as well as for plantar warts, we combined cure rates for these HPV types. Thus, we identified three subgroups of warts for which we could make reliable comparisons: common warts with HPV 2/27/57 (n=201), plantar warts with HPV 2/27/57 (n=174), and plantar warts with HPV 1 (n=85).
For common warts with HPV 2/27/57, the cure rate after a wait-and-see policy was 2/70 (3%, 95%CI 1-10). Cryotherapy was the most effective treatment for common warts with HPV 2/27/57: 30/44 (68%, 53-80) cured compared to 16/87 (18%, 12-28) cured after salicylic acid (Figure 9.2, Table 9.2).

Figure 9.2. Cure rates with 95% confidence intervals of the three largest groups of warts based on type of warts (common or plantar) and warts-associated HPV type (n=460).



For plantar warts, the subgroup with HPV 1 had a favourable natural course compared to those with HPV 2/27/57: 21/36 (58%, 95% CI 42-73) cured versus 4/58 (7%, 3-16) cured after a wait-and-see policy (Table 9.2). For plantar warts with HPV 2/27/57, salicylic acid [15/60, 25% (16-37) cured] was more effective compared to wait-and-see, whereas cryotherapy [6/56, 11% (5-21) cured] was not more effective than wait-and-see. For plantar warts with HPV 1, salicylic acid [24/26, 92% (76-98) cured] was also more effective compared to wait-and-see, whereas cryotherapy [15/23, 65% (45-81) cured] was not more effective than wait-and-see (Figure 9.2, Table 9.2).

In addition to the highly prevalent HPV types, plantar warts with HPV 4 from the gamma genus showed sufficient numbers (n=17) in the wait-and-see arm to reveal a specifically favourable natural course: 16/17 (94%, 73-99) of warts cured (Additional file 1). Per-protocol analysis did not reveal additional information. Cure rates per treatment arm in warts negative for HPV DNA (n=40) and warts with multiple HPV types (n=118) were similar to our analysis of cure rates of warts with single HPV types (n=562).

Table 9.2. Natural course and treatment response of the three largest groups* of warts based on type of wart (common or plantar) and wart-associated HPV type (n=460).

	Common warts	Plantar warts	
	HPV 2/27/57 (n=201)	HPV 2/27/57 (n=174)	HPV 1 (n=85)
Cure rates†			
Wait-and-see	2/70 3 (1-10)	4/58 7 (3-16)	21/36 58 (42-73)
Cryotherapy	30/44 68 (53-80)	6/56 11 (5-21)	15/23 65 (45-81)
Salicylic acid	16/87 18 (12-28)	15/60 25 (16-37)	24/26 92 (76-98)
Relative Risks‡			
Wait-and-see	1.0	1.0	1.0
Cryotherapy	23.9 (6.0 to 94.9)	1.6 (0.46 to 5.2)	1.1 (0.74 to 1.7)
Salicylic acid	6.4 (1.5 to 27.1)	3.6 (1.3 to 10.3)	1.6 (1.2 to 2.2)
Risk Differences‡			
Wait-and-see	0	0	0
Cryotherapy	65 (51 to 80)	4 (-7 to 14)	7 (-18 to 32)
Salicylic acid	16 (7 to 25)	18 (5 to 31)	34 (15 to 53)

* Numbers of warts >10 per treatment arm were considered sufficiently high to compare cure rates.
† Cure rates are number of warts cured at 13 weeks / number of warts; percentage (95% confidence intervals [CIs]).
‡ Relative risks (95% CIs) and Risk differences (95% CIs) of active treatments compared to wait-and-see policy as reference.

DISCUSSION

Main findings

HPV type influences the natural course and treatment response for plantar warts. The probability of cure after a wait-and-see policy was 8 times higher for HPV 1-associated plantar warts than for HPV 2/27/57-associated plantar warts. Using the HSL-PCR/MPG assay in our primary care study population, 80% of plantar warts provided a single HPV type of which 29% contained HPV 1. When treated, salicylic acid was more effective than cryotherapy for both HPV subgroups of plantar warts. However, for common warts, cryotherapy was most effective. Since the majority of common warts were associated with HPV 2/27/57, this study does not provide sufficient power to draw conclusions on the less prevalent HPV types.

Comparison with literature

This study confirms that treatment response in common warts is different from plantar warts,[10] even when associated with the same HPV type. Reasons for this difference are not fully understood at present. Conceivably, skin location specific factors such as callus are at play.

The short duration of warts with HPV 1 has been described earlier, but has never been prospectively investigated or related to treatment response.[24] Only one other trial has investigated the relation between cutaneous wart-associated HPV type and treatment effect. Tomson et al. (2010) studied the effect of cryotherapy on 54 common and plantar warts.[26] They found that the response to cryotherapy was unrelated to HPV type, but more likely the result of the individual's immune response to the virus. However, since all warts were treated with cryotherapy, they could not investigate differences between a wait-and-see policy or salicylic acid treatment. Furthermore, the low number of warts prevented drawing conclusions about HPV 1 associated warts.[26]

Compared to older HPV typing techniques, the HSL-PCR/MPG assay is able to distinguish closely-related HPV types 2, 27, and 57.[20] The similar cure rates of these types are probably in line with their high DNA homology in the alpha genus species 4,[18] and correspond with their similarity in relation to patient characteristics.[27] Only 7% of all swabs were negative for HPV DNA in which unknown HPV types could be involved. Alternatively, lesions (like callus) could have been misdiagnosed as warts, or residual hyperkeratotic lesions following HPV clearance could have been sampled. Therefore we could not use the swabs negative for HPV DNA for clinical prediction. The assay was also capable of detecting multiple HPV types per wart. It is likely that only one HPV type is responsible for the persistence of the wart; however, it is difficult to establish which one without using a technology such as laser capture microdissection for which biopsies instead of wart swabs are needed.[27-29] Consequently, we did not use swabs with multiple HPV types for clinical prediction.

