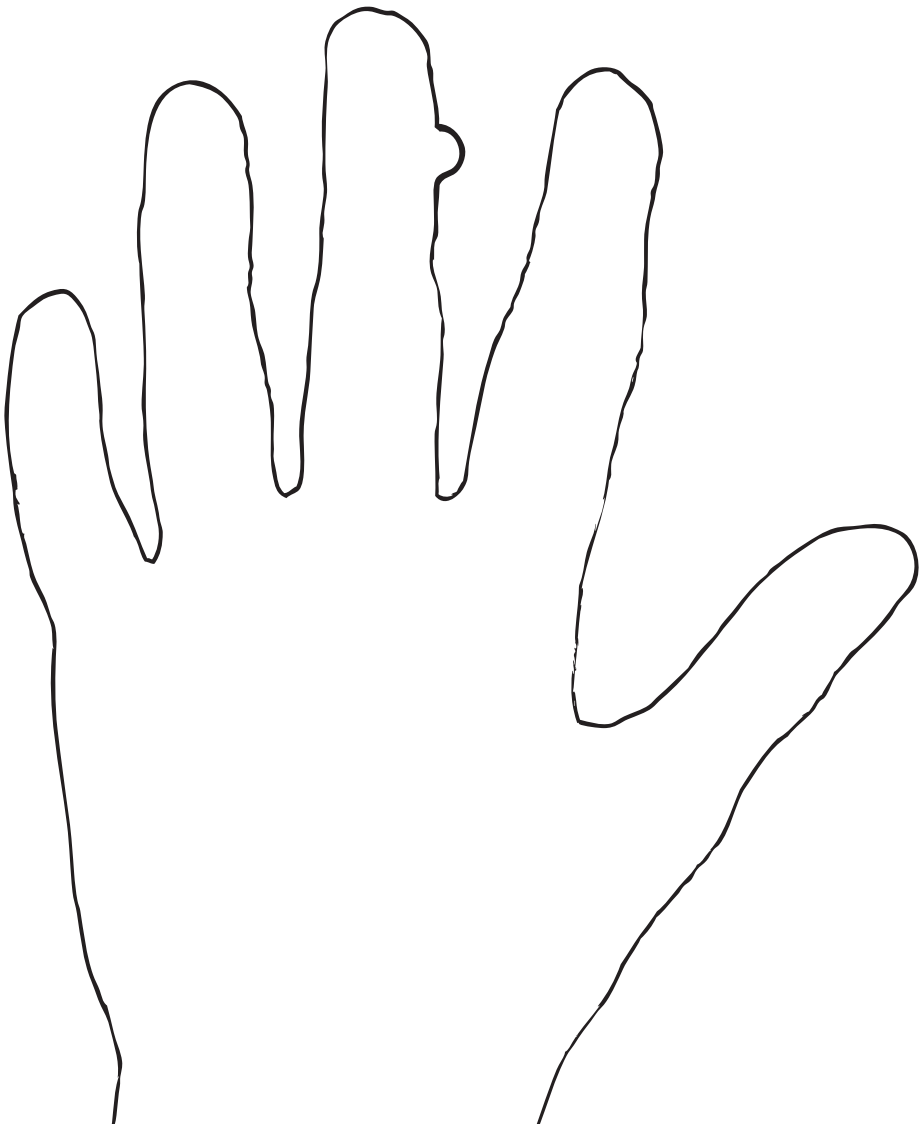


Final chapters

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

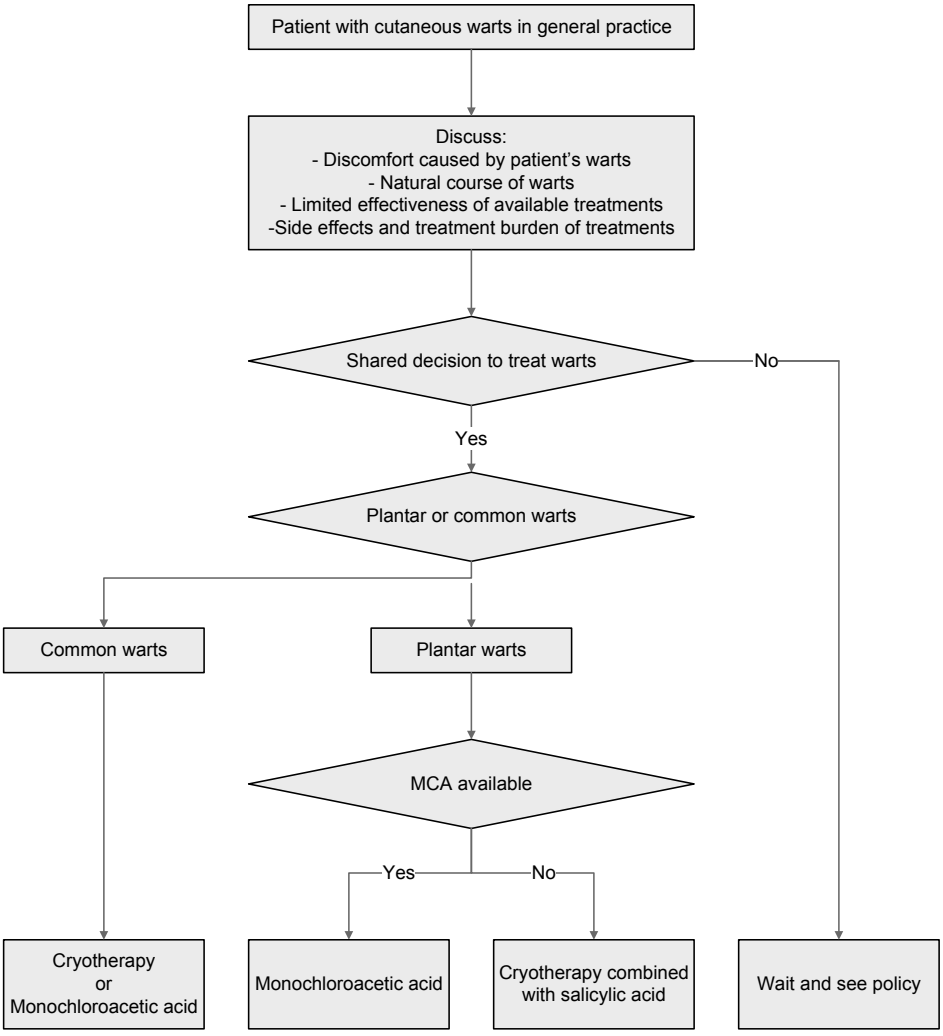
How did I get warts?