Strengths and limitations

This study combined the broad spectrum HSL-PCR/MPG assay and simple non-invasive swabs, which showed that HPV testing in practice can be easy, quick, and reliable. The study was embedded in a high quality randomised trial in primary care.[12] The two most frequently used treatments in dermatology as well as primary care practice were included.[9;11] However, the power of our analyses is lower compared to the original trial, since we studied cure rates in subgroups based on HPV types. Nevertheless, for the four most prevalent HPV types, numbers of warts per HPV type per treatment arm were high enough to make reliable comparisons. Although the original trial randomised the patients, we determined HPV type in separate warts. Because more than half of all patients had multiple warts, the

number of warts in the cryotherapy arm was less than the numbers in the other two arms due to chance.

This study allows us to conclude that the HPV type influences the natural course and treatment response, which is different from drawing conclusions about causal relations. One could argue that some wart characteristics are confounders, or are in fact in the causal pathway between HPV type and cure.[30] For example, HPV 1 is associated with a low number of warts per patient. HPV 1 often has endophytic growth patterns and high viral loads. It is hypothesised that this could trigger the immune system and limit the spread of warts, both of which could contribute to the favourable cure rates.[31] Increasing numbers of warts per patient may reflect poor immune responses to the HPV type inducing these warts. However, we did not study the immune response in this cohort of patients. Thus, for our research question related to prognosis only, we chose to present crude cure rates without adjustment.

Implications

This study reveals that HPV type may influence the choice of treatment for plantar warts. In daily practice, detection of HPV 1 in plantar warts implies a favourable natural course and may lead to advise the patient to wait-and-see. Detection of HPV 2/27/57 in plantar warts implies a persistent wart, which in most cases is resistant to treatment. However, when treatment is preferred, salicylic acid can be considered. For common warts, HPV typing does not yet contribute to the choice of treatment, because cryotherapy is effective in the majority of HPV2/27/57-associated warts. Future studies should reveal whether less prevalent HPV types causing common warts will be associated with lower cure rates. With our findings, we have opened a new direction to optimise wart treatment.

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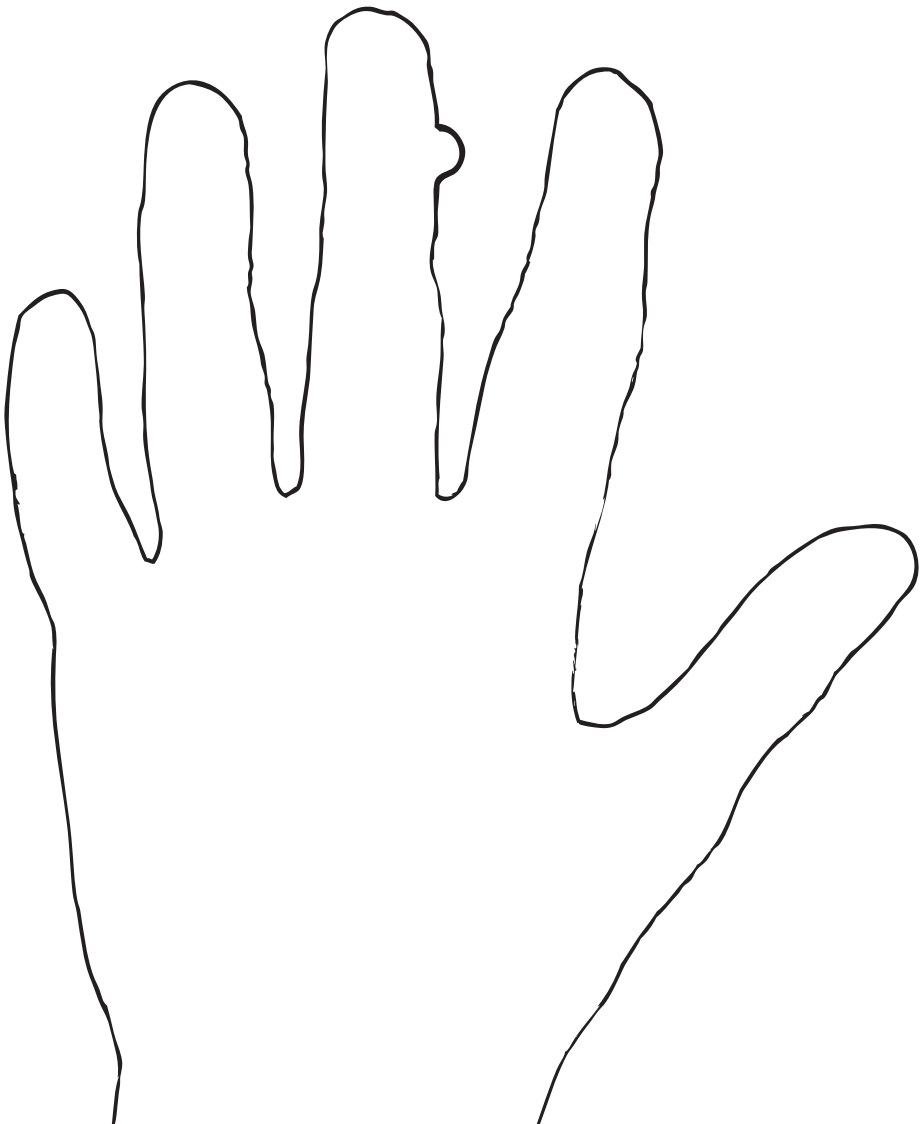
Appendix 9.1. Crude numbers of common and plantar warts cured at 13 weeks for all wart-associated HPV types (n=562)

Wart associated HPV			Common warts (n=271)			Plantar warts (n=291)		
Genus	Species	Type	Wait-and-see (n=84)	Cryotherapy (n=71)	Salicylic acid (n=116)	Wait-and-see (n=115)	Cryotherapy (n=84)	Salicylic acid (n=92)
Alpha	Species 2	HPV 3	-	6/7	3/3	-	-	-
		HPV 10	-	4/6	0/2	-	-	-
		HPV 28	0/2	-	0/11	-	-	-
	Species 4	HPV 2	1/32	10/15	7/33	0/12	0/2	8/21
		HPV 27	1/26	9/13	3/26	2/22	4/27	3/22
		HPV 57	0/12	11/16	6/28	2/24	2/27	4/17
	Species 8	HPV 7	-	-	0/3	-	-	-
Gamma	Species 1	HPV 4	0/4	4/6	0/1	16/17	-	0/1
		HPV 65	-	3/4	-	0/2	3/4	2/4
		HPV 95	0/1	-	-	-	-	-
Mu	Species 1	HPV 1	5/7	1/4	8/9	21/36	15/23	24/26
	Species 2	HPV 63	-	-	-	-	1/1	0/1
Nu	Species 1	HPV 41	-	-	-	0/2	-	-
All warts			7/84	48/71	27/116	41/115	25/84	41/92

Values are number of warts cured / number of warts in intention-to-treat analysis at 13 weeks.



Final chapters

CHAPTER 10

General discussion

Partially based on

Bruggink SC, Assendelft WJJ. For plantar warts, liquid nitrogen cryotherapy is more costly but not more effective than salicylic acid self-treatment. Evid Based Med 2012;17:156-57

and

Bouwes Bavinck JN, Eekhof JAH, Bruggink SC. Treatments for common and plantar warts. BMJ 2011;342:d3119

The studies presented in this thesis address the most apparent gaps in our knowledge on the *transmission* and *treatment* of warts in general practice. The main conclusions of the studies in this thesis are addressed in the Summary (Chapter 11) and specific methodological considerations of the studies are discussed in the corresponding chapters (Chapters 2-9). This general discussion first brings the conclusions back to daily practice, then presents explanations for the observed effects, and finally, provides recommendations for future research.

DAILY PRACTICE

Relevant clinical research has its roots and its implications in daily practice. The research presented in this thesis was fuelled by everyday cases of warts, such as the 10-year old girl - described in the introduction - who was suffering from a persistent plantar wart. Therefore, this section relates the study findings back to daily practice by presenting a point-by-point outline of what can be said and done to address the two important questions on transmission and treatment of warts. This aims to improve patient information for adequate reassurance and optimal shared decision-making.
Each point is marked according to the insight derived from studies in this thesis:
N – *New* insight directly derived from evidence emerging from this thesis
C – Insight already known but *confirmed* by evidence emerging from this thesis
K – Relevant insight already *known*, and not directly examined in this thesis

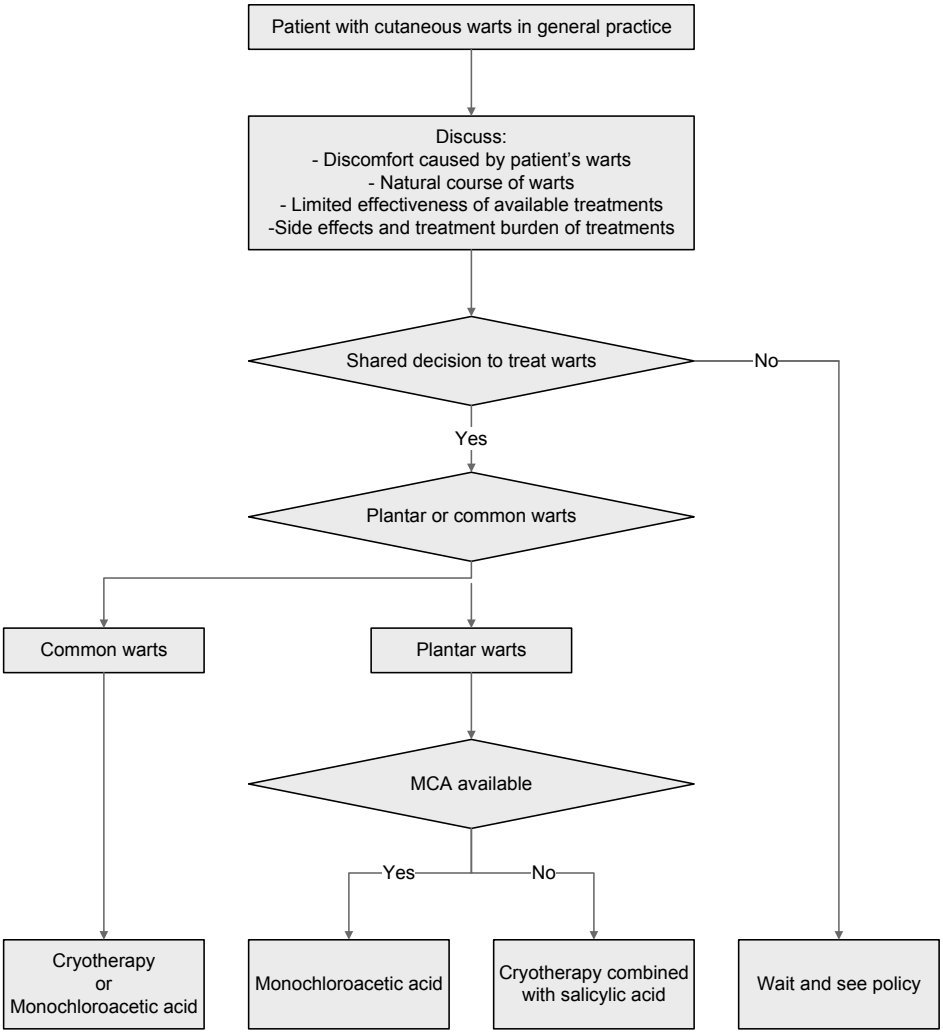
How did I get warts?

- Warts may be annoying but are completely harmless (C)
- Warts are caused by the human papillomavirus (HPV), of which four different types are most prevalent in general practice (N)
- Some people are more susceptible to HPV than others (C)
- Up to one third of children have warts (N)
- Parents are often not aware that their children have warts (N)
- Transmission usually occurs in the family or the school environment, whereas the spread in public places such as swimming pools is less likely (N)
- It is still unclear whether recommendations to prevent warts are effective (C)

How do I get rid of warts?