- 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

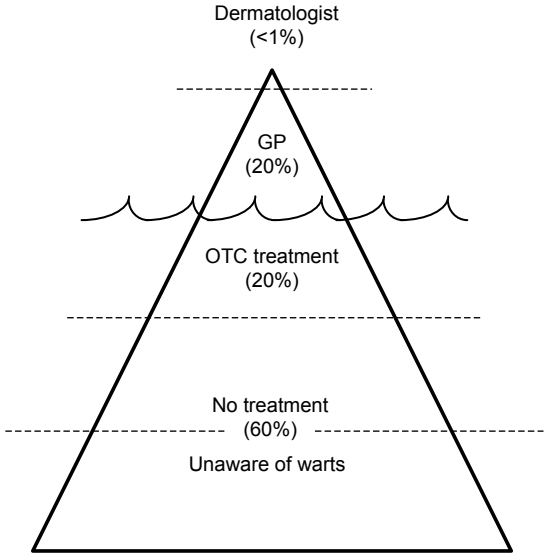
HPV types in the general practice population revealed that HPV types 1,2,27, and 57 are the most prevalent types responsible for the development of warts.

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.



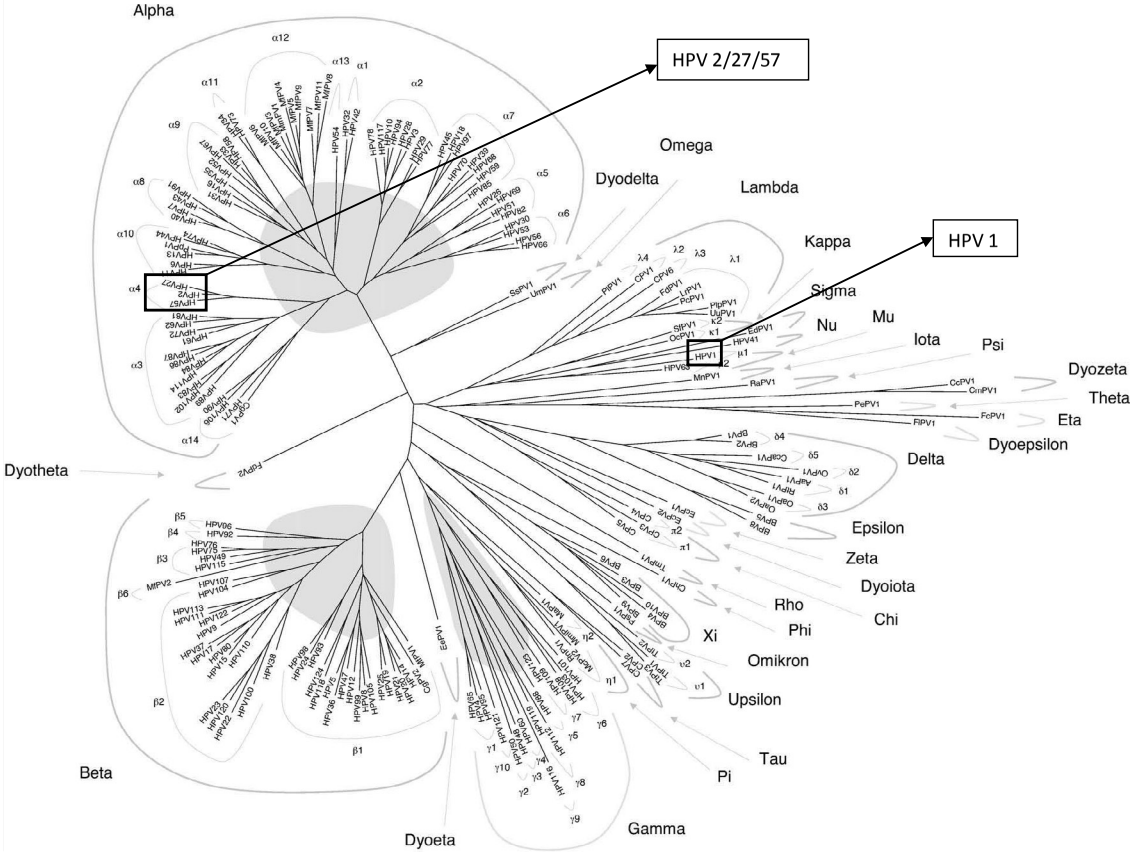
only 20% of all children with warts went to see the general practitioner (GP). Thus, the GP only sees the top of the iceberg of children with warts (Figure 10.2). This GP selection of children with warts is indeed different from the children not seeking medical advice. The primary school cohort showed 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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