- Half of all children with warts are cured after one year without treatment (N)

Figure 10.1. Flowchart for the treatment of cutaneous warts in general practice.



- Uncovering the discomfort caused by warts as well as treatment expectations ensures an open conversation (K)
- For common warts that are mostly located on the hands, cryotherapy is the most effective treatment with 50% of patients cured after 3 months. Monochloroacetic acid application is an effective alternative to avoid pain during cryotherapy application (N)
- For plantar warts, monochloroacetic acid application (50% of patients cured after 3 months) is preferred over cryotherapy combined with SA based on effectiveness, side effects and treatment burden. Cryotherapy and salicylic acid monotreatments are not more effective than a wait-and-see policy (N)

- For instructions for healthcare professionals to administer monochloric acid, go to http://www.youtube.com/watch?v=cTzkPCZaGW8
- Plantar warts are considerably more persistent in adolescents and adults than in children (C)
- Paring of warts might reduce symptoms, but radical excision is not advisable because of scarring and possible recurrence of warts (K)
- Research on HPV type-specific treatment seems promising, but is not yet available for practice (N)
- A wait-and-see policy is always an option (Figure 10.1). Treatment decisions are based on shared decision-making weighing the discomfort caused by warts, the effectiveness of treatment, the side effects of treatment, and the benign natural course (C)

UNDERSTANDING THE EFFECTS

In addition to reporting the effects found in our studies, ideally these effects can be explained by known mechanisms, or build on these mechanisms, in order to reach a deeper understanding. This section aims to achieve this by discussing views on the transmission of warts, the selection of patients with warts, the distinction between common and plantar warts, and HPV typing of warts.

Perspectives on transmission

The primary school cohort showed that the incidence for developing new warts is high in children, resulting in 3-68% of children with warts in different school classes. Risk factors for the development of warts were examined to establish a deeper understanding of the transmission of wart-associated human papillomavirus. Three main factors are likely to govern the transmission of warts.[1] Conceivably, the combined action of these three factors will determine the individual threshold for developing warts.

1. *The level of HPV exposure*. The level of individual HPV exposure theoretically depends on the viral load in a specific environment and the degree of contact with this specific environment. Analyses of the cohort of primary school children identified HPV exposure in the family and the school environment as the most important risk factors for the transmission of warts. The level of HPV exposure in public places was probably too low to detect such associations.
2. *Specific HPV type*. Different HPV types have different virulent abilities. For example, high numbers of HPV 1 may be present but will relatively infrequently cause warts, whereas relatively low numbers of HPV 2 may lead to multiple manifest infections.[2] Analyses of

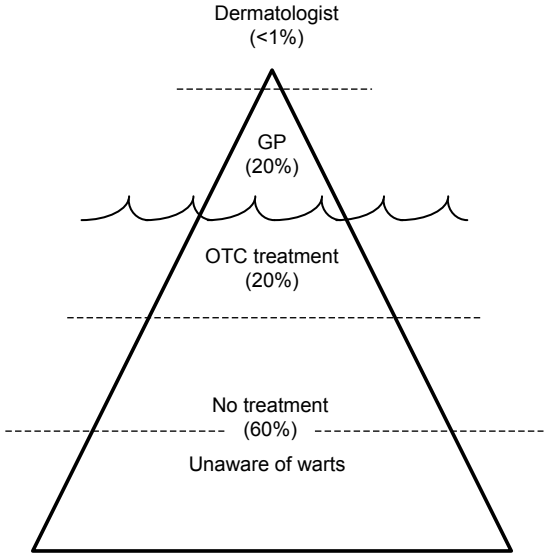
HPV types in the general practice population revealed that HPV types 1,2,27, and 57 are the most prevalent types responsible for the development of warts.

3. *Susceptibility of the host*. This largely depends on features of the individual skin and immune defence. These may be genetic traits, but may also vary over time. For example, the high prevalence of warts we found in children suggests that children may be more susceptible than adults because of their relatively immature immune defence.[3] Also, children are more likely to have damaged skin that may act as a port of viral entry. We also know that immunocompromised patients are highly susceptible to develop warts.[4]

Perspectives on patient selection

Generalizing the specific study results to larger populations is discussed in the respective chapters. However, in general, the findings of the thesis imply that it is important to realise which patient population is actually addressed when researching or managing patients with warts. In the cohort of primary school children, half of all children with warts were cured after one year. Awaiting the natural course of warts was no exception: less than half of all children with warts reported that their warts had not been treated that year. Although this may be a conscious decision, the parental questionnaires revealed that in more than half of all children with warts, parents were unaware that the children had warts. The children that did treat their warts mostly used over-the-counter treatment and

Figure 10.2. Schematic view of a general practitioner (GP) on the iceberg of warts in the population.



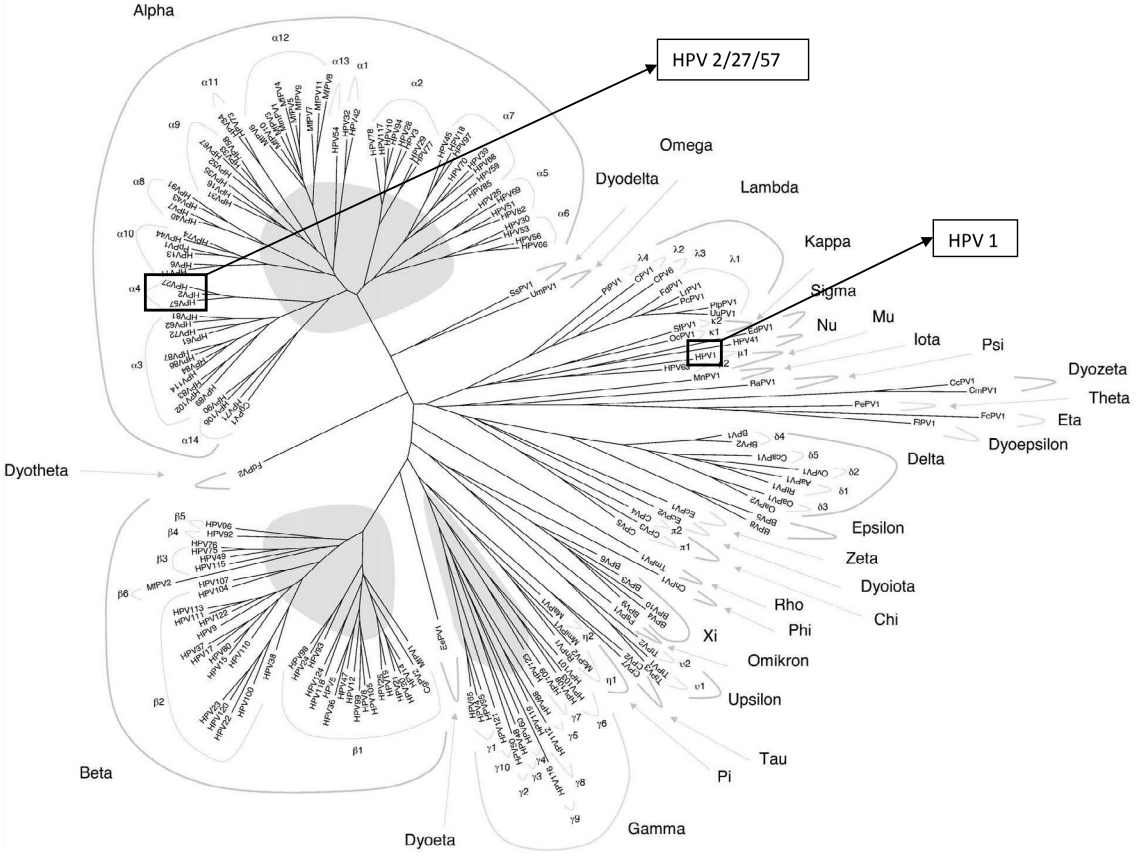
only 20% of all children with warts went to see the general practitioner (GP). Thus, the GP only sees the top of the iceberg of children with warts (Figure 10.2). This GP selection of children with warts is indeed different from the children not seeking medical advice. The primary school cohort showed that the GP selection of children have larger more persistent warts that cause more inconvenience and are more resistant to treatment than the warts of the other children. This implies that every study investigating warts should take into account the way the patients with warts were recruited.

Perspectives on common versus plantar warts

Our studies on risk factors for developing warts revealed no major differences between common and plantar warts. However, the trial clearly showed a distinction in the response to treatments: the survey among Dutch GPs showed that the preference for cryotherapy in practice is more evident for common warts than for plantar warts. This finding is noteworthy because, before publication of our trial, systematic reviews on treatments for warts did not make a distinction between common and plantar warts.[5-7] Following our trial, the 2012 update of the Cochrane review on topical treatments for cutaneous warts made a separate subgroup analysis for common and plantar warts.[8] For plantar warts, the relative risks (RRs) in the different comparisons in the review are generally in line with the WARTS-1 trial. However, the RR for salicylic acid compared to a wait-and-see policy showed significance in the pooled analysis: RR 1.29 (95% CI 1.07 to 1.55) vs. RR 1.43 (95% CI 0.72 to 2.87) in WARTS-1. The review therefore concludes that salicylic acid is (albeit modestly) effective for plantar warts. A recent large trial from the UK including only adult patients with plantar warts confirms our low cure rates for salicylic acid and cryotherapy in this specific population.[9] The conclusion that cryotherapy is most effective in common warts is in contrast with the few other trials comparing cryotherapy with no treatment [10] or salicylic acid.[11;12] This might be due to differences in patient selection and the methods used for treatment application.

Reasons for the difference in response to treatment between common and plantar warts are not yet elucidated. Although HPV-specific subgroup analysis of the trial showed that cure rates differed for HPV types, the difference between common and plantar warts remained when analyzing within a specific HPV type. Skin location specific factors are probably at play. Characteristics of the plantar skin due to its pressure bearing abilities might cause plantar warts to be less accessible for immune defences and for treatment.[13;14] It is feasible that monochloroacetic acid (with its strong corrosive capacity) is more capable than salicylic acid or cryotherapy to penetrate sufficiently deep in the callosity to destroy the HPV-containing cells and/or activate immune response.

Figure 10.3. Phylogenetic tree inferred from the L1 nucleotide sequences of 189 papillomavirus types illustrates close genetic relations between HPV 2, HPV 27, and HPV 57 from the alpha genus species 4.[15]



Perspectives on HPV typing

Of the most prevalent HPV types identified in general practice, the clinical profile (including the response to treatment) of HPV 1-associated warts from the mu genus showed marked differences from the HPV 2, 27, and 57 associated warts from the alpha genus. The clinical similarities of the HPV 2, 27, and 57 associated warts are in agreement with their genetic similarities (Figure 10.3).[15] Therefore, it is conceivable that the prognostic relations between clinical cure and HPV type are causal relations. However, one could argue that wart characteristics (such as age of the patient, wart location or the number of warts) are confounders, or are in fact in the causal pathway between HPV type and cure.[16] For example, HPV 1 is associated with a low number of warts per patient. HPV 1 often has endophytic growth patterns and high viral loads. It is hypothesised that this could trigger the immune system and limit the spread of warts, both of which could contribute to the favourable cure rates.[2] Thus, the exact causal relations remain unclear.

FUTURE RESEARCH

Although the most apparent gaps in the knowledge on warts have been addressed in this thesis, important questions still remain and new questions have arisen. This section discusses several important issues for future research to further optimise the prevention and treatment of warts.

Minor ailments in general practice

Cutaneous warts are a typical minor ailment, i.e. annoying but harmless. In general practice, about 60% of all consultations concern minor ailments.[17] In spite of the even higher prevalence in the general population and the considerable burden of disease, high-quality research on minor ailments is scarce.[18] This is surprising, because epidemiological research and treatment trials can easily be performed in view of the high attrition potential and easy comparison with a wait-and-see policy, with few ethical considerations. This should prompt researchers and policymakers to give higher priority to high-quality research on minor ailments. Daily practice would definitely benefit from this.

Synthesis of knowledge

Although general practice deals with the greater part of all patients with cutaneous warts, most of the research on warts is performed in dermatology or virology.[8;19;20] Due to good collaboration with researchers in other fields, the research in this thesis contains conclu-

sions related to microbiology, aetiology, natural history and interventions. Although all chapters explicitly share the view of the GP, these studies have been published in a large range of high-quality journals reaching researchers and clinicians in dermatology, virology, paediatrics and general medicine. Future research on warts should continue to synthesise knowledge from different disciplines with a general scope for optimal implementation of research findings in clinical practice.

HPV typing in warts

One of the innovative methods used in this thesis is the implementation of the HSL-PCR/MPG assay in primary care research. Collaboration with other researchers led to the development and validation of this novel assay that is capable of genotyping all known wart-associated HPV types. Previously, costly and time-consuming technology was needed for genotyping biopsies of warts.[21] Current bead-based luminex technology has facilitated the fast and reliable analysis necessary to analyze a high number of samples. This method also allows to take non-invasive swabs; this is an advantage as biopsies for all warts in primary care population with a high proportion of children would not have been feasible. This technology for genotyping cutaneous warts is promising for future research and may contribute to better prevention and more effective treatment of warts.

Prevention of warts

Firstly, investigating HPV-specific transmission patterns is necessary to further develop effective recommendations for the prevention of warts. Having identified family and the school environment as important risk factors for the development of warts, the first step would be to compare HPV types within families and schools. Also swabbing tables, door handles, bathroom shower drains, towels, etc. in family homes and schools might help identify objects carrying specific HPV types.

Secondly, research on the activity of the immune system against HPV would provide insight as to why some individuals develop warts and others do not.[22]

Finally, the recent large-scale introduction of immunization against cervical HPV 16/18 in female adolescents is of particular interest for research on the prevention of cutaneous warts.[23] This provides an opportunity to observe cross-immunity between different HPV types, i.e. the established herd immunity against HPV 16/18 might lead to immunity against cutaneous wart associated HPV types, especially against the closely related HPV 2/27/57 from the alpha genus.[24] This might cause a radical decrease in wart prevalence. Also, the knowledge from current HPV immunization may help to develop analogous vaccines against the cutaneous wart associated HPV types, especially valuable for immunocompromised patients at high risk for large numbers of persistent warts.[4]

Treatment of warts

This thesis has optimised wart treatment by offering realistic cure rates for cryotherapy, salicylic acid and monochloroacetic acid (MCA) for common and plantar warts. Nevertheless, it reveals that the even the most effective treatment fails in 50% of patients, offering no evidence-based treatment alternative for a large percentage of patients. Other promising treatments, such as 5-fluorauracil preparations, need to be thoroughly investigated in high-quality trials. Based on effectiveness, side- effects and treatment burden, MCA has now gained a role in the routine treatment of both common and plantar warts as long as healthcare professionals carefully administer it. However, MCA is not yet widely used in general practice and most pharmacies do not have MCA readily available. Future observational research needs to demonstrate whether current evidence will lead to widespread implementation of MCA.

In addition to research on new treatments, future research should also identify subgroups of patients for which specific treatment is effective as well as subgroups of patients with a favourable natural course.[25;26] The HPV research in this thesis identified a favourable natural course in the subgroup of HPV 1-associated plantar warts. Thus, detection of HPV 1 in plantar warts could support a wait-and-see policy rather than treatment. Although this opens a new direction to optimise treatment, it does not yet establish a solid basis for the routine implementation of HPV testing in daily practice. First, relations between HPV type, clinical characteristics of patients, and morphologic features of warts should be further clarified. If the morphology of warts proved to accurately predict HPV type or treatment response, HPV testing would have no added value for general practice. Also, the prevalence of HPV types and their relationship with cure should be confirmed in other primary care populations.

Based on the treatment evidence from WARTS-1 and WARTS-2, Figure 10.1 proposes a flowchart for the treatment of warts in general practice. However, ultimately, a more extensive evidence-based decision tool should be developed and implemented in general practice. This tool should guide patients on whether or not to visit general practice, and help physicians decide which treatment to use for specific patient groups. A subsequent recommendation for a wait-and-see policy for patients with a favourable natural course, or patients not responsive to treatment, could at least reduce treatment burden and unwarranted side effects. Although the costs for routine treatments are not particularly high,[9] development of the decision tool would preferably also include a cost-effectiveness analysis of different strategies, especially when effective strategies would turn out to include HPV testing.

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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 associates 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 prefered in practice while salicylic acid is prefered 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.

CHAPTER 12

Nederlandse samenvatting

Dankwoord

Curriculum Vitae

NEDERLANDSE SAMENVATTING

Wratten worden veroorzaakt door het humaan papillomavirus (HPV) en zijn één van de meest voorkomende redenen om naar de huisarts te gaan, zeker voor kinderen. Het meisje met voetzoolwratten uit de casus in **Hoofdstuk 1** illustreert dat patiënten vaak hulp zoeken omdat hun wratten fysieke en/of psychosociale klachten veroorzaken. De alledaagse vragen *Hoe ben ik aan mijn wratten gekomen?* en *Hoe kom ik van mijn wratten af?* leggen ons gebrek aan kennis bloot over de *transmissie* en *behandeling* van wratten. Dit proefschrift bestudeert daarom enerzijds de risicofactoren voor HPV transmissie om richting te geven aan evidence-based aanbevelingen voor de preventie van wratten (**Deel 1**), en anderzijds de effectiviteit van de meest gebruikte therapieën voor wratten om de behandeling van wratten in de huisartspraktijk te optimaliseren (**Deel 2**).

Deel 1: Transmissie

Omdat er maar weinig onderzoek gedaan is naar de epidemiologie en de transmissie van wratten, is het doel van **Hoofdstuk 2** om de prevalentie van wratten in een gemiddelde populatie basisschoolkinderen te bepalen en de relatie met risicofactoren in de omgeving te verkennen. In de observationele studie op vier basisscholen blijkt een derde van de bestudeerde basisschoolkinderen (n=1565) wratten te hebben: 20% heeft voetzoolwratten, 9% heeft handwratten en 4% heeft beide. De prevalentie stijgt met de leeftijd en is lager voor kinderen met een niet-blank huidtype. Opmerkelijk is dat de helft van de ouders van de kinderen met wratten niet weet dat hun kinderen wratten heeft. Omgevingsfactoren suggereren dat transmissie van wratten plaatsvindt in het gezin en de schoolklas, en niet zozeer in openbare gelegenheden waar aanbevelingen ter preventie van wratten zich momenteel op richten.

Gebaseerd op de cross-sectionele relaties met omgevingsfactoren uit Hoofdstuk 2, is in **Hoofdstuk 3** een theoretisch model ontworpen (Figuur 3.1) voor de mate van blootstelling aan HPV. Om dit model te testen worden de basisschoolkinderen uit Hoofdstuk 2 na een jaar wederom op de aanwezigheid van wratten onderzocht (n=1001). De incidentie van wratten blijkt 29 per 100 persoonsjaren 'at risk'. De verspreiding in het gezin en in de klas blijken belangrijk voor het krijgen van wratten; kinderen uit een gezin met minimaal één van de gezinsleden met wratten hebben een ruim tweemaal hogere kans op het ontwikkelen van wratten (hazard ratio 2,1) en kinderen in klassen met meer andere kinderen met wratten hebben een hogere kans op het krijgen van wratten (hazard ratio 1,2 per 10% stijging van prevalentie in de klas). Verscheidene factoren gerelateerd aan de transmissie in openbare gelegenheden blijken de kans op het krijgen van wratten niet te verhogen. Kortom, de verspreiding van wratten lijkt inderdaad meer in het gezin en in de

klas plaats te vinden dan in openbare gelegenheden. Aanbevelingen over de preventie van wratten zouden zich dan ook meer moeten focussen op het beperken van de transmissie in het gezin en in de klas in plaats van de transmissie in openbare gelegenheden zoals zwembaden.

Hoofdstuk 4 richt zich op de HPV virustypen die de wratten veroorzaken. Het doel is om de prevalentie van de specifieke HPV typen op wratten in de huisartspraktijk te bepalen en de relatie met patiëntfactoren te verkennen. Dit hoofdstuk introduceert een nieuw ontwikkelde techniek om alle bekende HPV types die wratten kunnen veroorzaken vast te stellen in uitstrijkjes van wratten. In de 744 wratten afkomstig van 246 patiënten uit de huisartspraktijk komen HPV 1, 2, 27, en 57 het meest voor. In slechts 14% van de wratten wordt een ander HPV type gevonden. In tegenstelling tot het klinisch profiel van wratten met HPV 2, 27, en 57 (die afstammen uit het alpha genus), komen wratten met HPV 1 (dat afstamt uit het mu genus) het meest voor bij kinderen, op de voetzolen, en zijn kort aanwezig voordat ze aan de huisarts getoond worden. In 74% van de patiënten met meerdere wratten delen alle wratten van één patiënt hetzelfde HPV type. Deze bevindingen zijn een belangrijk startpunt voor verder onderzoek naar HPV specifieke transmissiepatronen en HPV specifieke behandelingen.

Deel twee: Behandeling

Er is geen recent onderzoek beschikbaar over het natuurlijk beloop van wratten. **Hoofdstuk 5** beschrijft het natuurlijk beloop van de 333 kinderen met wratten uit het eerder beschreven observationele basisschoolcohort. De helft van alle kinderen met wratten heeft na een jaar geen wratten meer. Jonge leeftijd en een niet-blank huidtype voorspellen een snelle genezing. Twintig procent van de kinderen gaat met hun wratten naar de huisarts waar ze meestal behandeld worden met vloeibare stikstof of geconcentreerde salicylzuurzalf. Daarnaast gebruikt 18% van de kinderen alleen thuiszorgartikelen: vooral dimethyl/propaan bevriezing of zalf met lage dosis salicylzuur. Bij kinderen met grote wratten of wratten die veel hinder veroorzaken worden hun wratten vaker behandeld (thuis of bij huisarts). Deze bevindingen over het beloop van wratten levert nuttige informatie op voor de huisarts om samen met ouder en kind een afgewogen beslissing te maken over het al dan niet behandelen van wratten.

Een groot aantal verschillende behandelingen is beschikbaar voor wratten. Voordat het onderzoek uit dit proefschrift was verricht, leek salicylzuurzalfbehandeling op basis van schaars en tegenstrijdig bewijs in de literatuur de meest effectieve optie. Het doel van **Hoofdstuk 6** is om te onderzoeken of de keuzes die huisartsen maakten bij de behandeling van wratten in hun praktijk overeenkwamen met het toenmalige wetenschappelijk

bewijs. Een landelijke aselecte enquête onder 280 Nederlandse huisartsen laat zien dat stikstofbehandeling de eerste keuze is voor zowel hand- als voetwratten. Salicylzuur wordt minder vaak gebruikt, en als het wordt gebruikt dan is dit vaak in combinatie met stikstof. Een afwachtend beleid heeft de voorkeur van minder dan 20% van de huisartsen en monochloorazijnzuur van 3% van de huisartsen. Er blijkt dus een groot verschil te bestaan tussen de voorkeur voor stikstoftherapie in de praktijk en de voorkeur voor salicylzuurzalf in de literatuur. Dit wordt mogelijk verklaard door de lage kwaliteit van het bewijs waarop de literatuur is gebaseerd.

Hoofdstuk 7 presenteert de resultaten van de eerste Warts Randomised Treatment Study (WARTS-1). Deze pragmatische multicenter trial vergelijkt de effectiviteit van stikstoftherapie, salicylzuurbehandeling en een afwachtend beleid bij immunocompetente patiënten die met wratten bij de huisarts komen (n=250). Er blijkt een opvallend verschil in behandelingsresultaat te zijn tussen patiënten met handwratten en patiënten met voetzoolwratten. Stikstoftherapie is namelijk de meest effectieve behandeling voor handwratten (49% van de patiënten na 3 maanden genezen) met acceptabele bijwerkingen, de laagste behandelingsbelasting en de hoogste patiënttevredenheid. Voor voetzoolwratten zijn de beide actieve behandelingen niet effectiever dan een afwachtend beleid (23% van de patiënten genezen na 3 maanden). Ook blijken voetzoolwratten veel hardnekkiger bij adolescenten en volwassenen dan bij kinderen.

Op zoek naar een effectievere eerstelijns behandeling toont **Hoofdstuk 8** de resultaten van de tweede Warts Randomised Treatment Study (WARTS-2). Met de kennis uit WARTS-1 dat het behandelresultaat verschilt voor handwratten en voetzoolwratten is WARTS-2 opgezet als een pragmatisch multicenter trial met twee parallelle groepen. De effectiviteit en bijwerkingen van monochloorazijnzuur (MCA) worden voor de groep patiënten met handwratten vergeleken met stikstoftherapie (de beste gangbare therapie uit WARTS-1), en voor de groep patiënten met voetzoolwratten vergeleken met de combinatie van stikstoftherapie en salicylzuurbehandeling. Voor handwratten blijkt MCA een goed alternatief voor stikstoftherapie. De effectiviteit van MCA (43% van de patiënten genezen na 3 maanden) is vergelijkbaar met de effectiviteit van stikstoftherapie, maar MCA veroorzaakt minder pijn tijdens de behandeling. Dit kan aantrekkelijk zijn voor kinderen die bang zijn voor de pijn tijdens stikstoftherapie. Voor voetzoolwratten heeft MCA (46% van alle patiënten genezen na 3 maanden) de voorkeur boven de combinatie van stikstoftherapie en salicylzuurbehandeling (39% van de patiënten genezen na 3 maanden) op basis van effectiviteit, bijwerkingen en de belasting van behandeling.

Omdat we uit de bovenstaande trials weten dat de behandeling van wratten voor de helft van de patiënten niet werkt, lijkt het nuttig om subgroepen patiënten te identificeren die

wel op behandeling reageren. Het doel van **Hoofdstuk 9** is om binnen de WARTS-1 trial de relatie te onderzoeken tussen de effectiviteit van behandelingen en het specifieke HPV type dat de wrat veroorzaakt. Voor handwratten blijkt het HPV type in de praktijk weinig relevant, omdat het grootste deel van de wratten veroorzaakt wordt door de vergelijkbare HPV types 2, 27 en 57, waartussen geen verschil in behandelingeffect bestaat. Voor voetwratten met HPV 1 blijkt de kans op genezing na een afwachtend beleid 8 maal zo groot in vergelijking met HPV 2, 27, en 57. Verder blijkt salicylzuur effectiever dan een afwachtend beleid voor zowel de voetzoolwratten met HPV 1 als de voetzoolwratten met HPV 2, 27, en 57. Kortom, HPV typering van wratten is een nieuwe richting om behandeling van voetwratten te optimaliseren.

De algemene discussie in **Hoofdstuk 10** brengt de resultaten van dit proefschrift terug naar de dagelijkse praktijk. De belangrijkste bevinding om antwoord te geven op de vraag *Hoe ben ik aan mijn wratten gekomen?* is dat de transmissie van wratten vooral in het gezin en de klas plaatsvindt. Om tot een antwoord te komen op de vraag *Hoe kom ik van mijn wratten af?,* moeten patiënten worden geïnformeerd over het gunstige natuurlijk beloop, de beperkte effectiviteit van behandeling en de bijwerkingen ervan. Vervolgens kan de huisarts er samen met de patiënt voor kiezen om af te wachten, of behandeling te starten: stikstoftherapie of monochloorazijnzuur voor handwratten, monochloorazijnzuur of een combinatie van stikstoftherapie en salicylzuurbehandeling voor voetwratten. Tot slot is de belangrijkste aanbeveling van dit hoofdstuk om samen met de beroepsgroep een beslismodel voor de behandeling van wratten te ontwikkelen om patiënten optimaal te laten profiteren van de beschikbare kennis. Dit beslismodel kan patiënten adviseren wanneer het nuttig is met hun wratten naar de huisarts te gaan en kan artsen helpen de beste behandeling te kiezen voor specifieke groepen wratten of patiënten.

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CURRICULUM VITAE

Sjoerd Bruggink was born on October 11th 1980 in Alkmaar, the Netherlands. After graduating secondary school at the Murmellius Gymnasium Alkmaar in 1998, he studied medicine at the Leiden University Medical Center. Throughout his studies, he worked at the faculty of medicine developing questions for medical exams.

After finishing medical school in 2005, he completed the first year of the vocational training in tropical medicine as a house officer in general surgery at the Port Hospital in Rotterdam (J.H. van Dam). After travelling through South East Asia and New Zealand, he matched his broad interest in patient care and medical research in 2007 by combining the vocational training in general practice (M.L.T. Rodewijk and W.J.M. Vreijling) and this PhD project at the department of Public Health and Primary Care of the Leiden University Medical Center (J. Gussekloo, W.J.J. Assendelft, J.A.H. Eekhof).

He graduated as a general practitioner in 2011 and started as an independent contractor for practices in Leiden and Noordwijk. Since November 2012, Sjoerd works in a rural coastal general practice in Opunake, New Zealand, where he enjoys biking, surfing, and family life with Jiska and their two young daughters Sophie and Janne.